CLINICA PUBLICATION



DrNB / DNB NEUROSURGERY

EXIT EXAMINATION

SOLVED

QUESTION BANK

ALL 350 QUESTIONS ANSWERED IN FULL

SAMPLE EDITION

500 PAGES FROM ALL 9 VOLUMES

2020 – 2026 | 35 PAPERS | TOPIC-WISE | CITED

answers sourced from

Youmans and Winn Neurological Surgery

8th Edition · 2022

REVIEWED BY

Dr Sumit Mehra

Visit www.clinicapublication.com to order

National Board of Examinations · Neurosurgery (Part-II / Final) · Papers I, II & III

CLINICA PUBLICATION

Academic publishing for postgraduate medical examinations

DrNB / DNB NEUROSURGERY EXIT EXAMINATION

SOLVED Question Bank

All 350 questions answered · 2020 to 2026

VOLUME ONE

Chapter 1 · Neuroanatomy

ANSWERS SOURCED FROM

Youmans and Winn Neurological Surgery, 8th Edition (2022)

Examination sessions covered	**12**
Question papers	**35**
Questions answered in full	**350**
Topic chapters	**21**
Words of answer	**2,094,636**
Textbook figures reproduced	**1147 in 2280 places**
Tables built from the source	**953**
Distinct textbook pages cited	**2830**
Page citations in the text	**27,955**

REVIEWED BY

Dr Sumit Mehra

To order a printed & bound copy

Visit www.clinicapublication.com

Questions are reproduced from National Board of Examinations papers for academic revision only. Answers are the compiler's own summaries of material in the cited source and are not reproductions of it. Page numbers refer to the printed pagination of the 8th edition. This compilation is independent of, and not endorsed by, the National Board of Examinations or the publisher of the cited textbook.

Contents

How to use this book · the source rule 4
Examination pattern & papers covered 5
STATISTICS · what repeats, and how often 6

TOPIC CHAPTERS	QUESTIONS	
1. Neuroanatomy & Applied Anatomy	49	10
2. Neurophysiology, ICP & Cerebral Blood Flow	15	Vol Two
3. Head Injury & Neurotrauma	22	Vol Two
4. Craniovertebral Junction & Spinal Trauma	10	Vol Two
5. Neuro-Oncology: Gliomas, Intra-axial Tumours & Neuropathology	15	Vol Three
6. Skull Base, Meningioma & Orbital Lesions	15	Vol Three
7. Sellar, Suprasellar & Pituitary Region	8	Vol Three
8. Ventricular, Pineal & Posterior Fossa Lesions	10	Vol Four
9. Hydrocephalus, Shunts & CSF Disorders	15	Vol Four
10. Cerebrovascular I: Aneurysms & Subarachnoid Haemorrhage	14	Vol Four
11. Cerebrovascular II: AVM, Fistulae, Stroke & Venous Disease	18	Vol Five
12. Paediatric Neurosurgery & Craniofacial Anomalies	8	Vol Five
13. Spinal Dysraphism & Congenital Anomalies	11	Vol Five
14. Spine: Degenerative Disease, Spinal Tumours & Spinal Surgery	21	Vol Six
15. Neuro-Infections	18	Vol Six
16. Functional Neurosurgery, Epilepsy, Pain & Movement Disorders	30	Vol Seven
17. Peripheral Nerve & Brachial Plexus	13	Vol Eight
18. Neuroimaging, Neuromonitoring, Instruments & Technology	26	Vol Eight
19. Radiosurgery & Radiation in Neurosurgery	7	Vol Nine
20. Neuro-Critical Care, Neuro-Anaesthesia & Pharmacology	10	Vol Nine
21. Brain Death, Ethics, Research Methodology & History of Neurosurgery	15	Vol Nine

Appendix A · Paper-wise index (2020 – 2026) 350 Vol Nine
Appendix B · Youmans chapters used Vol Nine

How to use this book

Every question asked in the DrNB / DNB Neurosurgery exit (Part-II, Final) theory examination between June 2020 and April 2026 is answered here — thirty-five papers, three hundred and fifty questions, none omitted.

The source rule

Answers are written from Youmans and Winn Neurological Surgery, 8th Edition (2022), and from nothing else. Each factual block carries the printed page it came from, in the form [YW p.1339]; an e-page of the online edition cites as [YW p.615.e6]. A grey strip at the foot of every answer lists that answer's pages together, so you can go straight to the book and read around the point.

Where the textbook does not cover something — Indian legislation such as the THOTA Act, the biographies of Indian neurosurgeons, a handful of eponymous scales — the answer is not skipped and not guessed. It carries a red NOT IN YOUMANS flag, names the source actually used, and is answered anyway. 83 of the three hundred and fifty answers carry such a flag, most of them for one part only.

Where a current guideline is needed to complete an answer that the textbook leaves short, one tagged line is added, marked in red, for example [Guideline: BTF 4th ed., 2016]. This is deliberately rare. Where the textbook and another source disagree, the textbook is followed.

Reading an answer

Question block

The grey panel carries the question exactly as it was set, with its session, paper, question number and mark split.

Part headings

Teal bars mark each lettered part with its own marks, in the order the paper set them. Answer them in that order in the exam.

Tables

Anything the paper asks you to classify, compare, grade or differentiate is given as a table — write it as a table in the answer book.

Figures

Every picture in this book is the real figure, cropped from Youmans & Winn 8e at 350 dpi and printed with its source page. The italic line beneath each one lists exactly what to label when you reproduce it in the answer script.

HIGH-YIELD box

The green box closing each answer is the last-minute revision list for that question.

Citations

The small brown page numbers are for verification and further reading. Do not copy them into your answer script.

Printed copies

Printed and bound copies of this book are published by Clinica Publication.

Visit www.clinicapublication.com to order.

Examination pattern & papers covered

Three theory papers, each of three hours and 100 marks, each with ten compulsory questions of 10 marks. Papers from August 2021 onward were delivered in the computer-based format with the answer script written offline.

SESSION	PAPERS	No. OF PAPERS	QUESTIONS
JUN 2020	Paper I, Paper II, Paper III	3	**30**
DEC 2020	Paper I, Paper II, Paper III	3	**30**
JUN 2021	Paper I, Paper II, Paper III	3	**30**
DEC 2021	Paper I, Paper II, Paper III	3	**30**
JUN 2022	Paper I, Paper II, Paper III	3	**30**
DEC 2022	Paper I, Paper II, Paper III	3	**30**
APR 2023	Paper I, Paper II, Paper III	3	**30**
OCT 2023	Paper I, Paper II, Paper III	3	**30**
MAY 2024	Paper I, Paper II, Paper III	3	**30**
JAN 2025	Paper I, Paper II, Paper III	3	**30**
OCT 2025	Paper I, Paper II, Paper III	3	**30**
APR 2026	Paper I, Paper II	2	**20**
TOTAL		35	350

April 2026 is represented by Papers I and II; Paper III of that session was not available at the time of compilation. Fifteen pages of the source question papers existed only as scanned images and were transcribed by hand.

CHAPTER 1

Neuroanatomy & Applied Anatomy

49
QUESTIONS SOLVED

Internuclear Ophthalmoplegia & Brainstem Syndromes — 6 questions

a) Draw a labelled diagram of transverse section of the upper midbrain. [4]
b) Parinaud's syndrome and its clinical correlates. [4]
c) Aqueductoplasty. [2]

LONG | APR 2023 · Paper III · Q2 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 2 *Surgical Anatomy of the Brain*, §Basal Surface: Neural Relationships and §Brainstem, pp. 24, 35-38, 41 (Fig. 2.22, p. 24; Fig. 2.47, p. 36; Fig. 2.51, p. 38; Fig. 2.58, p. 41). Supplementary: Ch. 111 *Deep Brain Stimulation for Parkinson Disease*, §Targeting, p. 734 (Fig. 111.2, p. 734); Ch. 164 *Pineal Tumors*, §Clinical Presentation and §Diagnosis, p. 1149 (Fig. 164.1, p. 1149); Ch. 15 *Neuro-ophthalmology*, §Supranuclear, Internuclear, and Cerebellar and §Disorders of the Ocular Motor System, pp. 200.e19-200.e20, 200.e23, 200.e26 (Tables 15.3-15.4, pp. 200.e19-200.e20); Ch. 228 *Neuroendoscopy*, §Endoscopic Aqueductoplasty and §Indications, pp. 1730, 1732-1733; Ch. 45 *The Role of Endoscopic Third Ventriculostomy: A Critical Review*, §Third Ventricular Floor Fenestration, pp. 349-350 (Figs. 45.2-45.3, p. 349); Ch. 241 *Brainstem Gliomas*, §Midbrain, pp. 1825-1826 (Fig. 241.2, p. 1826).

(a) Draw a labelled diagram of a transverse section of the upper midbrain [4]

1. The organising sentence Youmans gives you — write this before you draw

- **The brainstem is divided into three parts: midbrain, pons and medulla** YW p.35. Say this first, because the examiner wants to see that you can place the section before you draw it.
- **The midbrain is divided by a midline sagittal plane into two cerebral peduncles.** Each peduncle is then divided into **three parts** YW p.35:
  - **An anterior part — the crus cerebri, or basis pedunculi.** The descending fibre mass (corticospinal, corticobulbar, corticopontine); this is the part visible from the front, forming the walls of the interpeduncular fossa.
  - **An intermediate part — the tegmentum.** Carries the red nucleus, the oculomotor and trochlear nuclei, the medial longitudinal fasciculus (MLF), the mesencephalic reticular formation and the ascending lemnisci.
  - **A posterior part, located behind the aqueduct — the tectum.** At the upper midbrain this is the **quadrigeminal plate**, i.e. the superior and inferior colliculi [YW pp. 35, 36].
- **The two boundaries between crus and tegmentum are both named, and both are examinable** YW p.35:
  - **The substantia nigra** separates crus cerebri from tegmentum internally.
  - **The lateral mesencephalic sulcus** separates them on the surface. It begins in the depth of the interpeduncular fossa as the **pontomesencephalic sulcus**, runs around the inferior margin of the crus cerebri, and passes behind the crus as the lateral mesencephalic sulcus [YW pp. 35, 36]. Superiorly it is joined by the interpeduncular (interbrachial) sulcus and ascends **to the medial geniculate body** YW p.38.

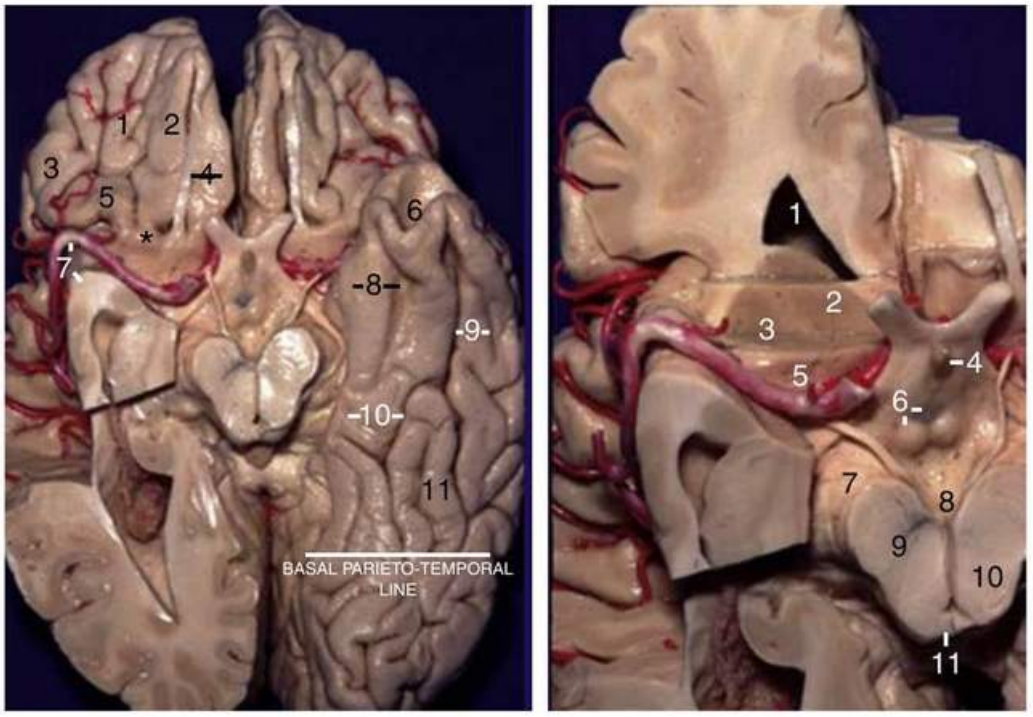


Figure 2.22. *Left,* Basal view. *1,* Anterior orbital gyrus; *2,* medial orbital gyrus; *3,* lateral orbital gyrus; *4,* rectus gyrus and olfactory tract; *5,* posterior orbital gyrus; *6,* temporal pole; *7,* genu of middle cerebral artery and insular pole; *8,* uncus and rhinal sulcus; *9,* occipitotemporal sulcus and inferior temporal gyrus; *10,* parahippocampal gyrus and collateral sulcus; *11,* fusiform gyrus; *, posteromedial orbital lobule. *Right,* Basal view. *1,* Frontal horn; *2,* caudate nucleus (head); *3,* lentiform nucleus; *4,* pituitary stalk; *5,* anterior perforated substance; *6,* tuber cinereum and mammillary body; *7,* crus cerebri; *8,* posterior perforated substance; *9,* substantia nigra; *10,* tegmentum; *11,* tectum.

*Reproduced from Youmans & Winn 8e, Fig. 2.22, p. 24 — Label when you reproduce the RIGHT panel (basal view of a sectioned specimen): 1 frontal horn, 2 head of caudate nucleus, 3 lentiform nucleus, 4 pituitary stalk, 5 anterior perforated substance, 6 tuber cinereum and mammillary body, 7 **crus cerebri**, 8 **posterior perforated substance**, 9 **substantia nigra**, 10 **tegmentum**, 11 **tectum**. Labels 7-11 are exactly the transverse-section layers of the upper midbrain as Youmans names them, seen in a real cut specimen — carry those five names across onto your own line drawing.*

2. What to put on the drawing, layer by layer, front to back

- **Interpeduncular fossa** in the anterior midline, bounded laterally by the two crura cerebri. **The oculomotor nerves emerge from the medial side of the crura cerebri in the interpeduncular fossa** YW p.35 — draw CN III leaving the medial surface of each crus.
- **Posterior perforated substance** forms the floor of the fossa; it is the entry site of the **posterior thalamoperforating arteries** arising from P1, which enter through the posterior perforated substance, the interpeduncular fossa and the medial crus cerebri YW p.27.
- **Crus cerebri (basis pedunculi)** — the anterior third of the section, drawn as a broad crescent on each side.
- **Substantia nigra** — a dark band immediately behind the crus, forming the internal boundary with the tegmentum YW p.35.
- **Tegmentum** — the middle third. At the level of the superior colliculus mark:

  - **Red nucleus.** Youmans uses the **anterior border of the red nucleus on an axial slice 4 mm below the midcommissural plane** as the working stereotactic landmark; a line drawn tangential to the anterior apex of the red nucleus is seen cutting through the subthalamic nucleus YW p.734. This is the most practical way to prove you know the level.
  - **Oculomotor nucleus** in the periaqueductal grey. Youmans localises the third-nerve nucleus to **periaqueductal grey matter at the level of the superior colliculus**, and notes that **the superior rectus subnucleus is contralateral and there is a single midline levator subnucleus** — hence a nuclear third-nerve lesion produces **bilateral ptosis and bilateral superior rectus palsy** YW p.200.e19.
  - **Fascicles of CN III**, which **pass through the decussating superior cerebellar peduncle, the substantia nigra and the medial cerebral peduncle** YW p.200.e19. Draw the fascicles crossing all three, because that is the anatomical basis of the three named fascicular syndromes (Table 2).
  - **Medial longitudinal fasciculus (MLF)**, paramedian, just ventral to the periaqueductal grey. The trochlear nucleus lies in **caudal periaqueductal grey matter, dorsal to the MLF** YW p.200.e20.
  - **Mesencephalic reticular formation** and **pretectum**, both named by Youmans as lying within the territory of the posterior thalamoperforating arteries YW p.27.
- **Cerebral aqueduct** in the midline, the landmark separating tegmentum from tectum YW p.35.
- **Tectum (quadrigeminal plate)** — the posterior third. **The posterior aspect of the midbrain presents superior and inferior colliculi (quadrigeminal plate)** YW p.36. At the *upper* midbrain these are the **superior colliculi**. Mark also the **medial geniculate body** laterally, because the lateral mesencephalic sulcus ascends to it YW p.38.
- **Trochlear nerve. The trochlear nerve exits the brainstem below the inferior colliculus** YW p.36 — so on an upper-midbrain (superior colliculus) section it has not yet emerged. Saying so separates a good answer from an average one.

Constructing the diagram. Youmans 8e teaches the midbrain section through real dissections (Figs. 2.22, 2.51, 2.58) and axial MRI (Fig. 111.2) rather than through a single stylised cross-sectional line drawing, so draw your own: a symmetrical oval; interpeduncular fossa and the two crura cerebri anteriorly with CN III emerging medially; a dark band of substantia nigra behind each crus; the tegmentum containing red nucleus, oculomotor nucleus in periaqueductal grey, paramedian MLF and mesencephalic reticular formation; the cerebral aqueduct in the midline; the tectum with the two superior colliculi posteriorly. Add the lateral mesencephalic sulcus on the surface between crus and tegmentum, and the medial geniculate body at its upper end.

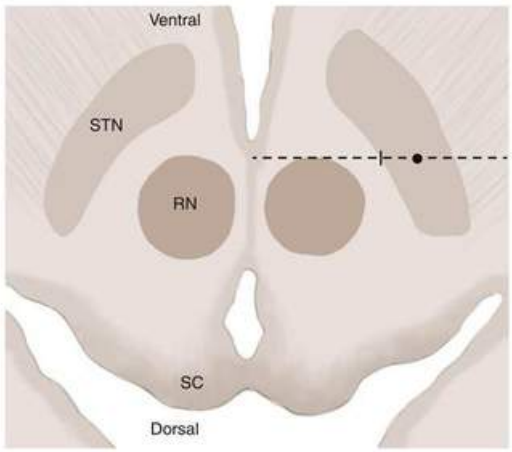


Figure 111.2. Midbrain at 4 mm below the midcommissural plane. The line parallel to the ventral border of the red nucleus *(RN; dashed line)* is extended to the midpoint of the subthalamic nucleus *(STN; black dot)* or, if the lateral border is difficult to interpret, at least 2 mm away from the STN medial border *(short vertical bar)* for targeting. *SC*, Superior colliculi.

ensure accessibility to the face from the unsterile side. After a skin incision just posterior to the planned skull entry location,

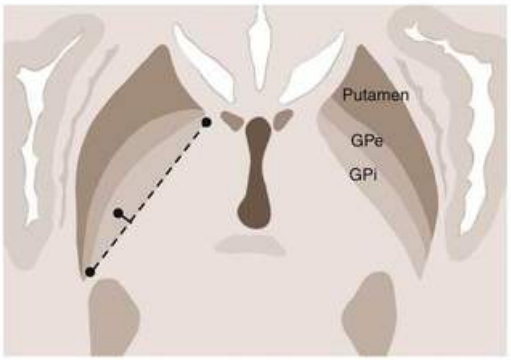


Figure 111.3. The axial cut at the midcommissural plane. The medial border of the globus pallidus interna *(GPi)* is split into thirds *(dashed line,)* and a point 3 to 4 mm lateral and perpendicular to the line at the junction of the posterior one-third and anterior two-thirds *(short vertical bar with black dot)* is used for targeting. *GPe*, Globus pallidus externa.

*Reproduced from Youmans & Winn 8e, Fig. 111.2, p. 734 — Imaging correlate — describe on this axial T2 fast spin echo image taken **4 mm below the midcommissural plane**: the **red nucleus (RN)** and the dashed tangent drawn parallel to its ventral border, the **subthalamic nucleus (STN)** that this line crosses, the **putamen**, the **globus pallidus externa and interna (GPe, GPi)**, and the **superior colliculi (SC)** posteriorly, with ventral marked anteriorly on the image. This is the upper midbrain as the stereotactic surgeon actually sees it.*

Table 1 · Upper midbrain — the parts of each cerebral peduncle, their boundaries, contents and vascular supply. Compiled from Youmans & Winn 8e, Ch. 2 pp. 24, 27, 35-36, 38 (Fig. 2.22, p. 24).

#	Layer (front to back)	Separated from the next by	Key contents to label	Arterial supply / territory at risk
1	**Crus cerebri (basis pedunculi)**	Substantia nigra internally; lateral mesencephalic sulcus on the surface	Descending corticospinal, corticobulbar and corticopontine fibres; CN III emerging medially into the interpeduncular fossa	Direct perforating arteries from P2A to the crus cerebri; anterior choroidal artery branches to the crus cerebri
2	**Substantia nigra**	— (it *is* the boundary)	Pigmented nucleus	Posterior thalamoperforating arteries (P1)
3	**Tegmentum**	Cerebral aqueduct posteriorly	Red nucleus; oculomotor nucleus in periaqueductal grey at the superior-colliculus level; trochlear nucleus caudally, dorsal to the MLF; MLF; mesencephalic reticular formation	Posterior thalamoperforating arteries (P1) — thalamus, hypothalamus, subthalamus, substantia nigra, red nucleus, oculomotor and trochlear nuclei and nerve, mesencephalic reticular formation, pretectum, rostromedial third-ventricular floor, posterior internal capsule
4	**Tectum (quadrigeminal plate)**	—	Superior colliculi (upper midbrain); inferior colliculi (lower midbrain); CN IV exits below the inferior colliculus	Long circumflex arteries from P1 reach the colliculi; medial posterior choroidal artery supplies crus cerebri, tegmentum, geniculate bodies, colliculi, pulvinar, pineal gland and medial thalamus

5	**Posterior perforated substance** (floor of interpeduncular fossa)	—	Entry site of perforators	Posterior thalamoperforating arteries from P1

3. Surface landmarks from the same section — worth the extra mark

- **Frontal (ventral) view**: interpeduncular fossa, the two crura cerebri, and the **pontomesencephalic sulcus separating midbrain from pons**, which originates in the depth of the interpeduncular fossa and runs around the inferior margin of the crus [YW pp. 35, 36].
- **Superior (dorsal) view**: crus cerebri laterally, the **anterior cerebellar incisura and cerebellomesencephalic fissure** behind (the brainstem fits into the anterior cerebellar incisura), the quadrigeminal plate, and the **interpeduncular or interbrachial sulcus** separating superior from middle cerebellar peduncle, which ascends from the bottom of the cerebellomesencephalic fissure [YW pp. 38, 41].
- **Posterolateral view**: **medial geniculate body, superior colliculi, superior cerebellar peduncle**, then middle cerebellar peduncle, in that order from above downward YW p.41.

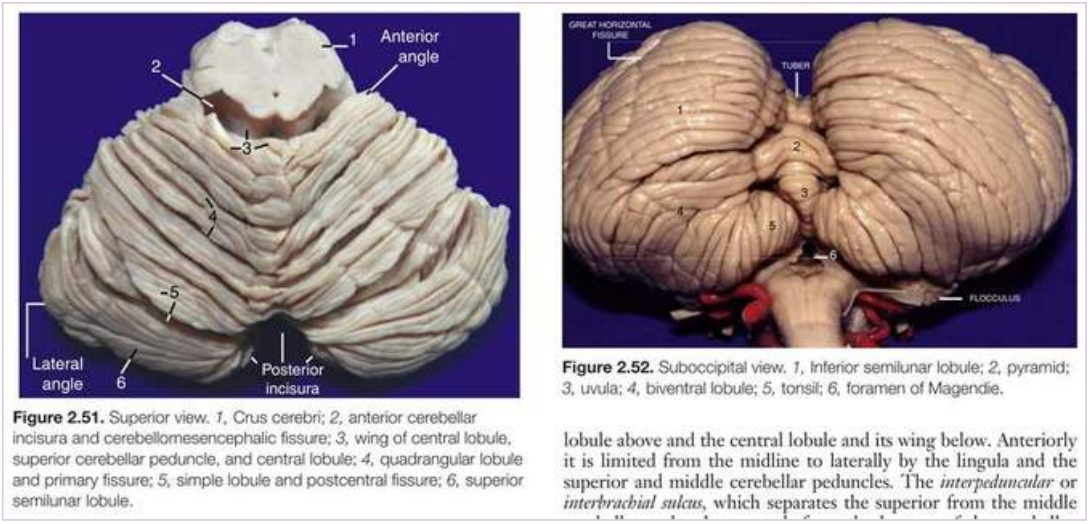


Figure 2.51. Superior view. *1*, Crus cerebri; *2*, anterior cerebellar incisura and cerebellomesencephalic fissure; *3*, wing of central lobule, superior cerebellar peduncle, and central lobule; *4*, quadrangular lobule and primary fissure; *5*, simple lobule and postcentral fissure; *6*, superior semilunar lobule.

Figure 2.52. Suboccipital view. *1*, Inferior semilunar lobule; *2*, pyramid; *3*, uvula; *4*, biventral lobule; *5*, tonsil; *6*, foramen of Magendie.

lobule above and the central lobule and its wing below. Anteriorly it is limited from the midline to laterally by the lingula and the superior and middle cerebellar peduncles. The *interpeduncular* or *interbrachial sulcus*, which separates the superior from the middle

*Reproduced from Youmans & Winn 8e, Fig. 2.51, p. 38 — Label when you reproduce it (superior view of midbrain and cerebellum): 1 **crus cerebri**, 2 anterior cerebellar incisura and cerebellomesencephalic fissure, 3 wing of central lobule, superior cerebellar peduncle and central lobule, 4 quadrangular lobule and primary fissure, 5 simple lobule and postcentral fissure, 6 superior semilunar lobule. This is the upper midbrain as seen down a supracerebellar infratentorial corridor.*

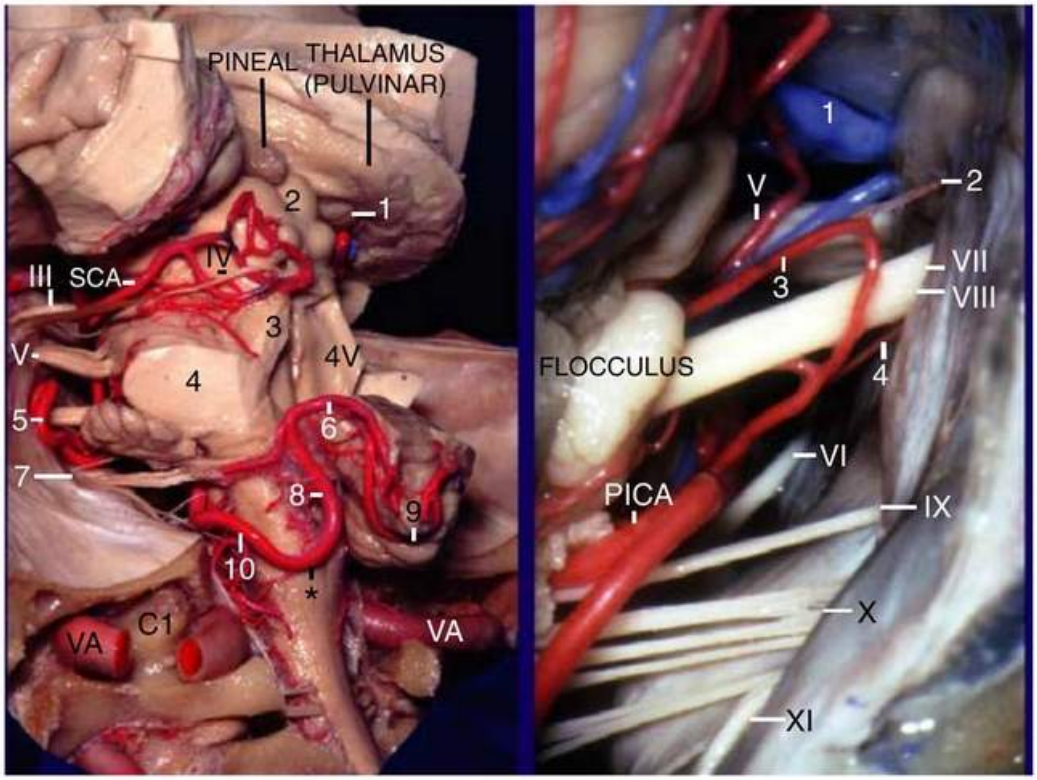


Figure 2.58. *Left,* Posterolateral view. *1,* Medial geniculate body; *2,* superior colliculi; *3,* superior cerebellar peduncle; *4,* middle cerebellar peduncle; *5,* anterior inferior cerebellar artery (AICA), cranial nerves VII and VIII; *6,* cranial loop of posterior inferior cerebellar artery (PICA) (supratonsillar segment); *7,* jugular foramen; *8,* PICA (posterior medullary segment); *9,* PICA (pyramidal loop); *10,* PICA (lateral medullary segment); *, caudal loop. *Right,* Retromastoid view of right cerebellopontine angle. *1,* Superior petrosal vein; *2,* subarcuate artery (AICA); *3,* AICA; *4,* internal auditory artery.

*Reproduced from Youmans & Winn 8e, Fig. 2.58, p. 41 — Label the LEFT panel (posterolateral view of the dorsal brainstem): 1 **medial geniculate body**, 2 **superior colliculi**, 3 **superior cerebellar peduncle**, 4 **middle cerebellar peduncle**, 5 AICA and cranial nerves; mark the trochlear (IV) and trigeminal (V) nerves, the flocculus and PICA. State in your label that CN IV emerges *below the inferior colliculus*, which is why it is absent from an upper-midbrain section.*

(b) Parinaud's syndrome and its clinical correlates [4]

4. Definition — Youmans gives it twice; quote both

- **Ch. 164 (the pineal surgeon's version):** *"Direct compression of the midbrain, particularly at the level of the superior colliculus, can cause disorders of extraocular movement, classically known as Parinaud syndrome. This syndrome can consist of paralysis of upgaze, convergence or retraction nystagmus, and light-near pupillary dissociation"* YW p.1149.
- **Ch. 15 (the neuro-ophthalmologist's version): the dorsal midbrain syndrome (Parinaud syndrome) is a constellation of signs including supranuclear upgaze palsy, convergence-retraction nystagmus (often elicited by attempts at upgaze), Collier sign (upper eyelid retraction), and pupillary light-near dissociation** YW p.200.e23.
- **The two lists are the same tetrad.** Present them as a numbered tetrad and you cannot lose the mark.

5. The anatomical correlate, sign by sign

- **Supranuclear upgaze palsy** — results from **involvement of projections from the vertical gaze centres travelling in the posterior commissure** YW p.200.e23. This is why the lesion is *dorsal* and *pretectal*, and why the palsy is supranuclear: the oculomotor nuclei and nerves themselves work, so the Bell phenomenon and the oculocephalic manoeuvre may still elevate the eyes.
- **Complete supranuclear vertical gaze palsy is a different, more rostral lesion:** *"when a complete supranuclear vertical gaze palsy is present, an intrinsic rostral midbrain lesion involving the rostral interstitial nuclei of the MLF is likely"* YW p.200.e23. Naming **riMLF** earns a mark on its own.
- **Convergence-retraction nystagmus** — elicited by attempts at upgaze; co-contraction of the horizontal recti retracts the globe into the orbit [YW pp. 200.e23, 1149].
- **Collier sign** — **upper eyelid retraction** from dorsal midbrain compression or infiltration; the same process may alternatively produce **ptosis** [YW pp. 200.e23, 1149].
- **Light-near dissociation** — the pupil reacts poorly to light but constricts to a near stimulus. Youmans lists the same phenomenon in **"blind" eyes**, in **Adie tonic pupil**, and **bilaterally in neurosyphilis (the Argyll Robertson pupil) or the dorsal midbrain syndrome** YW p.200.e26. Quote that list as the differential diagnosis of light-near dissociation.
- **Fourth nerve palsy with diplopia** — **less commonly** part of the picture YW p.1149. The trochlear nucleus lies in caudal periaqueductal grey dorsal to the MLF, and its **fascicles decussate in the anterior medullary velum**, so a dorsal midbrain lesion is well placed to catch them; a nuclear fourth-nerve lesion produces **internuclear ophthalmoplegia contralateral to the superior oblique weakness** because of the decussation, and **isolated fourth nerve nucleus lesions are very rare** YW p.200.e20.
- **Sylvian aqueduct syndrome** — **paralysis of downgaze or horizontal gaze from further midbrain compression, superimposed on Parinaud syndrome** YW p.1149. This is the "extra" the examiner is fishing for.
- **Raised ICP without a structural midbrain lesion can mimic the whole picture**: with downward diencephalic displacement, *"clinically, this results in findings resembling Parinaud syndrome"* YW p.2980.

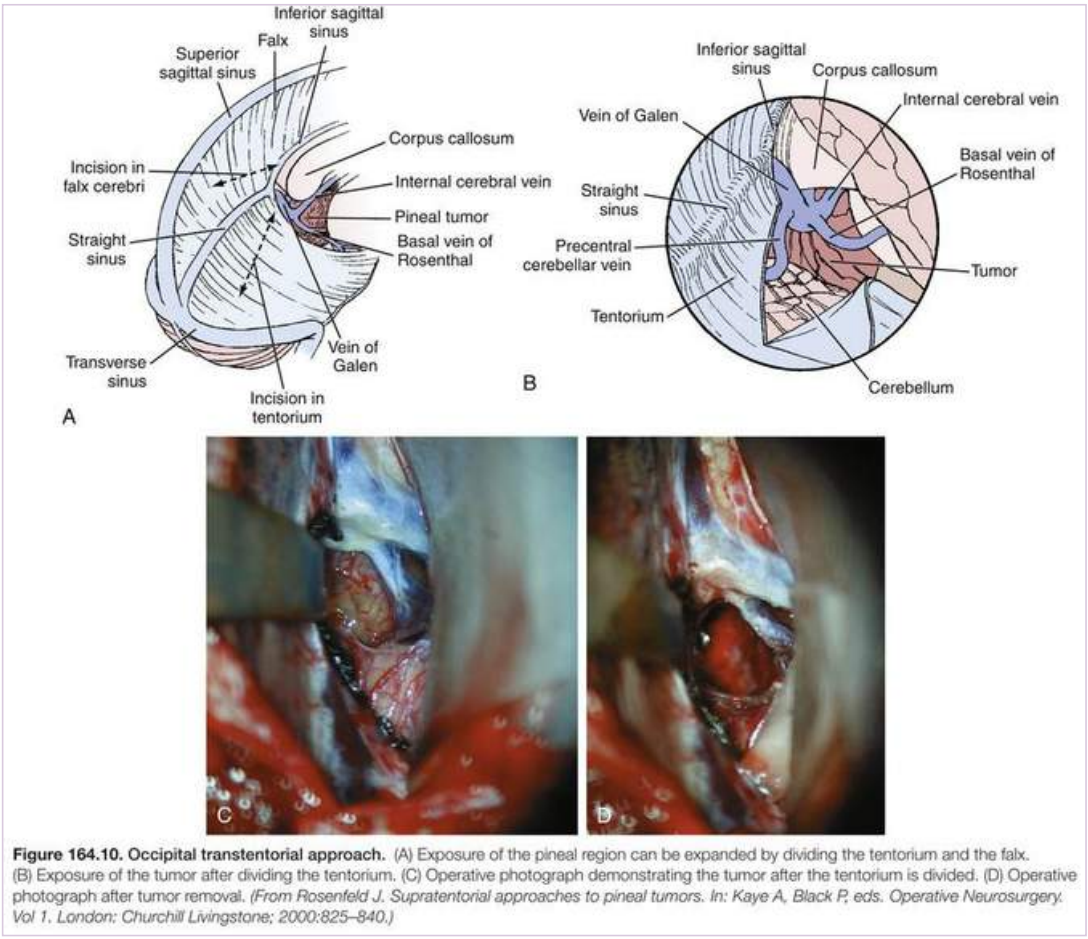


Figure 164.10. Occipital transtentorial approach. (A) Exposure of the pineal region can be expanded by dividing the tentorium and the falx. (B) Exposure of the tumor after dividing the tentorium. (C) Operative photograph demonstrating the tumor after the tentorium is divided. (D) Operative photograph after tumor removal. *(From Rosenfeld J. Supratentorial approaches to pineal tumors. In: Kaye A, Black P, eds. Operative Neurosurgery. Vol 1. London: Churchill Livingstone; 2000:825–840.)*

*Reproduced from Youmans & Winn 8e, Fig. 164.1, p. 1149 — Label when you reproduce it: (A) sagittal drawing — internal cerebral vein, velum interpositum, splenium, fornix, falx, inferior sagittal sinus, straight sinus, vein of Galen, superior vermian vein, tentorium, vermis of cerebellum, **corpora quadrigemina**, vein of the cerebellomesencephalic fissure, arachnoid, pineal gland, quadrigeminal cistern. (B) dorsal drawing — habenular commissure, pineal gland, **superior and inferior colliculi**, pineal vein, internal cerebral veins, medial and lateral posterior choroidal arteries, tela choroidea, fornix, basal vein of Rosenthal, vein of Galen, posterior cerebral artery, internal occipital vein. Use panel B to show the examiner *why* a pineal mass compresses the superior colliculus and the posterior commissure.*

6. Causes — organised, not listed at random

- **Common aetiologies (Ch. 15): stroke, pineal gland tumours, intrinsic brainstem tumours and hydrocephalus** YW p.200.e23.
- **For a complete vertical gaze palsy specifically: stroke — including bilateral paramedian midbrain-thalamic strokes from occlusion of the top of the basilar artery or the artery of Percheron; neurodegenerative disease — progressive supranuclear palsy, Niemann-Pick disease type C; and intrinsic tumours** YW p.200.e23. The **artery of Percheron** is worth a mark by itself.
- **Pineal and ventricular tumours** — Youmans lists Parinaud syndrome as a presenting feature of the **common ventricular tumours (glioma, dermoid cyst, germ cell tumour, meningioma)** YW p.1204 and of **intracranial germ cell tumours**, in which patients *"may exhibit a dorsal midbrain syndrome, known as Parinaud"* YW p.1833. In childhood cancers generally, **Parinaud syndrome** is listed alongside abducens-related gaze failure YW p.1760.e1. Cognitive dysfunction, headache and precocious puberty may accompany it YW p.988.
- **Pineal cysts and posterior third-ventricular expansion** — lesions here may present with **macrocephaly or Parinaud syndrome** YW p.1854; pineal apoplexy from haemorrhage into a pineal tumour can make symptoms appear abruptly YW p.1149.
- **Tectal glioma** — the archetypal upper-midbrain tumour. **Most upper midbrain tumours, such as tectal gliomas, are associated with obstructive hydrocephalus, so endoscopic third ventriculostomy or a ventriculoperitoneal shunt is the first line of therapy**; they usually do not require biopsy, adjuvant therapy or resection. **Tectal gliomas are**

poorly demarcated and rarely enhance, are hypointense on T1 and hyperintense on T2, and enhancing tectal lesions with tumour volume greater than 10 cm³ are usually associated with a worse prognosis [YW pp. 1825, 1826].

- **Iatrogenic — midbrain injury, Parinaud syndrome and cranial nerve palsies are reported complications of endoscopic aqueductoplasty**, especially for long-segment stenoses YW p.1733; endoscopy in the pineal region likewise risks **midbrain injury, Parinaud syndrome and cranial nerve** deficit YW p.1733.

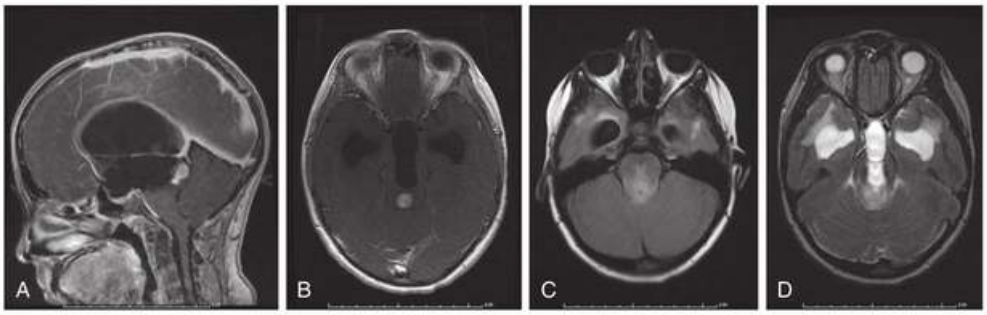


Figure 241.2. Magnetic resonance imaging of a tectal glioma with hydrocephalus. (A) Sagittal T1-weighted contrast-enhanced sequence demonstrating a tumor in the tectum with hydrocephalus. (B) Axial T1-weighted contrast-enhanced image of the tectal tumor. (C) Axial fluid-attenuated inversion recovery (FLAIR) sequence demonstrating a diffuse and infiltrating lesion in the tectum surrounding the aqueduct. (D) Axial T2-weighted image demonstrating the infiltrating lesion in the tectum and enlarged temporal horns with periventricular edema.

*Reproduced from Youmans & Winn 8e, Fig. 241.2, p. 1826 — Imaging correlate — describe on this four-panel MRI of a **tectal glioma with hydrocephalus**: (A) sagittal T1 post-contrast showing a tumour in the tectum with hydrocephalus; (B) axial T1 post-contrast of the tectal tumour; (C) axial FLAIR showing a diffuse infiltrating lesion in the tectum **surrounding the aqueduct**; (D) axial T2 showing the infiltrating tectal lesion with **enlarged temporal horns and periventricular oedema**. Say that the tectal location explains both the eye signs of Parinaud syndrome and the aqueductal obstruction, and that ETV — not resection — is the first-line treatment.*

Table 2 · Parinaud's syndrome — the tetrad, its anatomical substrate, and the neighbouring midbrain syndromes that must be distinguished. Compiled from Youmans & Winn 8e, Ch. 15 pp. 200.e19, 200.e20, 200.e23, 200.e26 (Tables 15.3-15.4) and Ch. 164 p. 1149.

Sign or syndrome	Anatomical substrate in Youmans	Clinical note
Supranuclear upgaze palsy	Projections from vertical gaze centres in the **posterior commissure**	Supranuclear — nuclei and nerves intact; Bell phenomenon preserved
Complete vertical gaze palsy	**Rostral interstitial nuclei of the MLF (riMLF)**, rostral midbrain	Suggests intrinsic rather than compressive lesion: top-of-basilar or artery of Percheron stroke, PSP, Niemann-Pick C, intrinsic tumour
Convergence-retraction nystagmus	Pretectum; elicited by attempted upgaze	Near-pathognomonic when present
Collier sign (lid retraction) — or ptosis	Dorsal midbrain compression or infiltration	Either may occur
Light-near dissociation	Pretectal afferent limb of the light reflex	Differential: blind eye, Argyll Robertson pupil (neurosyphilis), Adie tonic pupil
Fourth nerve palsy	Trochlear nucleus in caudal periaqueductal grey; fascicles decussate in the **anterior medullary velum**	Less common component; nuclear lesion gives contralateral superior oblique weakness
Sylvian aqueduct syndrome	Further midbrain compression	Adds **downgaze or horizontal gaze paralysis**
Weber syndrome	CN III fascicle + **cerebral peduncle**	Contralateral hemiparesis
Benedikt syndrome	CN III fascicle + **substantia nigra**	Contralateral parkinsonism
Claude syndrome	CN III fascicle + **superior cerebellar peduncle**	Ataxia

Nuclear CN III lesion	Periaqueductal grey at the superior colliculus	**Bilateral ptosis and bilateral superior rectus palsy** (crossed SR subnucleus, single midline levator subnucleus)

7. Investigation and management principles that follow

- **MRI with gadolinium is the principal diagnostic test for pineal tumours**, giving size, vascularity, homogeneity, anatomical relationships and degree of hydrocephalus; venous anatomy can be assessed for surgical planning YW p.1149.
- **Pineal tumours generally displace the deep venous system superiorly along the dorsal periphery of the tumour**; the exceptions — **meningiomas of the velum interpositum and epidermoid or other corpus callosum tumours — displace the deep venous system ventrally and inferiorly**, which is a diagnostic clue on MRI and determines the choice between an infratentorial and a supratentorial approach YW p.1149.
- **Approach corollary:** the **subtentorial supracerebellar approach** exposes the dorsal midbrain by retracting cerebellum and vermis caudally, **avoids any disruption of the deep venous system including the vein of Galen and internal cerebral veins**, and is the approach of choice for dorsal midbrain lesions; ventral midbrain lesions near the interpeduncular cistern are reached pterionally, and ventrolateral lesions subtemporally, with the disadvantage of prolonged temporal lobe retraction YW p.1825.

(c) Aqueductoplasty [2]

8. Definition, history and place in the endoscopic repertoire

- **Aqueductoplasty provides another method of endogenous CSF diversion in cases of hydrocephalus caused by membranous occlusion or short-segment stenosis of the aqueduct of Sylvius** YW p.1732.
- **First performed by Walter Dandy in 1920**; endoscopic aqueductoplasty, with and without stenting, offers an alternative or adjunct to third ventriculostomy in selected patients YW p.1732. Historically Dandy identified the obstruction and *"viewed third ventriculostomy as an advance on aqueductoplasty"* YW p.1729.e1.
- It sits alongside **ETV, choroid plexus cauterisation, cyst fenestration, septostomy, foraminoplasty** and shunt-catheter placement or removal as the standard neuroendoscopic operations for hydrocephalus YW p.1730.

9. Advantages over ETV — four, all quotable

- **Restores the physiological CSF pathway** YW p.1732.
- **Imparts no risk of basilar artery injury** YW p.1732 — compare the **catastrophic basilar injury rate of <0.2%** at ETV YW p.350.
- **Avoids hypothalamic injury** resulting from forceful fenestration of the third ventricular floor YW p.1732.
- **Negates consideration of arachnoidal adhesions, which do not occur around the aqueduct** YW p.1732 — i.e. no membrane of Liliequist and no secondary membranes to fenestrate.

10. Disadvantages, risks and complications

- **Additional risk of injury to the periaqueductal grey matter, the floor of the fourth ventricle and the tectal plate** YW p.1732.
- **Reported complications, especially in long-segment stenoses, include midbrain injury, Parinaud syndrome and cranial nerve palsies; in long-segment aqueductal stenosis ETV may be the more appropriate procedure** YW p.1733.
- **Failure to appreciate the curved nature of the aqueduct may result in injury of the tectal plate** YW p.1733.
- **Stent migration and local tissue reactions** are concerns when aqueductoplasty and stenting are combined YW p.1733.
- **Forniceal contusion** — relevant whenever a second intraventricular manoeuvre is added, since combining biopsy or aqueductoplasty with ETV carries a **visually evident forniceal contusion rate reported as high as 16.9%**; memory loss from forniceal injury most commonly follows bilateral insult and may be retrograde, anterograde or both YW p.1730 .

11. Technique, step by step

- **The bur hole for endoscopic aqueductoplasty is placed more anteriorly than for a standard ETV** YW p.1733 — the trajectory must line up with the aqueduct, not with the third ventricular floor. The same principle applies to visualising posterior third-ventricular structures: **a more anteriorly located bur hole or an angled lens improves the view of posterior landmarks, and the massa intermedia may obstruct the view** YW p.1730.
- **Identify the floor of the third ventricle in order from anterior to posterior**: optic recess, chiasm, infundibular recess, then the dorsum sellae, then the thin translucent floor posterior to it with the basilar apex and interpeduncular cistern beneath; a faint white line parallel and posterior to the dorsum sellae marks the attachment of the **Liliequist membrane** YW p.1730.
- **If using a Fogarty balloon catheter, the tip may be shaped with a gentle curve, because the aqueduct is not straight.** The catheter is then gently slid into the lumen of the aqueduct and the balloon carefully dilated YW p.1733.
- **A flexible endoscope may be useful for perforating a membranous obstruction, especially if the obstruction is in the distal aqueduct, which is not well visualised by a rigid endoscope** YW p.1733. More generally, **a flexible steerable ventriculoscope provides easier visual access to the posterior third ventricle, pineal region and cerebral aqueduct, but is more limited in terms of instrumentation** YW p.1730.
- **Stenting** is considered for patients at high risk of aqueductal restenosis or with a **trapped fourth ventricle**; routine stenting depends on surgeon preference YW p.1733.
- **Trapped fourth ventricle with slit-like lateral ventricles** — these shunted patients are **poor candidates for standard endoscopic aqueductoplasty**, and a **suboccipital approach for retrograde aqueductoplasty and stenting** is performed; because the restenosis risk is significant, **aqueductal stenting is advocated along with aqueductoplasty** in this group YW p.1733. A meta-analysis showed similar rates of improvement after **aqueductoplasty or stent placement in cases of fourth-ventricle** outflow obstruction YW p.268.

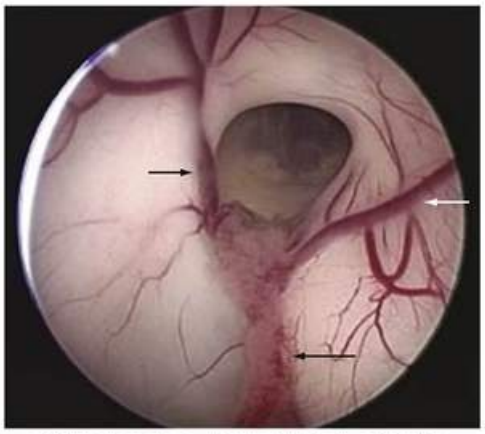


Figure 45.2. Endoscopic view into the right lateral ventricle. The thalamostriate vein *(white arrow)* runs along the lateral wall, converging with the anterior septal vein *(top short black arrow)* before converging and entering the foramen of Monro as the internal cerebral vein. The superior choroidal vein *(bottom long black arrow)* is also seen coursing through the choroid plexus. *(Courtesy T.T. Wong, MD.)*

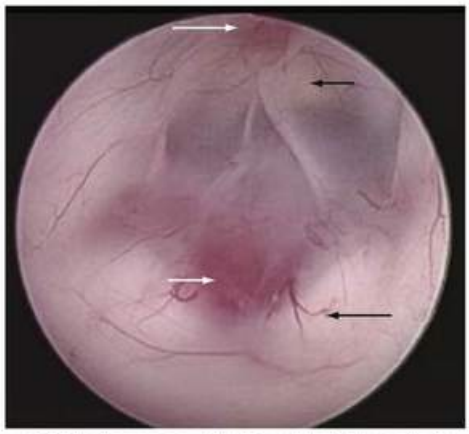


Figure 45.3. Endoscopic view of the floor of the third ventricle. The ideal spot for fenestration is in the midline, midway between the dorsum sella *(top short black arrow)* and the basilar artery *(bottom short white arrow)*. The paired mamillary bodies *(bottom long black arrow)* and the infundibular recess *(top long white arrow)* are also visible. *(Courtesy T.T. Wong, MD.)*

*Reproduced from Youmans & Winn 8e, Fig. 45.2, p. 349 — Reproduce the LEFT panel (endoscopic view into the right lateral ventricle) and label: **thalamostriate vein** running along the lateral wall, **anterior septal vein**, their confluence entering the foramen of Monro as the **internal cerebral vein**, and the **superior choroidal vein** coursing through the choroid plexus. Reproduce the RIGHT panel (endoscopic view of the floor of the third ventricle) and label: **dorsum sellae**, **basilar artery**, **paired mammillary bodies** and **infundibular recess**, marking the ideal fenestration point as *the midline, midway between the dorsum sellae and the basilar artery*. For aqueductoplasty, note in your label that the bur hole must be sited more anteriorly than the trajectory shown here.*

Table 3 · Endoscopic aqueductoplasty versus endoscopic third ventriculostomy — from Youmans & Winn 8e, Ch. 228 pp. 1730, 1732-1733, Ch. 45 pp. 349-350 and Ch. 34 p. 268.

Feature	Endoscopic aqueductoplasty	Endoscopic third ventriculostomy

Indication	**Membranous occlusion or short-segment aqueductal stenosis**; trapped fourth ventricle (retrograde route)	Any non-communicating hydrocephalus; long-segment aqueductal stenosis
Bur hole	**More anterior** than standard ETV	Standard precoronal
Instrument	Fogarty/balloon catheter with a **gently curved tip**; flexible scope for distal membranes	Blunt trocar, closed forceps or laser wire, then dilatation to 4-9 mm with double-balloon catheter, Fogarty, spreaders or forceps
Physiology	**Restores the physiological CSF route**	Creates a bypass into the interpeduncular cistern
Basilar artery risk	**None**	Catastrophic basilar injury <0.2%
Hypothalamic risk	**Avoided**	Hypothalamic injury — diabetes insipidus, pathological weight gain, amenorrhoea, precocious puberty
Arachnoid membranes	**Irrelevant** — none around the aqueduct	Membrane of Liliequist and multiple secondary membranes must be fenestrated
Specific risks	**Periaqueductal grey, fourth-ventricular floor and tectal plate injury; Parinaud syndrome; cranial nerve palsy; stent migration**	Fornix injury and memory loss, CSF leak, meningitis, seizure, haemorrhage
Short-term success	**>66% in most published series**	50-90% at 1 year in children; 50-86.5% in adult aqueductal stenosis
Durability	Poor — **88% radiographic restenosis at 10 years, 65% needed retreatment with ETV**; late failures at 4-10 years; higher restenosis in the young	Better; **phase-contrast MRI shows a significantly lower CSF flow rate through an aqueductoplasty than through an ETV stoma**
Youmans' verdict	*"Although conceptually attractive, ETV remains the preferred technique for endoscopic CSF diversion"*	Preferred

12. Outcome data to quote

- **Short-term success, defined as improvement in hydrocephalus-related symptoms, exceeds 66% in most published series** YW p.1733.
- **Significant risk of restenosis plagues endoscopic aqueductoplasty**, particularly if a stent is not placed concurrently or if it is performed for a trapped fourth ventricle YW p.1733.
- **Phase-contrast MRI reveals a significantly lower CSF flow rate through the aqueduct than through a ventriculostomy stoma after aqueductoplasty versus ETV**, which may contribute to eventual restenosis YW p.1733.
- **Younger patients restenose more often than adolescents and adults**, and although initial results can be excellent, **late failures are seen 4 to 10 years after aqueductoplasty**; in one series with 10-year follow-up the **radiographic restenosis rate was 88% and 65% required retreatment with ETV** YW p.1733.
- Youmans' bottom line: **"On the whole, although conceptually attractive, ETV remains the preferred technique for endoscopic CSF diversion"** YW p.1733.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Crus cerebri → substantia nigra → tegmentum → aqueduct → tectum.** Five layers, front to back; that is the whole of part (a) in one line YW p.35.
- **Two boundaries between crus and tegmentum**: the substantia nigra internally and the lateral mesencephalic sulcus on the surface — the latter running up to the medial geniculate body.
- **CN III leaves medially into the interpeduncular fossa; CN IV leaves below the inferior colliculus** — so CN IV does not appear on an upper-midbrain section.
- **A nuclear third-nerve lesion gives bilateral ptosis and bilateral superior rectus weakness**, because the superior rectus subnucleus is crossed and the levator subnucleus is single and midline.
- **Parinaud tetrad**: supranuclear upgaze palsy, convergence-retraction nystagmus, Collier sign, light-near dissociation. Add **Sylvian aqueduct syndrome** (downgaze or horizontal gaze palsy) for the extra mark.
- **Upgaze palsy = posterior commissure; complete vertical gaze palsy = riMLF.** Two different lesions, two

different answers.

- **Light-near dissociation differential**: dorsal midbrain syndrome, Argyll Robertson pupil, Adie tonic pupil, a blind eye.
- **Artery of Percheron occlusion** produces bilateral paramedian midbrain-thalamic infarction and a complete vertical gaze palsy.
- **An enhancing tectal glioma >10 cm³ carries a worse prognosis**, and ETV or shunt — not resection — is the first line of therapy.
- **Aqueductoplasty: no basilar risk, no hypothalamic risk, no arachnoid membranes — but tectal plate injury, Parinaud syndrome and 88% restenosis at 10 years.** ETV still wins.
- **Aqueductoplasty can itself cause Parinaud syndrome** — the link between parts (b) and (c) of this question.
- **Site the bur hole more anteriorly for aqueductoplasty than for ETV**, and curve the Fogarty tip, because the aqueduct is not straight.
- **Approach the dorsal midbrain supracerebellar-infratentorially** to spare the vein of Galen and internal cerebral veins.

Pages read for this answer — Youmans & Winn 8e: 27, 35, 36, 38, 41, 200.e19, 200.e20, 200.e23, 200.e26, 268, 350, 734, 988, 1149, 1204, 1729.e1, 1730, 1732, 1733, 1760.e1, 1825, 1826, 1833, 1854, 2980

a) Draw neat labelled diagram of floor of th fourth Ventricle. [4]
b) Internuclear ophthalmoplegia. [3]
c) Draw neat labelled diagram depicting deep venous system of brain. [3]

LONG | OCT 2023 · Paper I · Q4 | 10 marks

Also asked as: Neuroanatomy — also asked as APR 2026 · Paper II · Q6 (a) Surgical anatomy of deep venous system of brain [5]; (b) Anatomical subtypes of vein of Galen malformation [5].

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 2 *Surgical Anatomy of the Brain*, §Petrosal Surface of the Cerebellum and Fourth Ventricle, §Tentorial Surface of the Cerebellum and Fourth Ventricle, §Suboccipital Surface of the Cerebellum and Fourth Ventricle, §Veins of the Posterior Fossa and §Medial Surface: Venous Relationships, pp. 29-30, 37-40 (Figs. 2.48-2.50, p. 37; Figs. 2.51-2.52, p. 38; Figs. 2.53-2.55, p. 39; Figs. 2.36-2.37, pp. 29-30). Supplementary: Ch. 170 *Ventricular Tumors*, §Fourth Ventricle and §Venous Anatomy, pp. 1207, 1209-1210 (Figs. 170.8-170.9, pp. 1209-1210); Ch. 15 *Neuro-ophthalmology*, §Supranuclear, Internuclear, and Cerebellar, pp. 200.e19-200.e20, 200.e23-200.e24 (Tables 15.4-15.5, p. 200.e20; Fig. 15.36, p. 200.e24); Ch. 16 *Neurotology*, §Anatomy and §Physiology, p. 201.e11; Ch. 164 *Pineal Tumors*, §Anatomy, p. 1149 (Fig. 164.1, p. 1149); Ch. 247 *Vein of Galen Aneurysmal Malformation*, §Classification, p. 1869; Ch. 260 *Developmental Anomalies of the Craniovertebral Junction and Surgical Management*, §Clinical Presentation, p. 1961.

(a) Draw a neat labelled diagram of the floor of the fourth ventricle [4]

1. Set the scene in two sentences before drawing

- **The fourth ventricle is a tent-shaped midline structure surrounded mainly by the vermian components of the cerebellum.** A regular tent has a roof divided into two halves, a floor and two lateral walls; **the fourth ventricle resembles a turned-over tent with its base facing forward and two open lateral walls** YW p.36.
- **The floor is represented by the pons and medulla**; the superior cerebellar peduncles, the superior medullary velum and the adjacent lingula constitute the superior part of the roof; the inferior part of the roof is composed of the inferior medullary velum, tela choroidea, choroid plexus, uvula and nodule; the two open lateral walls are the lateral recesses, which communicate the fourth ventricle with the cerebellopontine angle YW p.36.
- **The floor of the fourth ventricle has a rhomboid shape** YW p.39 — hence the older name *rhomboid fossa*. It is exposed **after the removal of the tonsils and then the inferior portion of the roof of the fourth ventricle** YW p.38 — i.e. by the telovelar route.

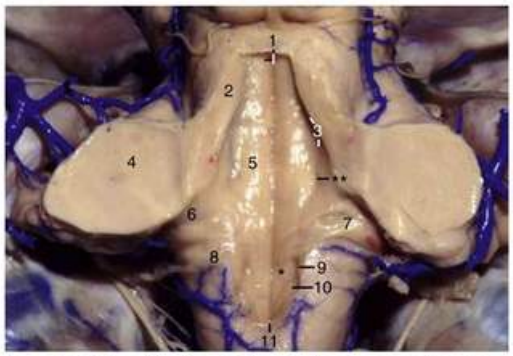


Figure 2.53. Floor of fourth ventricle, posterior view. *1*, Median sulcus and median eminence; *2*, superior cerebellar peduncle; *3*, sulcus limitans and vestibular area; *4*, middle cerebellar peduncle; *5*, facial colliculus; *6*, cochlear area; *7*, striae medullary; *8*, inferior cerebellar peduncle; *9*, inferior fovea; *10*, vagal trigone; *11*, obex and area postrema; *, hypoglossal trigone; **, superior fovea.

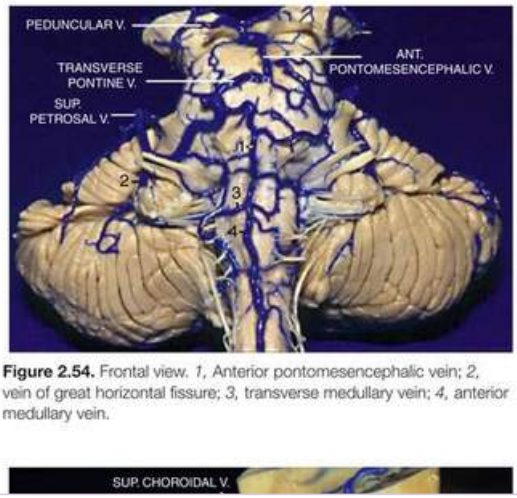


Figure 2.54. Frontal view. *1*, Anterior pontomesencephalic vein; *2*, vein of great horizontal fissure; *3*, transverse medullary vein; *4*, anterior medullary vein.

*Reproduced from Youmans & Winn 8e, Fig. 2.53, p. 39 — Label when you reproduce it (floor of the fourth ventricle, posterior view — this is the figure to copy): 1 **median sulcus and median eminence**, 2 **superior cerebellar peduncle**, 3 **sulcus limitans and vestibular area**, 4 **middle cerebellar peduncle**, 5 **facial colliculus**, 6 **cochlear area**, 7 **striae medullares**, 8 **inferior cerebellar peduncle**, 9 **inferior fovea**, 10 **vagal trigone**, 11 **obex and area postrema**, * **hypoglossal trigone**, ** **superior fovea**. Draw the rhomboid outline first, then the median sulcus, then the sulcus limitans, then the three transverse landmarks (striae medullares, facial colliculi, calamus scriptorius).*

2. The three longitudinal divisions

- **Median sulcus.** The three parts of the floor are **divided longitudinally into two symmetrical halves by the median sulcus** YW p.39.
- **Sulcus limitans.** *"The sulcus limitans, another longitudinal sulcus, divides each half of the floor into a raised median strip called the median eminence and a lateral strip called the area vestibularis"* YW p.39.
- **The single most examinable rule on this diagram: the motor nuclei of the cranial nerves are located medially to the sulcus limitans, and the sensory nuclei are located laterally to it** YW p.39. Write that sentence on the diagram itself.
- **At the junctional part the sulcus limitans is discontinuous** YW p.39 — a detail almost nobody quotes, and it earns a mark.

3. The three transverse parts

- **Junctional part. A strip between the lower margin of the cerebellar peduncles and the site of attachment of the tela choroidea, characterised by the medullary striae that extend into the lateral recesses** YW p.39. The **junctional part divides the floor into two unequal triangles** YW p.39.
- **Pontine part — the superior and larger triangle, with its apex directed to the aqueduct** YW p.39.
  - **Characterised by two rounded prominences, the facial colliculi, located on the median eminence, one on each side of the median sulcus** YW p.39.
  - **The facial colliculi are limited laterally by the superior fovea, a dimple formed by the sulcus limitans** YW p.39.
- **Medullary part — the inferior and smaller triangle, with its apex directed toward the obex** YW p.39.
  - **Presents the configuration of a feather, or pen nib, called the calamus scriptorius, with three triangular areas overlying the hypoglossal and vagus nuclei (hypoglossal and vagal trigones) and the area postrema** YW p.39.
  - **Just lateral to the hypoglossal trigone the sulcus limitans presents another dimple called the inferior fovea** YW p.39.

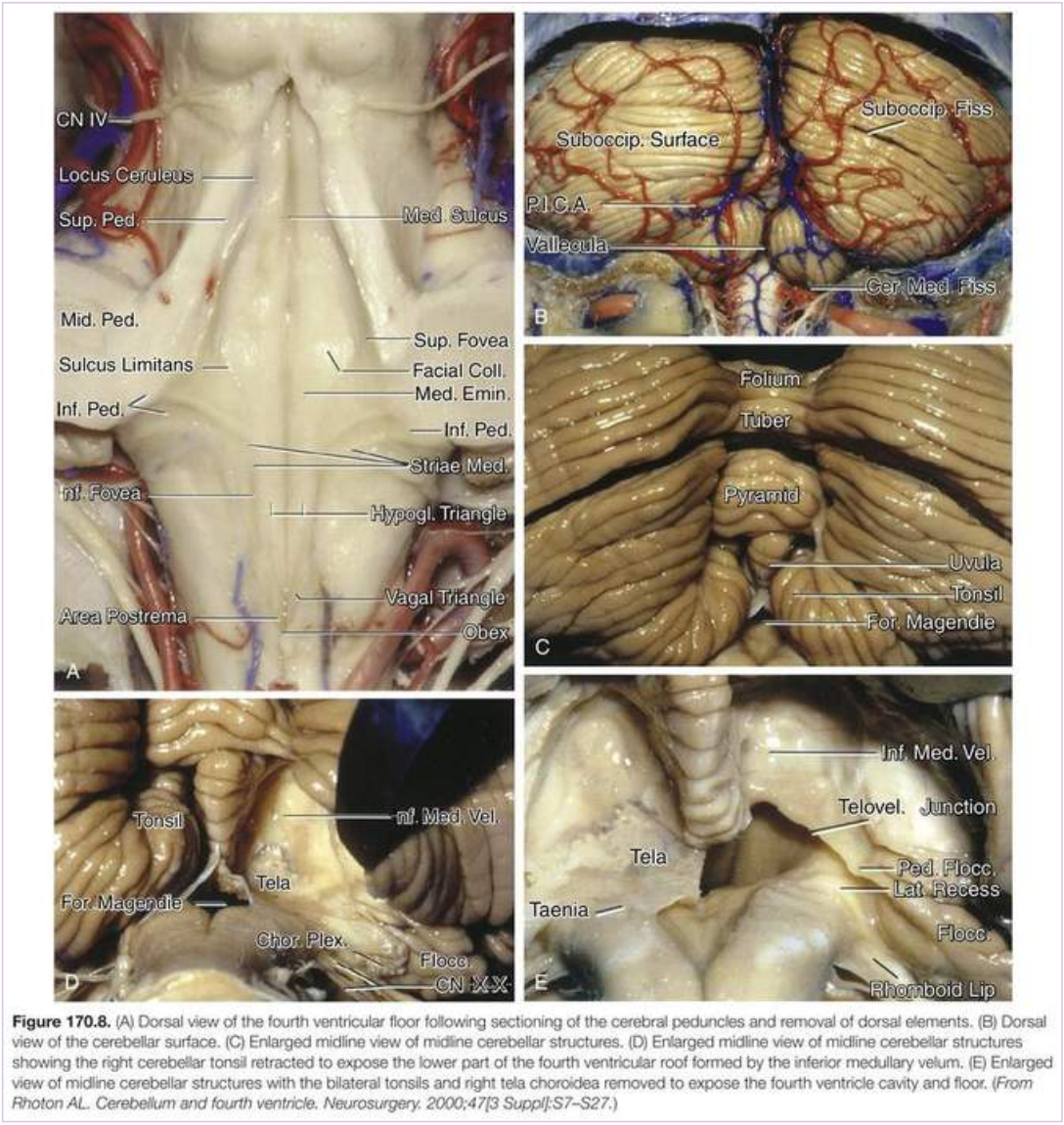


Figure 170.8. (A) Dorsal view of the fourth ventricular floor following sectioning of the cerebral peduncles and removal of dorsal elements. (B) Dorsal view of the cerebellar surface. (C) Enlarged midline view of midline cerebellar structures. (D) Enlarged midline view of midline cerebellar structures showing the right cerebellar tonsil retracted to expose the lower part of the fourth ventricular roof formed by the inferior medullary velum. (E) Enlarged view of midline cerebellar structures with the bilateral tonsils and right tela choroidea removed to expose the fourth ventricle cavity and floor. (*From Rhoton AL. Cerebellum and fourth ventricle. Neurosurgery. 2000;47[3 Suppl]:S7–S27.*)

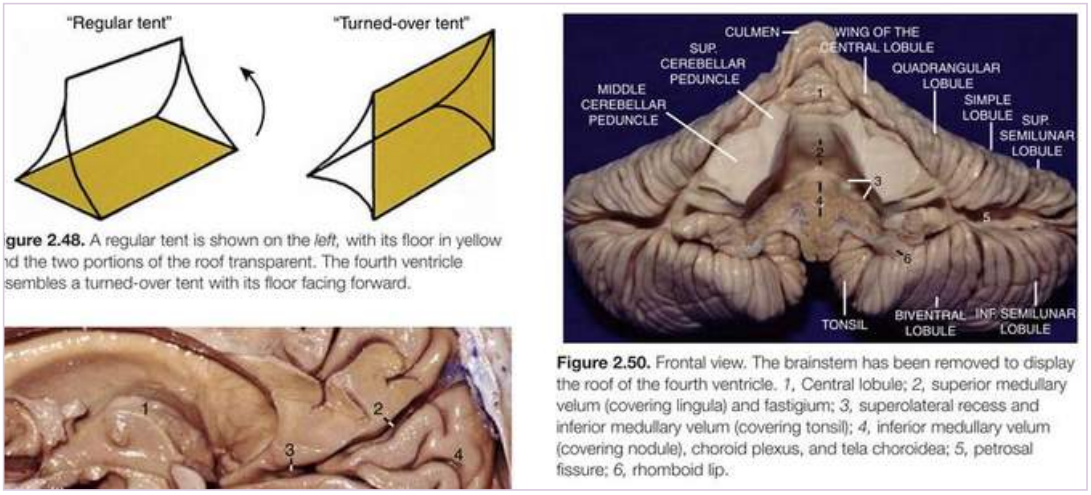
*Reproduced from Youmans & Winn 8e, Fig. 170.8, p. 1209 — Label when you reproduce PANEL A (dorsal view of the fourth ventricular floor after sectioning the cerebral peduncles and removing the dorsal elements — Rhoton's specimen): **CN IV**, **locus ceruleus**, **superior cerebellar peduncle (Sup. Ped.)**, **middle cerebellar peduncle (Mid. Ped.)**, **inferior cerebellar peduncle (Inf. Ped.)**, **superior fovea**, **sulcus limitans**, **facial colliculus**, **median eminence**, **striae medullares**, **inferior fovea**, **hypoglossal triangle**, **vagal triangle**, **area postrema**, **obex**, **median sulcus**. Panels D and E of the same figure show the telovelar exposure: **inferior medullary velum**, **tela choroidea**, **taenia**, **peduncle of the flocculus**, **lateral recess**, **foramen of Magendie**, **rhomboid lip**, **choroid plexus** and the retracted **tonsil** — label these to show how the floor is actually reached at operation.*

4. The lateral recess, the roof and the choroid plexus — the surroundings you must be able to name

- **The lateral recess is the lateral extension of the fourth ventricle and connects the fourth ventricle to the CP angle.** It is directed medially to laterally, slightly superiorly to inferiorly, and posteriorly to anteriorly, **forming an angle of about 45 degrees with the sagittal plane** YW p.37.
- **The lateral recess has an anterior, superior and posterior wall and a floor.** The anterior and superior walls are constituted by the **inferior cerebellar peduncle** as it runs upward and turns backward toward the cerebellum. **The floor is formed by the tela choroidea anteriorly, the choroid plexus in the middle and the inferior medullary velum posteriorly; at the foramen of Luschka the inferior medullary velum becomes thicker and is called the peduncle of the flocculus, constituting the posterior wall of the foramen of Luschka** YW p.37.
- **Superolateral recess — limited medially by the nodule and inferiorly by the superior pole of the tonsil covered by the inferior medullary velum**; above it the superior cerebellar peduncle presents a prominence, **the dentate tubercle**,

where the dentate nucleus reaches the surface. **The dentate nucleus can be considered the roof of the superolateral recess and the superior pole of the tonsil its floor** [YW pp. 37, 38].

- **Roof. The upper half of the roof is constituted by neural elements: the superior cerebellar peduncles, the superior medullary velum and the lingula.** The **lower half is composed of non-neural elements** and has a horizontal portion, the **inferior medullary velum** (covering the nodule and the superior pole of the tonsils), and a vertical portion, the **tela choroidea and choroid plexus** (covering the anterior aspect of the nodule, the uvula and partly the tonsils). **At the midline the upper and lower halves of the roof converge at the fastigium** YW p.37.
- **Choroid plexus. The morphology of the choroid plexus of the fourth ventricle resembles the letter "T" with two vertical bars.** The horizontal part that protrudes into the CP angle **resembles the horns of a bull**. **The vertical part and the proximal half of the horizontal part are usually supplied by PICA; the lateral half of the horizontal part and the choroid plexus at the CP angle are generally supplied by AICA** YW p.37.
- **Tonsillar spaces**, which you must know to reach the floor telovelarly: **supratonsillar space** (between the superior pole of the tonsil and the inferior medullary velum), **vallecula** (between the medial surfaces of the two tonsils), **cerebellomedullary fissure** (between the anterior surface of the tonsil and the medulla) and the **retrotonsillar space** (between the posterior surface of the tonsil and the adjacent vermis, formed by the **furrowed band of Reil** connecting uvula to tonsil and the **copula pyramidis** connecting pyramid to biventral lobule) [YW pp. 37, 38].



gure 2.48. A regular tent is shown on the *left*, with its floor in yellow nd the two portions of the roof transparent. The fourth ventricle sembles a turned-over tent with its floor facing forward.

Figure 2.50. Frontal view. The brainstem has been removed to display the roof of the fourth ventricle. *1*, Central lobule; *2*, superior medullary velum (covering lingula) and fastigium; *3*, superolateral recess and inferior medullary velum (covering tonsil); *4*, inferior medullary velum (covering nodule), choroid plexus, and tela choroidea; *5*, petrosal fissure; *6*, rhomboid lip.

*Reproduced from Youmans & Winn 8e, Fig. 2.50, p. 37 — Label when you reproduce it (frontal view with the brainstem removed, displaying the ROOF of the fourth ventricle — the mirror image of the floor): 1 **central lobule**, 2 **superior medullary velum (covering lingula) and fastigium**, 3 **superolateral recess and inferior medullary velum (covering tonsil)**, 4 **inferior medullary velum (covering nodule), choroid plexus and tela choroidea**, 5 **petrosal fissure**, 6 **rhomboid lip**. Add the **culmen, wing of the central lobule, quadrangular lobule, simple lobule, superior and inferior semilunar lobules, biventral lobule and tonsil** from the surrounding labels. Presenting the roof beside the floor proves you understand the "turned-over tent".*

Table 1 · Floor of the fourth ventricle — the three transverse parts and the two longitudinal sulci, with every named landmark. Reproduced from Youmans & Winn 8e, Ch. 2 pp. 37-39 (Fig. 2.53, p. 39) and Ch. 170 p. 1209 (Fig. 170.8).

Division	Limits	Named landmarks to label	Clinical / surgical significance
Pontine part (superior, larger triangle)	Apex directed to the **aqueduct**; base at the junctional part	**Facial colliculi** on the median eminence, one either side of the median sulcus; **superior fovea** lateral to each colliculus; **vestibular area** laterally; superior and middle cerebellar peduncles above and laterally	Facial colliculus = genu of CN VII over the abducens nucleus; must be identified and avoided (intraoperative stimulation helps)
Junctional part	Between the lower margin of the cerebellar peduncles and the attachment of the tela choroidea	**Striae medullares**, extending into the **lateral recesses**; the sulcus limitans is **discontinuous** here; **cochlear area** laterally; inferior cerebellar peduncle	Divides the floor into two unequal triangles; the landmark for the level of the lateral recess and foramen of Luschka

Medullary part (inferior, smaller triangle)	Apex directed to the **obex**	**Calamus scriptorius** (pen-nib configuration) with the **hypoglossal trigone**, **vagal trigone** and **area postrema**; **inferior fovea** just lateral to the hypoglossal trigone; **obex**	Hypoglossal and vagal nuclei lie immediately beneath — bradycardia, dysphagia and tongue weakness on manipulation
Median sulcus (longitudinal)	Aqueduct to obex	Divides the floor into two symmetrical halves	Midline; separates the two median eminences
Sulcus limitans (longitudinal)	Runs the length of each half, discontinuous at the junctional part	Divides each half into the **median eminence** (medial) and the **area vestibularis** (lateral); dimples into the **superior** and **inferior foveae**	**Motor cranial nerve nuclei lie medial to it, sensory nuclei lateral to it** — the single most examinable rule of the diagram
Lateral recess (lateral wall)	Extends laterally to the CP angle at **45 degrees to the sagittal plane**	Anterior/superior walls = inferior cerebellar peduncle; floor = tela choroidea, choroid plexus, inferior medullary velum; **peduncle of the flocculus** forms the posterior wall of the **foramen of Luschka**	Route of CSF egress; choroid plexus and flocculus protrude here; rhomboid lip nearby

5. Nuclei to mark on the floor — what actually lies beneath

- **Four principal vestibular nuclei lie in the floor of the fourth ventricle: the superior (Bechterew) nucleus, the lateral (Deiters) nucleus, the medial (Schwalbe) nucleus and the inferior (descending, spinal or Roller) nucleus** YW p.201.e11. These occupy the vestibular area lateral to the sulcus limitans.
- **The abducens nucleus lies on the floor of the fourth ventricle** and **contains internuclear neurons involved in horizontal gaze, so nuclear lesions produce an ipsilateral gaze palsy** rather than an isolated lateral rectus weakness YW p.200.e20. This is the direct link into part (b).
- **The facial colliculus overlies the genu of the facial nerve as it loops over the abducens nucleus** — Youmans specifically names **"identification and avoidance of the facial colliculus in the fourth ventricle"** as a use of intraoperative stimulation to avoid postoperative deficit YW p.3772.
- **Hypoglossal and vagal nuclei** lie beneath the hypoglossal and vagal trigones of the calamus scriptorius YW p.39.
- **Wernicke encephalopathy** produces increased T2/FLAIR signal in the **medial thalami, periaqueductal grey and floor of the fourth ventricle**, with mammillary body enhancement in chronic alcohol abuse — a radiological corollary of this anatomy YW p.200.e23.

(b) Internuclear ophthalmoplegia [3]

6. Definition and the responsible tract

- **An internuclear disorder affects the medial longitudinal fasciculus (MLF), causing internuclear ophthalmoplegia (INO) with an ipsilateral adduction deficit and abducting nystagmus of the contralateral eye** YW p.200.e19.
- **INO results from a lesion of the MLF either in the midbrain or the pons** YW p.200.e23.
- **Function of the MLF:** *"The MLF conveys the eye movement command from the sixth nerve nucleus to the contralateral third nerve nucleus, thereby allowing conjugate horizontal eye movements with simultaneous contraction of the ipsilateral lateral rectus and contralateral medial rectus muscles"* YW p.200.e23.
- **Why the deficit is ipsilateral: lesions of the MLF virtually always occur after the immediate decussation of the fibres originating in the sixth nerve nucleus, so the predominant clinical feature of impaired adduction is found ipsilateral to the lesion** [YW pp. 200.e23, 200.e24].
- **Wider role of the MLF:** it **connects the vestibular nuclei to all of the other cranial nerve nuclei, and of particular interest are the connections with CNs III, IV, VI and X** YW p.201.e11 — which is why INO so often keeps company with vestibular and gaze abnormalities.

7. Clinical signs, graded from florid to subtle

- **Classic unilateral INO: impaired adduction of the eye ipsilateral to the lesion and dissociated nystagmus of the contralateral abducting eye** YW p.200.e24.
- **Subtle INO: eye movements may appear full; subtle slowing of the adducting eye compared with the abducting eye during horizontal saccadic eye movements (adduction lag) may be the only clue** YW p.200.e24. Test saccades, not pursuit, to find it.
- **The single best discriminating manoeuvre: the adduction deficit in INO can often be overcome with convergence eye movements, whereas adduction deficits from other causes (e.g. third nerve palsy, ocular myasthenia) cannot** — this allows clinical differentiation from those entities YW p.200.e24.
- **Beware the mimic: ocular myasthenia gravis can have a clinical appearance that mimics other ocular motor disorders, such as pupil-sparing third nerve palsy or INO**, and complete ophthalmoplegia can occasionally be seen YW p.200.e19.

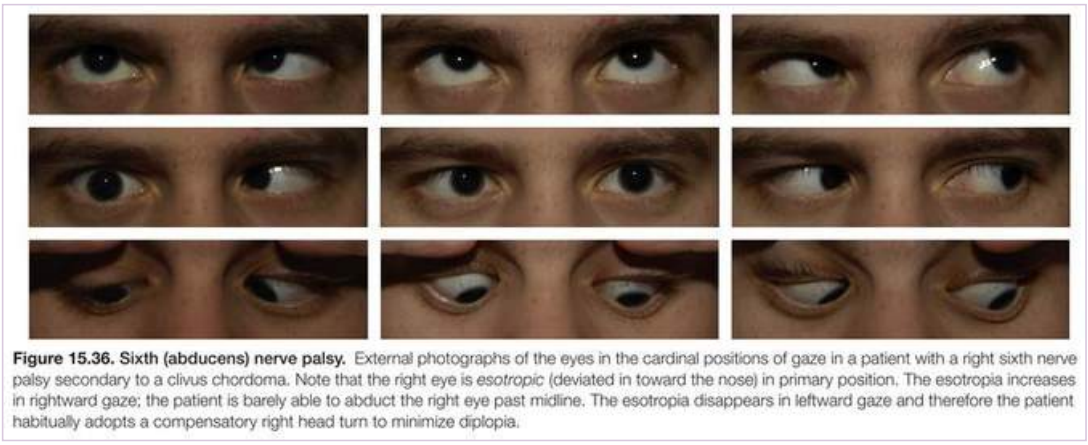


Figure 15.36. Sixth (abducens) nerve palsy. External photographs of the eyes in the cardinal positions of gaze in a patient with a right sixth nerve palsy secondary to a clivus chordoma. Note that the right eye is *esotropic* (deviated in toward the nose) in primary position. The esotropia increases in rightward gaze; the patient is barely able to abduct the right eye past midline. The esotropia disappears in leftward gaze and therefore the patient habitually adopts a compensatory right head turn to minimize diplopia.

*Reproduced from Youmans & Winn 8e, Fig. 15.36, p. 200.e24 — Imaging/clinical correlate — reproduce the nine-position photograph montage of a **right sixth (abducens) nerve palsy** and describe: the right eye **esotropic** in primary position, esotropia **increasing** in right gaze with the right eye barely able to abduct past the midline, esotropia **disappearing** in left gaze, and the **compensatory right head turn**. Use it as the contrast case for INO: here the failure is of *abduction* and it is the *lesioned* side, whereas in INO the failure is of *adduction* on the lesioned side with nystagmus of the *abducting* fellow eye — and a nuclear sixth-nerve lesion gives a complete ipsilateral gaze palsy because the nucleus contains the internuclear neurons that feed the MLF.*

8. Causes and localisation

- **Common causes of INO: multiple sclerosis, brainstem stroke, brainstem tumour and fourth ventricular tumour** YW p.200.e24.
- **In the case of stroke, the causative lesion can be very small and easily overlooked on neuroimaging** YW p.200.e24 — so a negative-looking MRI does not exclude it.
- **Nuclear fourth nerve lesion** — located in **caudal periaqueductal grey matter, dorsal to the MLF**; it produces **internuclear ophthalmoplegia contralateral to the superior oblique weakness** (because of the fourth nerve decussation), and is caused by haemorrhage, stroke, demyelination or trauma including neurosurgical trauma; **isolated fourth nerve nucleus lesions are very rare** YW p.200.e20.
- **Pontine abducens fascicular lesion at the pontomedullary junction — Millard-Gubler syndrome** comprises a **seventh nerve deficit and internuclear ophthalmoplegia**, while **Raymond-Cestan syndrome** adds contralateral hemiparesis; because the fascicles pass through the ventral brainstem, isolated sixth nerve palsies from this site are unusual YW p.200.e20.
- **Nuclear abducens lesion (Foville syndrome)** — pontine tegmentum involvement gives **fifth and seventh nerve deficits, Horner syndrome, ipsilateral reduction in taste and facial sensation, contralateral ataxia and ipsilateral gaze palsy**; the nucleus contains internuclear neurons for horizontal gaze, so **nuclear lesions produce an ipsilateral gaze palsy** YW p.200.e20.
- **Craniovertebral junction disease — "not uncommonly, internuclear ophthalmoplegia is present, leading to a**

misdiagnosis of mesencephalic and upper pontine disturbance" in basilar invagination; **downbeat nystagmus is present in strictly compressive lesions of the craniovertebral border with or without an associated Chiari malformation** YW p.1961. This is the trap: a treatable craniovertebral lesion masquerading as a brainstem one.

- **Raised intracranial pressure / central transtentorial herniation** — **"with progressive bilateral involvement, internuclear ophthalmoplegia may arise, and motor examination may show bilateral decerebrate posturing"** YW p.472.e8.
- **Chiari malformation** — downbeat nystagmus can be prominent and cause oscillopsia, and **it can improve or sometimes resolve following posterior fossa decompression** YW p.200.e24.

Table 2 · Internuclear ophthalmoplegia and the neighbouring brainstem gaze syndromes, by anatomical site. Reproduced from Youmans & Winn 8e, Tables 15.4 and 15.5, p. 200.e20, with Ch. 15 pp. 200.e19, 200.e23-200.e24, Ch. 260 p. 1961 and Ch. 69 p. 472.e8.

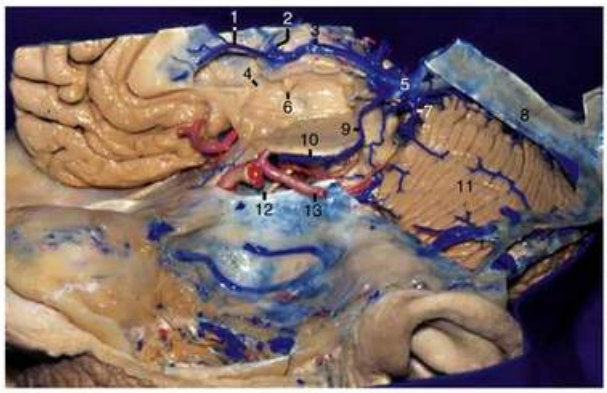
Site	Syndrome / finding	Associated features	Causes
MLF, midbrain or pons	**INO**	Ipsilateral adduction deficit (or adduction lag) + dissociated abducting nystagmus of the contralateral eye; adduction restored on convergence	MS, brainstem stroke, brainstem tumour, fourth ventricular tumour
Fourth nerve nucleus (caudal periaqueductal grey, dorsal to MLF)	INO **contralateral to superior oblique weakness**	Because of the fourth nerve decussation	Haemorrhage, stroke, demyelination, trauma (including neurosurgical); isolated nuclear lesion very rare
Fourth nerve fascicle (decussates in the anterior medullary velum)	Superior oblique weakness	**Horner syndrome contralateral to the superior oblique weakness**	Haemorrhage, stroke, trauma, cerebellar infarct with oedema and compression
Abducens nucleus (floor of the fourth ventricle)	**Foville syndrome / ipsilateral gaze palsy**	Fifth and seventh nerve deficits, Horner syndrome, ipsilateral loss of taste and facial sensation, contralateral ataxia	Stroke in the elderly, tumour in the young, occasionally demyelination
Abducens exit, pontomedullary junction	**Millard-Gubler syndrome**	Seventh nerve deficit **plus INO**; **Raymond-Cestan** adds contralateral hemiparesis	Ventral pontine lesions
Craniovertebral junction	INO mimicking mesencephalic/upper pontine disease	Downbeat nystagmus, dysphagia, sleep apnoea, central cord syndrome	Basilar invagination ± Chiari malformation
Diffuse, from raised ICP	INO with bilateral decerebrate posturing	Midposition fixed pupils, tachypnoea	Central transtentorial herniation
Neuromuscular junction	INO **mimic**	Fatigable ptosis, orbicularis oculi weakness; adduction *not* restored on convergence	Ocular myasthenia gravis

(c) Draw a neat labelled diagram depicting the deep venous system of the brain [3]

9. The two paired collectors and their confluence

- **The veins of the lateral ventricles typically drain into either the internal cerebral veins or the basal veins of Rosenthal** YW p.1207. Draw those two pairs first, then the vein of Galen.
- **Into the internal cerebral vein**, at the posterior margin of the foramen of Monro as it transitions into the third ventricle, drain the **anterior septal and caudate veins, the thalamostriate vein, the superior choroidal vein and the medial atrial vein** — these either anastomose with each other or drain directly YW p.1207.

- **Into the basal vein of Rosenthal** drain the **inferior choroidal vein, inferior ventricular vein, lateral atrial vein and the veins of the amygdala and hippocampus** YW p.1207.
- **The velum interpositum contains the internal cerebral veins, which drain posteriorly to the vein of Galen, and the medial posterior choroidal arteries** YW p.1207. The roof of the third ventricle is formed of four layers from dorsal to ventral: **the fornix, the two layers of tela choroidea (between which lies the velum interpositum) and the choroid plexus** YW p.1207.
- **The basal veins of Rosenthal combine with the internal cerebral veins to form the vein of Galen before draining** into the straight sinus YW p.1147.
- **Sacrifice of the internal cerebral vein or the basal vein of Rosenthal is not advised**; veins should be spared wherever possible to avoid venous infarct or haemorrhage YW p.1207.
- **Angiographic rule to quote: in the lateral view, the basal and internal cerebral veins delimit the thalamus and the hypothalamus** YW p.29.



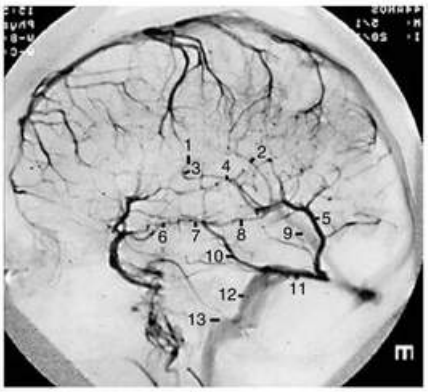


Figure 2.37. *Left*, Midsagittal view. *1*, Anterior septal vein; *2*, right thalamostriate vein; *3*, internal cerebral vein; *4*, foramen of Monro; *5*, vein of Galen; *6*, massa intermedia; *7*, precentral cerebellar vein; *8*, straight sinus; *9*, posterior mesencephalic segment of basal vein; *10*, peduncular segment of basal vein; *11*, tentorial surface of the cerebellum; *12*, oculomotor nerve; *13*, posterior cerebral artery. *Right*, Venous angiogram, lateral projection. *1*, Thalamostriate vein; *2*, inferior sagittal sinus; *3*, venous angle; *4*, internal cerebral vein; *5*, vein of Labbé; *6*, striate segment of basal vein; *7*, peduncular segment of basal vein; *8*, posterior mesencephalic segment of basal vein; *9*, straight sinus; *10*, temporosylvian vein; *11*, transverse sinus; *12*, sigmoid sinus; *13*, jugular bulb.

*Reproduced from Youmans & Winn 8e, Fig. 2.37, p. 30 — Label when you reproduce it — this is the figure to copy for part (c). LEFT panel (midsagittal dissection): 1 **anterior septal vein**, 2 **right thalamostriate vein**, 3 **internal cerebral vein**, 4 **foramen of Monro**, 5 **vein of Galen**, 6 **massa intermedia**, 7 **precentral cerebellar vein**, 8 **straight sinus**, 9 **posterior mesencephalic segment of basal vein**, 10 **peduncular segment of basal vein**, 11 tentorial surface of the cerebellum, 12 oculomotor nerve, 13 posterior cerebral artery. RIGHT panel (lateral venous angiogram): 1 **thalamostriate vein**, 2 **inferior sagittal sinus**, 3 **venous angle**, 4 **internal cerebral vein**, 5 vein of Labbé, 6 **striate segment of basal vein**, 7 **peduncular segment of basal vein**, 8 **posterior mesencephalic segment of basal vein**, 9 **straight sinus**, 10 temporosylvian vein, 11 transverse sinus, 12 sigmoid sinus, 13 jugular bulb. Draw the dissection and the angiogram side by side — that is exactly how the examiner wants the deep venous system presented.*

10. The basal vein of Rosenthal — three segments, learned by their tributaries

Youmans gives the basal vein as three segments; reproduce all three with their tributaries and relationships YW p.29:

- **First (anterior, or striate) segment. Originates from the junction of the anterior cerebral, inferior striate, olfactory, fronto-orbital and deep middle cerebral veins under the anterior perforated substance**, and runs posteriorly under the optic tract, medial to the anterior crus cerebri. **This point is the most medial and usually the most inferior part of the basal vein before its termination into the vein of Galen, and it indicates laterally the location of the apex of the uncus.**
- **Second (middle, or peduncular) segment.** Starts at the most medial point of the vein, usually where the **peduncular vein** joins it; runs laterally between the upper posteromedial uncus and the upper crus cerebri, under the optic tract, to the most lateral part of the crus cerebri — **usually where the inferior ventricular vein joins the basal vein, called the anterior peduncular segment by Huang and Wolf** — then turns medially, superiorly and posteriorly behind the crus to become the **posterior peduncular segment**. Main tributaries: **peduncular (interpeduncular), inferior ventricular, inferior choroidal, hippocampal and anterior hippocampal veins**.

- **Third (posterior, or posterior mesencephalic) segment.** Runs medially, superiorly and posteriorly from the lateral mesencephalic sulcus, under the pulvinar, into the quadrigeminal cistern to drain into the vein of Galen. Main tributaries: **lateral mesencephalic, posterior thalamic, posterior longitudinal hippocampal, medial temporal and medial occipital veins**; sometimes also the **precentral cerebellar, superior vermian, internal occipital, splenial, medial atrial and direct/lateral atrial subependymal veins**.
- **The "frog's legs" mnemonic is Youmans' own: in the angiographic frontal view the overall shape of both basal veins resembles the legs of a frog lying on its back with its toes directed anterolaterally** — **foot** = striate segment (related to the anterior perforated substance above, anterior uncus laterally, optic tract medially, carotid cistern below); **ankle** = crus cerebri anteriorly, uncal apex laterally, optic tract above; **leg** = anterior peduncular segment; **knee** = the most lateral aspect of the crus cerebri, related to the inferior choroidal point laterally and the optic tract just before the lateral geniculate body above; **thigh** = posterior peduncular plus posterior mesencephalic segments, related to the midbrain tegmentum medially, parahippocampal gyrus laterally and the pulvinar above YW p.29.

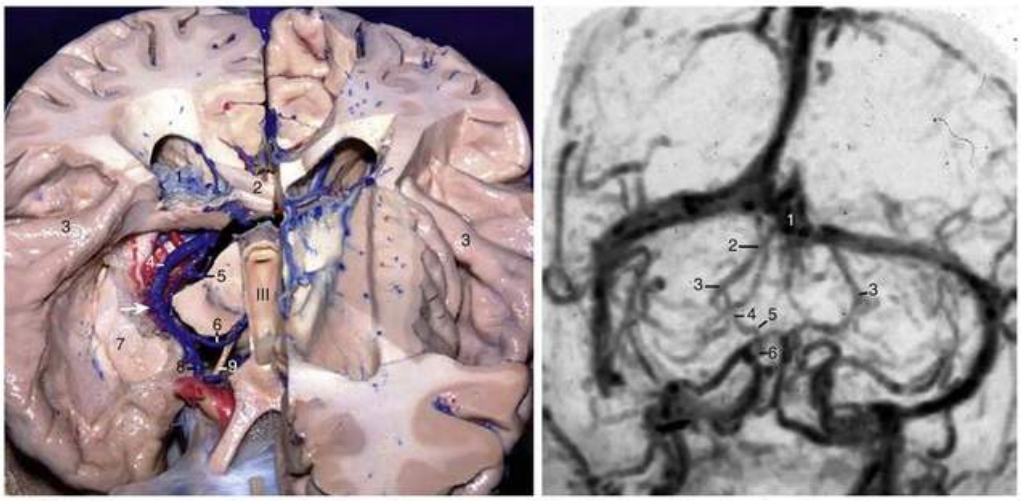


Figure 2.36. *Left,* Anatomic dissection as in frontal view of the angiography. *1,* Choroid plexus of the atrium; *2,* splenium of the corpus callosum; *3,* Heschl gyrus; *4,* posterior mesencephalic segment of basal vein; *5,* lateral mesencephalic sulcus; *6,* peduncular vein; *7,* head of the hippocampus; *8,* striate segment of the basal vein; *9,* oculomotor nerve; the *white arrow* indicates the inferior choroidal point. *Right,* Venous MR angiography, frontal view. *1,* Vein of Galen, *2,* posterior mesencephalic segment of basal vein; *3,* inferior choroidal point or drainage site of the inferior ventricular vein; *4,* peduncular segment of basal vein; *5,* apex of uncus; *6,* striate segment of basal vein.

*Reproduced from Youmans & Winn 8e, Fig. 2.36, p. 29 — Label when you reproduce it: LEFT panel (anatomical dissection in the frontal projection) — 1 choroid plexus of the atrium, 2 splenium of the corpus callosum, 3 Heschl gyrus, 4 **posterior mesencephalic segment of the basal vein**, 5 **lateral mesencephalic sulcus**, 6 **peduncular vein**, 7 head of the hippocampus, 8 **striate segment of the basal vein**, 9 oculomotor nerve, white arrow = **inferior choroidal point**. RIGHT panel (venous MR angiography, frontal view) — 1 **vein of Galen**, 2 posterior mesencephalic segment of basal vein, 3 **inferior choroidal point / drainage site of the inferior ventricular vein**, 4 peduncular segment of basal vein, 5 apex of uncus, 6 striate segment of basal vein. Use the MRV panel to demonstrate the "frog's legs" configuration.*

11. The galenic confluence and its posterior fossa tributaries

- **The superior or galenic group of posterior fossa veins drains into the vein of Galen** and comprises **(1) mesencephalic tributaries — the median and lateral anterior pontomesencephalic, lateral pontomesencephalic, lateral mesencephalic, peduncular, posterior mesencephalic and tectal veins; and (2) cerebellar tributaries — the precentral cerebellar vein and its variants, and the superior vermian vein** YW p.40.
- **Veins running on the surface of the midbrain drain to the galenic system**, unlike the rest of the anterior brainstem surface, which drains to the petrosal sinuses via the superior petrosal vein YW p.39.
- **The brachial veins running in the cerebellomesencephalic fissure can establish a communication between the petrosal and galenic groups via the pontotrigeminal and precentral cerebellar veins** YW p.40 — the anatomical basis of collateral rescue if the galenic system is compromised.
- **Tentorial-surface drainage pattern:** the midline cerebellomesencephalic fissure veins, the superior vermian veins near central lobule and culmen, and the anterior group of superior hemispheric veins **tend to drain into the vein of Galen**; the lateral group drains to the **superior petrosal sinus**; the posterior group drains to the **torcula, transverse sinus or a tentorial sinus** YW p.39.

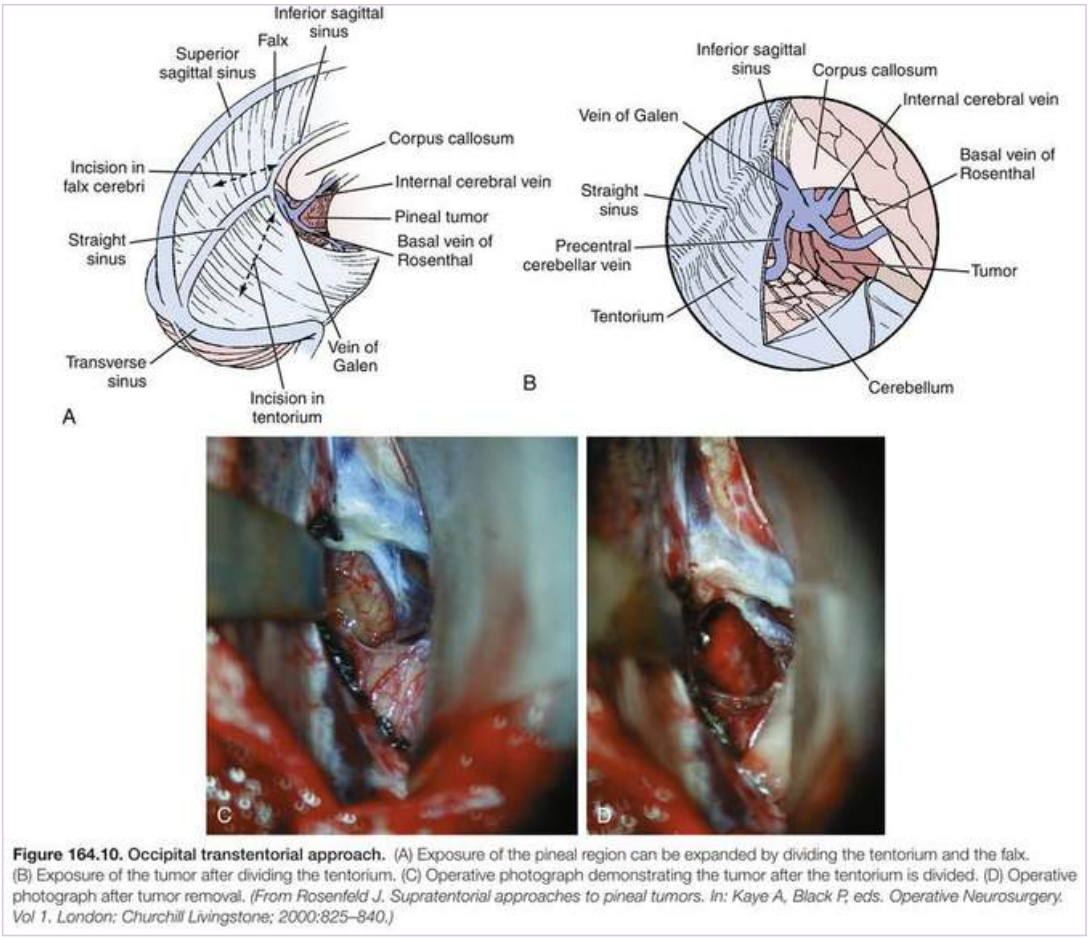


Figure 164.10. Occipital transtentorial approach. (A) Exposure of the pineal region can be expanded by dividing the tentorium and the falx. (B) Exposure of the tumor after dividing the tentorium. (C) Operative photograph demonstrating the tumor after the tentorium is divided. (D) Operative photograph after tumor removal. *(From Rosenfeld J. Supratentorial approaches to pineal tumors. In: Kaye A, Black P, eds. Operative Neurosurgery. Vol 1. London: Churchill Livingstone; 2000:825–840.)*

*Reproduced from Youmans & Winn 8e, Fig. 164.1, p. 1149 — Label when you reproduce it — PANEL A (sagittal drawing of the pineal region): **internal cerebral vein**, **velum interpositum**, splenium, **fornix**, falx, **inferior sagittal sinus**, **straight sinus**, **vein of Galen**, **superior vermian vein**, tentorium, vermis, corpora quadrigemina, **vein of the cerebellomesencephalic fissure**, arachnoid, pineal gland, quadrigeminal cistern. PANEL B (dorsal drawing): **internal cerebral veins**, velum interpositum, fornix, tela choroidea, habenular commissure, **medial and lateral posterior choroidal arteries**, pineal gland and **pineal vein**, superior and inferior colliculi, **basal vein of Rosenthal**, **vein of Galen**, posterior cerebral artery, **internal occipital vein**. This single figure gives the whole galenic confluence in two views.*

Table 3 · The deep venous system — collectors, tributaries and surgical rules. Compiled from Youmans & Winn 8e, Ch. 2 pp. 29-30, 39-40 and Ch. 170 pp. 1207, 1209.

Collector	Segments / course	Tributaries to name	Surgical rule
Internal cerebral vein (paired)	Formed at the posterior margin of the foramen of Monro; runs back in the **velum interpositum** between the two layers of tela choroidea, beneath the fornix, with the medial posterior choroidal arteries	**Anterior septal, caudate, thalamostriate, superior choroidal, medial atrial veins**	**Do not sacrifice.** The confluence of anterior septal and thalamostriate veins forms the angiographic **venous angle**

Basal vein of Rosenthal (paired)	**Striate → peduncular (anterior + posterior) → posterior mesencephalic**; "frog's legs" on frontal angiography	Striate: anterior cerebral, inferior striate, olfactory, fronto-orbital, deep middle cerebral. Peduncular: peduncular, **inferior ventricular**, inferior choroidal, hippocampal, anterior hippocampal. Posterior mesencephalic: lateral mesencephalic, posterior thalamic, posterior longitudinal hippocampal, medial temporal, medial occipital (± precentral cerebellar, superior vermian, internal occipital, splenial, medial/lateral atrial)	**Do not sacrifice.** Drains the temporal horn contents encountered in mesial temporal and pulvinar surgery
Vein of Galen	Union of both internal cerebral and both basal veins; drains to the **straight sinus**	**Precentral cerebellar vein, superior vermian vein**, tectal, lateral mesencephalic, peduncular and posterior mesencephalic veins; internal occipital and splenial veins	Displaced **superiorly** by most pineal tumours, but **ventrally/inferiorly** by velum interpositum meningiomas and corpus callosum epidermoids — the diagnostic clue that decides supra- versus infratentorial approach
Inferior sagittal sinus / straight sinus / torcula	Outflow	—	The **supracerebellar infratentorial approach** to the dorsal midbrain **avoids any disruption of the deep venous system, including the vein of Galen and internal cerebral veins**

12. Clinical corollaries of the deep venous anatomy — the marks beyond the diagram

- **Approach selection. Inferior displacement of the vein of Galen by a pineal region tumour increases the challenge and risk of the supracerebellar infratentorial approach** YW p.1210; conversely the **subtentorial supracerebellar approach to the dorsal midbrain avoids any disruption of the deep venous system, including the vein of Galen and internal cerebral veins** YW p.1825. At pineal surgery **it is important to identify and protect the vein of Galen, basal veins of Rosenthal and internal cerebral veins** YW p.1776.
- **Venous displacement pattern as a diagnostic sign. Pineal tumours generally displace the deep venous system superiorly along the dorsal periphery of the tumour; meningiomas arising from the velum interpositum and epidermoids or other tumours originating in the corpus callosum displace it ventrally and inferiorly** YW p.1149.
- **Cross-reference for the vein of Galen malformation question.** Lasjaunias defined **VGAM as arteriovenous fistulas draining to the median prosencephalic vein, the embryonic precursor of the vein of Galen, and subclassified VGAMs into the choroidal type and the mural type**; lesions dilating the *"true"* (embryologically mature) vein of Galen are instead **vein of Galen aneurysmal dilation (VGAD)** or **vein of Galen varix (VGV)** YW p.1869. **The mural type lies in the velum interpositum cistern or the quadrigeminal cistern, consists of single or multiple direct fistulas at the wall of the dilated posterior median prosencephalic vein, is usually fed by the quadrigeminal and/or posterior choroidal artery, has fewer fistulas and a rounder venous dilation, and presents later in infancy with macrocephaly, hydrocephalus or failure to thrive** YW p.1869.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Draw the rhomboid, then two longitudinal sulci, then three transverse parts.** Median sulcus and sulcus limitans; pontine, junctional and medullary parts.
- **Motor nuclei medial to the sulcus limitans, sensory nuclei lateral to it** — write that line on the diagram YW p.39.
- **Pontine part = facial colliculi + superior fovea; medullary part = calamus scriptorius (hypoglossal trigone, vagal trigone, area postrema) + inferior fovea; junctional part = striae medullares.**
- **The sulcus limitans is discontinuous at the junctional part** — a one-line detail that marks out a read answer.
- **The lateral recess lies at 45 degrees to the sagittal plane**; the inferior medullary velum thickens at the foramen of Luschka as the **peduncle of the flocculus**.
- **Fourth-ventricular choroid plexus is a "T with two vertical bars"** and the CP-angle portion resembles the **horns of a bull**; PICA supplies the vertical and proximal horizontal part, AICA the lateral part.
- **INO = ipsilateral adduction failure + contralateral abducting nystagmus**, because the MLF lesion is always distal to the decussation from the sixth nerve nucleus.
- **Convergence overcomes the adduction deficit in INO but not in third nerve palsy or myasthenia** — the single best bedside discriminator.
- **Adduction lag on saccades may be the only sign** of a subtle INO; the causative stroke can be too small to see on MRI.
- **Basilar invagination can present with INO** and be misdiagnosed as an upper pontine lesion — always look at the craniovertebral junction.
- **Deep venous system = internal cerebral veins (velum interpositum) + basal veins of Rosenthal (three segments) → vein of Galen → straight sinus.** Neither collector may be sacrificed.
- **The basal vein looks like a frog's legs on frontal angiography**: foot = striate, ankle/knee = peduncular, thigh = posterior mesencephalic.
- **On the lateral angiogram the basal and internal cerebral veins delimit the thalamus and hypothalamus**, and the **venous angle** (septal + thalamostriate) marks the foramen of Monro.
- **A pineal mass pushes the deep veins up; a velum interpositum meningioma pushes them down** — that one observation chooses the approach.

Pages read for this answer — Youmans & Winn 8e: 29, 36, 37, 38, 39, 40, 200.e19, 200.e20, 200.e23, 200.e24, 201.e11, 472.e8, 1147, 1149, 1207, 1210, 1776, 1825, 1869, 1961, 3772

a) Draw neat labelled diagrams of safe entry zones of brainstem. [5]
b) Brain stem auditory evoked potential monitoring. [5]

LONG | OCT 2023 · Paper II · Q3 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 461 *Microsurgery for Cerebral Cavernous Malformations*, §Microsurgical Technique, §Surgical Approaches, §Retrosigmoid Approach and §Far-Lateral Approach, pp. 3772-3775 (Fig. 461.4, p. 3772; Fig. 461.5, p. 3773; Fig. 461.6, p. 3775). Supplementary: Ch. 2 *Surgical Anatomy of the Brain*, §Brainstem, §Petrosal Surface of the Cerebellum and Fourth Ventricle, pp. 35-39, 41 (Fig. 2.47, p. 36; Fig. 2.53, p. 39; Fig. 2.58, p. 41); Ch. 170 *Ventricular Tumors*, §Fourth Ventricle, §Surgical Adjuncts and §Telovelar Approach, pp. 1209-1210, 1227 (Fig. 170.8, p. 1209); Ch. 241 *Brainstem Gliomas*, §Surgical Intervention and §Midbrain, pp. 1825-1827; Ch. 174 *Vestibular Schwannomas*, §Cranial Nerve VIII Monitoring and §Hearing Preservation, pp. 1281, 1284-1285, 1289 (Fig. 174.6, p. 1284); Ch. 16 *Neurotology*, §Auditory Brainstem Evoked Response Measures, pp. 201.e7, 201.e9; Ch. 408 *Neuroanesthesia for Microvascular and Interventional Cerebrovascular Procedures*, §Optimal Neurophysiologic Monitoring Environment, p. 3244.

(a) Draw neat labelled diagrams of the safe entry zones of the brainstem [5]

1. The principle first — why safe entry zones exist

- **The brainstem has no expendable tissue.** Youmans' governing statement is that **for brainstem cavernomas, multiple safe entry sites have been described that avoid critical nuclei and traversing white matter tracts**, and these **should be taken into consideration during surgical planning** YW p.3773.

- **The goal of brainstem surgery is defined before the incision:** *"One of the most important considerations for brainstem surgery is to define the goal of surgery, with the least amount of morbidity associated with it based on the understanding of the biology of the tumor and its anatomy. Therefore choosing a safe entry point is critical"* YW p.1825 .
- **Cystic focal lesions are easier than solid ones** because they can be identified and entered without aggressive manipulation of surrounding tissue YW p.1825.
- **Navigation and ultrasound are mandatory, not optional: "Neuronavigation and intraoperative ultrasound are extremely helpful and mandatory in choosing the site of entry into the brainstem and in resection so as to avoid neurological injury"** YW p.1825; intraoperative navigation is **particularly useful when approaching lesions that lack any cortical representation** YW p.3773.

2. Youmans' named list of safe entry zones — learn it verbatim

"For brainstem cavernomas, multiple safe entry sites have been described that avoid critical nuclei and traversing white matter tracts including the epitrigeminal, superior fovea triangle, interpeduncular fossa; anterior and lateral mesencephalic; inter-, supra-, and infracollicular; and lateral pontine and medullary zones, among others" YW p.3773. That is **ten named zones**; group them by level to draw them:

- **Midbrain (three ventral/lateral + three dorsal)**
  - **Interpeduncular fossa** — between the two crura cerebri, where **the oculomotor nerves emerge from the medial side of the crura cerebri** YW p.35. Reached pterionally: **lesions on the ventral aspect of the midbrain near the interpeduncular cistern can be reached via a pterional approach** YW p.1825.
  - **Anterior mesencephalic zone** — on the crus cerebri, medial to the corticospinal fibres and lateral to CN III.
  - **Lateral mesencephalic zone** — in the **lateral mesencephalic sulcus**, the surface groove that **separates the crus cerebri from the tegmentum** and ascends to the medial geniculate body [YW pp. 35, 38]. Reached subtemporally: **lesions on the ventrolateral aspect of the midbrain can be reached via a subtemporal approach, with the disadvantage of potentially requiring prolonged retraction on the temporal lobe** YW p.1825.
  - **Supracollicular, intercollicular and infracollicular zones** — on the **quadrigeminal plate**: above the superior colliculus, in the groove between superior and inferior colliculi, and below the inferior colliculus [YW pp. 36, 3773]. Remember **the trochlear nerve exits the brainstem below the inferior colliculus** YW p.36, so the infracollicular zone is the CN IV-bearing one. All three are reached by the **subtentorial supracerebellar approach, in which the cerebellum and vermis are retracted caudally to expose the dorsal mesencephalon; this allows direct access to the midbrain and avoids any disruption of the deep venous system, including the vein of Galen and internal cerebral veins** YW p.1825.
- **Pons (two)**
  - **Epitrigeminal zone** — the lateral pontine surface above and behind the trigeminal root entry zone. The surgical landmark is the emergence of CN V: **"just lateral to the lateral pontine sulcus is the emergence of the trigeminal nerve, with its smaller superomedial motor root and a larger inferolateral sensory root. From the microneurosurgical standpoint, the apparent origin of the trigeminal nerve can be considered as the limit between the pons and the middle cerebellar peduncle"** YW p.36. Reached retrosigmoid: **dissection along the petrotentorial junction and opening of the arachnoid over the superior petrosal vein provides access to the trigeminal nerve root entry zone** YW p.3774.
  - **Lateral pontine zone / middle cerebellar peduncle** — the workhorse. **"The middle cerebellar peduncle is a common entry point for accessing cavernous malformations of the pons"** YW p.3774.
  - **Superior fovea triangle** — on the *floor of the fourth ventricle*, in the pontine part. The superior fovea is **the dimple formed by the sulcus limitans lateral to the facial colliculus** YW p.39; entering here keeps the surgeon lateral to the facial colliculus and medial to the vestibular nuclei.
- **Medulla (one, plus the dorsal midline)**
  - **Lateral medullary zone** — the postolivary region. The anatomy to quote: **the rootlets of the accessory, vagus and glossopharyngeal nerves exit from the postolivary sulcus, the continuation of the posterolateral sulcus of the spinal cord**, and **the rootlets of the hypoglossal nerve exit from the preolivary (anterolateral) sulcus** YW p.36.

Approached far-laterally: **the far-lateral approach provides access to the vertebrobasilar junction, inferolateral pons, anterolateral medulla and upper cervical spinal cord** YW p.3774.

- The **dorsal midline of the medullary part of the fourth ventricular floor** is *not* a safe zone: the calamus scriptorius overlies the **hypoglossal and vagal trigones and the area postrema** YW p.39, and **manipulation of the floor of the fourth ventricle during surgery may result in hypotension, apnoea, or even cardiac arrest** YW p.1227.

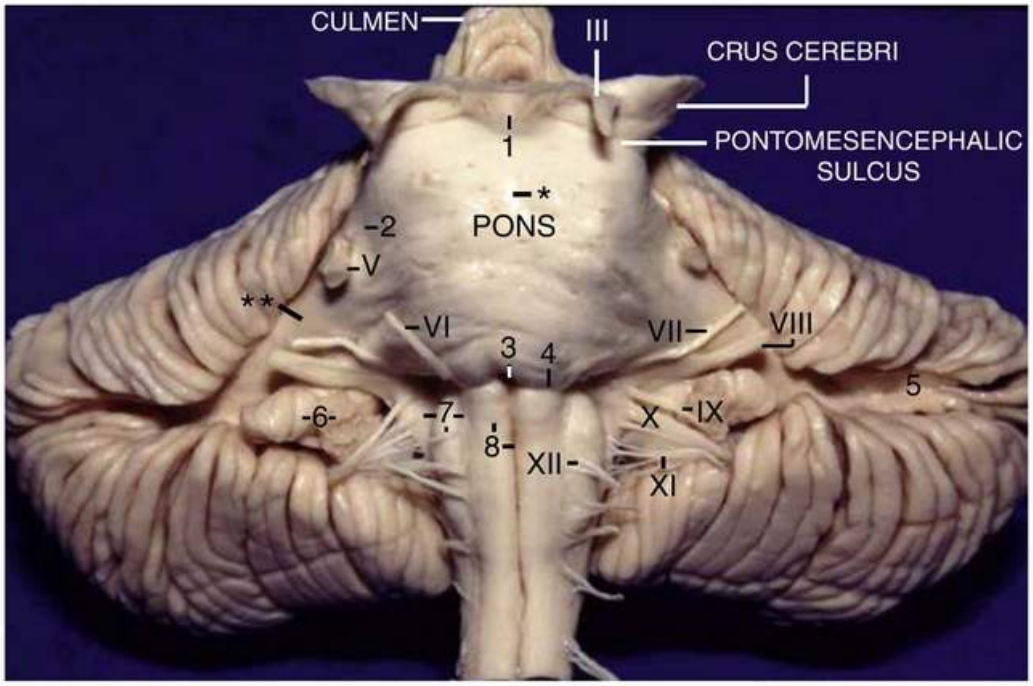


Figure 2.47. Frontal view. *1,* Interpeduncular fossa; *2,* lateral pontine sulcus; *3,* inferior foramen caecum; *4,* pontomedullary sulcus; *5,* great horizontal or petrosal fissure; *6,* flocculus and choroid plexus protruding from foramen of Luschka; *7,* supraolivary fossette, olive, and anterolateral sulcus; *8,* pyramid and anterior median fissure; *, basilar sulcus; **, middle cerebellar peduncle.

*Reproduced from Youmans & Winn 8e, Fig. 2.47, p. 36 — Label when you reproduce it (frontal/ventral view of the brainstem — the map of the VENTRAL entry zones): 1 **interpeduncular fossa**, 2 **lateral pontine sulcus**, 3 inferior foramen caecum, 4 **pontomedullary sulcus**, 5 great horizontal (petrosal) fissure, 6 flocculus and choroid plexus protruding from the foramen of Luschka, 7 **supraolivary fossette, olive and anterolateral (preolivary) sulcus**, 8 **pyramid and anterior median fissure**, * basilar sulcus, ** **middle cerebellar peduncle**; mark the emergence of **CN III** medial to the crus, **CN V** at the lateral pontine sulcus, **CN VI** at the junction of pontomedullary and preolivary sulci, and **CN VII, VIII** on the superior catheti with **CN IX, X, XI** on the hypotenuse of the supraolivary fossette. Then mark on it the **anterior mesencephalic**, **interpeduncular**, **epitrigeminal** and **lateral medullary** entry zones.*

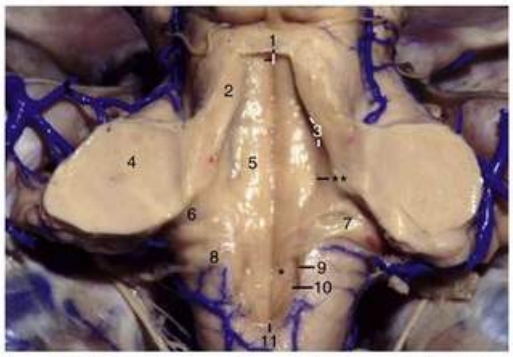


Figure 2.53. Floor of fourth ventricle, posterior view. *1*, Median sulcus and median eminence; *2*, superior cerebellar peduncle; *3*, sulcus limitans and vestibular area; *4*, middle cerebellar peduncle; *5*, facial colliculus; *6*, cochlear area; *7*, striae medullary; *8*, inferior cerebellar peduncle; *9*, inferior fovea; *10*, vagal trigone; *11*, obex and area postrema; *, hypoglossal trigone; **, superior fovea.

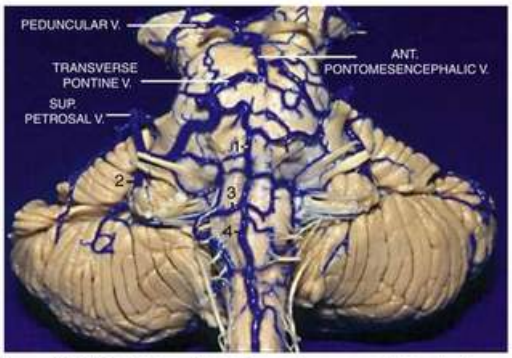


Figure 2.54. Frontal view. *1*, Anterior pontomesencephalic vein; *2*, vein of great horizontal fissure; *3*, transverse medullary vein; *4*, anterior medullary vein.

*Reproduced from Youmans & Winn 8e, Fig. 2.53, p. 39 — Label when you reproduce it (floor of the fourth ventricle, posterior view — the map of the DORSAL pontine and medullary entry zones): 1 median sulcus and median eminence, 2 superior cerebellar peduncle, 3 **sulcus limitans and vestibular area**, 4 middle cerebellar peduncle, 5 **facial colliculus**, 6 cochlear area, 7 striae medullares, 8 inferior cerebellar peduncle, 9 **inferior fovea**, 10 **vagal trigone**, 11 obex and area postrema, * **hypoglossal trigone**, ** **superior fovea**. Shade in the **superior fovea triangle** just lateral to the facial colliculus as the safe pontine dorsal entry, and cross-hatch the facial colliculus and the calamus scriptorius as the forbidden zones. Add the rule that motor nuclei lie medial and sensory nuclei lateral to the sulcus limitans.*

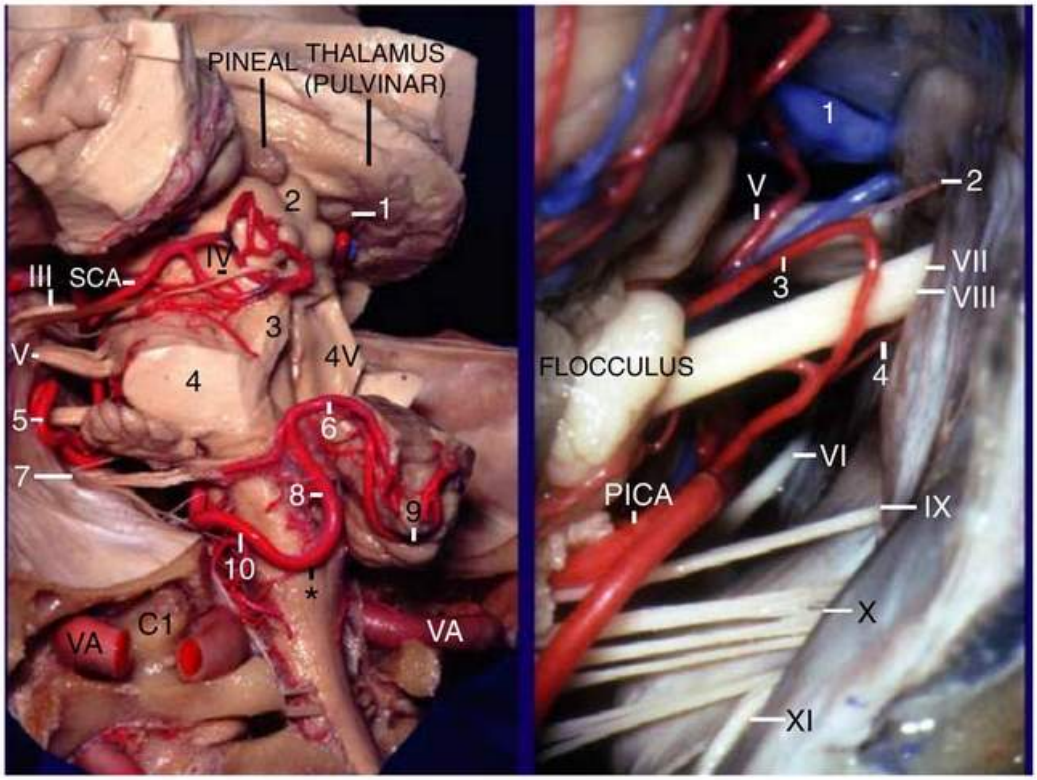


Figure 2.58. *Left,* Posterolateral view. *1,* Medial geniculate body; *2,* superior colliculi; *3,* superior cerebellar peduncle; *4,* middle cerebellar peduncle; *5,* anterior inferior cerebellar artery (AICA), cranial nerves VII and VIII; *6,* cranial loop of posterior inferior cerebellar artery (PICA) (supratonsillar segment); *7,* jugular foramen; *8,* PICA (posterior medullary segment); *9,* PICA (pyramidal loop); *10,* PICA (lateral medullary segment); *, caudal loop. *Right,* Retromastoid view of right cerebellopontine angle. *1,* Superior petrosal vein; *2,* subarcuate artery (AICA); *3,* AICA; *4,* internal auditory artery.

*Reproduced from Youmans & Winn 8e, Fig. 2.58, p. 41 — Label the LEFT panel (posterolateral view of the dorsal brainstem — the map of the MIDBRAIN dorsal entry zones): 1 **medial geniculate body**, 2 **superior colliculi**, 3 **superior cerebellar peduncle**, 4 **middle cerebellar peduncle**, 5 AICA and cranial nerves, with the trochlear (IV) and trigeminal (V) nerves, flocculus and PICA marked. Shade the **supracollicular**, **intercollicular** and **infracollicular** zones on the quadrigeminal plate, and draw the **lateral mesencephalic sulcus** running up to the medial geniculate body as the lateral mesencephalic zone. Note that CN IV emerges below the inferior colliculus and is therefore at risk in the infracollicular entry.*

3. The two-point method — how the zone is actually chosen

- **"Potential approach angles and thus surgical positioning can be evaluated using the two-point method. One point is placed in the center of the lesion, and a second is placed where the lesion most closely approaches the pial surface. The points are connected, and the resultant straight line can assist in determining the approach"** [YW pp. 3772, 3773].
- **The method has a named exception, and the examiner will want it:** *"There are exceptions to every rule, and the two-point method must be thoughtfully interpreted. For example, lesions in the pons are frequently closest to the ventral surface. However, these lesions are routinely approached via the middle cerebellar peduncle to reduce the risk of injury to the motor pathway"* YW p.3773.



Figure 461.4. Two-point method for surgical approach. A point in the center of the lesion is connected to a second point where the lesion most closely approaches the pial surface. The points are connected, and the resultant straight line determines the surgical approach. *(Used with permission from Barrow Neurological Institute, Phoenix, AZ.)*

*Reproduced from Youmans & Winn 8e, Fig. 461.4, p. 3772 — Label when you reproduce it: mark the **centre of the lesion** as point 1, the point where the **lesion most closely approaches the pial surface** as point 2, and the **straight line connecting them**, extended out through the skull, as the surgical trajectory. Annotate the exception: a pontine lesion closest to the ventral surface is still approached through the **middle cerebellar peduncle** to spare the corticospinal tract.*

4. Operative technique once the zone is selected

- **Pial opening. "Once a cortical entry point is determined, the pia is opened sharply with a blade or microscissors. Blunt-tipped forceps are then used to slowly and gently spread in the direction of the fiber tracts until the lesion is encountered"** YW p.3773.
- **Exophytic lesions** allow direct access; **when cavernomas approach but do not breach the surface there is frequently a hemosiderin-stained surface representation to guide the surgeon** YW p.3773.
- **Piecemeal internal decompression.** The lesion is entered sharply or with bipolar cauterisation, blood products evacuated with suction, irrigation and microforceps, and the lesion removed with microforceps, microdissectors, bipolar and sharp dissection: **"By focusing dissection within the cavernoma-brain interface and progressively shrinking the lesion into itself with bipolar electrocautery, the surgeon is able to maintain orientation and minimize the risk of leaving residual lesion"** YW p.3773. In the brainstem, a **suction cannula is used as a gentle retractor while a pituitary rongeur removes the lesion piecemeal** YW p.3773.
- **Developmental venous anomalies must be preserved. Special care must be taken to identify and avoid injury to any associated DVAs** YW p.3773; **any associated DVA should be preserved to reduce the risk of postoperative venous infarction** YW p.3772.
- **Do not chase the haemosiderin rim. No attempt should be made to resect the surrounding haemosiderin-laden brain unless the lesion is in non-eloquent cortex and the surgical indication is epilepsy** YW p.3772.
- **Systematic inspection of the cavity. "Breaking the lesional field into three-dimensional quadrants during this process provides a systematic method for inspection"**, and patience allows the cavity to collapse and be viewed

directly YW p.3773.

- **Instrument discipline. Avoid resting the back of an instrument on the craniotomy edge; rest a hand on the drapes and keep the instrument free of contact except at the surgical interface**, which gives tactile feedback and minimises transmitted force YW p.3773.
- **Counselling. Patients with deep-seated or brainstem cavernomas should be counselled regarding the risk of postoperative decline. Postoperative symptoms are typically similar to those experienced when the patient developed the haemorrhage, and tend to be worse after surgery in about one-half of patients with brainstem lesions** YW p.3772.

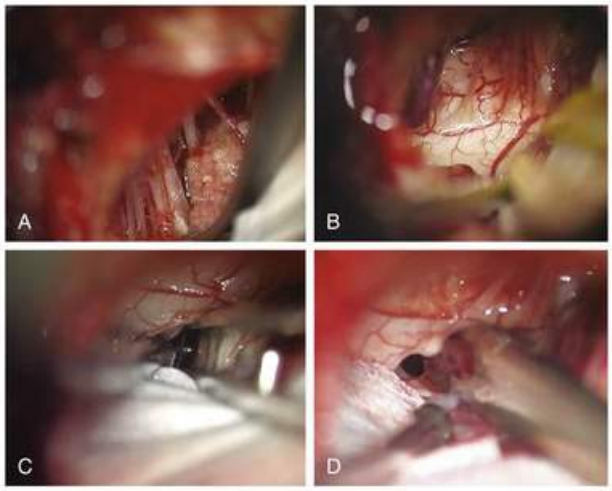


Figure 461.5. Microsurgical resection of a brainstem cavernous malformation (CM) through the left middle cerebellar peduncle. (A) The neurovascular structures (choroid plexus, lower cranial nerves, anterior inferior cerebellar artery, and posterior inferior cerebellar artery) of the cerebellopontine angle are dissected and mobilized. (B) The lateral cerebellar fissure is opened, and the middle cerebellar peduncle is exposed. (C) Using intraoperative neuronavigation, the entry point is selected and opened until the CM is found. (D) Using the suction cannula as a gentle retractor and with a pituitary rongeur, the CM is removed in a piecemeal fashion. Meticulous hemostasis and inspection of the cavity are mandatory at the end of the resection. *(Used with permission from Barrow Neurological Institute, Phoenix, AZ.)*

*Reproduced from Youmans & Winn 8e, Fig. 461.5, p. 3773 — Reproduce this four-panel operative photograph series (microsurgical resection of a brainstem cavernous malformation through the LEFT MIDDLE CEREBELLAR PEDUNCLE) and describe: (A) the neurovascular structures of the cerebellopontine angle — **choroid plexus, lower cranial nerves, AICA and PICA** — dissected and mobilised; (B) the **lateral cerebellar fissure opened and the middle cerebellar peduncle exposed**; (C) the entry point selected with **intraoperative neuronavigation** and opened until the CM is found; (D) the CM removed piecemeal with the **suction cannula used as a gentle retractor and a pituitary rongeur**, with meticulous haemostasis and inspection of the cavity at the end. State that this is the archetypal safe-entry-zone operation and the one that disproves the naive two-point rule.*

5. Approach-by-approach map — which craniotomy reaches which zone

- **Retrosigmoid — posterolateral pons, lateral middle cerebellar peduncle, superior lateral medulla and cerebellopontine angle** YW p.3774. To expose the lateral surface of the MCP, **the superior limb of the cerebellopontine fissure must be identified and the arachnoid of the fissure opened sharply, with care to preserve the vein of the superior cerebellopontine fissure; AICA typically passes between the facial and vestibulocochlear nerves and then runs along the surface of the MCP, providing another anatomical landmark** YW p.3774. Sequence of nerve identification: **CN XI at the foramen magnum followed cranially to X and IX; gentle retraction on the flocculus and the choroid plexus exiting the foramen of Luschka reveals the arachnoid over CN VII and VIII; the petrotentorial junction leads to the superior petrosal vein and thence to the trigeminal root entry zone; more medially CN IV is seen along the tentorial edge** YW p.3774.
- **Far-lateral — anterolateral trajectory to the brainstem; access to the vertebrobasilar junction, inferolateral pons, anterolateral medulla and upper cervical spinal cord**; first described by Heros. **Potential disadvantages: craniocervical instability, vertebral artery injury, CSF leak and injury to the low cranial nerves** YW p.3774.
- **Midline suboccipital / telovelar** — for the floor of the fourth ventricle. **The floor is exposed after removal of the tonsils and then of the inferior portion of the roof of the fourth ventricle** YW p.38. **Although advocated by Dandy as a safe approach, incision of the vermis can produce** cranial nerve, gait and focal motor disturbance, so the telovelar route is preferred; **manipulation of the floor of the fourth ventricle may result in hypotension, apnoea or**

even cardiac arrest YW p.1227.

- **Supracerebellar (suboccipital supracerebellar) infratentorial** — dorsal midbrain and collicular zones; **avoids disruption of the deep venous system including the vein of Galen and internal cerebral veins** [YW pp. 1825, 3774].
- **Orbitozygomatic / pterional** — ventral midbrain and interpeduncular fossa [YW pp. 1825, 3774].
- **Positioning.** For the retrosigmoid route Youmans prefers the **park-bench position** to avoid neurovascular compromise from turning the head laterally and to improve surgical access; **the park-bench position rolls the shoulder anteriorly and out of the way, which matters particularly when the surgeon's handedness matches the side of the craniotomy** YW p.3774. For brainstem gliomas, **the prone position provides excellent exposure of the brainstem except for upper midbrain tumours, and reduces the risk of venous air embolism and pneumocephalus** YW p.1825 .

Table 1 · Safe entry zones of the brainstem — Youmans' named list, their anatomical boundaries and the approach that reaches each. Compiled from Youmans & Winn 8e, Ch. 461 pp. 3773-3775, Ch. 2 pp. 35-39, 41 and Ch. 241 p. 1825.

Level	Safe entry zone	Anatomical limits / landmarks	Structures immediately at risk	Approach
Midbrain, ventral	**Interpeduncular fossa**	Between the two crura cerebri; floor = posterior perforated substance	**CN III** emerging from the medial crus; posterior thalamoperforating arteries	Pterional / orbitozygomatic
Midbrain, ventral	**Anterior mesencephalic zone**	On the crus cerebri, between CN III medially and the corticospinal fibres laterally	Corticospinal tract, CN III	Pterional / orbitozygomatic
Midbrain, lateral	**Lateral mesencephalic zone**	In the **lateral mesencephalic sulcus**, which separates crus from tegmentum and runs up to the medial geniculate body	Substantia nigra, medial geniculate body, basal vein of Rosenthal (posterior mesencephalic segment)	Subtemporal (prolonged temporal lobe retraction)
Midbrain, dorsal	**Supracollicular zone**	Above the superior colliculus on the quadrigeminal plate	Pretectum, posterior commissure → **Parinaud syndrome**	Supracerebellar infratentorial
Midbrain, dorsal	**Intercollicular zone**	Groove between superior and inferior colliculi	Colliculi, auditory and visual reflex pathways	Supracerebellar infratentorial
Midbrain, dorsal	**Infracollicular zone**	Below the inferior colliculus	**CN IV**, which exits below the inferior colliculus	Supracerebellar infratentorial
Pons, lateral	**Epitrigeminal zone**	Lateral pontine surface above/behind the CN V root entry zone; the apparent origin of CN V is the microsurgical limit between pons and MCP	CN V motor (superomedial) and sensory (inferolateral) roots; superior petrosal vein	Retrosigmoid
Pons, lateral	**Lateral pontine zone / middle cerebellar peduncle**	Lateral to the lateral pontine sulcus; open the superior limb of the cerebellopontine fissure; AICA runs on the MCP surface	Middle cerebellar peduncle fibres, CN VII/VIII, AICA, vein of the superior cerebellopontine fissure	Retrosigmoid — the workhorse for pontine cavernomas
Pons, dorsal	**Superior fovea triangle**	On the floor of the fourth ventricle, lateral to the facial colliculus, in the dimple of the sulcus limitans	**Facial colliculus** (CN VII genu over the abducens nucleus) medially; vestibular nuclei laterally	Midline suboccipital / telovelar
Medulla, lateral	**Lateral medullary zone**	Postolivary sulcus region, behind the olive	**CN IX, X, XI rootlets** from the postolivary sulcus; **CN XII** from the preolivary sulcus; PICA	Far-lateral

6. Adjuncts and monitoring for brainstem entry

- **Neuronavigation and intraoperative ultrasound are mandatory** for choosing the entry point and guiding resection

YW p.1825.

- **Intraoperative stimulation**, particularly for **identification and avoidance of the facial colliculus in the fourth ventricle**, can be beneficial — but **"there is no substitute for meticulous and disciplined surgical technique for the avoidance of postoperative deficits"** YW p.3772.
- **Monitoring changes are not a perfect guide: "postoperative neurological deficits are not always heralded by a change in monitored potentials. False-negative as well as false-positive potentials can complicate surgical procedures. However, changes from baseline recordings do require consideration intraoperatively"** YW p.3772.
- **Multimodal set-up for fourth-ventricular and brainstem work: SSEPs, MEPs, BAERs, facial nerve monitoring and lower cranial nerve monitoring** YW p.1227; **continuous brainstem auditory evoked responses provide information regarding the integrity of brainstem pathways and can be especially useful during fourth ventricular tumour surgery**, while **MEPs assess the pyramidal tracts** and **SSEPs detect reversible impending ischaemia from over-retraction** YW p.1210.
- **Closure.** The dura is closed watertight; if it cannot be closed primarily, a suturable dural substitute is placed **intradurally** and sutured in a sandwich fashion so that **CSF pressure and pulsatility assist in holding the repair together**, followed by fibrin glue, dry non-compressed Gelfoam epidurally, and a skull-base plate or titanium mesh YW p.3774. **Any violation into the mastoid air cells should be obliterated with bone wax to avoid CSF leak** YW p.3774. **If a postoperative CSF leak occurs, image and evaluate for hydrocephalus; if hydrocephalus is not suspected, place a lumbar drain, oversew the wound and divert CSF for 48 to 72 hours** YW p.3774.

(b) Brainstem auditory evoked potential monitoring [5]

7. Definition, stimulus and recording

- **The auditory brainstem response (ABR) is possibly the most powerful audiological test currently available for differentiating between cochlear and retrocochlear lesions, and is the auditory evoked potential most often assessed in site-of-lesion testing** YW p.201.e7.
- **The ABR is typically evoked with a short-duration pulse delivered to the ear at a predetermined intensity. At high-intensity levels the acoustic stimulus evokes as many as five amplitude peaks** YW p.201.e7.
- **The peaks were first identified and categorised by Jewett and Williston** YW p.201.e7 — quote the eponym.
- **Recording: BAERs depend on an auditory stimulus producing positive waves when measured via scalp electrodes in the 10 msec following the stimulus** YW p.1289; the display time window is **10 msec** YW p.201.e9.
- **The three major peaks are waves I, III and V**, generally accepted as corresponding to firing of **the first-order neurons of CN VIII (wave I), the superior olivary complex (wave III) and the inferior colliculus (wave V)**; **these three major waves are present at approximately 2-msec intervals in children and adults with normal hearing after the onset of the stimulus at high intensity** YW p.201.e7.

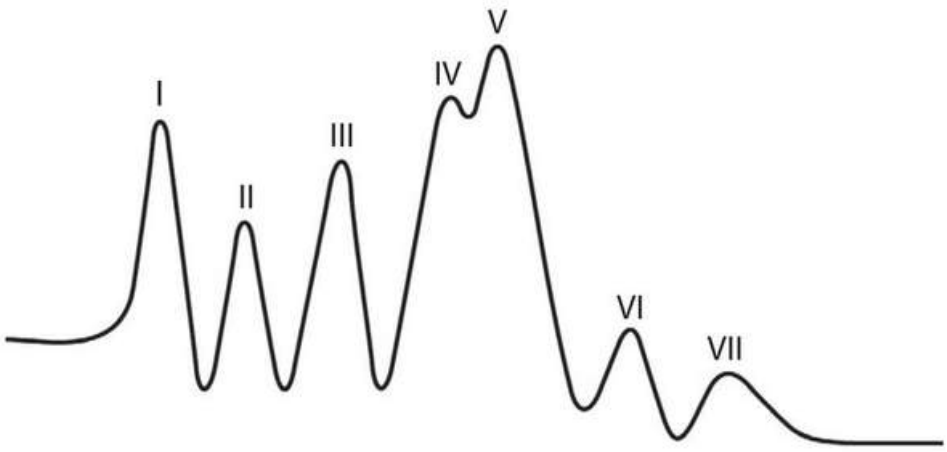


Figure 174.6. Brainstem auditory evoked potentials. The waves are thought to represent the activation of the acoustic nerve (wave I), cochlear nuclei (wave II), superior olives (wave III), lateral lemniscus tracts and nuclei (wave IV), and inferior colliculi (wave V). Waves VI and VII are presumed to arise from the medial geniculate body and the auditory radiations to the temporal lobe, respectively, although they are not considered clinically useful. (*Copyright Michael Gallagher, Department of Neurological Surgery, Northwestern Memorial Hospital, Chicago, IL.*)

*Reproduced from Youmans & Winn 8e, Fig. 174.6, p. 1284 — Reproduce this waveform schematic and label every generator: **wave I — acoustic (cochlear) nerve**; **wave II — cochlear nuclei**; **wave III — superior olives**; **wave IV — lateral lemniscus tracts and nuclei**; **wave V — inferior colliculi**; **wave VI — medial geniculate body**; **wave VII — auditory radiations to the temporal lobe**. Mark waves VI and VII as *"not considered clinically useful"*, and mark the 10-msec time base with the three major peaks (I, III, V) roughly 2 msec apart. This single figure answers the "generators" part of the question completely.*

8. Intensity-response behaviour — the graded data the examiner wants

- **As the intensity of the stimulus is decreased: the amplitude of all peaks decreases, the latency of each peak increases, and the replicability of the early waves (I and III) decreases. Only wave V is identifiable at threshold levels** YW p.201.e7.
- **The abnormal pattern in a retrocochlear lesion:** in a patient with a left cerebellopontine angle acoustic neuroma the left ear shows **poor replicability of waves III and V, increased latency of waves III and V, and consequently abnormal I-III and I-V interwave latencies** YW p.201.e9; the same ear shows **poor wave structure and a delay of wave V at 75-dB normalised hearing level** YW p.201.e9.
- **In vestibular schwannoma the sequence of deterioration is stereotyped: BAERs show increased latency initially in wave III and later in waves V and VI** YW p.1281.
- **Supporting audiological pattern:** the audiological examination in VS **typically shows loss of hearing at high frequencies with speech discrimination more affected than pure tone, indicating a retrocochlear lesion**; the acoustic reflex is **elevated or absent**, and **abnormal elevation or absence of the acoustic reflex in the presence of hearing loss at a less than 60-dB hearing level is audiological evidence of a retrocochlear site of the lesion**; **acoustic reflex adaptation is typically observed only in ears with a retrocochlear (CN VIII or low brainstem) disorder** [YW pp. 201.e7, 1281].

Table 2 · Brainstem auditory evoked potentials — wave generators, clinical value and the behaviour of each wave. Reproduced from Youmans & Winn 8e, Fig. 174.6, p. 1284 and Ch. 16 pp. 201.e7, 201.e9.

Wave	Generator (Youmans)	Approximate latency	behaviour	Clinical use

I	**Acoustic (cochlear) nerve** — first-order neurons of CN VIII	First peak; ~2 msec intervals between I, III and V	Monitors the **cochlea and CN VIII** — i.e. the peripheral, blood-supply-dependent limb
II	**Cochlear nuclei**	—	Inconsistent; not used in isolation
III	**Superior olives (superior olivary complex)**	**First to increase in latency in vestibular schwannoma**	One of the three major peaks; I-III interwave latency
IV	**Lateral lemniscus tracts and nuclei**	Often fused with wave V	—
V	**Inferior colliculi**	**The most robust wave; the only peak identifiable at threshold**; latency increases as intensity falls	The principal monitored peak; I-V interwave latency; delay of wave V is the classic retrocochlear sign
VI	**Medial geniculate body**	Latency increases late in vestibular schwannoma	**Not considered clinically useful**
VII	**Auditory radiations to the temporal lobe**	—	**Not considered clinically useful**

9. Clinical and intraoperative applications

- **Preoperative diagnosis. The ABR is often used in the preoperative evaluation of patients suspected of having CN VIII and low-brainstem disorders** YW p.201.e9.
- **Intraoperative monitoring, and exactly what each wave watches. "Under conditions in which a replicable ABR can be evoked preoperatively, it is common to use the procedure intraoperatively to monitor the integrity of the cochlea and CN VIII (wave I) and to evaluate more central auditory structures (waves III and V) as surgery progresses"** YW p.201.e9.
- **Hearing preservation surgery. "BAERs are monitored in any patient undergoing a hearing-preserving operation"** YW p.1285; **real-time information on the integrity and functional status of the cochlear nerve is critical while performing hearing-preserving surgery, and hearing status can be monitored in two ways: BAERs and direct stimulation** YW p.1289.
- **Brainstem and fourth-ventricular surgery. The use of continuous BAERs provides information regarding the integrity of brainstem pathways and can be especially useful during fourth ventricular tumour surgery** YW p.1210 ; the routine telovelar/transvermian neuromonitoring package is **SSEPs, MEPs, BAERs, facial nerve monitoring and lower cranial nerve monitoring** YW p.1227.
- **Postoperative documentation. Immediate postoperative ABR monitoring provides objective evidence of the integrity of the peripheral auditory system before final closure of the surgical field** YW p.201.e9.
- **Quantification. Intraoperative changes in ABR wave latencies can be used to quantify the effects of surgical procedures on transmission characteristics within the auditory system** YW p.201.e9.
- **Electrically evoked ABR (EABR) with cochlear implants — four peaks can be identified, the most robust being wave V; wave I is usually obliterated by the stimulus artefact at the beginning of the recording. EABR is affected by stimulus intensity, with a decrease in wave V amplitude and a slight increase in latency as current is decreased, and on average the latency of wave V is approximately 1.0 to 1.5 msec earlier than after the corresponding acoustic signal** YW p.201.e9.
- **Auditory neuropathy** — the combination of **absent or abnormal ABR with absent middle ear reflexes but normal outer hair cell function on otoacoustic emission testing and normal cochlear microphonics**, a term coined by **Starr and colleagues**, localising the abnormality to the level of the inner hair cells; pure-tone thresholds vary from normal to profound YW p.201.e9.

10. Limitations — the part most candidates omit

- **Not real-time. "Intraoperative changes in ABR wave latencies ... are not real-time measurements"** YW p.201.e9. The response requires **averaging over multiple stimulations; as a result, a change in the waveforms may be the consequence of manipulation that occurred seconds to minutes prior to the alert"** YW p.1284. Quantitatively,

"there is a lag of 2 to 3 minutes during the recording, which prevents the immediate identification of an injury" YW p.1289.

- **Useless when the baseline is poor. "It is commonly the case in patients harbouring large tumours that baseline BAERs are abnormal or absent, precluding their use as a surgical adjunct"** YW p.1284; **the response is often limited in the setting of large tumours because the baseline signal is often poor** YW p.1289.
- **Eighth-nerve monitoring does not deliver what facial nerve monitoring delivers. "Despite its widespread use, IOM of the vestibulocochlear nerve does not result in the same favourable outcomes as facial nerve monitoring. This likely reflects a combination of the inherent difficulty in monitoring the eighth cranial nerve as well as the need for improved IOM techniques"** YW p.1284.
- **False negatives and false positives. Postoperative neurological deficits are not always heralded by a change in monitored potentials; false-negative as well as false-positive potentials can complicate surgical procedures** YW p.3772.

11. The alternative — direct cochlear nerve action potential (CNAP)

- **In direct CNAP monitoring the cochlear action potential is measured directly from the eighth cranial nerve. After placement of a negative electrode at the contralateral mastoid and a scalp reference electrode, a recording electrode is placed directly on the nerve proximal to the tumour resection and an external auditory stimulus is applied** YW p.1284.
- **Unless a portion of normal nerve proximal to the tumour can be accessed, direct CNAP is not possible** YW p.1284.
- **The resulting action potential typically yields two high-amplitude negative peaks designated N1 and N2; changes in the latency or amplitude of the N1 peak suggest neural injury** YW p.1284.
- **Advantages and disadvantages. Compared to BAERs, direct CNAPs have the advantage of faster response times** and allow **immediate feedback plus confirmation of the structural and functional integrity of the nerve**; however **the recording electrode is relatively bulky**, it **requires a bipolar stimulator best suited to a suboccipital retrosigmoid approach**, and **because its use is limited to cases in which adequate exposure can be obtained it is often impractical during the middle cranial fossa approach** [YW pp. 1284, 1289].
- **Combination is better than either alone: the addition of CNAP monitoring to BAERs has been shown to improve hearing outcomes in small series** YW p.1289.

12. Anaesthetic requirements — a guaranteed sub-question

- **Intravenous anaesthesia has the least influence on all modalities. The susceptibility of monitoring modalities to the influence of inhalational anaesthetics increases in the following manner: brainstem auditory evoked response (BAER), SEP and MEP — with BAER most robust and MEP most susceptible** YW p.3244. Memorise the ordering.
- **Therefore low-dose inhalational agents (minimum alveolar concentration <1) are appropriate for SEP and BAER monitoring, whereas total intravenous anaesthesia with propofol and narcotic infusion is most appropriate if MEP monitoring is undertaken** YW p.3244.
- **Nitrous oxide is best avoided because it causes a profound decrease in MEP amplitude, although it has a negligible effect on SEP and BAER** YW p.3244.
- **Dexmedetomidine can be a useful adjunct**; **neuromuscular blockade should be avoided for optimal results** YW p.3244.
- **Technical cautions from the surgical side: electrocautery generates artefact, rendering IOM data transiently unreliable**, and there is a **risk of overstimulation of the nerve as well as iatrogenic injury from the probe**, so **low stimulation frequency and a pulsed (non-continuous) stimulus are recommended and electrocautery avoided when possible** YW p.1284.
- **Team requirement:** the monitoring team comprises **(1) a technologist who can set up patient and machine appropriately, (2) a knowledgeable expert neurophysiologist and (3) a physician licensed and privileged to supervise, give diagnostic interpretations and give medical advice about responses to change** — and **these apply across all areas of intraoperative neurophysiologic monitoring** YW p.2112.

Table 3 · BAER versus direct cochlear nerve action potential monitoring, and anaesthetic requirements. Compiled from Youmans & Winn 8e, Ch. 174 pp. 1284, 1289, Ch. 16 p. 201.e9 and Ch. 410 p. 3244.

	BAER / ABR	Direct CNAP
Electrode position	Scalp electrodes; response in the **10 msec** after the click	Recording electrode **directly on CN VIII proximal to the tumour**, negative electrode at contralateral mastoid, scalp reference
Waveform	Waves I-VII; **I, III, V** are the major peaks	Two high-amplitude negative peaks, **N1 and N2**
Response time	**Not real-time — 2-3 min lag**, averaged over many stimuli	**Immediate**
Fails when	**Large tumour with abnormal or absent baseline**	**No accessible normal nerve proximal to the tumour**; bulky electrode; impractical in the middle cranial fossa approach
Monitors	Cochlea and CN VIII (wave I); central auditory pathway (waves III, V)	Structural and functional integrity of the cochlear nerve
Best use	Any hearing-preservation operation; continuous monitoring of brainstem pathways in fourth-ventricular surgery	Suboccipital retrosigmoid approach; **added to BAER improves hearing outcomes**
Anaesthetic sensitivity (all modalities)	**BAER most robust → SEP → MEP most susceptible** to inhalational agents; MAC <1 acceptable for BAER and SEP; TIVA with propofol + narcotic if MEPs needed; avoid nitrous oxide (profound MEP amplitude loss, negligible effect on SEP/BAER); avoid neuromuscular blockade; dexmedetomidine useful adjunct	

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Youmans' safe entry zone list, verbatim:** epitrigeminal, superior fovea triangle, interpeduncular fossa, anterior and lateral mesencephalic, inter-, supra- and infracollicular, lateral pontine and medullary zones YW p.3773.
- **The two-point method** connects the centre of the lesion to the point where it comes closest to the pial surface — **but a ventrally placed pontine lesion is still entered through the middle cerebellar peduncle** to spare the corticospinal tract.
- **Open the pia sharply, then spread bluntly in the direction of the fibre tracts.**
- **Preserve every DVA; never chase the haemosiderin rim** outside non-eloquent cortex operated for epilepsy.
- **Superior fovea triangle is lateral to the facial colliculus** — the facial colliculus is the structure you are avoiding, and intraoperative stimulation helps identify it.
- **Infracollicular entry risks CN IV**, which exits below the inferior colliculus.
- **Manipulating the floor of the fourth ventricle can cause hypotension, apnoea or cardiac arrest** — the calamus scriptorius is not a safe zone.
- **BAEP generators**: I acoustic nerve, II cochlear nuclei, III superior olives, IV lateral lemniscus, V inferior colliculi, VI medial geniculate body, VII auditory radiations. **VI and VII are not clinically useful.**
- **Waves I, III and V are 2 msec apart; only wave V survives at threshold.** As intensity falls, amplitude falls, latency rises and early waves lose replicability.
- **In vestibular schwannoma wave III delays first, then V and VI.**
- **BAER is not real-time** — a 2-3 minute averaging lag, and it is useless when a large tumour has already abolished the baseline.
- **Anaesthetic robustness order: BAER > SEP > MEP.** MAC <1 for BAER/SEP; TIVA for MEP; nitrous oxide kills MEPs but not BAERs.
- **Direct CNAP (N1, N2) is immediate but needs accessible normal nerve** and a retrosigmoid exposure; **CNAP added to BAER improves hearing outcomes**.
- **Monitoring never replaces technique** — false-negative and false-positive potentials both occur, and *"there is no substitute for meticulous and disciplined surgical technique"*.

Pages read for this answer — Youmans & Winn 8e: 35, 36, 38, 39, 201.e7, 201.e9, 1210, 1227, 1281, 1284, 1285, 1289, 1825, 2112, 3244, 3772, 3773, 3774

a) Internuclear ophthalmoplegia. [3]
b) Draw axial section of midbrain at level of tectum. [4]
c) Clinical features of intrinsic brain stem lesions. [3]

LONG | MAY 2024 · Paper I · Q4 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 15 *Neuro-ophthalmology*, §Disorders of the Ocular Motor System and §Supranuclear, Internuclear, and Cerebellar, pp. 200.e19-200.e20, 200.e22-200.e25 (Tables 15.3-15.5, pp. 200.e19-200.e20; Fig. 15.31, p. 200.e22; Fig. 15.36, p. 200.e24). Supplementary: Ch. 2 *Surgical Anatomy of the Brain*, §Basal Surface: Neural Relationships and §Brainstem, pp. 24, 35-36, 38, 41 (Fig. 2.22, p. 24; Fig. 2.51, p. 38; Fig. 2.58, p. 41); Ch. 111 *Deep Brain Stimulation for Parkinson Disease*, §Targeting, p. 734 (Fig. 111.2, p. 734); Ch. 241 *Brainstem Gliomas*, §Focal Brainstem Glioma and §Diffuse Intrinsic Pontine Glioma, pp. 1825-1826, 1828-1829 (Figs. 241.1, 241.3, pp. 1825-1826); Ch. 16 *Neurotology*, §Vertigo of Central Origin and §Brainstem Lesions, pp. 201.e11, 201.e22; Ch. 260 *Developmental Anomalies of the Craniovertebral Junction and Surgical Management*, §Clinical Presentation, p. 1961; Ch. 69 *Physiology of the Cerebrospinal Fluid and Intracranial Pressure*, §Herniation Syndromes, p. 472.e8.

(a) Internuclear ophthalmoplegia [3]

1. Definition and the tract responsible

- **An internuclear disorder affects the medial longitudinal fasciculus (MLF), causing internuclear ophthalmoplegia (INO) with an ipsilateral adduction deficit and abducting nystagmus of the contralateral eye** YW p.200.e19. That single sentence is the definition; everything else is elaboration.
- **INO results from a lesion of the MLF either in the midbrain or the pons** YW p.200.e23. It is therefore a *localising* sign to the paramedian brainstem tegmentum, not to a nerve.
- **Function of the MLF, verbatim:** *"The MLF conveys the eye movement command from the sixth nerve nucleus to the contralateral third nerve nucleus, thereby allowing conjugate horizontal eye movements with simultaneous contraction of the ipsilateral lateral rectus and contralateral medial rectus muscles"* YW p.200.e23.
- **The MLF is far more than a gaze cable:** it **connects the vestibular nuclei to all of the other cranial nerve nuclei, and of particular interest are the connections with CNs III, IV, VI and X** YW p.201.e11. This is why INO so often travels with nystagmus, skew and vestibular symptoms.
- **Why the deficit is ipsilateral to the lesion: "Lesions of the MLF virtually always occur after the immediate decussation of the fibres originating in the sixth nerve nucleus, so the predominant clinical feature of impaired adduction is found ipsilateral to the lesion"** [YW pp. 200.e23, 200.e24].
- **Where the command starts: the abducens nucleus lies on the floor of the fourth ventricle and contains internuclear neurons involved in horizontal gaze, so nuclear lesions produce an ipsilateral gaze palsy** rather than an isolated lateral rectus weakness YW p.200.e20. An abducens *nuclear* lesion therefore gives a **conjugate gaze palsy**; an MLF lesion gives an **INO**. Contrast the two explicitly.

2. Signs, from florid to subtle, and the one manoeuvre that settles it

- **Classic unilateral INO: impaired adduction of the eye ipsilateral to the lesion and dissociated nystagmus of the contralateral abducting eye** YW p.200.e24.
- **Subtle INO: "eye movements may appear full; subtle slowing of the adducting eye compared with the abducting eye during horizontal saccadic eye movements (adduction lag) may be the only clue to the presence of an INO"** YW p.200.e24. Test **saccades**, not pursuit — ask the patient to look rapidly between two targets.
- **The discriminating test: "the adduction deficit in INO can often be overcome with convergence eye movements, whereas adduction deficits from other causes (e.g. third nerve palsy, ocular myasthenia) cannot, thereby allowing for clinical differentiation from these entities"** YW p.200.e24.
- **The commonest mimic: ocular myasthenia gravis can have a clinical appearance that mimics other ocular motor disorders, such as pupil-sparing third nerve palsy or INO**, and **complete ophthalmoplegia can sometimes be seen**

YW p.200.e19. Myasthenic weakness is **variable and asymmetrical**, worsens as the day progresses and improves after rest; look for **fatigable ptosis on 30 seconds of sustained upgaze** and **orbicularis oculi weakness** detected by prising the forcibly closed lids open [YW pp. 200.e19, 200.e21].

- **Confirm the mimic, do not assume it:** myasthenia is confirmed by **a positive edrophonium (Tensilon) or neostigmine (Prostigmin) test, serum acetylcholine receptor antibody assay, or repetitive nerve stimulation study — although these can be normal in ocular myasthenia; single-fibre electromyography has the greatest sensitivity but is technically difficult and may not be widely available** YW p.200.e21.

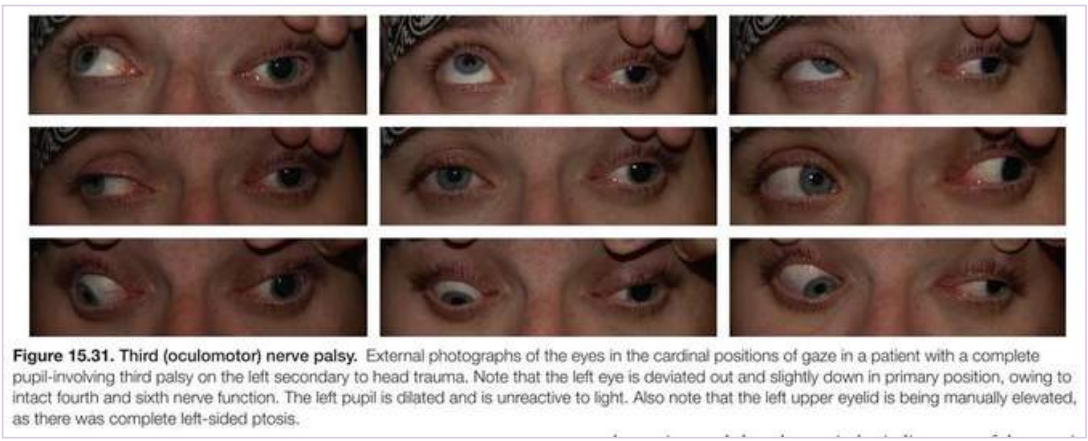


Figure 15.31. Third (oculomotor) nerve palsy. External photographs of the eyes in the cardinal positions of gaze in a patient with a complete pupil-involving third palsy on the left secondary to head trauma. Note that the left eye is deviated out and slightly down in primary position, owing to intact fourth and sixth nerve function. The left pupil is dilated and is unreactive to light. Also note that the left upper eyelid is being manually elevated, as there was complete left-sided ptosis.

*Reproduced from Youmans & Winn 8e, Fig. 15.31, p. 200.e22 — Reproduce this nine-position photograph montage of a **complete pupil-involving LEFT third nerve palsy** after head trauma, and describe: the left eye **deviated out and slightly down in primary position owing to intact fourth and sixth nerve function**, the **dilated unreactive left pupil**, and the **left upper eyelid being manually elevated because of complete ptosis**. Use it as the contrast case for INO: here adduction fails but **cannot be overcome by convergence**, the pupil is involved and there is ptosis — none of which occurs in a pure INO.*

3. Causes and their localisation

- **Common causes of INO: multiple sclerosis, brainstem stroke, brainstem tumour and fourth ventricular tumour** YW p.200.e24.
- **In the case of stroke the causative lesion can be very small and easily overlooked on neuroimaging** YW p.200.e24 — an unimpressive MRI does not exclude the diagnosis.
- **Nuclear fourth nerve lesion** — in **caudal periaqueductal grey matter, dorsal to the MLF** — gives **internuclear ophthalmoplegia contralateral to the superior oblique weakness**, because of the trochlear decussation; causes are **haemorrhage, stroke, demyelination and trauma (including neurosurgical)**, and **isolated fourth nerve nucleus lesions are very rare** YW p.200.e20.
- **Millard-Gubler syndrome** — abducens exit at the pontomedullary junction: a **seventh nerve deficit plus internuclear ophthalmoplegia**; **Raymond-Cestan syndrome** adds **contralateral hemiparesis**. Because the fascicles pass through the ventral brainstem, **isolated palsies are unusual** YW p.200.e20.
- **Craniovertebral junction disease** — the trap: **"not uncommonly, internuclear ophthalmoplegia is present, leading to a misdiagnosis of mesencephalic and upper pontine disturbance"** in basilar invagination; **downbeat nystagmus is present in strictly compressive lesions of the craniovertebral border with or without an associated Chiari malformation** YW p.1961.
- **Raised ICP with central transtentorial herniation — "with progressive bilateral involvement, internuclear ophthalmoplegia may arise, and motor examination may show bilateral decerebrate posturing"**; by this stage the **pupils have fallen into a midline fixed position** and respiration is tachypnoeic YW p.472.e8.
- **Compare with the supranuclear disorders** that share the territory: **the dorsal midbrain (Parinaud) syndrome** — supranuclear upgaze palsy, convergence-retraction nystagmus, Collier sign, light-near dissociation, from involvement of **projections from vertical gaze centres travelling in the posterior commissure**; and a **complete supranuclear vertical gaze palsy**, which implicates the **rostral interstitial nuclei of the MLF (riMLF)** YW p.200.e23.

(b) Draw an axial section of the midbrain at the level of the tectum [4]

4. Establish the level, then the layers

- **The brainstem is divided into three parts: midbrain, pons and medulla** YW p.35.
- **The midbrain is divided by a midline sagittal plane into two cerebral peduncles. Each peduncle is further divided into three parts: an anterior part consisting of the crus cerebri or basis pedunculi; an intermediate part, the tegmentum; and a posterior part located behind the aqueduct, the tectum** YW p.35. **The tectum is by definition the part behind the aqueduct** — so a section "at the level of the tectum" is a section through the quadrigeminal plate.
- **The substantia nigra and the lateral mesencephalic sulcus separate the crus cerebri from the tegmentum** YW p.35 — one internal, one on the surface.
- **The posterior aspect of the midbrain presents superior and inferior colliculi (quadrigeminal plate)** YW p.36. If the section is at the **superior colliculus** you are at the upper midbrain and the **oculomotor nucleus** is in the periaqueductal grey; if at the **inferior colliculus** you are at the lower midbrain, the **trochlear nucleus** is in the caudal periaqueductal grey dorsal to the MLF, and **CN IV exits the brainstem below the inferior colliculus** [YW pp. 36, 200.e19, 200.e20]. Say which level you have drawn.
- **Surface grooves to include. The pontomesencephalic sulcus, which separates the midbrain from the pons, originates in the depth of the interpeduncular fossa and runs around the inferior margin of the crus cerebri to join the lateral mesencephalic sulcus behind the crus cerebri** [YW pp. 35, 36]. The **interpeduncular or interbrachial sulcus separates the superior from the middle cerebellar peduncle, ascends from the bottom of the cerebellomesencephalic fissure toward the lateral aspect of the pons, where it is joined by the pontomesencephalic sulcus to proceed superiorly as the lateral mesencephalic sulcus to the medial geniculate body; the lateral mesencephalic sulcus separates the crus cerebri from the tegmentum** YW p.38.

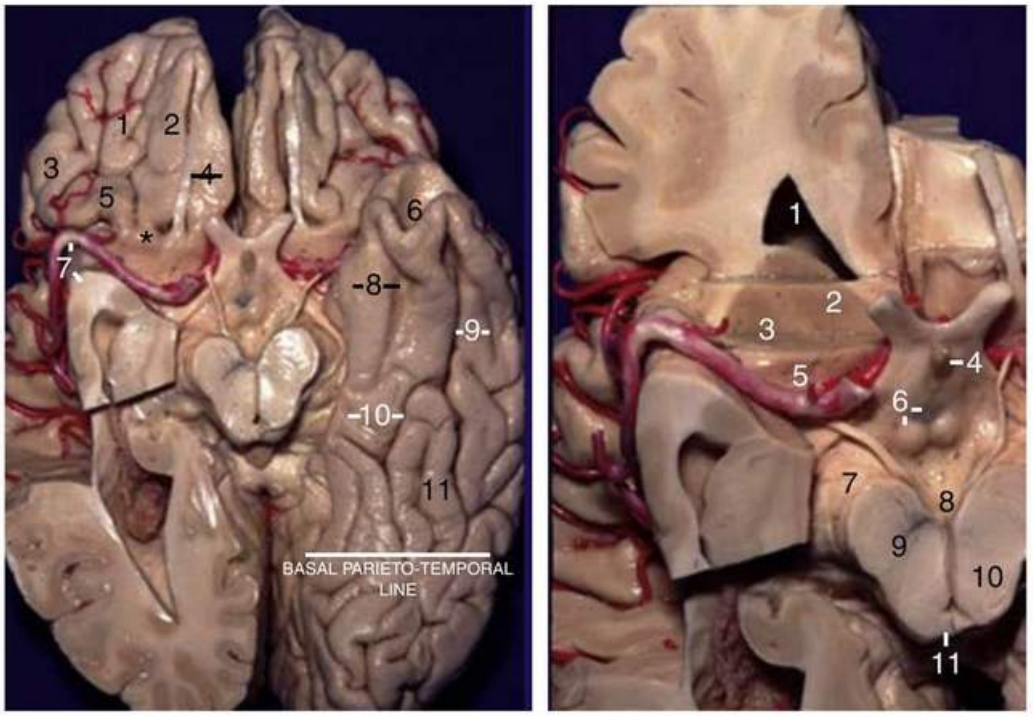


Figure 2.22. *Left,* Basal view. *1,* Anterior orbital gyrus; *2,* medial orbital gyrus; *3,* lateral orbital gyrus; *4,* rectus gyrus and olfactory tract; *5,* posterior orbital gyrus; *6,* temporal pole; *7,* genu of middle cerebral artery and insular pole; *8,* uncus and rhinal sulcus; *9,* occipitotemporal sulcus and inferior temporal gyrus; *10,* parahippocampal gyrus and collateral sulcus; *11,* fusiform gyrus; *, posteromedial orbital lobule. *Right,* Basal view. *1,* Frontal horn; *2,* caudate nucleus (head); *3,* lentiform nucleus; *4,* pituitary stalk; *5,* anterior perforated substance; *6,* tuber cinereum and mammillary body; *7,* crus cerebri; *8,* posterior perforated substance; *9,* substantia nigra; *10,* tegmentum; *11,* tectum.

*Reproduced from Youmans & Winn 8e, Fig. 2.22, p. 24 — Label when you reproduce the RIGHT panel (basal view of a sectioned specimen through the midbrain — the closest thing in Youmans to a real axial midbrain section): 1 frontal horn, 2 head of caudate nucleus, 3 lentiform nucleus, 4 pituitary stalk, 5 anterior perforated substance, 6 tuber cinereum and mammillary body, 7 **crus cerebri**, 8 **posterior perforated substance**, 9 **substantia nigra**, 10 **tegmentum**, 11 **tectum**. Labels 7-11 give you, in a real specimen, the exact layer sequence Youmans names in the text; carry them straight across onto your own drawing.*

5. What goes on the drawing — a checklist

- **Anteriorly, in the midline: interpeduncular fossa**, floored by the **posterior perforated substance**, which is the entry site for the **posterior thalamoperforating arteries** from P1 [YW pp. 27, 35].
- **Crus cerebri** on each side, with **CN III emerging from the medial side of the crura cerebri in the interpeduncular fossa** YW p.35.
- **Substantia nigra** as a dark band behind each crus YW p.35.
- **Tegmentum**, containing at the superior-colliculus level:
  - **Red nucleus** — Youmans' practical landmark: **the anterior border of the red nucleus is visualised on an axial slice 4 mm below the midcommissural plane, and a line drawn tangential to the anterior apex of the red nucleus is seen cutting through the subthalamic nucleus** YW p.734.
  - **Oculomotor nucleus** in **periaqueductal grey matter at the level of the superior colliculus**, with the **superior**

rectus subnucleus contralateral and a **single midline levator subnucleus** — hence **bilateral ptosis and bilateral superior rectus palsy** with a nuclear lesion YW p.200.e19.

- **Fascicles of CN III**, which **pass through the decussating superior cerebellar peduncle, the substantia nigra and the medial cerebral peduncle** YW p.200.e19.
- **Medial longitudinal fasciculus**, paramedian; the **trochlear nucleus lies dorsal to it in caudal periaqueductal grey** YW p.200.e20.
- **Mesencephalic reticular formation** and **pretectum** YW p.27.

- **Cerebral aqueduct** in the midline, the tegmentum-tectum boundary YW p.35.
- **Tectum**: **superior and inferior colliculi (quadrigeminal plate)**; add the **medial geniculate body** laterally as the upper end of the lateral mesencephalic sulcus, and the **superior cerebellar peduncle** posterolaterally [YW pp. 36, 38, 41].
- **Perforator territory to annotate** (it turns an anatomy drawing into a surgical one): **the posterior thalamoperforating arteries arise from P1 and enter through the posterior perforated substance, interpeduncular fossa and medial crus cerebri, supplying the anterior and part of the posterior thalamus, hypothalamus, subthalamus, substantia nigra, red nucleus, oculomotor and trochlear nuclei, oculomotor nerve, mesencephalic reticular formation, pretectum, rostromedial floor of the third ventricle and posterior portion of the internal capsule** YW p.27. **Short circumflex arteries terminate at the geniculate bodies and long circumflex arteries reach the colliculi**; **direct perforating arteries to the crus cerebri arise mainly from P2A** YW p.27. **The medial posterior choroidal artery supplies the crus cerebri, tegmentum, geniculate bodies (mainly medial), colliculi, pulvinar, pineal gland and medial thalamus** YW p.27.

Constructing the diagram. Youmans 8e teaches the midbrain section through real dissections (Figs. 2.22, 2.51, 2.58) and axial MRI (Fig. 111.2) rather than through a stylised cross-sectional line drawing, so draw your own and state which level you have chosen. Superior-colliculus level: symmetrical oval; interpeduncular fossa and posterior perforated substance anteriorly with CN III emerging from the medial crus; crus cerebri; substantia nigra; tegmentum with red nucleus, oculomotor nucleus in periaqueductal grey, paramedian MLF and mesencephalic reticular formation; cerebral aqueduct; tectum with the two superior colliculi. Add the lateral mesencephalic sulcus on the surface and the medial geniculate body at its upper end.

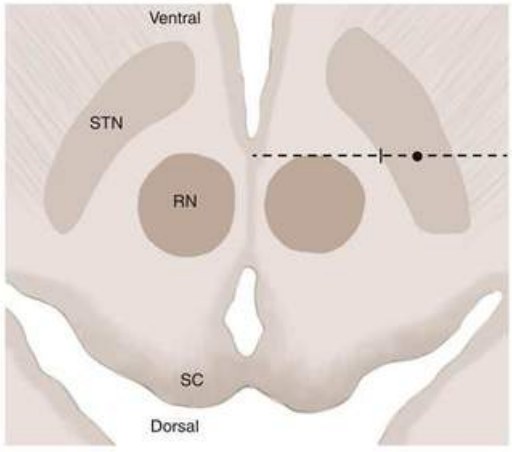


Figure 111.2. Midbrain at 4 mm below the midcommissural plane. The line parallel to the ventral border of the red nucleus *(RN; dashed line)* is extended to the midpoint of the subthalamic nucleus *(STN; black dot)* or, if the lateral border is difficult to interpret, at least 2 mm away from the STN medial border *(short vertical bar)* for targeting. *SC*, Superior colliculi.

ensure accessibility to the face from the unsterile side. After a skin incision just posterior to the planned skull entry location,

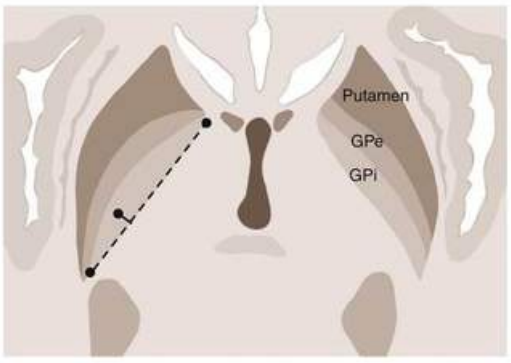


Figure 111.3. The axial cut at the midcommissural plane. The medial border of the globus pallidus interna *(GPi)* is split into thirds *(dashed line,)* and a point 3 to 4 mm lateral and perpendicular to the line at the junction of the posterior one-third and anterior two-thirds *(short vertical bar with black dot)* is used for targeting. *GPe*, Globus pallidus externa.

*Reproduced from Youmans & Winn 8e, Fig. 111.2, p. 734 — Imaging correlate — describe on this axial T2 fast spin echo image **4 mm below the midcommissural plane**: the **superior colliculi (SC)** posteriorly (confirming that this is a tectal-level section), the **red nucleus (RN)** with the dashed line drawn parallel to its ventral border, the **subthalamic nucleus (STN)** which that line crosses, the **putamen** and the **globus pallidus externa and interna (GPe, GPi)**. Note that ventral is marked anteriorly. This is how a tectal-level axial section looks in a living patient.*

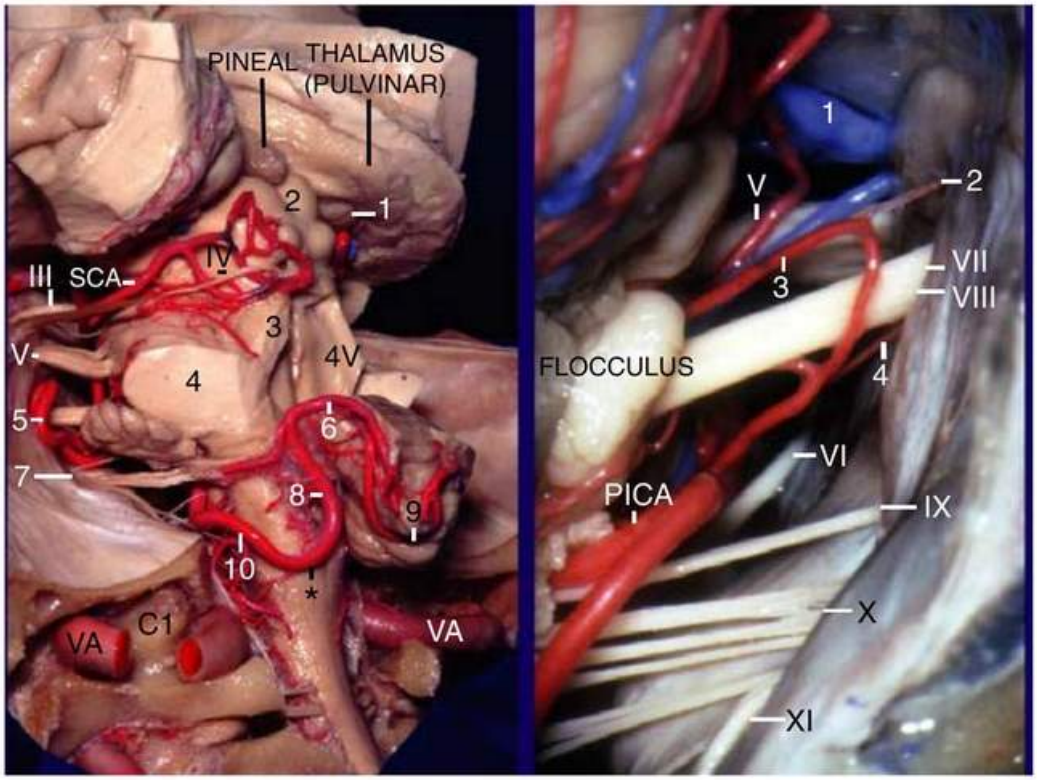


Figure 2.58. *Left,* Posterolateral view. *1,* Medial geniculate body; *2,* superior colliculi; *3,* superior cerebellar peduncle; *4,* middle cerebellar peduncle; *5,* anterior inferior cerebellar artery (AICA), cranial nerves VII and VIII; *6,* cranial loop of posterior inferior cerebellar artery (PICA) (supratonsillar segment); *7,* jugular foramen; *8,* PICA (posterior medullary segment); *9,* PICA (pyramidal loop); *10,* PICA (lateral medullary segment); *, caudal loop. *Right,* Retromastoid view of right cerebellopontine angle. *1,* Superior petrosal vein; *2,* subarcuate artery (AICA); *3,* AICA; *4,* internal auditory artery.

*Reproduced from Youmans & Winn 8e, Fig. 2.58, p. 41 — Label the LEFT panel (posterolateral view of the dorsal brainstem — the tectum seen from outside): 1 **medial geniculate body**, 2 **superior colliculi**, 3 **superior cerebellar peduncle**, 4 **middle cerebellar peduncle**, 5 AICA and cranial nerves; mark the **trochlear (IV)** and **trigeminal (V)** nerves, the flocculus and PICA. State in your label that CN IV emerges below the inferior colliculus, that the quadrigeminal plate is the tectum, and that the supra-, inter- and infracollicular safe entry zones sit on this surface.*

Table 1 · Axial section of the midbrain at the tectum — layers, contents and vascular territory. Compiled from Youmans & Winn 8e, Ch. 2 pp. 24, 27, 35-36, 38, 41 and Ch. 15 pp. 200.e19-200.e20.

Layer	Boundary with the next	Contents to label	Named artery / territory
Interpeduncular fossa + posterior perforated substance	Crura cerebri laterally	CN III emerging from the medial crus	Posterior thalamoperforating arteries (P1) enter here
Crus cerebri (basis pedunculi)	**Substantia nigra** internally; **lateral mesencephalic sulcus** on the surface	Corticospinal, corticobulbar, corticopontine fibres	Direct perforating arteries from **P2A**; anterior choroidal artery branches
Substantia nigra	— (it is the boundary)	Pigmented nucleus	Posterior thalamoperforating arteries

Tegmentum	**Cerebral aqueduct** posteriorly	Red nucleus; oculomotor nucleus (periaqueductal grey, superior colliculus level); trochlear nucleus (caudal, dorsal to MLF); MLF; mesencephalic reticular formation; pretectum	Posterior thalamoperforating arteries (P1)
Tectum (quadrigeminal plate)	—	**Superior colliculi** (upper midbrain) and **inferior colliculi** (lower midbrain); CN IV exits below the inferior colliculus	**Long circumflex arteries** reach the colliculi; **short circumflex arteries** terminate at the geniculate bodies; **medial posterior choroidal artery** supplies colliculi, tegmentum, geniculate bodies and pulvinar
Medial geniculate body (lateral)	—	Upper end of the lateral mesencephalic sulcus	Medial posterior choroidal artery; short circumflex arteries

(c) Clinical features of intrinsic brainstem lesions [3]

6. General behaviour of an intrinsic brainstem lesion

- **"Primary brainstem tumors, such as gliomas, usually grow slowly, infiltrate the brainstem nuclei and fiber tracts, and produce multiple signs and symptoms"** YW p.201.e22. That sentence is the concept: *multiple simultaneous deficits from a single small lesion.*
- **Epidemiology to quote: in adults they account for approximately 1% of intracranial tumours, but in children they are 5 to 10 times more common** YW p.201.e22.
- **"Vestibular and cochlear signs and symptoms are common and occur in approximately 50% of patients"**, and **"the brainstem site of origin can usually be determined from the other associated neurological findings"** YW p.201.e22.
- **Symptoms correspond to the tumour location** YW p.1825 — so answer by level, not as an undifferentiated list.
- **Adjacent (extrinsic) lesions must be excluded: tumours adjacent to the fourth ventricle can produce vestibular signs by compressing the vestibular nuclei — medulloblastoma, ependymoma, papilloma, teratoma, epidermoid cyst and cysticercosis** YW p.201.e22.

7. Focal brainstem glioma — the indolent presentation

- **"Patients with FBSG usually present with minor symptoms that may have been present for years"** YW p.1825.
- **Commonly seen symptoms: neck pain and stiffness, cranial nerve palsies, contralateral hemiparesis, and hemichorea** YW p.1825.
- **Hydrocephalus may occur in exophytic tumours extending posteriorly, tectal gliomas, and tumours arising from the posterior aspect of the rostral midbrain** YW p.1825.
- **Torticollis is a common presentation in older children with exophytic tumours, due to chronic tonsillar herniation** YW p.1825.
- **Medullary gliomas may present with dysphagia or apnoea, whereas cervicomedullary gliomas usually present with upper and/or lower motor neuron lesions** YW p.1825.

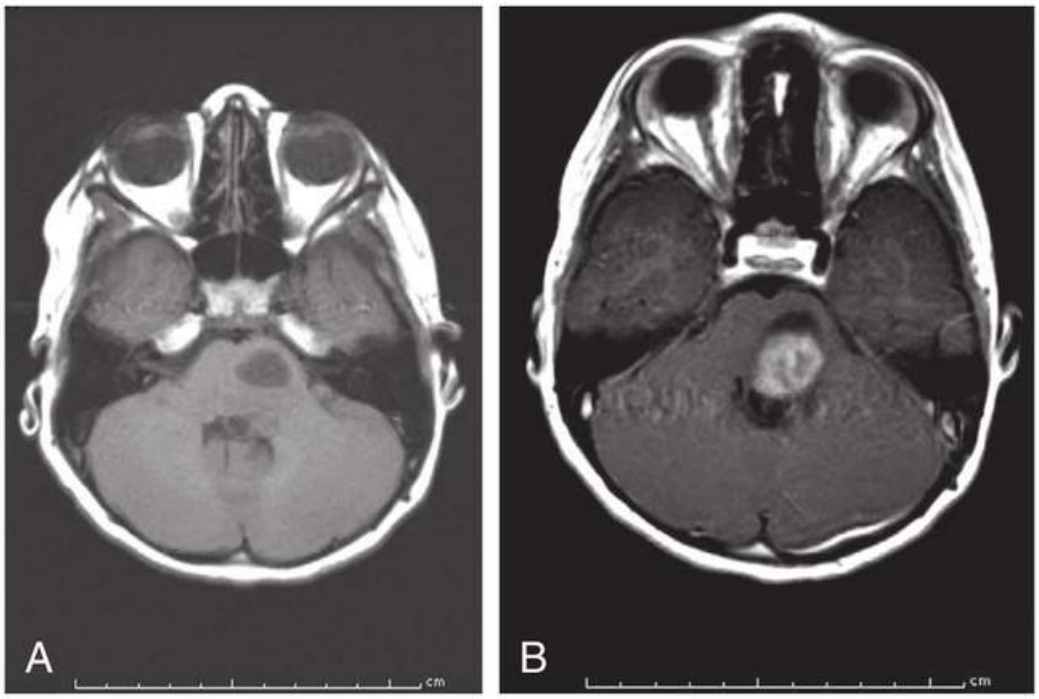


Figure 241.1. Magnetic resonance imaging of a focal midbrain and pontine tumor. (A) T1-weighted axial sequence demonstrating a poorly defined tumor in the pons and midbrain with anterior cyst. (B) T1-weighted contrast-enhanced image demonstrating avid enhancement of the tumor.

*Reproduced from Youmans & Winn 8e, Fig. 241.1, p. 1825 — Imaging correlate — describe this two-panel MRI of a **focal midbrain and pontine tumour**: (A) T1-weighted axial sequence showing a **poorly defined tumour in the pons and midbrain with an anterior cyst**; (B) T1-weighted contrast-enhanced image showing **avid enhancement of the tumour**. Add the radiographic criteria for focal brainstem glioma: **well-demarcated borders, minimal or no vasogenic oedema, isointense or hypointense on T1, hyperintense on T2, and homogeneous contrast enhancement**, with **diffusion tensor imaging a crucial diagnostic tool — a DTI measure of white-matter tract integrity that is decreased when tracts are disrupted indicates a poor prognosis**.*

8. Diffuse intrinsic pontine glioma — the aggressive presentation and the triad

- **"Patients with DIPG present with a short duration of symptoms/signs due to the aggressive nature of the disease"** YW p.1828. Contrast this directly with the years-long history of a focal glioma.
- **The classical clinical presentation of DIPG is a triad** YW p.1828:
  - **Cerebellar symptoms — ataxia, dysmetria and/or dysarthria.**
  - **Long tract impairment — sensory loss, increased tone, hemiparesis, clonus, Babinski sign and/or hyperreflexia.**
  - **Cranial nerve palsy — facial asymmetry and diplopia due to impaired extraocular movement.**
- **"The most common cranial nerve palsies include VI and VII; however, cranial nerves III, IV, IX, and X may be affected as well"** YW p.1828.
- **"Less than 10% of patients with DIPG present with hydrocephalus, in the later stages of the disease, due to expansion of the pons or exophytic tumour growth leading to obstruction of the fourth ventricle"** YW p.1828. Hydrocephalus is therefore *not* a typical presenting feature of DIPG — an examinable discriminator against a tectal or exophytic tumour.
- **Imaging features: on CT, DIPG appears isodense or hypodense with no calcifications, and the presence of calcification usually implies an atypical brainstem glioma**; on MRI **indistinct margins, isointense or hypointense on T1, hyperintense on T2, heterogeneous contrast enhancement, usually increased diffusion, diffuse expansion**

of the pons with signal possibly extending to midbrain, thalamus and cerebellum, a commonly seen exophytic component, and frequent encirclement of the basilar artery. **Petechial haemorrhages are common and best detected by susceptibility-weighted imaging**, while **obstructive hydrocephalus and dissemination are not common** [YW pp. 1828, 1829].

- **Spectroscopy: MRS can distinguish DIPG from focal brainstem glioma using the choline/N-acetyl aspartate ratio and measure the risk of more rapid progression; detection of lactate and N-acetyl aspartate at diagnosis predicts a poor prognosis; areas of T2 hypointensity that enhance and show restricted diffusion may represent anaplasia and are good stereotactic biopsy targets** [YW pp. 1828, 1829].

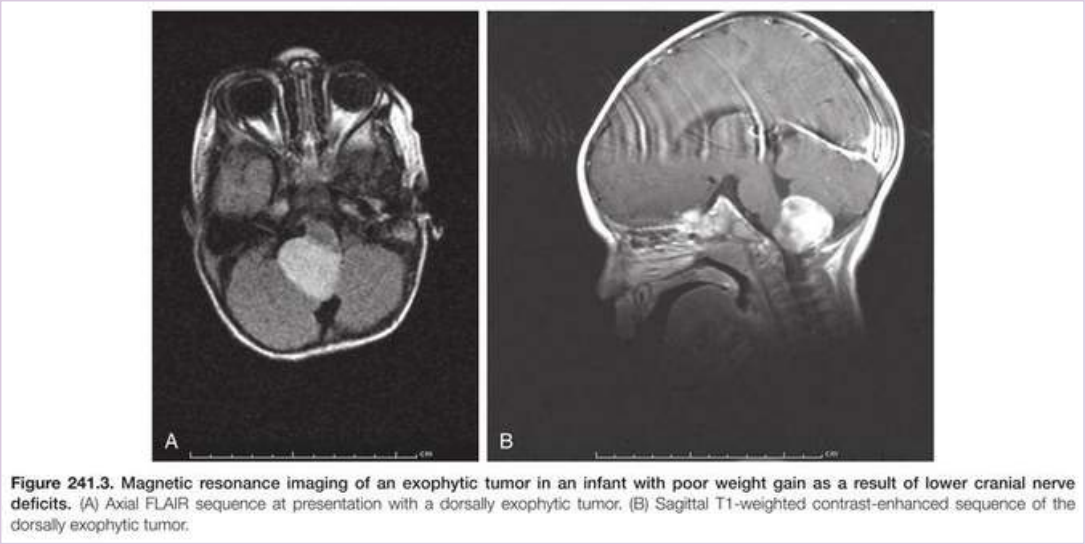


Figure 241.3. Magnetic resonance imaging of an exophytic tumor in an infant with poor weight gain as a result of lower cranial nerve deficits. (A) Axial FLAIR sequence at presentation with a dorsally exophytic tumor. (B) Sagittal T1-weighted contrast-enhanced sequence of the dorsally exophytic tumor.

*Reproduced from Youmans & Winn 8e, Fig. 241.3, p. 1826 — Imaging correlate — describe this two-panel MRI of a **dorsally exophytic brainstem tumour in an infant presenting with poor weight gain from lower cranial nerve deficits**: (A) axial FLAIR at presentation showing the dorsally exophytic tumour; (B) sagittal T1 post-contrast of the same lesion. Link it to the clinical rule that **dorsally exophytic brainstem gliomas arise from the subependymal glial tissues with the main bulk of the tumour residing within the fourth ventricle**, and that failure to thrive, dysphagia and apnoea are the medullary/lower cranial nerve presentation.*

9. Localising syndromes — answer by level

These are the named syndromes Youmans tabulates; give them as a table, because that is how the marks are allocated.

Table 2 · Named intrinsic brainstem syndromes by level, with their components. Reproduced from Youmans & Winn 8e, Tables 15.3-15.5, pp. 200.e19-200.e20, and Ch. 16 p. 201.e22.

Level	Syndrome	Components as Youmans gives them
Midbrain, CN III fascicle + cerebral peduncle	**Weber**	Contralateral hemiparesis
Midbrain, CN III fascicle + substantia nigra	**Benedikt**	Contralateral parkinsonism
Midbrain, CN III fascicle + decussating superior cerebellar peduncle	**Claude**	Ataxia
Midbrain, CN III nucleus (periaqueductal grey at superior colliculus)	Nuclear third nerve palsy	**Bilateral ptosis, bilateral superior rectus palsy** (crossed SR subnucleus, single midline levator subnucleus)
Dorsal midbrain / pretectum	**Parinaud (dorsal midbrain) syndrome**	Supranuclear upgaze palsy, convergence-retraction nystagmus, Collier sign, light-near dissociation
Rostral midbrain, riMLF	Complete supranuclear vertical gaze palsy	Top-of-basilar or **artery of Percheron** stroke, PSP, Niemann-Pick C, intrinsic tumour
Lower midbrain, CN IV nucleus	Nuclear fourth nerve palsy	Superior oblique weakness with **INO contralateral** to it; isolated lesions very rare

Anterior medullary velum, CN IV fascicle	Fascicular fourth nerve palsy	**Horner syndrome contralateral to the superior oblique weakness**
Pontine tegmentum, CN VI nucleus	**Foville**	Fifth and seventh nerve deficits, **Horner syndrome**, ipsilateral reduction of taste and facial sensation, contralateral ataxia, **ipsilateral gaze palsy**
Pontomedullary junction, CN VI exit	**Millard-Gubler**	Seventh nerve deficit **plus INO**
Pontomedullary junction, ventral	**Raymond-Cestan**	Contralateral hemiparesis with seventh nerve deficit and INO
MLF, midbrain or pons	**INO**	Ipsilateral adduction deficit, contralateral abducting nystagmus; adduction restored on convergence
Lateral medulla (ipsilateral vertebral artery occlusion)	**Wallenberg (lateral medullary) syndrome**	Symptoms: **vertigo, nausea, vomiting, intractable hiccups, ipsilateral facial pain, diplopia, dysphagia, dysphonia**. Signs: **ipsilateral Horner syndrome; ipsilateral loss of facial pain and temperature; ipsilateral paralysis of palate, pharynx and larynx; ipsilateral facial and lateral rectus weakness; ipsilateral dysmetria, dysrhythmia and dysdiadochokinesia; contralateral loss of pain and temperature on the body**. **The lesion is caudal to the cochlear nuclei and cochlear nerve root entry zone, so hearing loss is not characteristic.** The body and extremities **strongly deviate toward the side of the lesion**
Dorsolateral pontomedullary region (AICA occlusion)	AICA syndrome	**Severe vertigo, nausea, vomiting, unilateral hearing loss, tinnitus, facial paralysis**; examination shows **ipsilateral hearing loss, facial weakness, cerebellar dysfunction, ipsilateral facial pain and temperature loss, decreased body pain and temperature**. **The labyrinthine artery arises from AICA in 80-90%, so infarction of the membranous labyrinth is common** — hence hearing loss, unlike Wallenberg
Cerebellum alone (VA, PICA or AICA)	Cerebellar infarct	**Severe vertigo, vomiting and ataxia with absent brainstem signs** — often misdiagnosed as a peripheral vestibular disorder; **the unique differentiating feature is the presence of cerebellar signs**

10. Eye-movement features that localise an intrinsic brainstem lesion in a comatose or obtunded patient

- **Ocular bobbing — non-rhythmic, rapid, conjugate downward movements of the eyes followed by a slow return to the midline. Ocular bobbing always localises to the pons** and typically occurs with large destructive lesions such as pontine haemorrhage, although it can result from pontine dysfunction caused by large compressive cerebellar lesions YW p.200.e25.
- **Because the centres controlling horizontal gaze are also in the pons, horizontal eye movements cannot usually be elicited with the doll's-eye manoeuvre in the presence of ocular bobbing** YW p.200.e25.
- **Other vertical variants — ocular dipping, reverse bobbing — have less reliable localising value** YW p.200.e25.
- **Ping-pong gaze** — slow horizontal ocular oscillations alternating direction every few seconds; results from **diffuse bilateral hemispheric injury** and **portends a poor prognosis** YW p.200.e25. **Periodic alternating gaze deviation**, with reversals over minutes rather than seconds, occurs with **hepatic encephalopathy and midline cerebellar disease** YW p.200.e25.

- **Gaze deviation rules**: a **destructive lesion in one frontal eye field causes ipsilateral gaze deviation ("looks toward the lesion")**; an **irritative lesion such as focal seizure causes contralateral deviation ("looks away")**; **thalamic lesions often result in "wrong-way" eyes** YW p.200.e25.
- **Wernicke encephalopathy** — the classic triad is **confusion, ophthalmoplegia and ataxia**; **horizontal gaze dysfunction including sixth nerve palsy is common, and nystagmus is the only ocular motility abnormality occurring more frequently than sixth nerve palsy**; most patients have both. The nystagmus is usually a **combination of upbeat and gaze-evoked nystagmus, which can convert to downbeat with time**. MRI shows **increased T2/FLAIR signal in the medial thalami, periaqueductal grey and floor of the fourth ventricle**, with **mammillary body enhancement** in chronic alcohol abuse. **Improvement often begins within hours to days of thiamine, but recovery is often incomplete if treatment is delayed** YW p.200.e23.
- **Cerebellar signs that accompany intrinsic posterior fossa disease: downbeat nystagmus, gaze-evoked nystagmus, saccadic intrusions and oscillations; dysmetric (hypermetric or hypometric) saccades causing difficulty reading; impaired pursuit producing "saccadic" or "cogwheel" pursuit; tonic inward deviation of both eyes or esotopia from midline cerebellar lesions that can be misdiagnosed as bilateral sixth nerve palsy; and alternating skew deviation that changes direction with lateral gaze** YW p.200.e24. In Chiari malformation, **downbeat nystagmus can be prominent and cause oscillopsia, and can improve or resolve following posterior fossa decompression** YW p.200.e24.

Table 3 · Focal brainstem glioma versus diffuse intrinsic pontine glioma — the clinical and radiological discriminators. Reproduced from Youmans & Winn 8e, Ch. 241 pp. 1825-1826, 1828-1829.

	Focal brainstem glioma (FBSG)	Diffuse intrinsic pontine glioma (DIPG)
Symptom duration	**Minor symptoms present for years**	**Short duration — aggressive**
Typical features	Neck pain and stiffness, cranial nerve palsies, contralateral hemiparesis, **hemichorea**; torticollis in older children with exophytic tumours (chronic tonsillar herniation); dysphagia or apnoea with medullary tumours; UMN and/or LMN signs with cervicomedullary tumours	**Triad**: cerebellar symptoms (ataxia, dysmetria, dysarthria) + long-tract impairment (sensory loss, increased tone, hemiparesis, clonus, Babinski, hyperreflexia) + cranial nerve palsy (facial asymmetry, diplopia)
Cranial nerves	Location-dependent	**VI and VII most common**; also III, IV, IX, X
Hydrocephalus	Common with **exophytic posterior, tectal and posterior rostral midbrain** tumours	**<10%, late**, from pontine expansion or exophytic obstruction of the fourth ventricle
MRI	**Well-demarcated borders, minimal or no vasogenic oedema**, T1 iso/hypointense, T2 hyperintense, **homogeneous** enhancement	**Indistinct margins**, T1 iso/hypointense, T2 hyperintense, **heterogeneous** enhancement, increased diffusion, diffuse pontine expansion, exophytic component, **encircles the basilar artery**, petechial haemorrhage on SWI
CT	—	Isodense or hypodense **with no calcification** — calcification implies an atypical brainstem glioma
Pathology / genetics	Mostly **pilocytic or fibrillary astrocytoma**, non-invasive, low mitotic activity; **7q34 duplication with KIAA1549-BRAF fusion in 66-80% of juvenile pilocytic astrocytoma (62% of brainstem ones)**; **BRAF V600E in 9% of juvenile pilocytic astrocytoma**	Aggressive high-grade; MRS **choline/NAA ratio** separates it from FBSG
DTI / prognosis	**Decreased white-matter tract integrity on DTI indicates a poor prognosis**	Lactate and NAA detection at diagnosis predicts poor prognosis
Differential	Cavernoma, AVM, epidermoid cyst, lipoma; **focal brainstem encephalitis, tuberculoma, brainstem abscess** in endemic areas; **Alexander disease** and **neuromyelitis optica**	As for FBSG

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **INO = ipsilateral adduction failure + contralateral abducting nystagmus**, because the MLF lesion always lies distal to the decussation from the abducens nucleus.
- **An abducens *nuclear* lesion gives a conjugate gaze palsy, not a sixth nerve palsy**, because the nucleus houses the internuclear neurons of the MLF.
- **Convergence overcomes the adduction deficit in INO but not in third nerve palsy or myasthenia** — the single best bedside discriminator.
- **Adduction lag on saccades may be the only sign** of a subtle INO, and the causative infarct may be invisible on MRI.
- **Tectum = the part behind the aqueduct.** Superior colliculus level → oculomotor nucleus; inferior colliculus level → trochlear nucleus, and CN IV exits below the inferior colliculus.
- **The lateral mesencephalic sulcus runs up to the medial geniculate body** and separates crus from tegmentum on the surface; the substantia nigra does it internally.
- **P1 posterior thalamoperforators supply the red nucleus, substantia nigra, CN III and IV nuclei and the pretectum** — one occluded perforator explains a whole midbrain syndrome.
- **Intrinsic brainstem lesions produce multiple simultaneous deficits from a small lesion** because they infiltrate nuclei and fibre tracts together; vestibular or cochlear symptoms occur in ~50%.
- **FBSG: years of minor symptoms. DIPG: weeks.** Learn the DIPG triad — cerebellar, long-tract, cranial nerve — and that CN VI and VII lead.
- **Hydrocephalus in <10% of DIPG and only late**; it belongs to tectal and dorsally exophytic tumours instead.
- **Wallenberg spares hearing** (the lesion is caudal to the cochlear nuclei); **AICA occlusion does not**, because the labyrinthine artery arises from AICA in 80-90%.
- **Ocular bobbing always localises to the pons**; **ping-pong gaze means diffuse bilateral hemispheric injury and a poor prognosis**.
- **Destructive frontal eye field → looks toward the lesion; seizure → looks away; thalamic lesion → "wrong-way" eyes.**
- **Wernicke: confusion, ophthalmoplegia, ataxia**, with T2/FLAIR change in medial thalami, periaqueductal grey and the floor of the fourth ventricle.
- **Calcification on CT argues against DIPG**, and an enhancing tectal lesion >10 cm³ argues for a worse prognosis.

Pages read for this answer — Youmans & Winn 8e: 27, 35, 36, 38, 41, 200.e19, 200.e20, 200.e21, 200.e23, 200.e24, 200.e25, 201.e11, 201.e22, 472.e8, 734, 1825, 1828, 1829, 1961

Internuclear ophthalmoplegia:

a) Provide anatomical localization with diagram. [5]

b) Clinical examination technique. [3]

c) Discuss associated syndromes. [2]

LONG | OCT 2025 · Paper I · Q2 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 15 *Neuro-ophthalmology*, §Disorders of the Ocular Motor System, §Cranial Nerve: Third (Oculomotor) Nerve, §Supranuclear, Internuclear, and Cerebellar, §Eye Movements in Coma and §The Pupil, pp. 200.e18-200.e26 (Box 15.4, p. 200.e18; Tables 15.2-15.6, pp. 200.e19-200.e20, 200.e26; Fig. 15.28, p. 200.e18; Fig. 15.31, p. 200.e22; Fig. 15.36, p. 200.e24). Supplementary: Ch. 2 *Surgical Anatomy of the Brain*, §Petrosal Surface of the Cerebellum and Fourth Ventricle and §Brainstem, pp. 35-36, 39, 41 (Fig. 2.53, p. 39; Fig. 2.58, p. 41); Ch. 170 *Ventricular Tumors*, §Fourth Ventricle, p. 1209 (Fig. 170.8, p. 1209); Ch. 16 *Neurotology*, §Anatomy and §Vertigo of Central Origin, pp. 201.e11, 201.e22; Ch. 260 *Developmental Anomalies of the Craniovertebral Junction and Surgical Management*, §Clinical Presentation, p. 1961; Ch. 69 *Physiology of the Cerebrospinal Fluid and Intracranial Pressure*, §Herniation Syndromes, p. 472.e8.

(a) Internuclear ophthalmoplegia — anatomical localisation, with diagram [5]

1. Terminology — fix the four tiers before localising anything

Youmans divides ocular motor disorders into four anatomical tiers, and INO is the third. Give the whole ladder, because the examiner is testing whether you understand what "internuclear" means YW p.200.e19:

- **Orbital (mechanical) processes** — trauma, thyroid eye disease — mechanically restrict globe movement.
- **Neuromuscular junction dysfunction** — ocular myasthenia — **can mimic any pattern of ocular motor deficit**.
- **Nuclear / infranuclear (cranial nerve) disorders** — third, fourth and sixth nerve palsies **affect motility in predictable patterns related to the muscles that they innervate**.
- **Supranuclear disorders** — intracranial disease affecting the **gaze control centres**, often producing **conjugate gaze palsies**.
- **Internuclear disorder** — **"An internuclear disorder affects the medial longitudinal fasciculus (MLF), causing internuclear ophthalmoplegia (INO) with an ipsilateral adduction deficit and abducting nystagmus of the contralateral eye"** YW p.200.e19. *Internuclear* means **between two nuclei** — between the abducens nucleus of one side and the oculomotor nucleus of the other.

2. The circuit, in the order the impulse travels

- **Origin — the abducens nucleus. "The nucleus lies on the floor of the fourth ventricle"** and **"the nucleus contains internuclear neurons involved in horizontal gaze, so nuclear lesions produce ipsilateral gaze palsy"** YW p.200.e20. The abducens nucleus is therefore the **final common horizontal gaze centre**: it drives the ipsilateral lateral rectus directly *and* sends internuclear neurons across the midline into the MLF.
- **Immediate decussation. "Lesions of the MLF virtually always occur after the immediate decussation of the fibers originating in the sixth nerve nucleus, so the predominant clinical feature of impaired adduction is found ipsilateral to the lesion"** [YW pp. 200.e23, 200.e24]. This single fact determines the whole clinical picture and must be stated.
- **Conduction — the MLF. "The MLF conveys the eye movement command from the sixth nerve nucleus to the contralateral third nerve nucleus, thereby allowing conjugate horizontal eye movements with simultaneous contraction of the ipsilateral lateral rectus and contralateral medial rectus muscles"** YW p.200.e23.
- **Termination — the medial rectus subnucleus of the oculomotor nucleus**, which lies in **periaqueductal grey matter at the level of the superior colliculus**; in the same nucleus **the superior rectus subnucleus is contralateral and there is a single midline levator subnucleus** YW p.200.e19.
- **Effector.** The third nerve **innervates all of the extraocular muscles except the lateral rectus and superior oblique, innervates the levator palpebrae superioris, and carries parasympathetic efferent fibres to the pupillary sphincter and ciliary muscle through the ciliary ganglion** YW p.200.e21. In a pure INO **none of these is affected** — only adduction, and only in the conjugate (yoked) mode.
- **The MLF's wider connections, which explain the company INO keeps. "The medial longitudinal fasciculus connects the vestibular nuclei to all of the other cranial nerve nuclei, and of particular interest are the connections with CNs III, IV, VI, and X"** YW p.201.e11. **Four principal vestibular nuclei lie in the floor of the fourth ventricle: the superior (Bechterew), lateral (Deiters), medial (Schwalbe) and inferior (descending, spinal or Roller) nuclei** YW p.201.e11. **The vestibulocerebellar and vestibulospinal tracts** connect the same nuclei to cerebellum and cord YW p.201.e11.
- **Surface landmark of the abducens nucleus.** On the floor of the fourth ventricle **the pontine part is characterised by two rounded prominences, the facial colliculi, located on the median eminence, one on each side of the median sulcus; the facial colliculi are limited laterally by the superior fovea, a dimple formed by the sulcus limitans**, and **the motor nuclei of the cranial nerves are located medially to the sulcus limitans while the sensory nuclei are located laterally to it** YW p.39. The abducens nucleus therefore lies **medial to the sulcus limitans, beneath the facial colliculus**, with the vestibular nuclei in the area vestibularis lateral to it — exactly as shown in a real specimen YW p.1209. The midbrain end of the tract lies in the **tegmentum**, the intermediate part of each cerebral peduncle between the substantia nigra and the aqueduct YW p.35, with the oculomotor nucleus in periaqueductal grey and **CN III emerging from the medial side of the crura cerebri in the interpeduncular fossa** [YW pp. 35, 36]. Seen from

behind, the same segment presents, from above downward, the **medial geniculate body, superior colliculi and superior cerebellar peduncle** YW p.41.

- **Longitudinal extent. "INO results from a lesion of the MLF either in the midbrain or the pons"** YW p.200.e23 — so the MLF is a *paramedian tegmental* tract running the length of the upper brainstem, and an INO localises to that column, from the abducens nucleus in the fourth ventricular floor up to the oculomotor nucleus in periaqueductal grey.

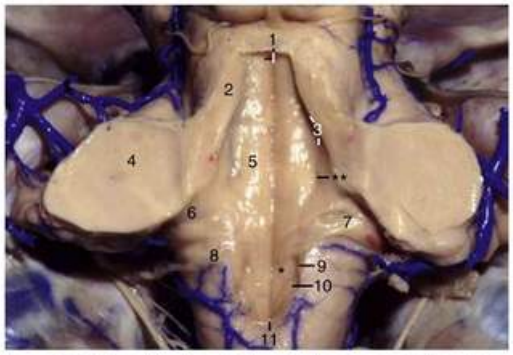


Figure 2.53. Floor of fourth ventricle, posterior view. *1*, Median sulcus and median eminence; *2*, superior cerebellar peduncle; *3*, sulcus limitans and vestibular area; *4*, middle cerebellar peduncle; *5*, facial colliculus; *6*, cochlear area; *7*, striae medullary; *8*, inferior cerebellar peduncle; *9*, inferior fovea; *10*, vagal trigone; *11*, obex and area postrema; *, hypoglossal trigone; **, superior fovea.

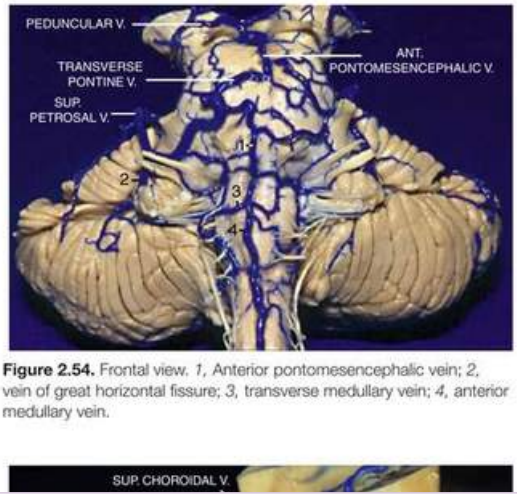


Figure 2.54. Frontal view. *1*, Anterior pontomesencephalic vein; *2*, vein of great horizontal fissure; *3*, transverse medullary vein; *4*, anterior medullary vein.

*Reproduced from Youmans & Winn 8e, Fig. 2.53, p. 39 — Label when you reproduce it (floor of the fourth ventricle, posterior view — the lower end of the MLF circuit): 1 **median sulcus and median eminence**, 2 superior cerebellar peduncle, 3 **sulcus limitans and vestibular area**, 4 middle cerebellar peduncle, 5 **facial colliculus**, 6 cochlear area, 7 striae medullares, 8 inferior cerebellar peduncle, 9 inferior fovea, 10 vagal trigone, 11 obex and area postrema, * hypoglossal trigone, ** **superior fovea**. On your copy, write "abducens nucleus" beneath the facial colliculus (the facial nerve genu loops over it), mark the **four vestibular nuclei** in the vestibular area lateral to the sulcus limitans, and add the rule that **motor nuclei lie medial and sensory nuclei lateral to the sulcus limitans**.*

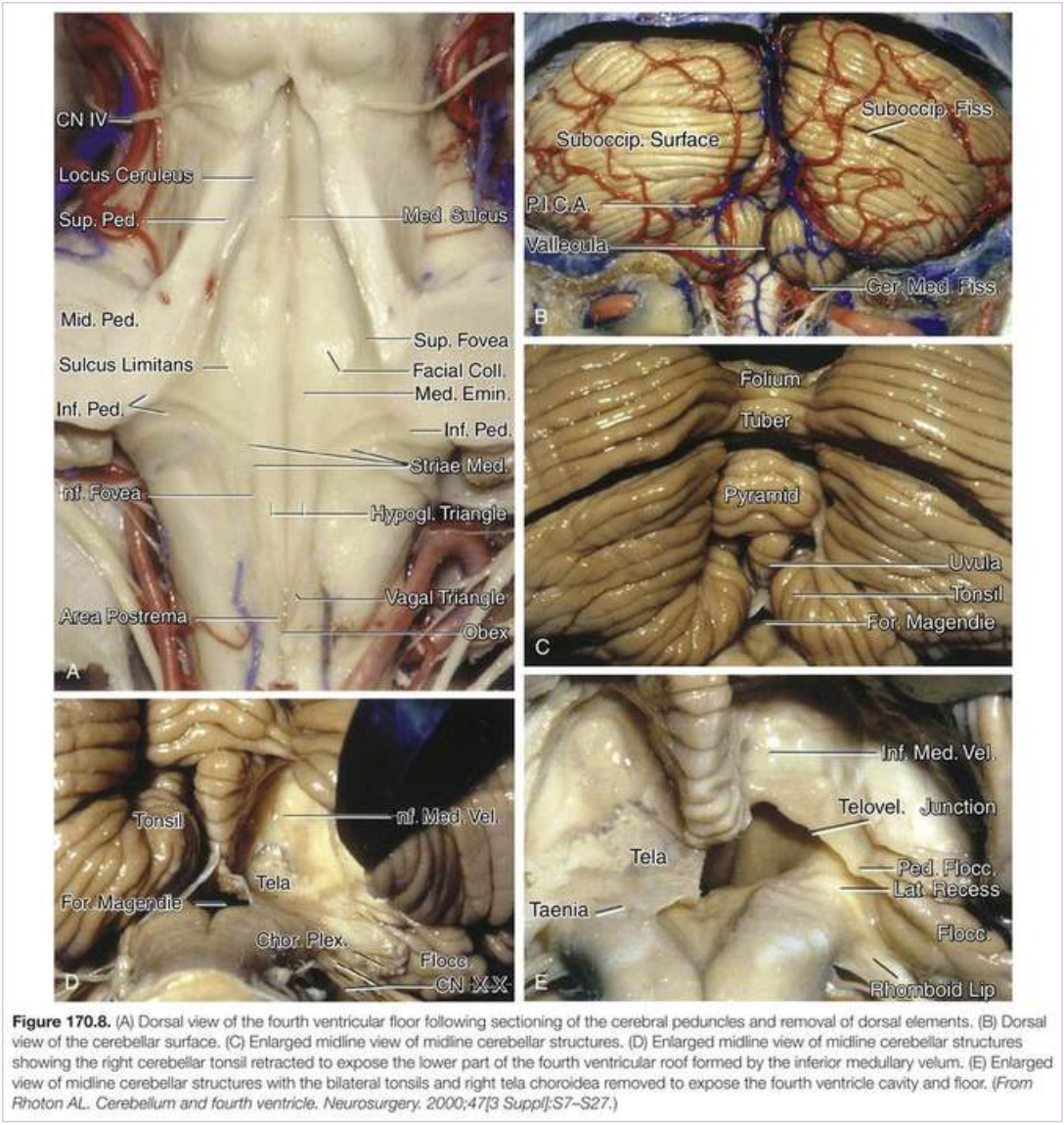


Figure 170.8. (A) Dorsal view of the fourth ventricular floor following sectioning of the cerebral peduncles and removal of dorsal elements. (B) Dorsal view of the cerebellar surface. (C) Enlarged midline view of midline cerebellar structures. (D) Enlarged midline view of midline cerebellar structures showing the right cerebellar tonsil retracted to expose the lower part of the fourth ventricular roof formed by the inferior medullary velum. (E) Enlarged view of midline cerebellar structures with the bilateral tonsils and right tela choroidea removed to expose the fourth ventricle cavity and floor. (*From Rhoton AL. Cerebellum and fourth ventricle. Neurosurgery. 2000;47[3 Suppl]:S7–S27.*)

*Reproduced from Youmans & Winn 8e, Fig. 170.8, p. 1209 — Label PANEL A when you reproduce it (dorsal view of the fourth ventricular floor after sectioning the cerebral peduncles — Rhoton's specimen, the same anatomy in a real dissection): **CN IV**, **locus ceruleus**, superior, middle and inferior cerebellar peduncles, **superior fovea**, **sulcus limitans**, **facial colliculus**, **median eminence**, **striae medullares**, inferior fovea, **hypoglossal triangle**, **vagal triangle**, area postrema, obex, median sulcus. Use it to show that the abducens nucleus, the MLF and the vestibular nuclei are all crowded into a few millimetres of paramedian tegmentum — which is why a tiny lesion produces an INO with vestibular and gaze signs together.*

3. Drawing the diagram — what earns the five marks

Constructing the diagram. Youmans 8e does not carry a single wiring diagram of the MLF, so draw one and label it from the text. Draw a coronal/schematic brainstem in outline with the fourth ventricle above the pons and the aqueduct above the midbrain. Then: (1) place the **abducens nucleus** on the floor of the fourth ventricle beneath the **facial colliculus**, with the **facial nerve genu** looping over it; (2) draw the **motor neurons** of that nucleus running forward and out at the **junction of the pontomedullary and preolivary sulci** to the **ipsilateral lateral rectus**; (3) draw the **internuclear neurons** from the same nucleus **decussating immediately** in the pontine tegmentum and ascending as the **MLF**, paramedian, just ventral to the periaqueductal grey; (4) end the MLF in the **medial rectus subnucleus of the contralateral oculomotor nucleus**, in periaqueductal grey at the level of the superior colliculus; (5) draw the oculomotor nerve leaving **medial to the crus cerebri in the interpeduncular fossa** to reach the **medial rectus**; (6) add the **four vestibular nuclei** in the fourth ventricular floor with their MLF connections to CN III, IV, VI and X; (7) add the **riMLF** rostrally as the vertical gaze centre. Then mark a lesion on one MLF and show, with arrows, adduction failure on that side and abducting nystagmus of the fellow eye on gaze *away* from the lesion.

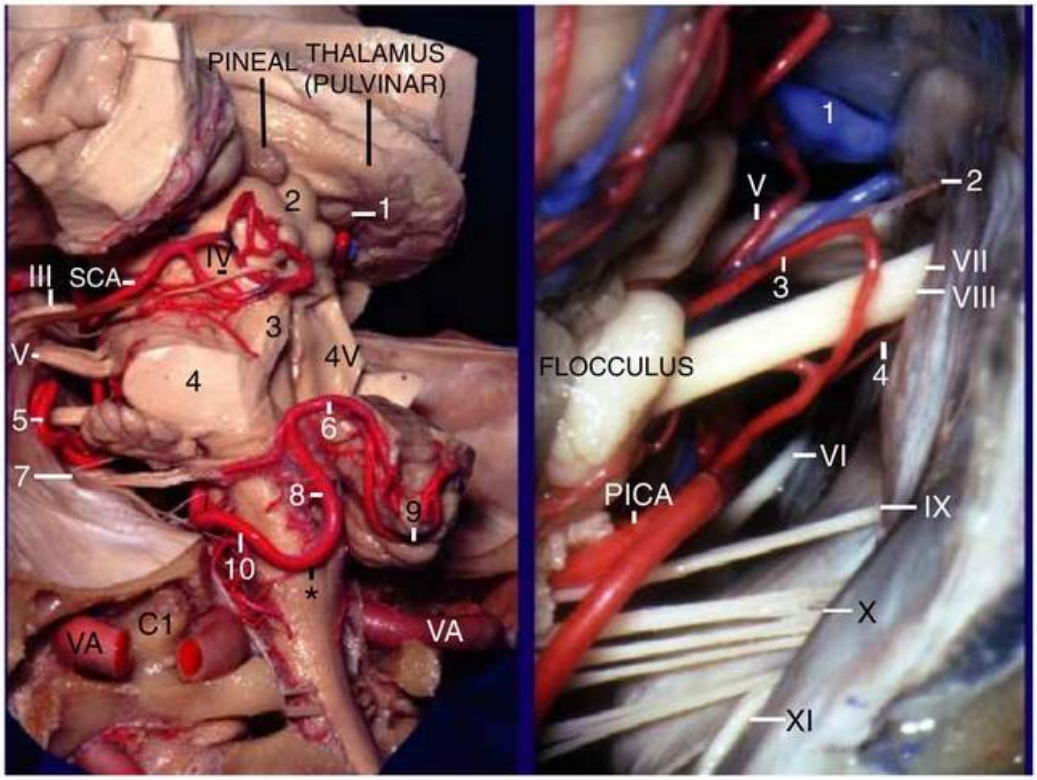


Figure 2.58. *Left,* Posterolateral view. *1,* Medial geniculate body; *2,* superior colliculi; *3,* superior cerebellar peduncle; *4,* middle cerebellar peduncle; *5,* anterior inferior cerebellar artery (AICA), cranial nerves VII and VIII; *6,* cranial loop of posterior inferior cerebellar artery (PICA) (supratonsillar segment); *7,* jugular foramen; *8,* PICA (posterior medullary segment); *9,* PICA (pyramidal loop); *10,* PICA (lateral medullary segment); *, caudal loop. *Right,* Retromastoid view of right cerebellopontine angle. *1,* Superior petrosal vein; *2,* subarcuate artery (AICA); *3,* AICA; *4,* internal auditory artery.

*Reproduced from Youmans & Winn 8e, Fig. 2.58, p. 41 — Label the LEFT panel (posterolateral view of the dorsal brainstem — the upper end of the circuit): 1 **medial geniculate body**, 2 **superior colliculi**, 3 **superior cerebellar peduncle**, 4 **middle cerebellar peduncle**, 5 AICA and cranial nerves; mark the **trochlear (IV)** and **trigeminal (V)** nerves. Annotate that the **oculomotor nucleus lies in periaqueductal grey at the level of the superior colliculus** (the MLF's destination) and that the **trochlear nucleus lies in caudal periaqueductal grey dorsal to the MLF**, so a nuclear fourth-nerve lesion produces an INO contralateral to the superior oblique weakness.*

4. Localisation by clinical pattern — the table the examiner wants

Table 1 · Localisation of an adduction deficit — INO and its anatomical neighbours and mimics. Reproduced from Youmans & Winn 8e, Tables 15.3-15.5, pp. 200.e19-200.e20, with Ch. 15 pp. 200.e19, 200.e21, 200.e23-200.e24 and Ch. 16 p. 201.e11.

Site	Sign produced	How to recognise it	Youmans' listed causes
MLF (pons or midbrain)	**INO** — ipsilateral adduction deficit + dissociated nystagmus of the contralateral abducting eye	**Adduction restored by convergence**; pupil normal; no ptosis	**MS, brainstem stroke, brainstem tumour, fourth ventricular tumour**; in stroke the lesion **can be very small and easily overlooked on neuroimaging**

Abducens nucleus (floor of the fourth ventricle)	**Ipsilateral conjugate gaze palsy** (not a sixth nerve palsy), because the nucleus contains the internuclear neurons	Pontine tegmentum signs: fifth and seventh nerve deficits, Horner syndrome, ipsilateral loss of taste and facial sensation, contralateral ataxia (**Foville syndrome**)	Stroke in elderly persons, tumour in the young, occasionally demyelination
Abducens exit, pontomedullary junction	**Millard-Gubler** — seventh nerve deficit **with INO**; **Raymond-Cestan** adds contralateral hemiparesis	Fascicles traverse ventral brainstem, so isolated palsies are unusual	Ventral pontine lesions
Trochlear nucleus (caudal periaqueductal grey, dorsal to MLF)	Superior oblique weakness with **INO contralateral** to it	Because the fourth nerve decussates; **isolated nuclear lesions are very rare**	Haemorrhage, stroke, demyelination, trauma including neurosurgical
Oculomotor nucleus (periaqueductal grey, superior colliculus level)	**Bilateral ptosis and bilateral superior rectus palsy**	Crossed SR subnucleus, single midline levator subnucleus	Tumour (e.g. glioma), stroke, demyelination
Oculomotor fascicle	Weber (cerebral peduncle → contralateral hemiparesis), Benedikt (substantia nigra → contralateral parkinsonism), Claude (superior cerebellar peduncle → ataxia)	Fascicles pass through all three	Stroke, tumour, rarely demyelination
Oculomotor nerve, subarachnoid	Complete "down and out" eye with dilated unreactive pupil and ptosis; **adduction NOT restored by convergence**	**Pupillary fibres run superficially and medially** and are preferentially compressed	**PCOM aneurysm or uncal herniation until proved otherwise**; meningitis
Neuromuscular junction	**INO mimic**, or pupil-sparing third nerve palsy mimic	Fatigable ptosis on 30 s upgaze, orbicularis oculi weakness, diurnal variation, relief after rest; convergence does **not** restore adduction	Ocular myasthenia gravis
Orbit / orbital apex	Mechanical restriction, proptosis, periorbital and conjunctival oedema, multiple nerve involvement	Third, fourth, fifth (V1) and sixth nerves and the optic nerve together	Tumour, trauma, inflammation, infection (**fungal until proved otherwise in a diabetic patient**)
Craniovertebral junction	INO masquerading as brainstem disease	**"Not uncommonly, internuclear ophthalmoplegia is present, leading to a misdiagnosis of mesencephalic and upper pontine disturbance"**; downbeat nystagmus in strictly compressive lesions ± Chiari	Basilar invagination, developmental craniovertebral anomalies
Diffuse, from raised ICP	INO with bilateral decerebrate posturing and midposition fixed pupils	Central transtentorial herniation sequence	Any mass with downward diencephalic shift

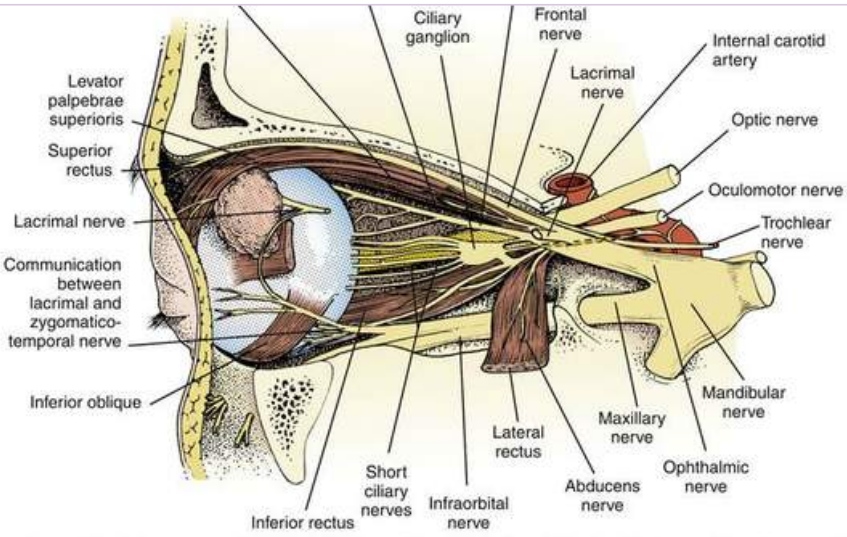


Figure 15.28. Anatomy of the globe, extraocular muscles, and cranial nerves in the orbit and orbital apex. (*From Standring S. Gray's Anatomy. 40th ed. Churchill Livingstone; 2008.*)

*Reproduced from Youmans & Winn 8e, Fig. 15.28, p. 200.e18 — Label when you reproduce it (anatomy of the globe, extraocular muscles and cranial nerves in the orbit and orbital apex): **optic nerve**, **oculomotor nerve**, **trochlear nerve**, **abducens nerve**, **ophthalmic, maxillary and mandibular divisions of the trigeminal nerve**, **frontal, lacrimal and nasociliary nerves**, **long and short ciliary nerves**, **ciliary ganglion**, **anterior ethmoidal nerve**, **infraorbital nerve**, **internal carotid artery**, **levator palpebrae superioris**, **superior rectus**, **inferior rectus**, **lateral rectus**, **inferior oblique**, and the communication between the lacrimal and zygomaticotemporal nerves. Use this figure to prove that the **medial rectus is the only muscle failing in INO**, and to show the orbital-apex crowding that explains the multiple-nerve mimics in the table above.*

(b) Clinical examination technique [3]

5. Youmans' own examination sequence — Box 15.4, reproduced in order

Youmans sets out the examination of eye movements and eyelid position as a six-step box; give it step by step YW p.200.e18:

- **Step 1 — eyelids and pupils in the centre position. "Evaluate the eyelid position and the pupils for asymmetry with the eyes in the center position, making note of any ptosis (possible third nerve palsy, myasthenia), pupillary dilation (possible third nerve palsy or Adie tonic pupil), or mild ptosis with pupillary constriction (possible Horner syndrome)."** A normal lid and pupil here is the first positive finding in favour of INO.
- **Step 2 — pursuit and nystagmus. "Look for nystagmus and smoothness of pursuit by having the patient fixate a slowly moving target in the horizontal and vertical directions."** This is where **dissociated abducting nystagmus** of the fellow eye is seen.
- **Step 3 — range of movement. "Observe the range of horizontal and vertical eye movements, making note of any limitations in the range of movement."** In INO the limitation is of **adduction** and it is **ipsilateral to the lesion**.
- **Step 4 — adduction versus abduction for vertical limitation. "Note whether the vertical range limitation is worse when the eye is adducted or abducted; the superior and inferior oblique muscles are more important for vertical movement when the eye is adducted, whereas the superior and inferior rectus muscles are more important for vertical movement when the eye is abducted."**
- **Step 5 — the patient's own report. "The patient's report of which positions produce diplopia and determination of the severity of the diplopia in these positions can complement the clinician's observations."**
- **Step 6 — dissociate the eyes. "Dissociating the two eyes with a red Maddox rod over the right eye helps patients report their observations."**

6. The three additional manoeuvres that clinch an INO

- **Test saccades, not just pursuit. "With a subtle INO, eye movements may appear full; subtle slowing of the adducting eye compared with the abducting eye during horizontal saccadic eye movements (adduction lag) may**

be the only clue to the presence of an INO" YW p.200.e24. Ask the patient to refixate rapidly between two widely separated targets and watch the *velocity* of the two eyes, not the endpoint.

- **Test convergence — the decisive test. "The adduction deficit in INO can often be overcome with convergence eye movements, whereas adduction deficits from other causes (e.g., third nerve palsy, ocular myasthenia) cannot, thereby allowing for clinical differentiation from these entities"** YW p.200.e24. Bring a target to the patient's nose; if adduction appears, the medial rectus and its nucleus and nerve are intact and the lesion is internuclear.
- **Test fatigability.** Because **ocular myasthenia can mimic INO** YW p.200.e19, examine for **fatigable ptosis after prolonged upgaze for 30 seconds** and for **orbicularis oculi weakness — have the patient forcefully close the eyes while the examiner tries to pry them open; if the examiner is able to open the eyes while the patient is giving good effort, orbicularis weakness is present** YW p.200.e21.

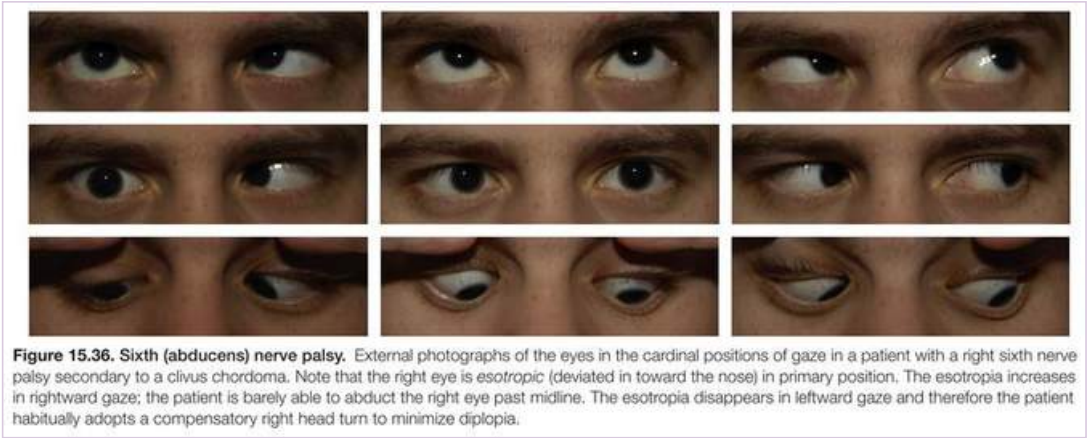


Figure 15.36. Sixth (abducens) nerve palsy. External photographs of the eyes in the cardinal positions of gaze in a patient with a right sixth nerve palsy secondary to a clivus chordoma. Note that the right eye is *esotropic* (deviated in toward the nose) in primary position. The esotropia increases in rightward gaze; the patient is barely able to abduct the right eye past midline. The esotropia disappears in leftward gaze and therefore the patient habitually adopts a compensatory right head turn to minimize diplopia.

*Reproduced from Youmans & Winn 8e, Fig. 15.36, p. 200.e24 — Reproduce this nine-position photograph montage of a **right sixth (abducens) nerve palsy** (secondary to a clivus chordoma) and describe: the right eye **esotropic in primary position**, the **esotropia increasing in right gaze** with the right eye **barely able to abduct past the midline**, the **esotropia disappearing in left gaze**, and the **compensatory right head turn**. Present it beside your INO findings as the mirror-image abnormality: in a sixth nerve palsy **abduction** fails on the side of the lesion, whereas in INO **adduction** fails on the side of the lesion and the *fellow, abducting* eye shows nystagmus.*

7. Completing the examination — what else must be documented

- **Pupil. Anisocoria is never caused by visual loss; the pupils remain equal even if one eye is blind. Anisocoria results from an efferent problem affecting the ocular sympathetic or parasympathetic innervation of the iris musculature or the iris itself** YW p.200.e25. Determine first **whether the larger or the smaller pupil is abnormal**: with a **parasympathetic lesion the ipsilateral pupil is larger and the difference is most apparent in bright light**; with a **sympathetic lesion the ipsilateral pupil is smaller and the difference is most apparent in the dark**. **Physiologic (simple or benign) anisocoria occurs in up to 20% of the normal population, with a difference of less than 1 mm remaining constant in light and dark or slightly more prominent in the dark** YW p.200.e26. **A normal pupil is a positive finding in favour of INO.**
- **Lid. The third nerve innervates the powerful levator palpebrae superioris, whereas the sympathetic system innervates smooth muscle in the eyelid (Müller muscle), providing a few millimetres of additional eyelid elevation** YW p.200.e26 — hence a few millimetres of ptosis with a small pupil means Horner, not third nerve.
- **Test the yoked partner.** Because the abducens nucleus is the final common horizontal gaze centre, always check for a **conjugate gaze palsy** on the side of the adduction deficit; a gaze palsy *plus* an INO on the same side means a nuclear rather than an MLF lesion YW p.200.e20.
- **Cerebellar eye signs.** Examine deliberately for **downbeat nystagmus, gaze-evoked nystagmus, saccadic intrusions and oscillations, dysmetric (hypermetric or hypometric) saccades, "saccadic" or "cogwheel" pursuit, tonic inward deviation of both eyes or esotropia that can be misdiagnosed as bilateral sixth nerve palsy, and alternating skew deviation that changes direction with lateral gaze** YW p.200.e24.
- **In the unresponsive patient. Assessment of eye movements in coma has three major components: the resting position of the eyes, description of any abnormal spontaneous eye movements, and induction of reflexive eye**

CHAPTER 2

Neurophysiology, ICP & Cerebral Blood Flow

15
QUESTIONS SOLVED

Cerebral Blood Flow & Autoregulation

5 questions

a) Draw a pressure volume curve.
b) Define cerebral compliance.
c) Effect of cerebral perfusion pressure on compliance in traumatic brain injury.
d) Risks and benefits of ICP monitoring.

LONG | DEC 2020 · Paper I · Q2 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 69 *Physiology of the Cerebrospinal Fluid and Intracranial Pressure*, §General Physiology of Intracranial Pressure, §Steady-State Intracranial Pressure and Cerebrospinal Fluid Dynamics, §Non-Steady-State Dynamics, §Effects of Elevated Intracranial Pressure and §Intracranial Pressure Monitoring, pp. 472, 472.e1-472.e11 (Figs. 69.1-69.3, pp. 472.e2-472.e3; Figs. 69.5-69.8, pp. 472.e6-472.e7; Table 69.2, p. 472.e9). Supplementary: Ch. 384 *Clinical Pathophysiology of Traumatic Brain Injury*, §Cerebral Blood Flow, Cerebral Blood Volume, Arteriovenous Difference in Oxygen, and Autoregulation, pp. 2977-2979 (Figs. 384.4-384.5, pp. 2977-2978; Tables 384.11-384.12, pp. 2978-2979); Ch. 388 *Invasive Physiologic Monitoring for Traumatic Brain Injury*, §Cerebral Perfusion Pressure, §Parameters Derived From ICP, MAP, CPP and the ICP Waveform and §Monitoring of Intracranial Compliance and Elastance, pp. 3028, 3030-3032 (Figs. 388.1-388.3, pp. 3028-3032); Ch. 37 *Intracranial Pressure Monitoring*, §General Principles and §Current Intracranial Pressure Monitoring Technology, pp. 288-293 (Figs. 37.1-37.2, pp. 289-290); Ch. 391 *Critical Care Management of Traumatic Brain Injury*, pp. 3062, 3067.

(a) Draw a pressure-volume curve [2]

1. What the curve is, and the doctrine that generates it

- **The pressure-volume curve is the graphical expression of the Monro-Kellie doctrine.** Youmans writes the doctrine as a conservation-of-volume equation: **V1CSF + V1BLOOD + V1BRAIN + V1OTHER = VINTRACRANIAL SPACE = V2CSF + V2BLOOD + V2BRAIN + V2OTHER**, where VOTHER is any abnormal component such as tumour or haematoma. Because the dura distends only minimally, **a change in the volume of one compartment must occur at the expense of the other two if ICP is to stay constant** [YW pp. 472, 472.e4].
- **The historical statements are worth quoting.** Monro (turn of the 19th century, Edinburgh) argued that "the substance of the brain… is nearly incompressible, [so] the quantity of blood within the head must be the same, or very nearly the same at all times." Kellie, to the Medico-Chirurgical Society of Edinburgh, added that no portion of circulating fluid can be withdrawn "without its place being simultaneously occupied by some equivalent" YW p. 472.e1.
- **The relationship between added volume and ICP is not linear.** In the normal adult it is a **hyperbola**; with ICP above 50 mm Hg and as ICP approaches MAP the curve flattens again, so **the complete curve is sigmoid rather than hyperbolic** YW p. 472.e5.

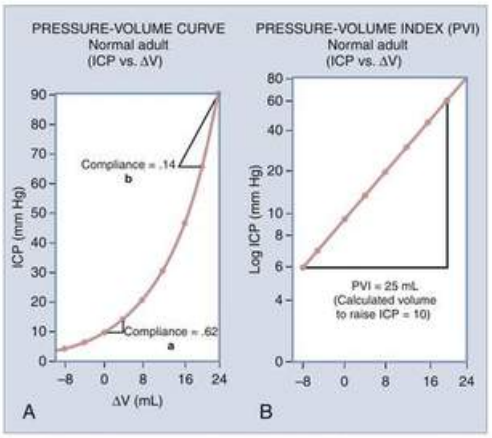


Figure 69.3. The pressure-volume curve and the pressure-volume index *(PVI)* describe the response of intracranial pressure *(ICP)*

TABLE 69.1 Concentrations of Solutes (mEq/kg H_2O) in Plasma and Lumbar Cerebrospinal Fluid in Humans

Substance	Plasma	CSF
Sodium (Na^+)	150	147
Potassium (K^+)	4.63	2.86
Magnesium (Mg^{2+})	1.61	2.23
Calcium (Ca^{2+})	4.7	2.28
Chloride (Cl^-)	99	113
Bicarbonate (HCO_3^-)	26.8	23.3
Amino acids	2.62	0.72
Osmolality	289.0	289.0
pH	7.397	7.30

Data from Hendry EB. The osmotic pressure and chemical composition of human body fluids. Clin Chem. 1962;8:246-265; Bradley RD, Semple SJG. A comparison of certain acid-base characteristics of arterial blood, jugular venous blood and cerebrospinal fluid in man, and the effect on them of some acute and chronic acid-base disturbances. J Physiol. 1962;160(3):381–391.
CSF, *Cerebrospinal fluid.*

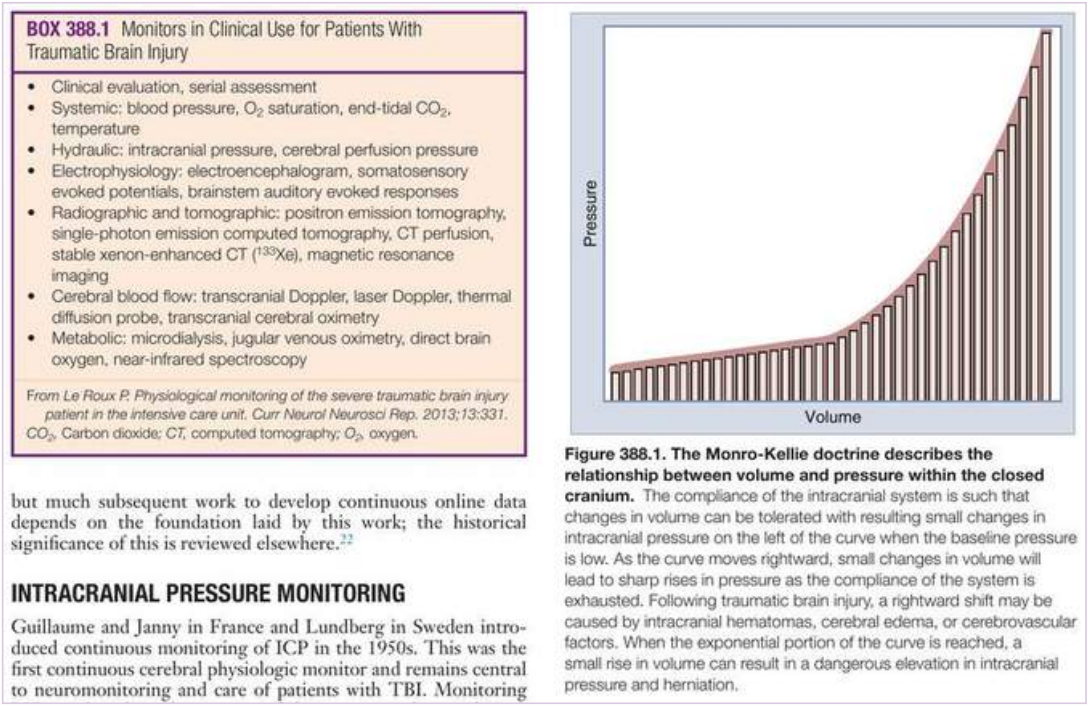
69

approximately 15% of the total brain volume. Total CSF is considered to include compartmental CSF and the extracellular space.

*Reproduced from Youmans & Winn 8e, Fig. 69.3, p. 472.e3 — Label when you reproduce it: (A) ICP (mm Hg, y-axis, 0-90) against ΔV (mL, x-axis, −8 to +24); mark point *a* on the flat limb (compliance = 0.62, the period of **spatial compensation**) and point *b* on the steep limb (compliance = 0.14, the period of **spatial decompensation**). (B) the same data with **log ICP** on the y-axis, giving a straight line whose slope is the **pressure-volume index (PVI = 25 mL)** — the notional volume needed to raise ICP tenfold.*

2. The two limbs — name them, because that is where the marks are

- **Flat limb = period of spatial compensation.** Along this portion, increases in volume affect ICP minimally because compensatory mechanisms keep ICP in the normal range YW p. 472.e5.
- **Steep limb = period of spatial decompensation.** As volume is added the pressure change per unit volume becomes increasingly large and compliance falls; the slope of the curve rises rapidly YW p. 472.e5.
- **Terminal plateau.** Above ~50 mm Hg, and as ICP approaches MAP, the curve flattens — the point at which cerebral perfusion is critically low and bleeding from a ruptured aneurysm slows because ICP has met arterial pressure [YW pp. 472.e5, 472.e5].
- **Which compartment buffers first?** Although the brain occupies **80%** of the intracranial space, that volume is available for compensation **only when VOTHER increases slowly**; with rapid change the brain shifts and herniates instead. Blood and CSF occupy less space but **can be reduced more rapidly, and therefore change first** in compensation YW p. 472.e6.



BOX 388.1 Monitors in Clinical Use for Patients With Traumatic Brain Injury

- Clinical evaluation, serial assessment
- Systemic: blood pressure, O_2 saturation, end-tidal CO_2, temperature
- Hydraulic: intracranial pressure, cerebral perfusion pressure
- Electrophysiology: electroencephalogram, somatosensory evoked potentials, brainstem auditory evoked responses
- Radiographic and tomographic: positron emission tomography, single-photon emission computed tomography, CT perfusion, stable xenon-enhanced CT (^{133}Xe), magnetic resonance imaging
- Cerebral blood flow: transcranial Doppler, laser Doppler, thermal diffusion probe, transcranial cerebral oximetry
- Metabolic: microdialysis, jugular venous oximetry, direct brain oxygen, near-infrared spectroscopy

From Le Roux P. Physiological monitoring of the severe traumatic brain injury patient in the intensive care unit. Curr Neurol Neurosci Rep. 2013;13:331.
CO_2, Carbon dioxide; CT, computed tomography; O_2, oxygen.

but much subsequent work to develop continuous online data depends on the foundation laid by this work; the historical significance of this is reviewed elsewhere.[22]

INTRACRANIAL PRESSURE MONITORING

Guillaume and Janny in France and Lundberg in Sweden introduced continuous monitoring of ICP in the 1950s. This was the first continuous cerebral physiologic monitor and remains central to neuromonitoring and care of patients with TBI. Monitoring

Figure 388.1. The Monro-Kellie doctrine describes the relationship between volume and pressure within the closed cranium. The compliance of the intracranial system is such that changes in volume can be tolerated with resulting small changes in intracranial pressure on the left of the curve when the baseline pressure is low. As the curve moves rightward, small changes in volume will lead to sharp rises in pressure as the compliance of the system is exhausted. Following traumatic brain injury, a rightward shift may be caused by intracranial hematomas, cerebral edema, or cerebrovascular factors. When the exponential portion of the curve is reached, a small rise in volume can result in a dangerous elevation in intracranial pressure and herniation.

Reproduced from Youmans & Winn 8e, Fig. 388.1, p. 3028 — Label when you reproduce it: pressure on the y-axis, volume on the x-axis; the flat compensated left-hand portion where compliance absorbs added volume, the knee, and the exponential right-hand portion where a small volume increment produces a dangerous pressure rise. Annotate that after TBI the whole curve is shifted rightward by intracranial haematoma, cerebral oedema or cerebrovascular factors.

3. The numbers to write on the axes

- **Upper limit of normal ICP in adults and older children: 15-20 mm Hg.** Supine healthy adults: **7-15 mm Hg**. Erect: may become **negative, as low as −15 mm Hg**. Coughing or sneezing transiently exceeds **30-50 mm Hg** with rapid return to baseline YW p. 472.e2.
- **Normal intracranial volume distribution (1500 mL):** brain **87%**, compartmental CSF (ventricles, cisterns, subarachnoid space) **9%**, blood **4%** YW p. 472.e3. Ch. 70 gives it by absolute volume: brain **1250-1500 mL**, CSF **125-150 mL**, blood **125-150 mL** YW p. 473.e1.
- **PVI in normal adults: 25-30 mL.** Values **<13 mL are clearly abnormal**. PVI is age-dependent: **normal infants have a PVI below 10 mL and the adult value of 25 mL is reached at about 14 years** YW p. 472.e5.
- **Steady-state ICP obeys ICP = (If × Ro) + Pd** — the product of CSF formation rate and outflow resistance, plus dural sinus pressure. Mathematical modelling shows **(If × Ro) contributes only ~10% of total ICP**; the remainder is dural sinus pressure, which is why even small rises in sagittal sinus pressure are transmitted directly to the CSF and raise resting ICP [YW pp. 472.e4, 472.e5].

Table 1 · The Monro-Kellie compartments, their normal volumes and the therapy that targets each — compiled from Youmans & Winn 8e, Ch. 69 pp. 472, 472.e3-472.e4 and Table 69.2, p. 472.e9, with volumes from Ch. 70 p. 473.e1.

Compartment	Normal volume / share	Commonest pathological increase	Therapeutic modalities (Table 69.2)
V_{BRAIN}	1250-1500 mL (87%, "80% of intracranial space")	Cerebral oedema (cytotoxic ± vasogenic)	CPP management, Lund protocol, antihypertensives, fluid resuscitation, corticosteroids, barbiturates, osmotic agents, diuretics, hypothermia
V_{CSF}	125-150 mL (9%)	Hydrocephalus, choroid plexus papilloma, IIH	Acetazolamide, furosemide, corticosteroids, external drainage, internal drainage
V_{BLOOD}	125-150 mL (4%)	Post-traumatic hyperaemia, vasodilatation from low CPP or high PaCO₂	Hyperventilation, head elevation, barbiturates

V_{OTHER}	Tumour, haematoma (extradural, subdural, subarachnoid, intraparenchymal)	Surgical evacuation, craniectomy

(b) Define cerebral compliance [2]

4. Elastance first, then compliance — the examiner wants both

- **Elastance is the system parameter defined by the pressure change per unit of volume change** — the pressure rise produced by any given volume increase in craniospinal contents. It is **not necessarily linear across all volumes and not necessarily constant under all physiological conditions** YW p. 472.e3.
- **Compliance is the inverse of elastance** — ΔV/ΔP, the volume change per unit pressure change YW p. 472.e3. Restated on the curve: **the reciprocal of the slope of the pressure-volume curve (ΔV/ΔP) represents the compliance of the system, which is maximal in the period of spatial compensation** YW p. 472.e5. Ch. 388 gives the working clinical definition: "**Intracranial compliance is the change in volume per unit change in pressure**, and knowing where a patient lies on this exponential curve at a given time can convey important information about the risk for a rapid increase in ICP or herniation" YW p. 3032.
- **Elastance arises from two mechanisms — distention and displacement.** As volume is added there are two routes for compensation: **distention of the spinal dura mater**, and **displacement of CSF and blood** YW p. 472.e3.
- **Why compliance is more useful than absolute ICP.** "Knowledge of the absolute pressure coupled with some expression of the slope of the ICP-volume curve at any given time point provides a more complete description of the stability or instability of ICP" — and a patient with poor compliance is at much greater risk than a patient with normal compliance and **the same ICP** [YW pp. 472.e6, 3032].

5. How compliance is measured and expressed — five named indices

- **Pressure-volume index (PVI).** Plotting **log ICP against volume yields a straight line**; its slope is the PVI, the calculated volume in millilitres needed to raise ICP by a factor of 10. Normal **25-30 mL**; **<13 mL clearly abnormal**. Measured clinically by infusion or withdrawal of small fluid boluses into the CSF space with concomitant pressure measurement. **CSF outflow resistance can also be calculated from the rate of decay of the pressure peak after a bolus infusion.** Continuous PVI methods using multiple time-averaged small-volume pulses generate less perturbation but **tend to underestimate compliance** [YW pp. 472.e5, 3032].
- **Volume-pressure ratio (VPR).** "A measure of brain compliance is the volume-pressure ratio (VPR). The VPR represents the slope of the pressure-volume curve" YW p. 2979.
- **Volume pressure response (Leech and Miller).** The ICP response to a **rapid bolus injection of saline into the CSF space**; it depends on the rate of injection and yields different values for slow, medium and rapid boluses YW p. 3032.
- **RAP index** (R = correlation coefficient, A = pulse amplitude of ICP, P = ICP) — the moving correlation between mean ICP wave amplitude and mean ICP; **varies from +1 to −1**. RAP **0** = no synchronisation, i.e. good compensatory reserve; RAP → **+1** = synchrony, so small rises in volume produce large rises in ICP; RAP < **0** = ICP amplitude now falls as ICP rises, meaning **compensatory reserve is exhausted and autoregulation has collapsed**. RAP is vulnerable to **baseline effect errors** because it relies on absolute ICP [YW pp. 472.e6, 3032].
- **RAC index** (R, A = pulse amplitude of ICP, C = CPP) — the analogous relationship between ICP pulse amplitude and CPP. CENTER-TBI data show **both PRx and RAC predict 6- and 12-month mortality** in adults with severe TBI YW p. 3032.
- **Practical caveat.** Direct compliance/elastance measurement "has not gained widespread clinical use, in large part because [it requires] injection of fluid into an EVD, which can be time-consuming and associated with risk." Compliance is therefore inferred from **waveform analysis, derived indices (RAP, RAC) and the therapeutic intensity level** — how much treatment is needed to control ICP YW p. 3032.

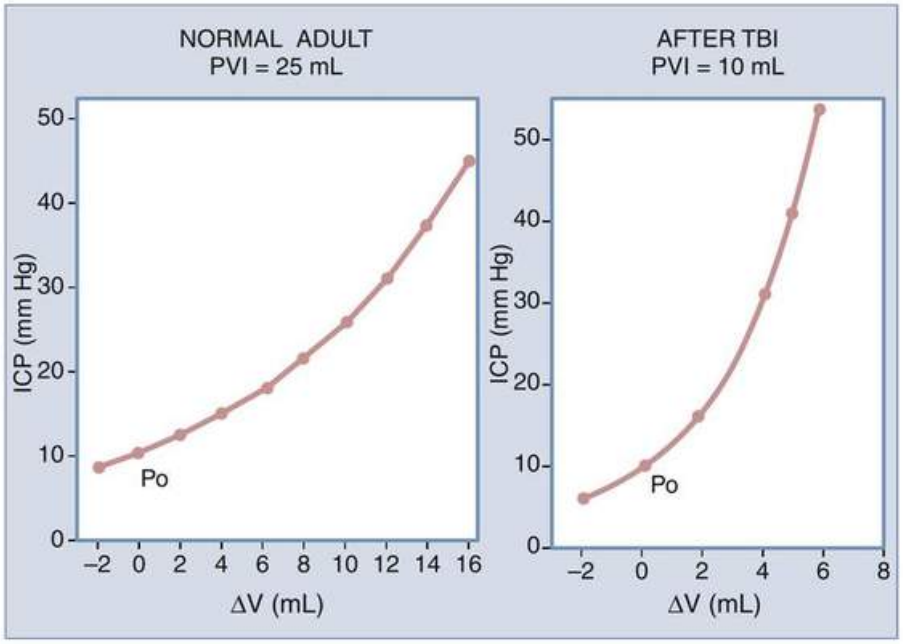


Figure 69.5. Pressure-volume curves. *Left,* From a normal adult. *Right,* From an adult with cerebral edema. In the pathologic state, the curve is steeper and the pressure-volume index *(PVI)* is greatly reduced as a result of V_{OTHER} (the abnormal component of the skull). *ICP,* Intracranial pressure; *Po,* steady state; *TBI,* traumatic brain injury; *V,* volume.

*Reproduced from Youmans & Winn 8e, Fig. 69.5, p. 472.e6 — Label when you reproduce it: two pressure-volume curves side by side. **Left** — normal adult, PVI = 25 mL, steady state P_o at ~8 mm Hg, ΔV axis running to +16 mL. **Right** — adult with cerebral oedema after TBI, PVI = 10 mL, the curve visibly steeper and the ΔV axis compressed to +8 mL. The point to write underneath: in the pathological state the same small volume increment produces a far larger pressure rise because V_{OTHER} has consumed the compensatory reserve.*

(c) Effect of cerebral perfusion pressure on compliance in traumatic brain injury [3]

6. The two directions of the CPP-compliance interaction

- **Definition and identity.** Perfusion pressure in any tissue bed is MAP minus mean venous pressure; **in the brain mean venous pressure closely approximates ICP, hence CPP = MAP − ICP**. ICP is transmitted to the compliant cerebral veins, which is why the ICP term is the correct subtrahend [YW pp. 3030, 472.e6].
- **Falling CPP reduces compliance (the key statement).** "When a reduction of CPP is caused by increased ICP, **brain compliance decreases**, an action that also serves to increase pulsatile transmission" YW p. 472.e6.
- **Falling CPP also increases pulse transmission through the vessel wall.** "When CPP decreases, the **wall tension of reactive brain vessels decreases, thereby increasing the transmission of the arterial pulse wave to the intracranial contents**." Taken together, a decrease in CPP produces an increase in **both** blood-pressure and ICP pulsatility. This relationship is **highly predictive of fatal outcome**, because a levelling off or decrease in ICP pulse amplitude implies the cerebral vessels are **no longer pressure-reactive** YW p. 472.e6.
- **Autoregulatory reserve quantifies the margin.** Autoregulatory reserve is the difference between the current CPP and the lower limit of autoregulation. With a lower limit in the range **50-70 mm Hg**, a CPP of **90 mm Hg gives a reserve of 20-40 mm Hg**; a CPP below the autoregulatory threshold exhausts the reserve YW p. 472.e6.
- **The vicious circle.** If ICP rises, CPP falls; if the lower limit of autoregulation is exhausted, CBF falls and causes ischaemia; ischaemia creates **cytotoxic oedema**, which adds to VBRAIN, raises ICP further and lowers CPP again. "Clearly a vicious circle of edema and ICP elevation can ensue if treatment attempts do not prevent it." When it cannot

be broken with available medical treatment the state is called **refractory intracranial hypertension**, and the end point of unchecked ICP elevation is "a positive feedback loop terminating in herniation and brain death" [YW pp. 472, 472.e7].

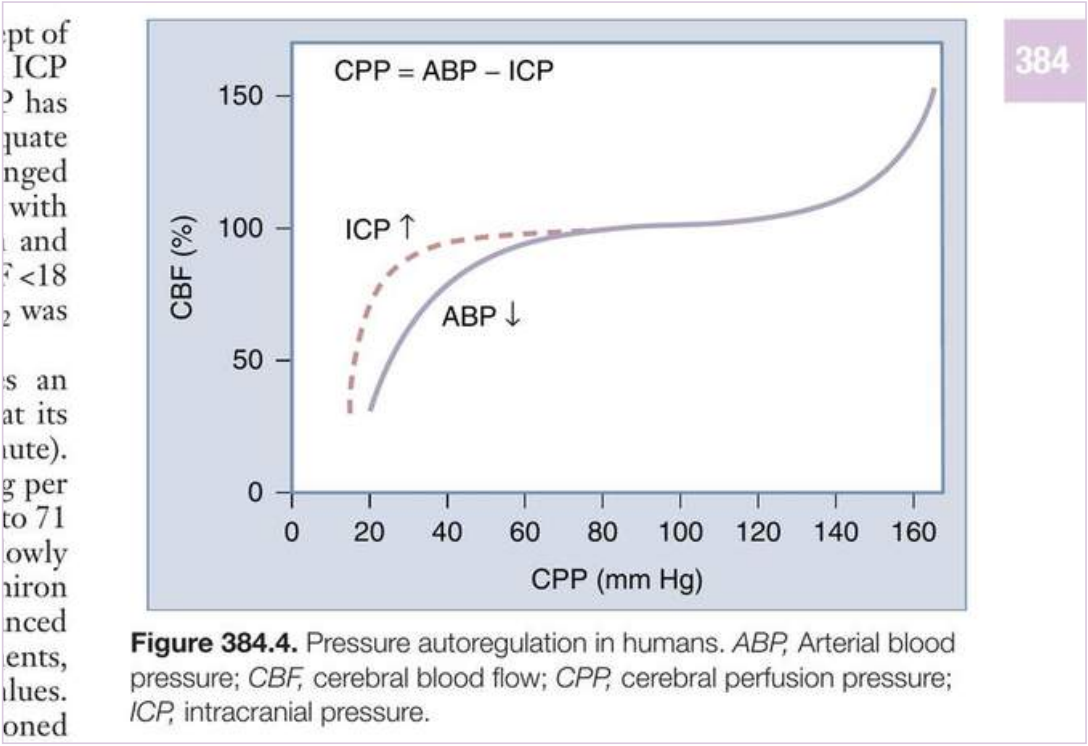


Figure 384.4. Pressure autoregulation in humans. *ABP*, Arterial blood pressure; *CBF*, cerebral blood flow; *CPP*, cerebral perfusion pressure; *ICP*, intracranial pressure.

*Reproduced from Youmans & Winn 8e, Fig. 384.4, p. 2977 — Label when you reproduce it: CBF as % of normal on the y-axis against CPP (mm Hg) on the x-axis; write the identity **CPP = ABP − ICP** in the panel. Draw the solid curve for a fall in CPP produced by falling **ABP** and the broken curve for a fall produced by rising **ICP** — note that the ICP-driven curve breaks away at a *higher* CPP, i.e. autoregulation fails earlier when the insult is intracranial hypertension rather than systemic hypotension.*

7. Autoregulatory status decides whether ICP- or CPP-directed therapy is right

- **Pressure passivity after TBI.** "Normal cerebral pressure autoregulation is impaired in a large percentage of patients with severe traumatic brain injury." Such patients are termed **pressure passive**: CBF follows CPP, so a sharp rise in CPP raises CBF and hence CBV and can produce a dangerous rise in ICP, while a sharp fall in CPP produces inadequate tissue perfusion YW p. 3032.
- **Why a shifted curve matters for compliance.** In pathological states the autoregulation curve is commonly **shifted to the right and made more linear**, which reduces the autoregulatory reserve for any given CPP YW p. 472.e7.
- **PRx — the bedside index of pressure reactivity.** PRx is the **moving correlation coefficient between 40 consecutive 5-second averages of ICP and MABP captured at ≥60 Hz** (Czosnyka). Alternatively expressed as the running correlation between MAP and ICP over a **3- to 4-minute** interval. **PRx is negative when autoregulation is intact** (a MAP rise does not change CBF, CBV or ICP) and **positive when autoregulation is impaired** (ICP follows MAP). **A PRx greater than 0.2 for more than 6 hours is associated with increased mortality.** PRx works best with an intact cranium — **after decompressive craniectomy cranial compliance is altered**, so CBF/CBV changes no longer translate into ICP changes [YW pp. 472.e6, 3031, 3032].
- **Howells' comparison is the examinable answer to part (c).** When cerebral autoregulation was **preserved**, a strategy maintaining a **higher CPP** was beneficial; in patients with **impaired autoregulation**, **ICP-targeted care with CPP in the 50-60 mm Hg range** was preferable YW p. 3031.
- **Target CPP has moved with the evidence.** Early recommendations favoured CPP >70 mm Hg; trials using that population target reduced the incidence of cerebral ischaemia but showed **no outcome benefit because fluids and vasopressors to hold CPP >70 caused a fivefold increase in pulmonary complications**. BTF 3rd edition: CPP 50-70 with avoidance of active elevation above 70. **BTF 4th edition: target CPP 60-70 mm Hg.** Current thinking favours an **individualised CPP-opt**, since levels both above and below a patient's CPP-opt are associated with worse outcome, and

time spent **below** CPP-opt may be particularly harmful in impaired autoregulation (COGiTATE is testing PRx/RAP-derived CPP-opt targets prospectively) [YW pp. 3031, 3032].

- **ICP threshold.** Saul and Ducker showed benefit treating ICP above 15 versus 25 mm Hg; Marmarou's logistic regression on 428 patients found the threshold most predictive of 6-month outcome was **20 mm Hg**; current BTF guidelines recommend treatment for persistent ICP **above 22 mm Hg**, with CPP as a second variable targeted at **60-70 mm Hg** YW p. 472.e9. Lazaridis used a **PRx >0.2** to derive individual ICP thresholds that were **more predictive of outcome than a standard 20 or 25 mm Hg dose** YW p. 3032.
- **Mechanistic corollary for CBV.** Low CPP stimulates arteriolar vasodilatation, increasing both CBV and ICP; conversely, raising CPP with vasopressors stimulates pressure autoregulation to vasoconstrict, **reducing CBV and ICP** — but "this argument appears to hold only when pressure autoregulation remains intact" YW p. 472.e11. The opposing view is the **Lund concept**, which deliberately reduces CPP and hydrostatic force in damaged capillary beds YW p. 472.e11.

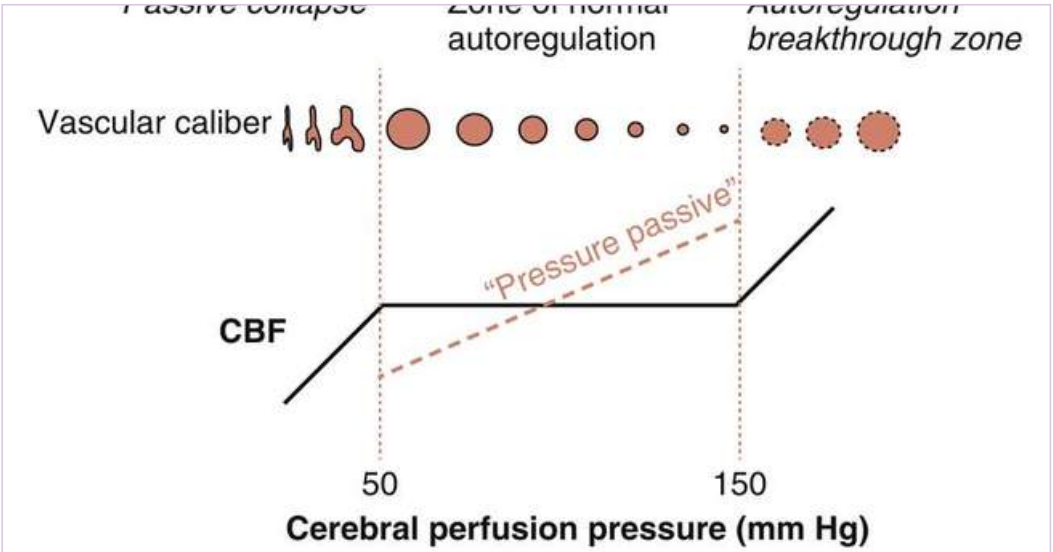


Figure 388.3. Classical cerebral pressure autoregulation curve that describes the relationship between cerebral perfusion pressure (CPP) and cerebral blood flow (CBF). Over a wide range of CPP, CBF remains essentially constant if autoregulation is preserved. This regulatory mechanism occurs at the level of the arterioles, which constrict with increasing pressure to regulate CBF and maintain flow at a constant rate. Below the lower limit of autoregulation (CPP of about 50 mm Hg in adults), there is vascular collapse, and CBF declines with falling perfusion pressure. Above the upper limit of cerebral pressure autoregulation (CPP of about 150 mm Hg in adults), CBF will rise with increasing perfusion pressure. However, normal cerebral pressure autoregulation is impaired in a large percentage of patients with severe traumatic brain injury. When autoregulation is impaired, changes in pressure within the normal autoregulatory range of 50 to 150 mm Hg will lead to changes in CBF. Patients with this disturbance in normal pressure autoregulation are termed *pressure passive* because their CBF will be dependent on CPP. A sharp rise in CPP in these patients can result in elevation of CBF and thus cerebral blood volume, which can result in a dangerous rise in intracranial pressure. Conversely, a sharp drop in CPP in a patient who is pressure passive can result in a substantial decrease in CBF that can lead to inadequate tissue perfusion. Because of these relationships between autoregulation status, CPP, and CBF, the target CPP in patients severe traumatic brain injury can often depend on whether cerebral autoregulation status is preserved or impaired.

*Reproduced from Youmans & Winn 8e, Fig. 388.3, p. 3032 — Label when you reproduce it: three zones across the CPP axis — **passive collapse** (below ~50 mm Hg), **zone of normal autoregulation** (50-150 mm Hg) and **autoregulation breakthrough zone** (above ~150 mm Hg); the row of arterioles showing vascular calibre constricting across the plateau; the flat CBF plateau; and the broken "pressure passive" diagonal that replaces the plateau when autoregulation is lost after severe TBI.*

Table 2 · Indices of intracranial compliance and pressure reactivity — what each measures, its normal value and its prognostic meaning. From Youmans & Winn 8e, Ch. 69 pp. 472.e5-472.e6 and Ch. 388 pp. 3031-3032; VPR from Ch. 384 p. 2979.

Index	What it is	Normal / favourable	Abnormal and what it means

PVI	Slope of log ICP vs volume; volume needed to raise ICP 10-fold	25-30 mL adult (<10 mL in normal infants; adult value by ~14 y)	<13 mL clearly abnormal — small volume changes give large pressure changes
VPR	Slope of the pressure-volume curve (volume-pressure ratio)	Low	Rising VPR = falling compliance
Volume pressure response	ICP response to rapid saline bolus into CSF space (Leech and Miller)	Small	Large; value depends on injection rate
RAP	Correlation between mean ICP wave amplitude and mean ICP	≈0 at normal ICP = good compensatory reserve	→+1 poor reserve; <0 reserve exhausted, autoregulation collapsed
RAC	Correlation between ICP pulse amplitude and CPP	—	Predicts 6- and 12-month mortality (CENTER-TBI)
PRx	Moving correlation of 40 consecutive 5-s averages of ICP and MABP at ≥60 Hz	Negative	Positive = impaired autoregulation; **>0.2 for >6 h = increased mortality**; unreliable after craniectomy
ICP pulse amplitude	Amplitude of the pulsatile ICP component	Rises as compliance falls	Levelling off or fall = vessels no longer pressure-reactive, highly predictive of fatal outcome

(d) Risks and benefits of ICP monitoring [3]

8. Benefits — the case for monitoring

- **The premise.** "The decision to monitor a patient's ICP is based on the premise that intracranial hypertension reduces CPP both focally and globally and can cause ischemia. The final results of elevated ICP are brain herniation and death… Monitoring ICP allows such problems to be detected and treated much earlier" YW p. 472.e8.
- **The epidemiological case.** Intracranial hypertension is found in **40% to 60% of severe head injuries** and is a major factor in death in **50% of all fatalities**. Traumatic Coma Data Bank data show that the **proportion of hourly ICP recordings greater than 20 mm Hg is highly significant in predicting outcome**. A **mean ICP increase of 10 mm Hg in the first 48 hours after injury carries an adjusted odds ratio of 3.12 for mortality** YW p. 472.e8.
- **Therapeutic dividend.** If a ventriculostomy is used there is the added advantage that ICP elevation can be **treated** by CSF drainage — and one study demonstrated clinical benefit for ventriculostomy over a fibreoptic ICP monitor in TBI, probably because of that therapeutic drainage [YW pp. 472.e8, 472.e9].
- **Guideline support.** BTF: ICP and CPP monitoring are recommended to reduce **in-hospital and 2-week postinjury mortality**. Unsupported BTF criteria in adults: **GCS 3-8 with abnormal CT**; with a normal CT, two or more of **age >40 years, unilateral or bilateral motor posturing, systolic BP <90 mm Hg**. Patients with GCS >8 may benefit if CT shows significant mass lesions or if treatment is needed for associated injuries YW p. 472.e8. ACS TQIP best-practice guidelines still advocate monitoring for **GCS ≤8 with structural brain injury on CT**, and suggest it for higher GCS with structural injury at high risk of progression (large contusions, coagulopathy) or when urgent surgery for extracranial injury is required [YW pp. 288, 289]. Neurocritical Care Society and ESICM consensus statements **strongly recommend** ICP monitoring for other acute brain injuries such as SAH and encephalitis within structured protocols YW p. 289.
- **Non-traumatic uses.** ICP monitoring has been used in TBI, SAH, intracranial tumour, intracranial haemorrhage, stroke, hydrocephalus, CNS infection and **fulminant hepatic failure**. With intracranial tumours, ventricular catheters provide temporary therapeutic decompression before and after resection and a rational means of testing re-establishment of normal CSF pathways postoperatively [YW pp. 288, 472.e8].
- **Systems benefit.** Observational studies suggest significant outcome benefit, particularly for **mortality**, when severe-TBI protocols that use ICP monitoring are introduced, and that this is **cost-effective**; a treatment response to first- or second-tier therapy is itself associated with reduced mortality. In BEST TRIP, **use of an ICP monitor was**

associated with more efficient care [YW pp. 3030, 3030].

9. Risks — procedural, device-related and conceptual

- **EVD malposition: 4% to 20%**; most misplaced drains cause no significant clinical sequelae but about **4% require replacement**. Freehand cannulation success was only **82%** even among practising neurosurgeons [YW pp. 290, 290].
- **EVD haemorrhage:** reported range **0% to 15%, average 1.1%**; most patients are asymptomatic; **clinically significant haemorrhage requiring surgical evacuation occurs about 0.5%** of the time (intracerebral, subdural or extradural). Coagulopathy, therapeutic anticoagulants and antiplatelet agents increase risk. Laceration of a cortical artery can cause a **traumatic pseudoaneurysm** YW p. 290. Ch. 69 quotes intraventricular monitoring haemorrhage rates of **<2% to 22%**, with a risk of haemorrhage at drain removal YW p. 472.e9.
- **EVD infection — the most significant risk.** Range **0% to 22%** across all series with a **cumulative incidence of 8.8%** . **Biofilms have been isolated on 73% of EVD catheters after a median use of just 4 days.** Few infections occur in the first 5 days but the rate rises significantly after **5 to 10 days**. Risk factors: intraventricular haemorrhage, SAH, craniotomy, CSF leakage, systemic infection, increased CSF output, diabetes mellitus, depressed skull fracture; technical factors are duration of catheterisation and catheter irrigation [YW pp. 290, 472.e9]. Ch. 69 quotes infectious complications of **3% to 22%** depending on classification YW p. 472.e9.
- **Occlusion** by brain matter or clot occurs frequently, especially with intraventricular haemorrhage or SAH; most resolve with flushing YW p. 290.
- **Measures that do and do not help. Prophylactic catheter exchange does not reduce infection and is not recommended** — retrospective series and one randomised trial found a *higher* incidence in routinely exchanged catheters. Subcutaneous **tunnelling** (>5 cm; most modern kits include a trocar for this) reduces leakage and infection. **Antibiotic-impregnated catheters** (minocycline-rifampicin) reduced infection from **9.4% to 1.3%** in Zabramski's RCT. Silver-impregnated catheters show mixed data and no randomised trials. BTF guidelines **do not recommend antibiotic prophylaxis** for EVD placement or catheterisation. Venue of insertion (operating room vs ICU vs emergency department) makes no significant difference [YW pp. 290, 291, 472.e9].
- **Parenchymal (microtransducer) monitors — lower risk, different problems.** Infectious complication rate **<1%**. Camino series of >1000 patients: **haemorrhage 2.5%, all clinically silent, no clinical infection**; other series 0% to 5.1% with surgical evacuation needed in one patient overall. But: **microtransducers cannot be recalibrated externally**; **zero drift** of 0.5-3.2 mm Hg per day is reported with maximal drift usually **>20 mm Hg**; **mechanical malfunction in 10-23% early, ~5% more recently** from cable breakage or probe dislocation; and **all intraparenchymal monitors are prone to regional inaccuracy** because elevated ICP is variably pronounced within the parenchyma and **compartmental pressure differentials exist between regions** [YW pp. 291, 292, 472.e9]. A 2019 meta-analysis (Volovici) of EVD versus intraparenchymal monitors found poor study quality but a **higher rate of complications with EVD and no difference in mortality or functional outcome** YW p. 291.
- **Telemetric monitors.** In 185 patients monitored 3-409 days (mean 60.7), overall complication rate **5.9%** (one intracranial abscess, two superficial infections), **haemorrhage of any size 15.6%** with only one causing deficit, and **postimplantation cerebral oedema in 46.9%** [YW pp. 292, 293].
- **The conceptual risk — monitoring is not therapy.** "High-quality clinical data have not been able to make the link between ICP monitoring and improved outcomes." **BEST TRIP** (324 patients >13 years, severe TBI, South American ICUs) found **no outcome benefit** comparing ICP-monitor-triggered care with imaging/clinical-examination-guided care; a meta-analysis of 14 studies could not demonstrate significant mortality benefit. Youmans' own reading is that **BEST TRIP was not a trial of whether to monitor ICP but a comparison of two management strategies**, that most patients never developed raised ICP, that internal validity was good but external validity limited, and that **consensus interpretation advises against changing practice where ICP is already routinely monitored** [YW pp. 288, 472.e8, 3030].
- **The other conceptual risk — treating a number.** "Simply treating a numerical threshold (ICP >20 mm Hg) is a vast oversimplification of a complex problem… an ICP number per se is not the target, but rather a warning sign of an underlying pathophysiologic process that needs targeted and ideally mechanistic treatment" YW p. 3033. Miller suggested as early as 1981 that elevated ICP might be a **marker of injury severity** rather than the primary cause of poor outcome YW p. 3033.

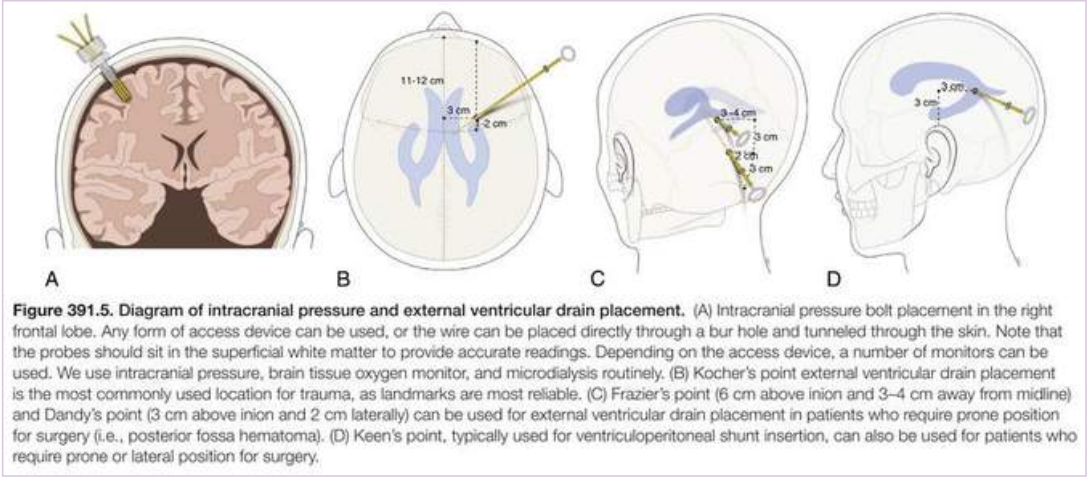


Figure 391.5. Diagram of intracranial pressure and external ventricular drain placement. (A) Intracranial pressure bolt placement in the right frontal lobe. Any form of access device can be used, or the wire can be placed directly through a bur hole and tunneled through the skin. Note that the probes should sit in the superficial white matter to provide accurate readings. Depending on the access device, a number of monitors can be used. We use intracranial pressure, brain tissue oxygen monitor, and microdialysis routinely. (B) Kocher's point external ventricular drain placement is the most commonly used location for trauma, as landmarks are most reliable. (C) Frazier's point (6 cm above inion and 3–4 cm away from midline) and Dandy's point (3 cm above inion and 2 cm laterally) can be used for external ventricular drain placement in patients who require prone position for surgery (i.e., posterior fossa hematoma). (D) Keen's point, typically used for ventriculoperitoneal shunt insertion, can also be used for patients who require prone or lateral position for surgery.

*Reproduced from Youmans & Winn 8e, Fig. 391.5, p. 3068 — Label when you reproduce it: (A) intracranial pressure bolt in the right frontal lobe with probes sitting in **superficial white matter**; (B) **Kocher's point** EVD placement — 11-12 cm behind the nasion, 3 cm from midline, the commonest trauma site because landmarks are most reliable; (C) **Frazier's point** (6 cm above inion, 3-4 cm from midline) and **Dandy's point** (3 cm above inion, 2 cm laterally) for the prone patient, e.g. posterior fossa haematoma; (D) **Keen's point**, typically for VP shunt insertion, usable in prone or lateral positioning.*

Table 3 · Risk-benefit ledger for the two workhorse ICP monitors — from Youmans & Winn 8e, Ch. 37 pp. 289-292 and Ch. 69 pp. 472.e8-472.e9.

	External ventricular drain (gold standard)	Intraparenchymal microtransducer
Accuracy / calibration	Fluid-coupled external strain gauge, **recalibratable without manipulating the catheter**; ease of calibration is why it is the gold standard	**Cannot be recalibrated externally**; zero drift 0.5-3.2 mm Hg/day, maximum usually >20 mm Hg; Camino may overestimate by a mean 9 mm Hg vs EVD
Therapeutic capability	**Yes** — CSF drainage lowers ICP; also allows dynamic testing; monitor of first choice per ACS TQIP	No
Placement	Freehand cannulation success 82%; impossible with small or shifted ventricles	Easy; usable with compressed ventricles or midline shift; right frontal region usual
Infection	0-22%, cumulative 8.8%; biofilm on 73% at median 4 days; rate rises after 5-10 days	**<1%**; colonisation frequent but meningitis rare
Haemorrhage	0-15%, average 1.1%; surgical evacuation 0.5%; risk also at removal	2.5% in >1000-patient Camino series, all silent; range 0-5.1%
Malposition / mechanical	Malposition 4-20%, 4% replaced; occlusion frequent	Mechanical malfunction 10-23% early, ~5% recent; regional inaccuracy from compartmental pressure gradients
Zeroing reference	Typically zeroed at the **foramen of Monro**, using the **external acoustic meatus** as landmark; no defined ICU reference level exists	Same convention

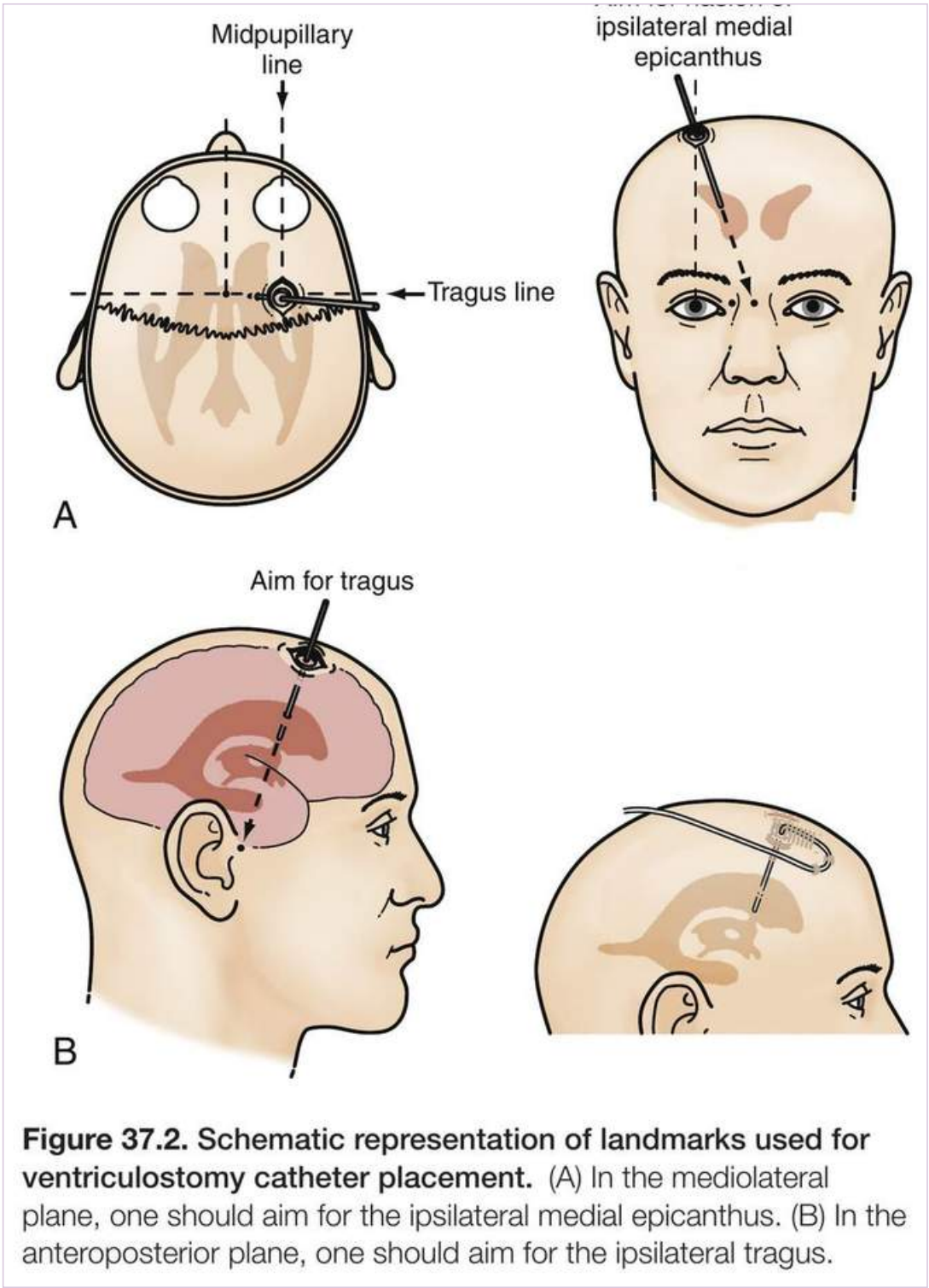


Figure 37.2. Schematic representation of landmarks used for ventriculostomy catheter placement. (A) In the mediolateral plane, one should aim for the ipsilateral medial epicanthus. (B) In the anteroposterior plane, one should aim for the ipsilateral tragus.

*Reproduced from Youmans & Winn 8e, Fig. 37.2, p. 290 — Label when you reproduce it: (A) the mediolateral plane — midpupillary line and tragus line, **aim for the nasion or ipsilateral medial epicanthus**; (B) the anteroposterior plane — **aim for the ipsilateral tragus**. State that the catheter tip should lie at the foramen of Monro and that the catheter is then tunnelled subcutaneously to minimise CSF leakage and infection.*

10. Points that earn extra marks

- **Zeroing.** There is **no defined reference level** for the transducer in the ICU, although the device is typically zeroed at the level of the **foramen of Monro**, using the **external acoustic meatus** as the anatomical landmark YW p. 472.e9.
- **AAMI standard.** The American National Standard for ICP Monitoring Devices specifies a **pressure range of 0-100 mm Hg, accuracy of 2 mm Hg over 0-20 mm Hg, and maximal error of 10% over 20-100 mm Hg** YW p. 289.

Lundberg's own requirements still apply: minimal trauma at placement, negligible infection risk, no CSF leakage, easy handling, reliability, and continued function during diagnostic and therapeutic procedures YW p. 289.

- **Non-invasive surrogate.** Ultrasound **optic nerve sheath diameter** measured **3 mm deep to the posterior pole**; **ONSD 4.5-5.5 mm indicates raised ICP**; ultrasound ONSD has better diagnostic accuracy than MRI or CT ONSD, and admission ONSD correlates with mortality — but the critical cut-off differs between studies, limiting use. CT characteristics, clinical examination and epidural pressure have all been shown to be **unreliable surrogates** [YW pp. 292, 293, 472.e9].
- **SIBICC tiers** give the treatment architecture that monitoring feeds: **Tier 0** (all monitored patients) sedation/analgesia, core temperature <38°C, CPP >60; **Tier 1** increased sedation, CSF drainage via EVD, bolus mannitol or hypertonic saline, PaCO₂ at the low end of normal, EEG and seizure prophylaxis; **Tier 2** mild hypocapnia (PaCO₂ 32-35), neuromuscular blockade trial, **MAP challenge to assess autoregulation**; **Tier 3** secondary decompressive craniectomy, pentobarbital/thiopental coma, mild hypothermia 35-36°C. Inter-tier checks: re-examine, repeat CT, reconsider surgery, exclude extracranial causes, verify physiology, consider transfer YW p. 3030.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Draw the curve, then name the limbs** — flat = period of *spatial compensation*, steep = period of *spatial decompensation*, terminal flattening above 50 mm Hg makes the full curve **sigmoid, not hyperbolic**.
- **Compliance = ΔV/ΔP = the reciprocal of the slope of the pressure-volume curve, and is the inverse of elastance.** Elastance arises from *distention* (spinal dura) plus *displacement* (CSF and blood).
- **PVI 25-30 mL normal, <13 mL clearly abnormal, <10 mL in normal infants, adult value reached at 14 years** — the single most quotable compliance number.
- **CPP = MAP − ICP**, because mean cerebral venous pressure closely approximates ICP.
- **Falling CPP lowers brain compliance and raises pulse transmission**; a *levelling off or fall* in ICP pulse amplitude means the vessels are no longer pressure-reactive and is highly predictive of fatal outcome.
- **PRx > 0.2 for more than 6 hours predicts increased mortality** — and PRx is unreliable after decompressive craniectomy because cranial compliance is altered.
- **Howells' rule:** autoregulation preserved → CPP-targeted care with a higher CPP; autoregulation impaired → ICP-targeted care with CPP 50-60 mm Hg.
- **Treat persistent ICP >22 mm Hg (BTF 4th edition), target CPP 60-70 mm Hg** — but Marmarou's outcome-derived threshold was 20 mm Hg.
- **Intracranial hypertension occurs in 40-60% of severe head injuries and is a major factor in death in 50% of fatalities**; a 10 mm Hg mean ICP rise in the first 48 h gives an adjusted OR of 3.12 for mortality.
- **EVD infection cumulative 8.8% (range 0-22%), biofilm on 73% of catheters by day 4; prophylactic catheter exchange is harmful, tunnelling >5 cm and minocycline-rifampicin impregnation (9.4% → 1.3%) help.**
- **Parenchymal monitors: infection <1%, haemorrhage 2.5%, but zero drift 0.5-3.2 mm Hg/day and no external recalibration** — and they measure a region, not the whole cranium.
- **BEST TRIP did not show ICP monitoring is useless** — it compared two strategies, most patients never had raised ICP, and consensus advises no practice change where monitoring is routine.

Pages read for this answer — Youmans & Winn 8e: 288, 289, 290, 291, 292, 293, 472, 472.e1, 472.e2, 472.e3, 472.e4, 472.e5, 472.e6, 472.e7, 472.e8, 472.e9, 472.e11, 473.e1, 2979, 3030, 3031, 3032, 3033

a) Describe cerebral blood flow and its regulation. [5]
b) Define brain death and its diagnosis. [5]

LONG | APR 2023 · Paper I · Q4 | 10 marks

Also asked as: Neurophysiology — also asked as OCT 2023 · Paper I · Q1 (a: Blood brain barrier [5]; b: Regulation of cerebral blood flow [3]; c: Intracranial pressure waves [2]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 403 *Cerebral Blood Flow and Metabolism and Cerebral Ischemia*, §Cerebral Autoregulation, §Regulation of Cerebral Blood Flow by Blood Gases, §Cerebral Neurovascular Coupling and §Ischemic Penumbra, pp. 3207.e9, 3207.e11-3207.e16, 3207.e21 (Figs. 403.3-403.5, pp. 3207.e13-3207.e15; Table 403.1, p. 3207.e14; Table 403.2, p. 3207.e21). Supplementary: Ch. 69 *Physiology of the Cerebrospinal Fluid and Intracranial Pressure*, §Steady-State ICP and CSF Dynamics, p. 472.e5; Ch. 384 *Clinical Pathophysiology of Traumatic Brain Injury*, pp. 2976-2978 (Fig. 384.4, p. 2977; Table 384.11, p. 2978); Ch. 404 *Cerebral Ischemia*, p. 3209 (Fig. 404.1, p. 3209); Ch. 211 *Neurocritical Care in Children*, §The Diagnosis of Brain Death in Children, pp. 1608-1609 (Table 211.3, p. 1609); Ch. 410 *Neurosonology*, §Transcranial Doppler as a Confirmatory Test for Brain Death, p. 3258 (Fig. 410.5, p. 3258); Ch. 82 *Electroencephalography*, p. 502.e8; Ch. 388 *Invasive Physiologic Monitoring for TBI*, pp. 3033-3034.

(a) Describe cerebral blood flow and its regulation [5]

1. Normal values — open with the numbers

- **Mean normal adult CBF is 53 mL/100 g per minute** YW p. 472.e5. Note that this figure is not an absolute: "there is no absolute CBV or CBF value that is normal per se; these parameters are rather defined by the metabolic activity of the brain itself" — 53 mL/100 g/min "may be considered hyperemic in the anesthetized brain or ischemic in a portion of brain with elevated metabolic need" YW p. 472.e10.
- **Normal CMRO₂ is 3.4 mL/100 g per minute** YW p. 3033. The brain is about **2% of body weight but consumes about 20% of the oxygen consumed by the body** YW p. 3033; Ch. 70 frames the same point as the brain being **2-3% of total body mass yet requiring ~20% of the total circulating blood volume** YW p. 473.e1.
- **The determinants.** CBV and CBF "are essentially functions of the cerebral arteriovenous pressure difference and cerebrovascular resistance, which is largely determined by vessel caliber" YW p. 472.e5. **Most of the CBV resides within the pial vessels and veins, but the precapillary arterioles control CBF** YW p. 472.e10.
- **What tone responds to.** Vascular tone is influenced by both **physical (biomechanical force)** and **chemical (pH, PCO₂)** signals, with the aim of maintaining CBF across a wide range of arterial blood pressures (**50 to 160 mm Hg**) and levels of tissue metabolism (**PaCO₂ 20 to 70 mm Hg**) YW p. 472.e5.
- **Relation to ICP.** "CBF and ICP are related by the Monro-Kellie doctrine" YW p. 3207.e9; CBF and CBV are maintained within narrow limits by autoregulation despite rhythmic cardiorespiratory changes in blood volume YW p. 472.e5.

2. Cerebral autoregulation — definition, limits and the four hypotheses

- **Definition.** "The brain maintains its regional and total blood flow (and therefore perfusion) at a fairly constant rate over a wide range of systemic blood pressure by a vasomotor phenomenon known as cerebral autoregulation. Autoregulation involves the sustained constriction or dilation of cerebral resistance vessels, **principally the precapillary arterioles, purely in response to changes in transmural pressure** caused by variations in CPP" YW p. 3207.e13.
- **Limits.** In normal individuals CPP varies directly with MAP because ICP is constant, so **the brain is protected over a MAP range of 60 to 150 mm Hg**; beyond these limits CPP passively follows MAP YW p. 3207.e13. Ch. 388 gives the lower limit of preserved autoregulation as **50-60 mm Hg in adults, decreasing in an age-related fashion in children, and the upper limit as 150 mm Hg** YW p. 3030.
- **The limits are not fixed. Right shift** in chronic hypertension (increased sympathetic tone) and states with increased renin release. **Left shift** in sleep, "physiologic hypotension" in athletes, "pathologic hypotension" from haemorrhage, and with ACE inhibitors, prolonged hypoxaemia or hypercapnia. Autoregulation may be **disturbed** in acute severe hypotension or hypertension and **profoundly impaired or abolished** in severe cerebral ischaemia, within arteriovenous malformation beds, in TBI and after aneurysmal SAH YW p. 3207.e13.
- **Time course.** Not instantaneous — pial artery measurements give **5 to 10 seconds**; in vitro evaluations give a longer **60**

to 120 seconds between intraluminal pressure change and arteriolar dilation YW p. 3207.e13.

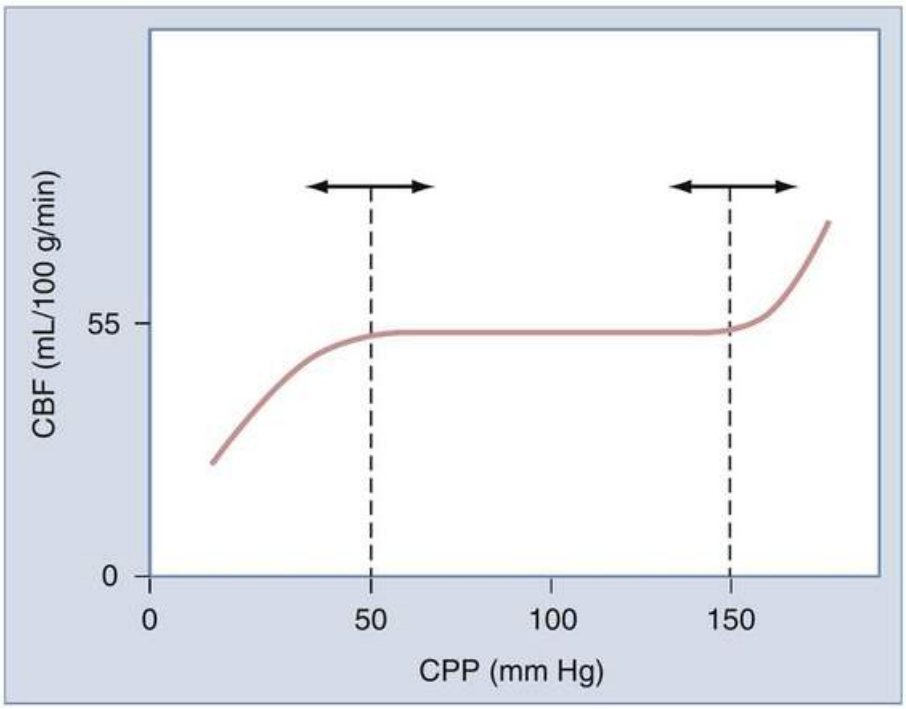


Figure 403.3. Classic cerebral autoregulation curve. Cerebral autoregulation maintains a relatively constant rate of cerebral blood flow (CBF) across a wide range of cerebral perfusion pressure (CPP), as shown (plateau). The normal pressure limits of autoregulation *(vertical broken lines)* may be shifted to the left or right in certain conditions *(arrows)* and impaired or abolished in others (see text for details). Note the respective relatively steep rise and fall in CBF as CPP changes above and below the normal limits of autoregulation.

range
resolu
cours
chang
autor
may
produ
withi
120-s
respo
(i.e.,
still p
wall).
do in
becau
recep
sugge
but pr
Th
role t
Arter
deper
to inc
to de
that r
influe
contr
entry

*Reproduced from Youmans & Winn 8e, Fig. 403.3, p. 3207.e13 — Label when you reproduce it: CBF (mL/100 g/min) on the y-axis with the plateau marked at **55**, CPP (mm Hg) on the x-axis 0-150; the two vertical broken lines marking the **normal pressure limits of autoregulation**; the horizontal double-headed arrows showing that these limits may shift left or right; and the relatively steep rise and fall of CBF beyond the limits.*

- **Myogenic hypothesis** — "accords a key role to the inherent response of VSM to mechanical stimulation." Arterioles show partial contraction dependent on intraluminal pressure: pressure up → contraction up, pressure down → contraction down. The sequence is **depolarisation of VSM cells → Ca²⁺ entry through L-type voltage-gated calcium channels → calcium-induced calcium release from sarcoplasmic reticulum → Ca²⁺-dependent myosin light-chain phosphorylation → actin-myosin contraction.** Candidate mechanosensors are **stretch-activated channels** — the TRP superfamily members **TRPC6, TRPV2 and TRPM4**, whose antisense downregulation significantly attenuates pressure-induced depolarisation — and **VSM integrins** acting through dense plaques, since integrin-specific peptide sequences are potently vasoactive and integrin signalling alters L-type Ca²⁺ current [YW pp. 3207.e13, 3207.e13].
- **Endothelial hypothesis** — the endothelium responds to physical stimuli such as pulsatile stretch and shear stress and has a critical vasomodulatory role through synthesis and release of **EDRFs (NO, prostaglandin I₂, EDHF)** and **EDCFs (endothelin-1, thromboxane A₂)**. An increase in flow rate and shear stress without a rise in transmural pressure induces vasodilation, most likely through endothelial NO release. Against it: some studies find that **disruption of the endothelium does not impair transmural pressure-induced arteriolar constriction** [YW pp. 3207.e13, 3207.e14].
- **Neurogenic hypothesis** — attributes cerebrovascular resistance to neurotransmitter release from perivascular nerve fibres, which arborise throughout the adventitia and come from **extrinsic** (remote) or **intrinsic** (local) sources.

Sympathetic innervation of extracerebral arteries "probably serves to **shift the upper limit of the autoregulatory curve to higher pressures**," partly mediated by **neuropeptide Y**, protecting the brain against sympathetically driven hypertension. But parasympathetic stimulation, though a strong endothelium-dependent vasodilator via acetylcholine and NO, "does not seem to play any role in autoregulation," and the trigeminovascular CGRP system "has no known role in autoregulation" [YW pp. 3207.e14, 3207.e14].

- **Metabolic hypothesis** — largely argued *against* for autoregulation specifically: (1) microdialysis measurements of extracellular and perivascular **H⁺, K⁺ and adenosine** normally do **not** change in response to CPP alterations within the autoregulatory range; (2) the time course of autoregulation may be too rapid to depend on metabolite generation; (3) the autoregulatory response is preserved in isolated perfused vessels in vitro. Counterpoints: dialysis has poor time resolution, Winn and colleagues did demonstrate adenosine changes within the autoregulatory range, and autoregulation is significantly decreased in **adenosine receptor knockout mice**. Conclusion: "metabolic factors may play a role in autoregulation, but probably not the dominant role under physiologic conditions" [YW pp. 3207.e13, 3207.e13].

Table 1 · Origins of neurovascular innervation — reproduced in full from Youmans & Winn 8e, Table 403.1, p. 3207.e14.

Classification	Subdivision	Source	Neurotransmitter	Vasomotor effect
Extrinsic — autonomic ganglionic	Sympathetic	Superior cervical ganglion	ATP / Neuropeptide Y / Noradrenaline	Vasoconstriction / Vasoconstriction / Vasoconstriction (α)
	Parasympathetic	Pterygopalatine (sphenopalatine) and otic ganglia	Acetylcholine / Nitric oxide / Vasoactive intestinal peptide	Vasodilation (all three)
Extrinsic — non-autonomic ganglionic peptidergic	Trigeminovascular	Gasserian (trigeminal) ganglion	Calcitonin gene-related peptide / Neurokinin A / Substance P	Vasodilation (all three)
Extrinsic — nuclear monoaminergic	Catecholaminergic	Locus caeruleus, ventrolateral medulla	Noradrenaline	Vasodilation (β₂)
	Serotoninergic	Raphe nuclei	Serotonin	Vasodilation or vasoconstriction
Intrinsic — local peptidergic	Adventitial local neurons	—	Neuropeptide Y / Vasoactive intestinal peptide	Vasoconstriction / Vasodilation

3. Chemical regulation — CO₂, then O₂

- **CO₂ is the most important physiological variable in chemoregulation.** PaCO₂ exerts profound effects on CBF, **particularly across the physiological range of 30 to 50 mm Hg**, and the relationship is **linear** there. Hypercapnia causes cerebral vasodilation at all ages; hypocapnia the reverse. **Inhalation of 5% to 7% CO₂ is associated with an almost exponential increase in CBF of 50% to 100%**, making CO₂ one of the most potent vasodilatory influences on the cerebral circulation. When PCO₂ alterations are sustained for **3 to 5 hours** there is an adaptive return of CBF toward baseline [YW pp. 3207.e14, 3207.e15].
- **Clinical rule of thumb:** "In adults, a **1-torr change in PaCO₂ is associated with a 3% change in CBF**" YW p. 472.e10.
- **The pH hypothesis — the mechanism to quote.** A direct effect of CO₂ on brain vessels has been disproved by experiments showing that PCO₂ manipulations are not vasoactive when CSF pH is held constant. **When PaCO₂ increases, molecular CO₂ — but not HCO₃[−] or H⁺ — diffuses across the BBB; perivascular PCO₂ rises; astrocytes convert CO₂ to HCO₃[−] and H⁺ via carbonic anhydrase; extracellular/perivascular H⁺ rises (local pH falls).** The resulting VSM sequence is **increased potassium conductance → K⁺ efflux → hyperpolarisation →**

closure of voltage-gated calcium channels → reduced cytosolic Ca²⁺ → relaxation, probably via K_{ATP} or K_{Ca} channels or increased H⁺/K⁺ exchange. Adaptation is associated with a gradual return of CSF pH and HCO₃[−] toward normal [YW pp. 3207.e14, 3207.e15].

- **Oxygen — a threshold phenomenon, not a linear one.** Elevated inspired oxygen elicits cerebral vasoconstriction and decreases CBF; a fall in PaO₂ causes vasodilation. **The response of CBF to PaO₂ is a threshold phenomenon evident only when PaO₂ falls below the normal physiological range**; the relationship is hyperbolic, and only with marked hypoxia is there a dramatic compensatory rise in CBF. Hypoxia acts both directly (inhibiting sarcoplasmic Ca²⁺ uptake, favouring EDRF over EDCF) and indirectly by increasing **K⁺, H⁺ and adenosine**. Arterial chemoreceptors do **not** contribute (hypoxic vasodilation persists after deafferentation of cranial nerves IX and X), though oxygen-sensing neurons in the **rostral ventrolateral medulla** may contribute neurogenic vasodilation. **NO signalling is probably not involved in mild-to-moderate hypoxia but may be involved in severe hypoxia (PaO₂ <35 mm Hg)** [YW pp. 3207.e15, 3207.e15].

later in the context of flow-metabolism coupling. Cortical CBF has been shown to increase with increasing H^+ concentration or

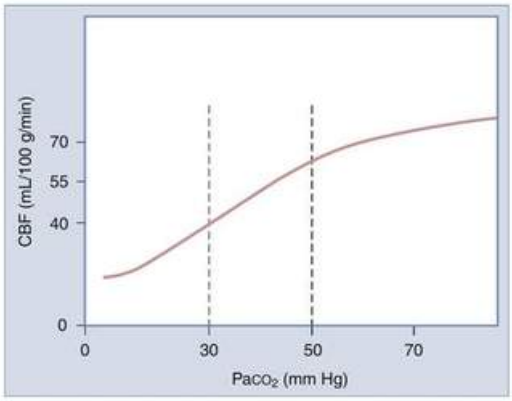


Figure 403.4. Effect of arterial partial pressure of CO_2 ($PaCO_2$) on cerebral blood flow (CBF). Note that there is a linear relationship between CBF and $PaCO_2$ across the physiologic range of $PaCO_2$ as marked by the *vertical broken lines.*

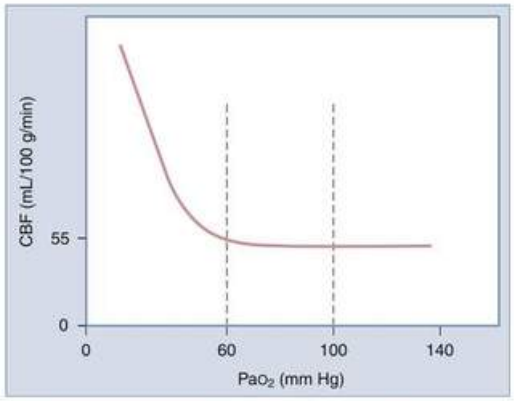


Figure 403.5. Effect of the arterial partial pressure of oxygen (PaO_2) on cerebral blood flow (CBF). Note that there is a hyperbolic relationship between CBF and PaO_2. However, in the physiologic range of PaO_2, marked by the *vertical broken lines,* CBF remains relatively constant despite marked changes in PaO_2. Only when PaO_2 falls to levels indicative of marked hypoxia is there a compensatory (and relatively dramatic) increase in CBF.

*Reproduced from Youmans & Winn 8e, Fig. 403.4, p. 3207.e15 — Label when you reproduce it: CBF (mL/100 g/min, plateau value 55, upper value 70) on the y-axis against PaCO₂ (mm Hg, 0-70) on the x-axis; mark the two vertical broken lines at **30 and 50 mm Hg** bounding the physiological range, and note that the relationship is **linear** across that range.*

4. Named chemical mediators — the list the examiner wants

- **Nitric oxide** — eNOS regulated by Ca²⁺-calmodulin and by serine (and in specific situations tyrosine/threonine) phosphorylation; Hsp90 assists phosphorylation of eNOS by Akt YW p. 3207.e11.
- **Eicosanoids** — 20-carbon mediators produced by regulated oxygenation of arachidonic acid, which must first be released from the sn-2 position of glycerophospholipids, principally by **phospholipases of the A₂ type** YW p. 3207.e11.
- **EDHF** — acetylcholine, UTP and ATP continue to dilate cerebral arterioles after complete inhibition of NOS and COX. EDHF action is characterised by resistance to NOS and COX inhibition, an intact endothelium, **hyperpolarisation of VSM cells by approximately 15 mV**, and blockade by inhibitors of **Ca²⁺-activated K⁺ (K_{Ca}) channels**. Candidate identities: an **epoxyeicosatrienoic acid** from cytochrome P-450 epoxygenase, or **K⁺** itself acting on barium-sensitive K_{ir} channels [YW pp. 3207.e11, 3207.e11].
- **Endothelin-1** — low concentrations act on endothelial **ET_B** receptors to dilate via NO; with endothelium removed or ET-1 injected into the subarachnoid cisterns it produces **profound and long-lasting vasoconstriction via VSM ET_A receptors** through PLC/IP₃, Rho/Rho kinase and ERK-1/2. ET-1 "does not appear to have a substantial role in CBF except in pathologic states" and does not contribute to basal tone; its action is

considerably augmented in cerebral ischaemia and in vasospasm after SAH, where NO signalling is defective. NO and ET-1 are physiological antagonists [YW pp. 3207.e11, 3207.e12].

- **Adenosine** — free brain concentration **50 to 300 nmol/L**; rises sharply with increased neuronal activity, seizures, hypoxia and ischaemia. **G_{i/o}-coupled A₁ receptors** on neurons inactivate adenylate cyclase, reduce cyclic AMP, reduce Ca^{2+} influx, increase K^{+} efflux and hyperpolarise — inhibitory presynaptic autoreceptors. **G_s-coupled A₂ receptors** in VSM and endothelium elicit **cyclic AMP-mediated vasodilation**; A_{2a} stimulation releases NO from endothelium and astrocytes. Through these combined actions adenosine minimises the energy deficit from CBF-metabolism mismatch and is implicated both as a **mediator of flow-metabolism coupling** and as a **neuroprotective agent in ischaemia** YW p. 3207.e12.
- **Potassium** — "among the most potent vasodilatory signals in the brain" and a key mediator of neurovascular coupling. **Perivascular K^{+} of 3 to 15 mmol/L hyperpolarises the VSM membrane via increased K_{ir} (particularly $K_{ir}2.1$) conductance and Na^{+},K^{+}-ATPase in pial artery VSM**, closing voltage-gated calcium channels and relaxing the muscle. **Above about 15 mmol/L, K^{+} becomes a vasoconstrictor** because excessive accumulation depolarises and activates VSM VGCCs. Excess perineuronal K^{+} is prevented by astrocytic uptake and spatial buffering toward perivascular end-feet YW p. 3207.e12.
- **Hydrogen ions** — the mediator of the well-known vasodilatory action of CO_2. H^{+} arises from local CO_2 production during oxidative glucose metabolism and from lactate. Extracellular acidification causes vasodilation **and reduced neuronal excitability**; attention has focused on K_{ATP} channel activation (openers dilate, glibenclamide blocks) and/or facilitation of NO release YW p. 3207.e12.

5. Neurovascular (flow-metabolism) coupling

- **Roy and Sherrington** enunciated the concept more than a century ago; increased cerebral activity is accompanied by **rapid (within 1 to 2 seconds) and regionally specific increases in oxygen and glucose uptake and metabolism**, delivered by increased capillary blood flow — **functional hyperaemia** or **neurovascular coupling** YW p. 3207.e15.
- **Why the classic metabolite theory is insufficient.** A simple local build-up of metabolites "fails to anticipate any effect on the upstream resistance vessels or arterioles," so the vascular response must be **retrogradely propagated** — possibly through gap junctions between endothelial cells or between endothelial and VSM cells, or by flow-mediated vasodilation YW p. 3207.e16.
- **Astrocytic end-feet as vasoregulatory units.** Binding of glutamate to **metabotropic glutamate receptors** activates PLC and generates **IP_3**, which releases Ca^{2+} from endoplasmic reticulum *and* causes a spatially restricted rise in $[Ca^{2+}]_i$ through Ca^{2+} release channels associated with **end-foot IP_3 receptors** — a localised large-amplitude signal that immediately precedes dilation of an approximately **30-µm segment of arteriole**. **TRPV4** has been linked to vasodilation through agonist-induced astrocyte Ca^{2+} oscillations. **Vasoconstriction is induced with large Ca^{2+} increases, vasodilation with moderate increases**, both mediated by a Ca^{2+}-sensitive potassium channel. Candidate effectors are **K^{+}** (end-foot big-conductance K_{Ca} → K^{+} into ECS → K_{ir} activation → VSM hyperpolarisation) and **arachidonic acid metabolites** [YW pp. 3207.e15, 3207.e16].
- **GABAergic interneurons** richly innervate microvessels and can **both increase and decrease** the diameter of neighbouring microvessels through **vasoactive intestinal polypeptide, NOS and somatostatin** — a plausible mechanism for redistributing perfusion to activated networks against a background of stable global perfusion YW p. 3207.e16.
- **Metabolic modulation of the astrocytic unit.** When oxygen availability is low and astrocyte $[Ca^{2+}]_i$ is elevated, **astrocyte glycolysis is maximised, accumulating extracellular lactate and adenosine**; lactate attenuates transporter-mediated uptake of the vasorelaxant **prostaglandin E_2** from the ECS and blocks astrocyte-mediated constriction — both favouring vasodilation YW p. 3207.e16.

6. CBF thresholds — the clinically decisive table

Table 2 · Cerebral blood flow thresholds — reproduced in full from Youmans & Winn 8e, Table 403.2, p. 3207.e21.

Ischaemic threshold	Rate of CBF (mL/100 g/min)	Neurological manifestation
Normal	50-60	No deficit
First	25-30	Mild to moderate deficit from electrical impairment
Second	16-20	Severe deficit from electrical failure
Third	10-12	Profound deficit from pump failure and cytotoxic oedema
Fourth	<10	Impending death from gross metabolic failure

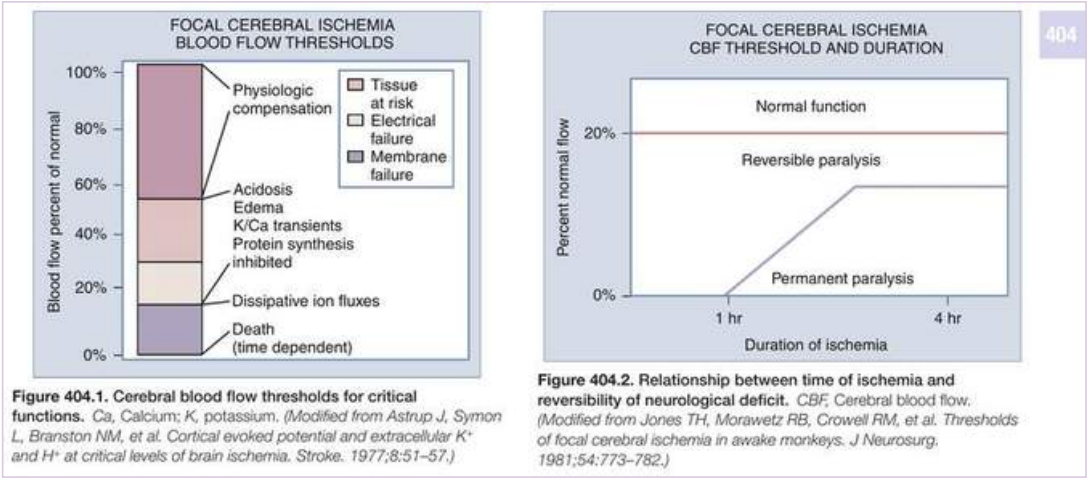


Figure 404.1. Cerebral blood flow thresholds for critical functions. *Ca, Calcium; K, potassium. (Modified from Astrup J, Symon L, Branston NM, et al. Cortical evoked potential and extracellular K^+ and H^+ at critical levels of brain ischemia. Stroke. 1977;8:51–57.)*

Figure 404.2. Relationship between time of ischemia and reversibility of neurological deficit. *CBF, Cerebral blood flow. (Modified from Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg. 1981;54:773–782.)*

*Reproduced from Youmans & Winn 8e, Fig. 404.1, p. 3209 — Label when you reproduce it: blood flow as percent of normal on the y-axis with the three stacked bands — **physiologic compensation** at the top, then **electrical failure**, then **membrane failure** at the bottom; against them write the biochemical events in descending order — *acidosis, oedema, K/Ca transients, protein synthesis inhibited* (electrical failure band), *dissipative ion fluxes*, and *death (time dependent)* at the base.*

- **The penumbra.** A peripheral area around the core that may be saved from infarction by reperfusion or pharmacological intervention; it has **maximal volume at the onset of ischaemia and progressively shrinks with time**. In awake macaques the infarction threshold rose from about **5 mL/100 g/min for 2-hour MCA occlusion to about 18 mL/100 g/min for permanent occlusion**. Despite critically low perfusion the penumbra's glucose metabolism tends to be maintained, producing marked elevation of the **glucose metabolism/blood flow ratio — metabolism-flow uncoupling** — with **peri-infarct depolarizations**; when ATP is completely depleted the penumbra becomes irreversibly depolarised and indistinguishable from core. Molecular penumbras are identified by **Hsp70 and hypoxia-inducible factor-1** expression [YW pp. 3207.e21, 3207.e21].
- **CBF after head injury.** Measurements within 6 hours of severe head trauma (GCS ≤8) are **reduced (22.5 ± 5.2 mL/100 g/min)** and correlate well with GCS and outcome; this is commoner with bilateral diffuse injury. **Between 45% and 65% of head injury victims exhibit hyperaemia in the 12 to 24 hours after injury.** CBF generally **stabilises by 36 to 48 hours** after injury. Extremes of CBF, both low and high, are seen in patients with poor outcome [YW pp. 472.e10, 472.e10].

(b) Define brain death and its diagnosis [5]

NOT COVERED IN YOUMANS — answered from the source named below

Youmans & Winn 8e has no dedicated chapter or section on adult brain death. Searching the text for "brain death", "apnea test", "determination of death by neurological criteria" and "Harvard criteria" returns a full account only in **Ch. 211 *Neurocritical Care in Children*, §The Diagnosis of Brain Death in Children, pp. 1608-1609**, plus confirmatory-test material in **Ch. 410 *Neurosonology* p. 3258** (TCD), **Ch. 82 p. 502.e8** (cEEG) and **Ch. 388 p. 3034** (PbtO2). The definition, the examination, the apnea test, the observation periods and the ancillary tests below are therefore taken from that paediatric section, which Youmans states is **"consistent with the report by the Quality Standards Subcommittee of the American Academy of Neurology"** and "addresses additional aspects… that are unique to children." Where a value is paediatric-specific it is flagged as such.

7. Definition and legal frame

- **The core definition.** National policy and state law established in **1981** indicate that "**irreversible absence of brain function (including the brainstem) is synonymous with death**" YW p. 1608.
- **Historical lineage.** Guidelines for determining death by neurological criteria "have developed over time at many institutions on the basis of the **Harvard criteria**." Paediatric criteria were published in **1987** by the **American Academy of Pediatrics**, consistent with the AAN Quality Standards Subcommittee report, and were **revised in 2011** by a committee under the auspices of the **Society of Critical Care Medicine, the American Academy of Pediatrics and the Child Neurology Society** [YW pp. 1608, 1608].
- **The physiological end point.** Youmans' ICP chapter describes the terminal sequence explicitly: unchecked ICP elevation is "a positive feedback loop terminating in herniation and brain death" YW p. 472; in central transtentorial herniation, "as hypoxia ensues the pupils dilate, and **brain death follows shortly thereafter**" YW p. 472.e8.

8. Prerequisites — what must be established or excluded first

- **An irreversible cause must be known.** "Before the determination of brain death, the patient must be known to have an **irreversible disease that can cause brain death**" YW p. 1608.
- **Reversible mimics must be ruled out**: "drug poisoning, toxicity, metabolic disorder, severe electrolyte disturbances, **hypothermia**, and **shock**" YW p. 1608.
- **Temperature.** "Brainstem reflexes can be **lost at a body temperature of 32°C**." A temperature of **36.5°C or lower** prompts the controversial need to correct arterial blood gas values for temperature, a concern avoided at normothermia. Because normothermia is hard to achieve in children with loss of brain function, and because data supporting a specific lower limit are scarce, **a threshold of 35°C can be considered feasible and appropriate** YW p. 1608.

9. The clinical examination — complete loss of brain function

- **Motor.** No spontaneous movement or vocalisation; no response to noxious stimuli; **no decorticate or decerebrate posturing** YW p. 1608.
- **Spinal reflexes that may legitimately persist** — this is a favourite discriminator: "Rudimentary spinal reflex responses may remain, including **deep tendon reflexes, plantar reflexes, triple flexion of the legs, and superficial abdominal reflexes**" YW p. 1608.
- **Pupils.** "May be either widely dilated or midway between constriction and dilation, and **stimulation with a bright light must fail to produce any pupillary constriction**" YW p. 1608.
- **Eye movements.** The eyes must be motionless; **oculocephalic (doll's eye) and oculovestibular (ice water caloric) reflexes must be absent** YW p. 1608.
- **Bulbar reflexes.** "The **gag, cough, sucking and rooting reflexes** must be absent" YW p. 1608.
- **Apnoea.** "In order to document the absence of spontaneous ventilatory efforts, an **apnea test should be performed with each examination, if there is no contraindication**" YW p. 1608.

10. The apnoea test, step by step

- **Pre-oxygenation.** "Before ventilation is interrupted, the patient should be **ventilated with 100% oxygen for at least 5 minutes** to minimize the risk of hypoxia" YW p. 1608.

- **Baseline blood gas.** Obtain arterial blood gas to demonstrate **adequate acid-base balance and acceptable ventilation (PCO₂ 35-45 mm Hg) and oxygenation (PO₂ ≥ 100 mm Hg)**. "If any of these criteria are not met, the patient may not tolerate the apnea test without developing hypoxia" [YW pp. 1608, 1609].
- **Technique.** One described method is transition from the mechanical ventilator to a **self-inflating resuscitation bag**, which may reduce the risk of barotrauma and hypoxia; the bag is set with **100% oxygen and PEEP approximating the patient's current ventilator settings** YW p. 1609.
- **Duration and threshold.** "The patient is then observed constantly for **10 to 15 minutes**. If **no spontaneous effort at ventilation is observed at a PCO₂ of 60 mm Hg or 20 mm Hg above baseline**, the test result is interpreted as consistent with absence of brainstem function" YW p. 1609.
- **Modification for lung disease.** In patients with lung disease or chronic CO₂ retention the observation period should be **shorter: at least 2 to 3 minutes, and preferably 5 minutes** YW p. 1609.
- **Stopping rules.** Discontinue for **oxygen saturation falling below 85%-90%, hypotension, any arrhythmia associated with haemodynamic instability, or observed respiratory effort**. "If circulatory instability occurs at any time, the patient should be reconnected to the ventilator" YW p. 1609.

Table 3 · Recommended observation periods for the diagnosis of brain death, by age — reproduced from Youmans & Winn 8e, Table 211.3, p. 1609, with the adult rule from the accompanying text.

Age group	Number of examinations	Inter-examination observation period
Neonates (37 weeks gestational age to full-term 30 days of age)	Two, each with apnoea testing	**24 hours**
Infants and children (>30 days to 18 years)	Two, each with apnoea testing	**12 hours**
18 years and older	An interval between the two required evaluations is **optional**	—

- **Why two examinations in children.** "An interval period of time between the two required brain death evaluations is **optional in patients 18 years of age and older**. Because of the difficulties in performing a brain death examination in younger patients, however, **two examinations — including apnea testing with each examination, separated by an observation period — are required**" YW p. 1609.

11. Ancillary (confirmatory) tests — when, and their limits

- **Which tests.** "Ancillary tests such as a **nuclear medicine perfusion scan, EEG, cerebral angiography, and transcranial Doppler imaging** can be used when required, although these ancillary tests have limitations" YW p. 1609.
- **The four permitted indications** (2011 revision committee): ancillary studies may be used **(1) when components of the examination or apnoea testing cannot be completed; (2) if there is uncertainty about components of the neurological examination; (3) if a medication effect may be present; (4) to reduce the observation period between examinations** YW p. 1609.
- **They do not replace the clinical diagnosis.** "When ancillary studies are used, **a second clinical examination and apnea test should still be performed**, and components that can be completed must yield results that are consistent with brain death." **A nuclear medicine perfusion scan may be preferred when drugs that may suppress the EEG are present (e.g. pentobarbital)** YW p. 1609.
- **Transcranial Doppler.** "The true diagnosis of brain death is a **clinical diagnosis**, and blood flow studies such as cerebral angiography, radioisotope scanning, and TCD are **confirmatory tests**." Most studies comparing TCD with clinical criteria indicate **sensitivities and specificities approaching 100%**. Per the President's Commission, confirmatory tests "can be used to **shorten the observation period**" in patients who fulfil clinical criteria, before organ retrieval or withdrawal of ventilation. **False negatives** occur when massive brainstem destruction from destructive or posterior fossa lesions leaves the patient clinically brain dead with **preserved supratentorial blood flow**, so EEG activity may persist and TCD waveforms may indicate preserved flow. TCD is especially useful when the clinical diagnosis is difficult because of extensive trauma, cranial nerve damage or paralytic agents, and "may be helpful in avoiding unnecessary surgery in this situation" [YW pp. 3258, 3258].

- **EEG.** Continuous EEG "can be used as an **additive test** for the diagnosis of brain death" YW p. 502.e8; diagnosis of brain death is one of the listed indications for EEG in the ICU [YW pp. 502, 502.e1].
- **Brain tissue oxygen.** "A PbtO₂ of 0 mm Hg can be seen in clinical brain death" YW p. 3034.

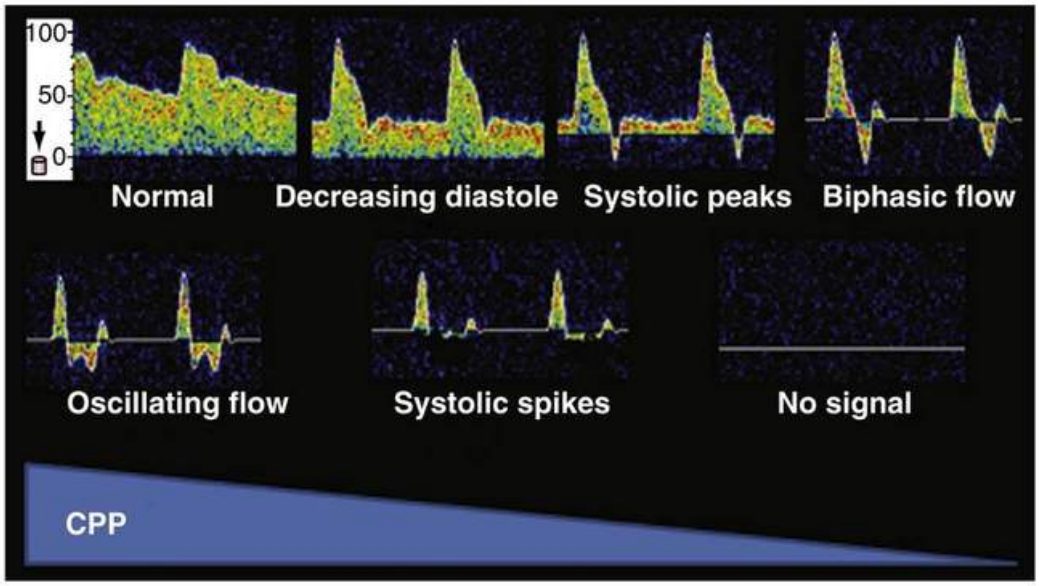


Figure 410.5. Tracing indicating progression of the velocity waveform from a normal pattern to one seen with cerebral circulatory arrest. With decreasing cerebral perfusion pressure *(CPP)* or increased resistance to flow, there is a progressive decrease in the diastolic velocity, progressing to oscillating flow, and finally to small systolic peaks, and to zero flow. The *lower panel* indicates transcranial Doppler findings in cerebral circulatory arrest. (*Modified from Hassler W, Steinmetz H, Pirschel J. Transcranial Doppler study of intracranial circulatory arrest. J Neurosurg. 1989;71[2]:195–201.*)

*Reproduced from Youmans & Winn 8e, Fig. 410.5, p. 3258 — Label when you reproduce it: the six TCD velocity waveform stages in order as CPP falls — **normal → decreasing diastole → systolic peaks → biphasic flow → oscillating flow → systolic spikes → no signal** — with the descending CPP wedge beneath. Say in words that oscillating (reverberating) flow, isolated short systolic spikes, and absent signal (with a previously obtainable window) are the patterns of **cerebral circulatory arrest**.*

12. After the determination

- **Documentation and communication.** "Once the determination of brain death is made, the medical team should add appropriate documentation to the patient's medical record, and should communicate findings with the patient's family" YW p. 1609.
- **Organ donation.** "At this point, it may also be appropriate to discuss the **recovery of organs for humanitarian purposes**. Permission from the family may be requested for evaluation of the patient by an **organ and tissue procurement agency**" YW p. 1609.

GUIDELINE UPDATE

World Brain Death Project / AAN 2023 practice guideline — Youmans 8e predates the current unified adult-and-paediatric determination-of-death-by-neurologic-criteria guideline, which harmonises prerequisites (including a minimum MAP/SBP and exclusion of drug effect by five half-lives), fixes one examination by a suitably qualified clinician for adults, and lists radionuclide perfusion scintigraphy and four-vessel angiography as the preferred ancillary tests over EEG. Quote it only if the examiner asks for current practice; the Youmans material above is the answer to the question as set.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Mean normal adult CBF is 53 mL/100 g/min; normal CMRO₂ is 3.4 mL/100 g/min** — the brain is 2% of body weight and consumes 20% of the body's oxygen.
- **Autoregulation protects the brain over a MAP of 60-150 mm Hg (Ch. 403) / a CPP of 50-150 mm Hg (Ch. 388)** , and operates at the **precapillary arterioles** in response to **transmural pressure**.
- **Four hypotheses — myogenic, endothelial, neurogenic, metabolic.** Youmans favours myogenic; H⁺, K⁺ and adenosine do *not* change within the autoregulatory range, which is the argument against the metabolic hypothesis.
- **Right shift of the curve: chronic hypertension and increased renin. Left shift: sleep, athletes, haemorrhagic hypotension, ACE inhibitors, prolonged hypoxaemia, hypercapnia.**
- **CO₂ is the most potent chemoregulator — linear across PaCO₂ 30-50 mm Hg; 1 torr = 3% change in CBF; 5-7% inhaled CO₂ raises CBF by 50-100%.**
- **The pH hypothesis:** molecular CO₂ crosses the BBB, astrocytic carbonic anhydrase makes H⁺, and perivascular H⁺ hyperpolarises VSM by raising K⁺ conductance.
- **Oxygen is a threshold, not a gradient** — CBF rises only when PaO₂ falls below the physiological range.
- **Potassium is biphasic: 3-15 mmol/L perivascular K⁺ dilates via K_{ir}2.1; above ~15 mmol/L it constricts by depolarising VSM.**
- **Memorise Table 403.2:** normal 50-60, electrical impairment 25-30, electrical failure 16-20, pump failure and cytotoxic oedema 10-12, death <10 mL/100 g/min.
- **Brain death = irreversible absence of brain function including the brainstem, and is synonymous with death** (1981 US national policy and state law).
- **Spinal reflexes are compatible with brain death** — deep tendon, plantar, triple flexion of the legs and superficial abdominal reflexes may all persist.
- **Apnoea test:** 100% O₂ for ≥5 min, baseline PCO₂ 35-45 and PO₂ ≥100, observe 10-15 min, positive if no effort at **PCO₂ 60 mm Hg or 20 above baseline**; abort for SpO₂ <85-90%, hypotension, arrhythmia or any respiratory effort.
- **Observation periods (paediatric):** 24 hours for neonates 37 weeks to 30 days; 12 hours for >30 days to 18 years; optional interval at ≥18 years.
- **Brainstem reflexes can be lost at 32°C** — always exclude hypothermia before declaring death.
- **Ancillary tests are confirmatory only, and TCD can be falsely negative** when the brainstem is destroyed but supratentorial flow persists; choose a radionuclide perfusion scan when barbiturates may suppress the EEG.

Pages read for this answer — Youmans & Winn 8e: 472, 472.e5, 472.e8, 472.e10, 473.e1, 502, 502.e1, 502.e8, 1608, 1609, 3030, 3033, 3034, 3207.e9, 3207.e11, 3207.e12, 3207.e13, 3207.e14, 3207.e15, 3207.e16, 3207.e21, 3258

a) Blood brain barrier. [5]
b) Regulation of cerebral blood flow. [3]
c) Intracranial pressure waves. [2]

LONG | OCT 2023 · Paper I · Q1 | 10 marks

Also asked as: Neurophysiology — also asked as APR 2023 · Paper I · Q4 (a: Describe cerebral blood flow and its regulation [5]; b: Define brain death and its diagnosis [5]) and MAY 2024 · Paper I · Q7 (a: Draw a diagram of blood brain barrier [4]; b: Monro Kellie doctrine [3]; c: Lund hypothesis for cerebral perfusion pressure management [3]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 68 *The Blood-Brain Barrier*, §Functional Anatomy of the Blood-Brain Barrier and §Transport Across the Blood-Brain Barrier, pp. 471.e1-471.e6 (Figs. 68.1-68.5, pp. 471.e2-471.e8; Box 68.1, p. 471.e2; Table 68.1, p. 471.e5). Supplementary: Ch. 70 *Cerebral Edema*, §Blood-Brain Barrier and §Glymphatic System, pp. 473, 473.e1-473.e2 (Figs. 70.1-70.2, pp. 473.e2-473.e4); Ch. 42 *Physiology of the Choroid Plexus and Cerebrospinal Fluid*, p. 322.e2 (Fig. 42.1, p. 322.e2); Ch. 141 *Delivery of Drugs to Brain Tumors*, §The Blood-Cerebrospinal Fluid Barrier, p. 972 (Fig. 141.1, p. 972); Ch. 403 *Cerebral Blood Flow and Metabolism and Cerebral Ischemia*, §Cerebral Autoregulation and §Regulation of Cerebral Blood Flow by Blood Gases, pp. 3207.e12-3207.e15 (Fig. 403.3, p. 3207.e13; Table 403.1, p. 3207.e14); Ch. 69 *Physiology of the CSF and Intracranial Pressure*, §Intracranial Pressure Waveforms and §Non-Steady-State Dynamics, pp. 472.e2, 472.e6-472.e7 (Figs. 69.1-69.2, p. 472.e2; Figs. 69.7-69.8, p. 472.e7); Ch. 71 *Extracellular Fluid Movement and Clearance in the Brain*, p. 474.e4 (Fig. 71.3, p. 474.e4).

(a) Blood brain barrier [5]

1. Definition — the BBB is a neurovascular unit, not a membrane

- **Youmans' opening definition.** "The blood-brain barrier (BBB) is a '**neurovascular unit**' composed of **microvascular endothelium, basement membrane, neurons, and neuroglial structures: astrocytes, pericytes, and microglia**" YW p. 471.e1. The Key Concepts box repeats it with the extracellular matrix: "a neurovascular unit that consists of microvascular endothelium, neurons, basement membrane, and neuroglial structures, including astrocytes, pericytes, and microglia" YW p. 471.e1.
- **It is dynamic, not passive.** "The BBB is a **dynamic gatekeeper** that anatomically connects and interacts with peripheral intravascular signals, cerebrospinal fluid, and the parenchymal environment to mediate a complex system of exchange, transport, and clearance." More recently, "cells involved in the production and reabsorption of CSF also need to be considered as members of the neurovascular unit" YW p. 471.e1.
- **Historical proof. Ehrlich (1885)** showed that intravenously injected dye stained visceral structures but not normal brain; **Goldmann (1913)** showed that intraventricular dye stained brain but not systemic tissues. Together these indicated a barrier between the systemic circulation and brain YW p. 473.e1.
- **The structural foundation.** "The **foundation of the blood-brain barrier is the tight junctions between the cerebral vascular endothelial cells**" YW p. 473.e1. "The anatomic BBB is formed by a **monolayer of microvascular endothelial cells that line the intraluminal space of brain capillaries and are supported by astrocyte end-feet**" YW p. 471.e1.

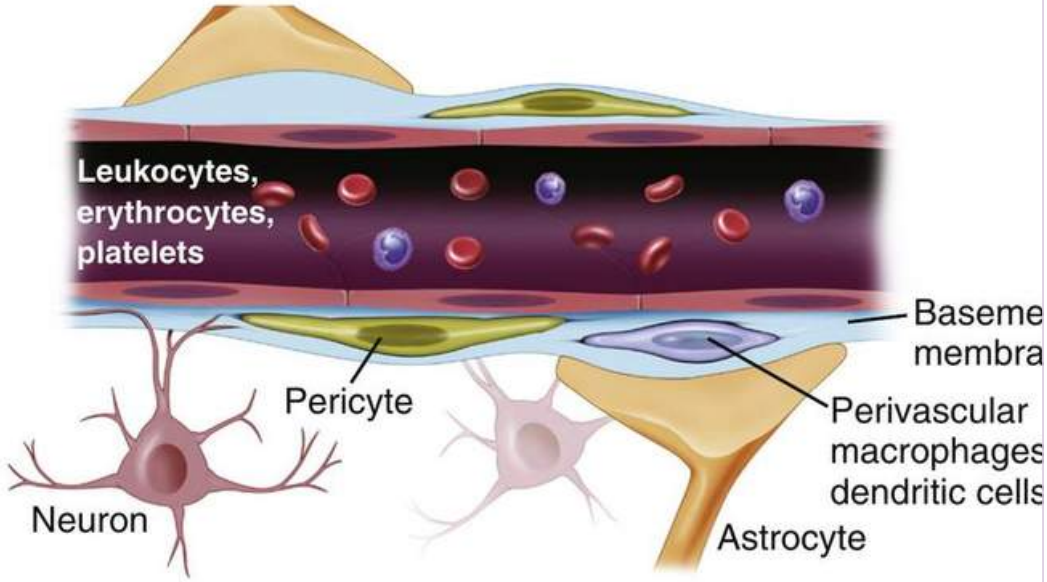


Figure 68.1. Schematic of a "neurovascular unit," which consists of endothelial cells, astrocytes, pericytes, macrophages, microglia, neurons, the basement membrane, and the extracellular matrix.

*Reproduced from Youmans & Winn 8e, Fig. 68.1, p. 471.e2 — Label when you reproduce it: the capillary lumen containing leukocytes, erythrocytes and platelets; the endothelial monolayer; the **basement membrane**; a **pericyte** sharing that basement membrane; **perivascular macrophages and dendritic cells**; an **astrocyte** with its end-foot on the vessel; a **neuron**; and (from the caption) microglia and the extracellular matrix. This is the six-cell "neurovascular unit" the examiner wants named.*

2. Ultrastructure — the three ways brain endothelium differs from peripheral endothelium

- **Youmans states them as a numbered list** YW p. 471.e5:
  - **1. "The BBB lacks fenestrations and is characterized by low pinocytotic activity, both of which markedly impair fluid uptake."** Brain microvascular endothelial cytoplasm has **rare pinocytotic vesicles** [YW pp. 471.e5, 471.e2].
  - **2. "TJs are ubiquitous in brain ECs and impede paracellular transport of large or hydrophobic molecules across the BBB into the brain parenchyma."**
  - **3. "Mitochondria are present at a much higher concentration, which provides the energy needed for active transport of various proteins and factors required by the brain."**
- **Junctional molecular inventory. Tight junctions regulate paracellular transport and consist of occludin, claudin and junctional adhesion molecules. Adherens junctions mediate cell spacing and transmit cytoskeletal signals and include cadherin, catenins, vinculin and actinin** [YW pp. 471.e1, 471.e2]. The detailed schematic adds **claudin-3, -5 and -12 forming the primary seal by homotypic binding to claudins on adjacent cells; occludin as a dynamic regulatory protein whose presence correlates with increased transendothelial electrical resistance and decreased paracellular permeability; JAMs, which with PECAM regulate leukocyte migration; and the accessory scaffolds ZO-1, ZO-2, ZO-3, cingulin and 7H6**, with **VE-cadherin** at the adherens junction on the basolateral side YW p. 471.e8.
- **Geometry to quote.** The **average total surface area of the brain microvasculature is 20 m²**; cerebral capillary endothelial surface area is **100 cm²/g tissue**; **total length 650 km**; **inner capillary lumen 6 µm**; in cortex **capillaries lie 20 µm apart**. The endothelial cell has a **luminal and abluminal membrane separated by 300 to 500 nm of cytoplasm** [YW pp. 471.e5, 471.e1]. Ch. 70 gives the capillary network total area as **12-20 m²** with a **mean intercapillary distance of approximately 40 microns** YW p. 473.e1.
- **The permeability threshold.** Tight junctions "restrict the passage of most **large (greater than 180 Da), hydrophilic, and/or charged molecules** by restricting paracellular movement." Molecules that *do* cross include **gases (oxygen,**

carbon dioxide), small lipophilic structures (methanol, ethanol) and nutrients (glucose, ascorbic acid) YW p. 473.e1.

- **Coverage figures.** "**More than 90% of astrocyte foot processes surround ECs**" and astrocyte end-feet "densely surround TJs, reducing the size of the gap between ECs." Pericyte projections "penetrate the basal lamina and cover **20% to 30% of the microvascular circumference**"; pericytes are **most abundant on venules** [YW pp. 471.e2, 471.e3].
- **More than 99% of brain capillaries have a BBB**, the exception being the **circumventricular organs** YW p. 471.e5.

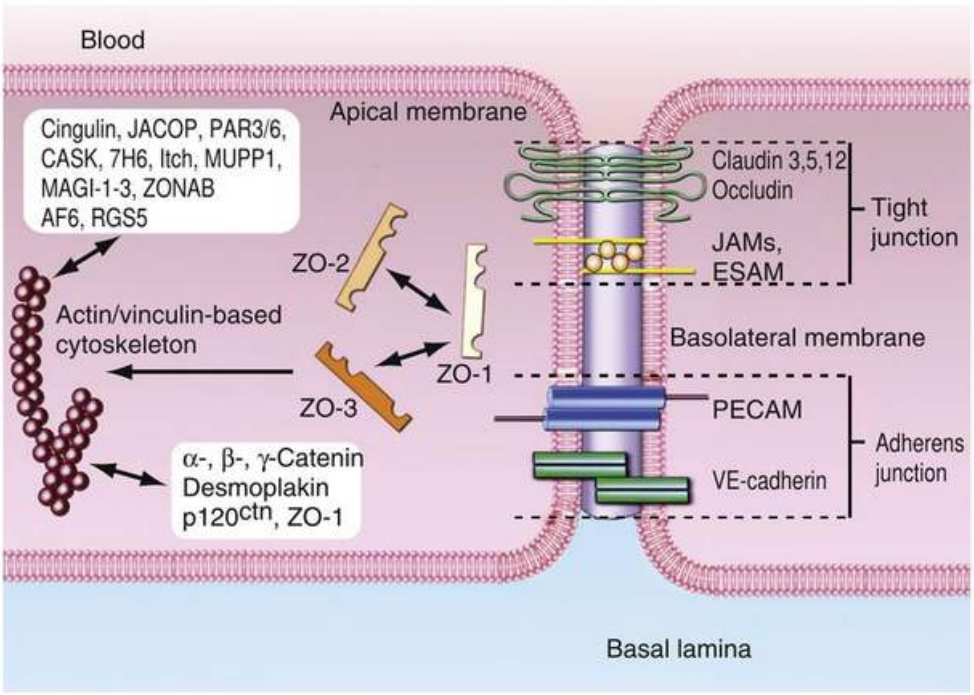


Figure 68.5. Schematic of a tight junction at the blood-brain barrier (BBB). Claudins make up the backbone of the tight junction strands, form dimers, and bind homotypically to claudins on adjacent cells to produce the primary seal of the tight junction. Occludin functions as a dynamic regulatory protein the presence of which at the BBB is correlated with increased transendothelial electrical resistance and decreased paracellular permeability. Junctional adhesion molecules (JAMs) are localized at the tight junction and, in association with platelet endothelial cellular adhesion molecule-1 (PECAM), regulate leukocyte migration across the BBB. Several accessory proteins also contribute to its structural support, such as zona occludens-1 (ZO-1) through ZO-3, cingulin, and 7H6. Adherens junctions are located near the basolateral side of the endothelial cells and are not specific for cerebral endothelial junctions. *ESAM,* Endothelial cell–selective adhesion molecule; *VE,* vascular endothelial.

*Reproduced from Youmans & Winn 8e, Fig. 68.5, p. 471.e8 — Label when you reproduce it: the capillary lumen (Blood) at the top, the **apical membrane**, the **tight junction** with **claudin 3, 5, 12** and **occludin** spanning the cleft, **JAMs** and **ESAM**, the scaffolding complex (**ZO-1, ZO-2, ZO-3, cingulin, 7H6, MAGI-1-3, MUPP1, PAR3/6, CASK, AF6, PDZ**), the **actin/vinculin-based cytoskeleton**, then the **basolateral membrane** carrying **PECAM** and **VE-cadherin** at the **adherens junction**, with **α-, β-, γ-catenin, desmoplakin and p120^{ctn}**, sitting on the **basal lamina**.*

3. The cellular members and what each contributes

- **Endothelial cells** — the anatomical barrier; also the site of **charge polarity** between abluminal and luminal surfaces, which influences permeability and is regulated in part by tight junctions. Differential receptor and transporter expression allows **directional transport** of solutes such as glucose and of Na⁺, K⁺ and Ca²⁺. **Na⁺,K⁺-ATPase, the Na⁺/H⁺ exchanger and the Na⁺-amino acid transporter are predominantly abluminal; GLUT1 is concentrated abluminally (three to four times higher than luminal); P-glycoprotein (MDR1) is concentrated luminally; alkaline phosphatase and γ-glutamyl transpeptidase are concentrated luminally**. **EC polarity generates interstitial fluid and maintains homeostatic gradients**, and perturbation of transporter activity has been implicated as a cause of oedema after ischaemic stroke YW p. 471.e2.
- **Astrocytes** — reinforce barrier function and contact ECs on the **abluminal** side. Associated with adrenergic, cholinergic and peptide-responsive nerve terminals. They can **induce both barrier and permeability properties**: Stewart and Wiley (1981) showed coelomic vessels acquire BBB characteristics in contact with neural grafts; Janzer and Raff showed astrocytic aggregates induce a functional BBB in non-brain ECs in the anterior chamber of the eye; astrocyte-conditioned media induce BBB-like properties in vitro. **BBB polarity is additionally maintained by astrocytes, in which distribution of aquaporin-4 plays a significant role in water absorption and potentially in edema formation** [YW pp. 471.e2, 471.e3].
- **Pericytes** — undifferentiated contractile connective tissue cells localising to capillary walls, sharing the endothelial basement membrane, aiding regulation of EC growth and modulating capillary integrity; they act as a **secondary BBB**, monitoring the perivascular space and phagocytosing unwanted substances. Although they lack contractile actin they are implicated in CBF regulation and in the **no-reflow phenomenon** after ischaemic stroke. They synthesise laminin and fibronectin, express **PDGFR** (targeted unsuccessfully with imatinib in GBM), and **migrate away from the site of injury in conditions that increase BBB permeability such as trauma or seizures** YW p. 471.e3.
- **Neurons** — their role at the BBB "is primarily **enzymatic**." They upregulate catalytic factors specific to ECs and provide **noradrenergic, serotoninergic, cholinergic and GABAergic innervation** to astrocytes and their associated ECs; PET and fMRI detect regional increases in CBF, glucose and oxygen consumption coupled to local neuronal activity YW p. 471.e3.
- **Microglia** — resident macrophages providing **immunosurveillance** of the CNS and perivascular space; they act as **antigen-presenting cells** to T cells, secrete proinflammatory cytokines and proliferate rapidly. Central in stroke, trauma, multiple sclerosis and neurodegeneration; microglial clearance of amyloid plaques suggests stimulation may sometimes be beneficial YW p. 471.e3.
- **Extracellular matrix** — provides physical stability and is "a critical anchoring site that mediates polarity at the EC-astrocyte interface." Integrity is maintained through **laminin, collagen type IV and integrins**; matrix proteins also **upregulate TJ protein expression**, and ECM disruption impairs BBB structural integrity YW p. 471.e3.

4. The enzymatic barrier — the second barrier people forget

- **Three main catalytic agents regulate transportation across the BBB: γ-glutamyl transpeptidase, alkaline phosphatase and aromatic L-amino acid decarboxylase**, all concentrated in cerebral vessels YW p. 471.e2.
- **Cytochrome P-450.** CYP enzymes at the BBB and neurovascular unit "provide a potent mechanism of biotransformation **in proximity to neurons**" even though total brain CYP is less than hepatic. They catalyse formation of neurosteroids and eicosanoids and metabolise vitamins A and D, centrally acting drugs, anaesthetics and environmental neurotoxins, controlling **neurotrophic support, neuroprotection, control of cerebral blood flow and brain cholesterol homeostasis**. Brain CYPs have **unique regional induction patterns regulated independently of hepatic isoforms**; the worked example is **metabolism of carbamazepine into a proconvulsant toxic metabolite** YW p. 471.e2.
- **Levodopa is the classic exploitation of the enzymatic barrier.** Levodopa is structurally similar to a neutral amino acid and enters ECs via the **large neutral amino acid carrier**; **ECs contain dopa decarboxylase**, which converts it to dopamine, so "the amount of dopamine generated in the brain is limited by EC expression of dopa decarboxylase." Other BBB-regulated enzymes: **monoamine oxidase A and B, catechol O-methyltransferase and**

pseudocholinesterase YW p. 471.e6.

5. Transport across the BBB — the four (or five) mechanisms

- **Youmans' four primary mechanisms** YW p. 471.e5:
  - **1. Paracellular aqueous diffusion** — small water-soluble molecules through the extracellular pathway, regulated by tight junctions.
  - **2. Transcellular lipophilic diffusion** — a transmembrane process; substances cross **at a rate proportional to their molecular weight and lipid solubility**.
  - **3. Adsorptive transcytosis** — endocytosis mediated by **clathrin-coated pits** and to a lesser extent caveolae; **generally selective for cationic molecules** and **the predominant mechanism for passage of HIV-1 into the brain** .
  - **4. Saturable transport** — subdivided into **(a) receptor-mediated transcytosis**, which can work against a concentration gradient but requires energy, and **(b) channel-mediated transport** via transport proteins.
- **Carrier systems present at the BBB:** hexoses (glucose, galactose); neutral, basic and acidic amino acids; monocarboxylic acids (lactate, pyruvate); purines (adenine, guanine); nucleosides (adenosine); amines; and ions. **Uptake of larger molecules including insulin and transferrin occurs via receptor-mediated endocytosis** YW p. 471.e5.
- **Glucose. GLUT1 is a 45- to 55-kD protein** depending on glycosylation, present in high concentration in endothelium of arterioles, venules and capillaries, facilitating movement of **D-glucose enantiomers**. Transport across the BBB is **the rate-limiting step of primary energy acquisition** and **the rate of transport is proportional to CBF**. Five sodium-independent brain glucose transporters exist, including **GLUT1 (endothelial cells), GLUT3 (neurons) and GLUT5 (microglia)**, each able to transport 2-deoxyglucose, 3-O-methylglucose, mannose, galactose and glucose. **GLUT1 expression is altered by hypoglycaemia, diabetes, epilepsy, trauma and tumours** YW p. 471.e5.
- **Amino acids — four systems** [YW pp. 471.e5, 471.e6]:
  - **L type** — large neutral amino acids, preference for leucine residues; **sodium independent, saturable, stereospecific**.
  - **A type** — small neutral amino acids; **sodium dependent**.
  - **Independent transporters for acidic and basic amino acids** — basic and large neutral amino acid transfer rates are high because of high brain requirement.
  - **A sodium-dependent system for alanine, serine, cysteine and threonine**, whose primary role appears to be to **transport amino acids out of the brain**.
- **Glutamate handling.** Glutamate is the most abundant CNS amino acid, stored intracellularly against its gradient; it is removed from extracellular fluid by local astrocytes **and by endothelial cells at the BBB**, which use a **sodium-dependent abluminal excitatory amino acid transporter**. The BBB also participates in glutamate metabolism. Precursors **tryptophan, tyrosine and histidine** cross and are then converted to **serotonin, dopamine/noradrenaline and histamine** respectively YW p. 471.e6.
- **Permeability is bidirectionally modulated.** Table 68.1 lists agents that **decrease** permeability — intracellular cAMP, steroids, adrenomedullin, noradrenaline, GDNF, bFGF, polyunsaturated fatty acids, TGF-β — and a far longer list that **increase** it: bradykinin, histamine, serotonin, thrombin, glutamate, ATP/ADP/AMP, endothelin-1, adenosine, platelet-activating factor, phospholipase A₂, arachidonic acid, prostaglandins, leukotrienes, IL-1α, IL-1β, IL-6, TNF-α, MIP-1 and MIP-2, C3a-desArg, free radicals and nitric oxide YW p. 471.e5.

Table 1 · The four transport mechanisms of the blood-brain barrier, with worked examples — from Youmans & Winn 8e, Ch. 68 p. 471.e5 and Fig. 68.4, p. 471.e6.

#	Mechanism	What crosses	Notes
1	Paracellular aqueous diffusion	Small water-soluble molecules	Regulated by tight junctions; only very small amounts permitted

2	Transcellular lipophilic diffusion	Lipid-soluble agents (and vinca alkaloids, cyclosporine, zidovudine at the efflux pumps)	Rate proportional to molecular weight and lipid solubility
3	Transport proteins (channel-mediated, saturable)	Glucose, amino acids, purine bases, nucleosides, cholines, monocarboxylic acids, ions	GLUT1 abluminal, 3-4× luminal level; rate proportional to CBF
4a	Receptor-mediated transcytosis	Insulin, transferrin	Energy-dependent; can work against a concentration gradient
4b	Adsorptive transcytosis	Albumin and other plasma proteins; **HIV-1**	Clathrin-coated pits > caveolae; selective for cationic molecules

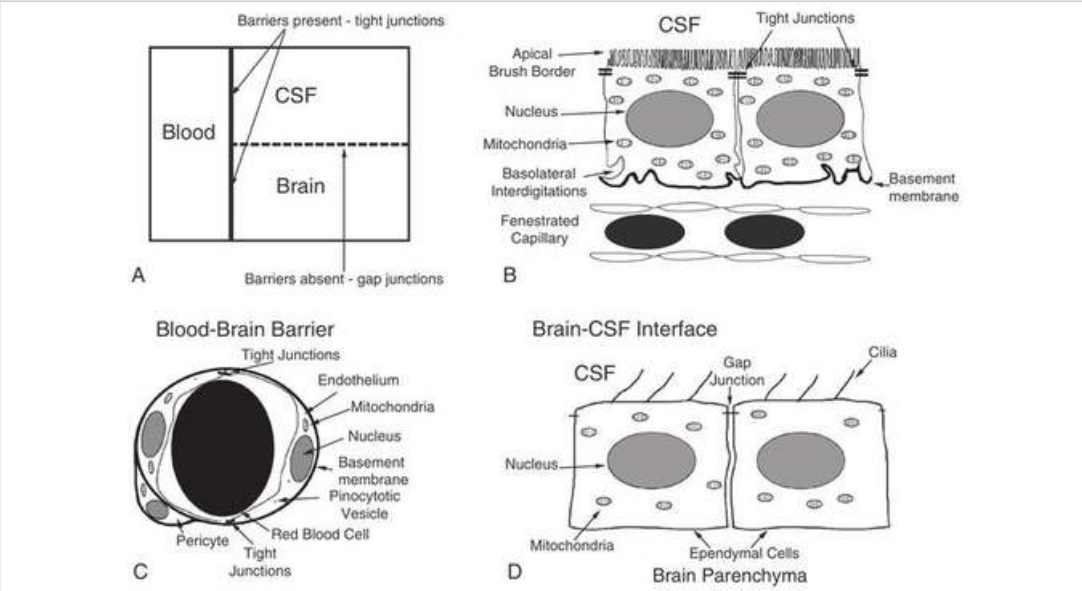


Figure 42.1. Structural configuration of transport interfaces in the adult central nervous system. (A) Restrictive tight junctions at the choroidal blood–cerebrospinal fluid (CSF) barrier (BCSFB) demarcate blood from ventricular CSF. A 10-fold tighter barrier (than the choroid plexus) separates brain capillary blood from tissue *(bold solid line)*. The permeable ependyma, with gap junctions, divides ventricular CSF from the brain's internal face *(broken line)*; similarly, the leaky pia-glia membrane overlies the external cortical surface. (B) The choroidal BCSFB has a single epithelial layer spot-welded by zonulae occludentes tight junctions at the apices of the cells. Choroidal capillaries permit large molecules to penetrate the interstitium up to the basolateral membrane. Lush microvilli at the CSF-facing apical membrane provide a great area for transport. There is also marked surface area in the interdigitating basolateral membranes. Copious mitochondria energize the dynamic transport of ions and substrates. (C) The anatomic substrate for the blood-brain barrier is the tight junctions between endothelial cells. A profusion of mitochondria powers bidirectional solute transport across abluminal and luminal endothelial faces. Transendothelial movement of molecules into the brain also occurs by pinocytosis. The microvessel wall is expansively covered by astrocyte foot processes and pericytes, furnishing added regulation of transport and permeability. (D) The CSF-brain interface contains ependyma, with gap junctions highly permeable to macromolecules distributing readily between ventricles and brain interstitial fluid. Transependymal bidirectional distribution of solutes allows the CSF to act as a nutritional source as well as an excretory sink for cerebral catabolites. (*From Smith DE, Johanson CE, Keep RF. Peptide and peptide analog transport systems at the blood-CSF barrier. Adv Drug Deliv Rev. 2004;56[12]:1765–1791.*)

*Reproduced from Youmans & Winn 8e, Fig. 42.1, p. 322.e2 — Label when you reproduce it: panel **C** — the anatomic substrate of the blood-brain barrier: endothelium with **tight junctions** at the apices, **mitochondria**, **nucleus**, **basement membrane**, sparse **pinocytotic vesicles**, a **pericyte**, and a red blood cell in the lumen; panel **D** — the **CSF-brain interface**: ependymal cells joined by **gap junctions**, permeable to macromolecules, permitting transependymal bidirectional distribution of solutes so that CSF acts as both a nutritional source and an excretory sink for cerebral catabolites.*

6. Regional exceptions and the neighbouring barriers

- **The BBB phenotype develops along the vascular tree.** "The precise vascular localization of the functional term blood-brain barrier might be extended beyond the capillary segments to CNS microvessels." As penetrating pial vessels become capillaries, permeability falls in steps: **diapedesis under normal conditions and permeability to most small molecules at the pial level → reduced passage of proteins → drastically reduced passage of cellular elements and impermeability to most hydrophilic molecules → negligible permeability, polarised phenotype and active drug exclusion at the BBB proper** [YW pp. 471.e5, 471.e6].
- **Circumventricular organs** — the parts of the brain **without** a BBB: "**median eminence, pituitary gland, choroid plexus, subfornical organ, lamina terminalis and area postrema**," which "are important for **peripheral chemosensing**" YW p. 471.e5.

- **The blood-CSF barrier.** The specialised **tight junctions of choroid plexus epithelial cells** — not endothelium — separate CSF from blood; **zonulae occludentes seal neighbouring epithelial choroidal cells continuously**, strongly restricting paracellular solute movement and limiting diffusion of polar drugs. **The choroid plexus capillaries themselves are fenestrated and provide little resistance to small molecules.** The blood-CSF barrier does not contribute significantly to drug entry into brain parenchyma because **its surface area is approximately 1000-fold smaller than that of the BBB**. Like the BBB it contains drug-metabolising enzymes [YW pp. 972, 972].
- **The blood-tumour barrier.** The endothelial tight junction component "can be compromised significantly in the enhancing part of a glioma, which results in the hallmark of contrast enhancement on CT or MRI," but other physiological and physical barriers still restrict delivery: distended capillaries with leaky walls and sluggish flow, radial drug clearance shunting drug away from the tumour, and hypoxia-driven resistance YW p. 972.
- **The glymphatic system — the efflux limb.** "Whereas the blood-brain barrier represents a fluid **input** pathway to brain interstitial tissue, the glymphatic system represents a fluid pathway for **eliminating** excess brain fluid and solutes." CSF is driven along **periarterial (Virchow-Robin) spaces** by arterial pulsation, a pressure gradient, respiration and vasomotor motility; movement into the brain interstitium is facilitated by **aquaporin-4 water channels on astrocyte foot processes** that envelop the microvasculature; fluid then moves **by convection to the perivenous spaces of the deep cerebral veins** and drains out via **cervical lymphatics, arachnoid granulations and the perineural space of cranial nerves** [YW pp. 473.e1, 473.e2].

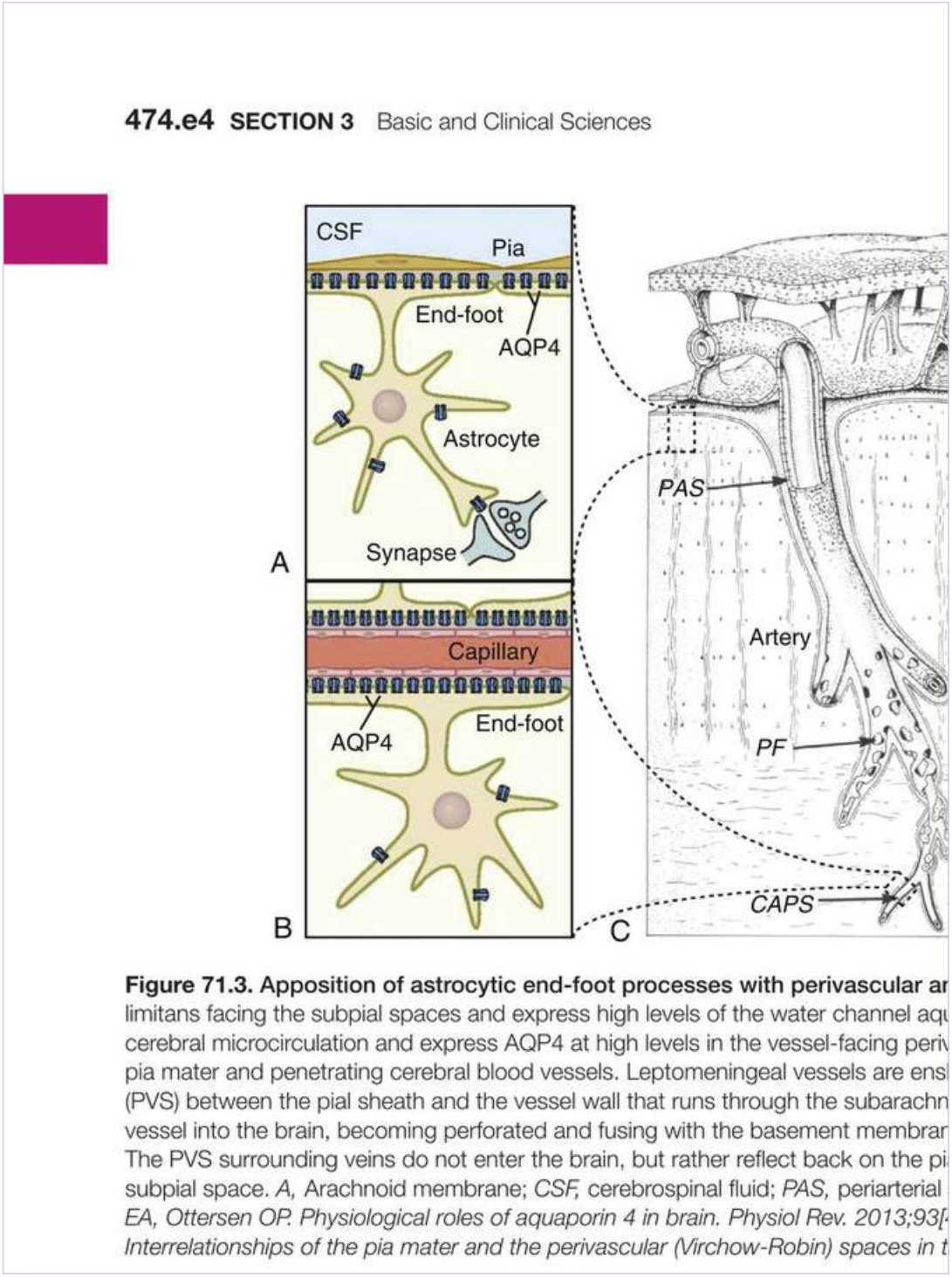


Figure 71.3. Apposition of astrocytic end-foot processes with perivascular ar
limitans facing the subpial spaces and express high levels of the water channel aqu
cerebral microcirculation and express AQP4 at high levels in the vessel-facing perivi
pia mater and penetrating cerebral blood vessels. Leptomeningeal vessels are ens
(PVS) between the pial sheath and the vessel wall that runs through the subarachn
vessel into the brain, becoming perforated and fusing with the basement membrar
The PVS surrounding veins do not enter the brain, but rather reflect back on the pi
subpial space. *A,* Arachnoid membrane; *CSF,* cerebrospinal fluid; *PAS,* periarterial
EA, Ottersen OP. Physiological roles of aquaporin 4 in brain. Physiol Rev. 2013;93[
Interrelationships of the pia mater and the perivascular (Virchow-Robin) spaces in t

*Reproduced from Youmans & Winn 8e, Fig. 71.3, p. 474.e4 — Label when you reproduce it: (A) the subpial compartment — **CSF**, **pia**, astrocyte **end-foot** expressing **AQP4** at high level on the vessel-facing surface, **synapse**; (B) the capillary level — **AQP4** on both end-feet flanking the capillary; (C) the anatomy of the **perivascular (Virchow-Robin) space (PAS/PVS)** between the pia mater sheath and the penetrating artery, becoming perforated and fusing with the basement membrane before the terminal capillary bed, and the **perivenous (PF)** return route.*

- **Drug delivery consequences.** Of **6304 medications** analysed (excluding diagnostic dyes), **only 6% were used for treatment of the CNS** despite heavy CNS pharmaceutical research. The BBB's selectivity is "a double-edged sword": "The evolution of the BBB fortunately makes large increases in intracranial pressure rare occurrences," and it prevents harmful toxins reaching the brain, but it blocks therapy [YW pp. 471.e10, 471.e10].

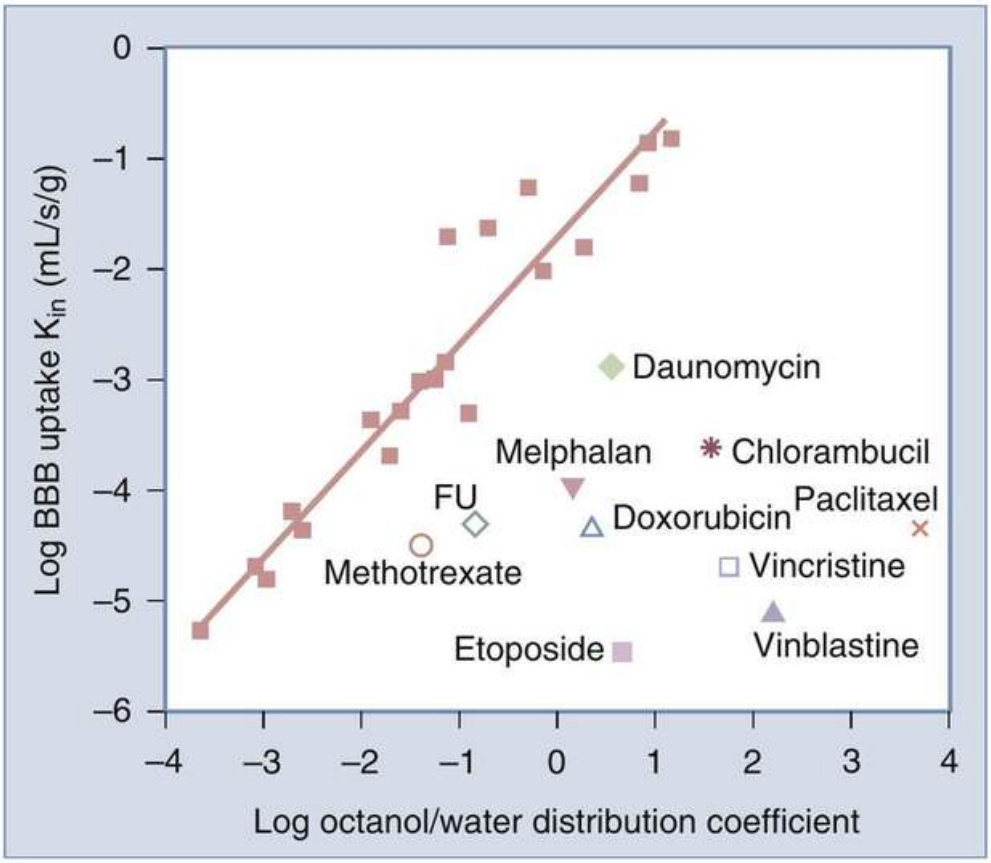


Figure 141.1. Relationship between blood-brain barrier permeability and the octanol/water partition coefficient of chemotherapeutic agents. The *solid line* is the least-squares fit to the data for agents that are not actively taken up by the brain or pumped out by the blood-brain barrier (BBB). *FU,* Fluorouracil; K_{in}, unidirectional transfer coefficient. (*Modified from Smith QR. A review of blood-brain barrier transport techniques. In: Nag S, ed. Methods in Molecular Medicine. Vol. 89: The Blood-Brain Barrier: Biology and Research Protocols. Totowa, NJ: Humana Press; 2003.*)

*Reproduced from Youmans & Winn 8e, Fig. 141.1, p. 972 — Label when you reproduce it: log BBB uptake K_{in} (mL/s/g) on the y-axis against log octanol/water distribution coefficient on the x-axis; the least-squares line for agents neither actively taken up nor pumped out; and the named outliers falling **below** the line because they are substrates of efflux pumps — **methotrexate, fluorouracil, etoposide, doxorubicin, daunomycin, vincristine, vinblastine, paclitaxel, melphalan, chlorambucil**. The teaching point: lipophilicity predicts BBB uptake, and every drug below the line is being actively excluded.*

(b) Regulation of cerebral blood flow [3]

7. Autoregulation — pressure

- **Definition.** "The brain maintains its regional and total blood flow (and therefore perfusion) at a fairly constant rate over a wide range of systemic blood pressure by a vasomotor phenomenon known as **cerebral autoregulation**." It involves sustained constriction or dilation of **the precapillary arterioles, purely in response to changes in transmural pressure** caused by variations in CPP YW p. 3207.e13.
- **Range.** "In effect, the brain is protected from fluctuations in perfusion over a **MAP range of 60 to 150 mm Hg**. Beyond these limits, CPP passively follows MAP." In normal individuals CPP varies directly with MAP because ICP is constant YW p. 3207.e13. Ch. 69 gives the working ranges of tone regulation as **arterial blood pressure 50 to 160 mm**

Hg and **PaCO₂ 20 to 70 mm Hg**, with **mean normal adult CBF 53 mL/100 g per minute** YW p. 472.e5.

- **Shifts and failures. Right-shifted** in chronic hypertension (increased sympathetic tone) and increased renin states; **left-shifted** in sleep, physiological hypotension in athletes, haemorrhagic hypotension, and with ACE inhibitors, prolonged hypoxaemia or hypercapnia. **Profoundly impaired or abolished** in severe cerebral ischaemia, AVM beds, TBI and after aneurysmal SAH YW p. 3207.e13. After injury the curve is typically **shifted to the right and made more linear**, which reduces the autoregulatory reserve for any given CPP YW p. 472.e7.
- **Mechanisms — four hypotheses. Myogenic** (VSM depolarisation → L-type VGCC Ca²⁺ entry → calcium-induced calcium release → myosin light-chain phosphorylation → contraction; mechanosensors are the stretch-activated **TRPC6, TRPV2, TRPM4** channels and VSM integrins); **endothelial** (shear stress and pulsatile stretch → EDRFs: NO, PGI₂, EDHF; EDCFs: ET-1, thromboxane A₂); **neurogenic** (perivascular nerves, with sympathetic innervation shifting the **upper** limit rightward partly via neuropeptide Y); and **metabolic** (largely argued against, because extracellular H⁺, K⁺ and adenosine do not change within the autoregulatory range) [YW pp. 3207.e13, 3207.e14].
- **Time course. 5 to 10 seconds** in pial arteries in vivo; **60 to 120 seconds** in vitro YW p. 3207.e13.

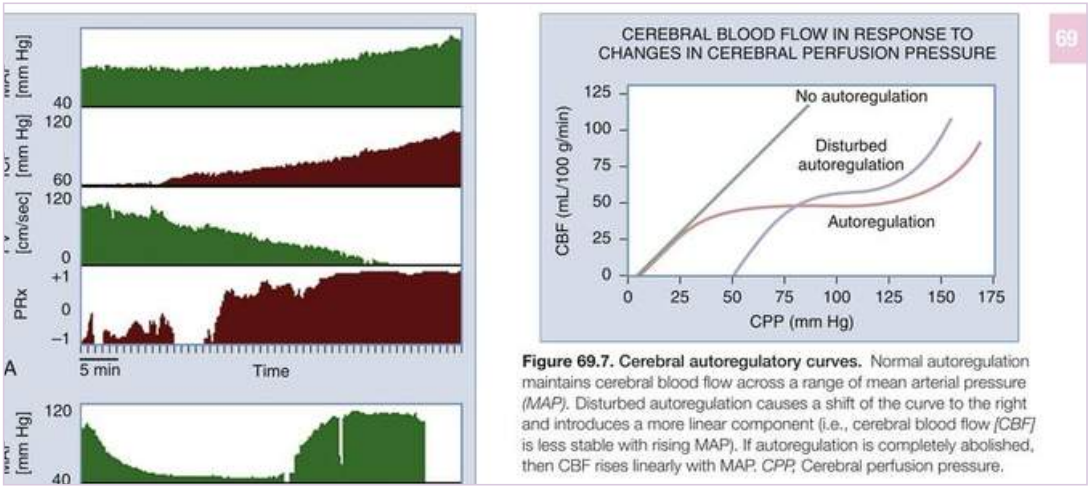


Figure 69.7. Cerebral autoregulatory curves. Normal autoregulation maintains cerebral blood flow across a range of mean arterial pressure *(MAP)*. Disturbed autoregulation causes a shift of the curve to the right and introduces a more linear component (i.e., cerebral blood flow *[CBF]* is less stable with rising MAP). If autoregulation is completely abolished, then CBF rises linearly with MAP. *CPP,* Cerebral perfusion pressure.

*Reproduced from Youmans & Winn 8e, Fig. 69.7, p. 472.e7 — Label when you reproduce it: CBF (mL/100 g/min, 0-125) against CPP (mm Hg, 0-175); three curves — **normal autoregulation** (flat plateau), **disturbed autoregulation** (right-shifted with a more linear component, so CBF is less stable with rising MAP), and **no autoregulation** (a straight line through the origin, CBF rising linearly with MAP).*

8. Chemical regulation — CO₂, O₂, and the local mediators

- **CO₂ is "the most important physiologic variable in chemoregulation,"** acting **linearly across the physiological PaCO₂ range of 30 to 50 mm Hg**; **inhalation of 5% to 7% CO₂ raises CBF by 50% to 100%, almost exponentially**. Sustained PCO₂ change for 3 to 5 hours produces adaptive return of CBF toward baseline. Clinically, **a 1-torr change in PaCO₂ gives a 3% change in CBF** [YW pp. 3207.e14, 472.e10].
- **The pH hypothesis.** Extracellular rather than intracellular acidosis, and not molecular CO₂ itself, is the determinant: manipulating PCO₂ is **not** vasoactive when CSF pH is held constant. **Molecular CO₂ crosses the BBB → perivascular PCO₂ rises → astrocytic carbonic anhydrase converts CO₂ to HCO₃[−] + H⁺ → perivascular H⁺ rises → increased VSM potassium conductance and K⁺ efflux → hyperpolarisation → closure of voltage-gated calcium channels → reduced cytosolic Ca²⁺ → relaxation** [YW pp. 3207.e14, 3207.e15].
- **Oxygen is a threshold phenomenon.** Raised inspired oxygen constricts and lowers CBF; a fall in PaO₂ dilates, but only **below the normal physiological range**. Hypoxia acts directly (inhibits sarcoplasmic Ca²⁺ uptake, favours EDRF over EDCF) and indirectly by generating **K⁺, H⁺ and adenosine**; **arterial chemoreceptors are not involved** (vasodilation persists after deafferentation of IX and X),

though **rostral ventrolateral medullary oxygen-sensing neurons** may add neurogenic vasodilation. **NO signalling is probably not involved in mild-to-moderate hypoxia but may be in severe hypoxia (PaO₂ <35 mm Hg)** YW p. 3207.e15.

- **Named local mediators. Adenosine** (free brain level 50-300 nmol/L; inhibitory A₁ on neurons, vasodilator cAMP-mediated A₂ on VSM and endothelium; a mediator of flow-metabolism coupling and a neuroprotectant); **potassium** (biphasic — dilates at perivascular 3-15 mmol/L via K_{ir}2.1 and Na⁺,K⁺-ATPase, constricts above ~15 mmol/L by depolarising VSM); **hydrogen ions** (dilate and simultaneously reduce neuronal excitability, probably via K_{ATP} channels and/or NO release); **endothelin-1** (ET_B-mediated dilation at low dose, powerful long-lasting ET_A-mediated constriction when endothelium is disrupted — important in ischaemia and post-SAH vasospasm, not in basal tone); **EDHF** (hyperpolarises VSM by ~15 mV, blocked by K_{Ca} inhibitors) [YW pp. 3207.e11, 3207.e12].
- **Neurovascular coupling.** Roy and Sherrington's principle, refined: increased activity produces **regionally specific increases in oxygen and glucose uptake within 1 to 2 seconds** (functional hyperaemia). **Astrocytic end-feet act as vasoregulatory units** — glutamate on metabotropic receptors → PLC → IP_3 → spatially restricted end-foot Ca^{2+} rise → dilation of a ~30-µm arteriolar segment; **moderate Ca^{2+} rises dilate, large rises constrict**, both via a Ca^{2+}-sensitive potassium channel. **GABAergic interneurons** can both dilate and constrict adjacent microvessels via VIP, NOS and somatostatin [YW pp. 3207.e15, 3207.e16].
- **Viscosity.** Table 384.11 makes the haemorheological point cleanly: **lower blood viscosity with intact autoregulation leaves CBF unchanged but reduces CBV (and hence ICP); with defective autoregulation, low viscosity raises CBF and lowers AVDO₂** YW p. 2978.

Table 2 · Status of cerebral blood flow, cerebral blood volume and arteriovenous difference of oxygen under various clinical conditions — reproduced in full from Youmans & Winn 8e, Table 384.11, p. 2978.

Feature with primary reduction	CBF	CBV (ICP)	AVDO₂
Decreased $CMRO_2$ (within physiologic limits)	↓	↓	=
Low CPP (autoregulation intact)	=	↑	=
Low CPP (autoregulation defective)	↓	↓	↑
Lower blood viscosity (autoregulation intact)	=	↓	=
Low blood viscosity (autoregulation defective)	↑	=	↓
Low $PaCO_2$ (hyperventilation)	↓	↓	↑
Small cerebral artery diameter (cerebral vasospasm)	↓	↑	↑

(c) Intracranial pressure waves [2]

9. The normal waveform — three components, then five peaks

- **The three major components.** "The ICP waveform is normally pulsatile and can be divided into **three major components**. The **average level** is commonly referred to as the ICP, whereas **rhythmic fluctuations** in pressure superimposed on this level are associated with **cardiac** and **respiratory** activity. To completely describe ICP, one should specify the **magnitude of the baseline or 'steady-state' level** and the **amplitude and periodicity of the pulsatile components**" YW p. 472.e2.
- **Cardiac component.** Created by cyclical changes in cerebral blood volume. **Left ventricular contraction contributes the cardiac component, at a frequency similar to the peripheral arterial pulse.** The transmitting vessels remain unsettled — early studies implicated the choroid plexus and pial arteries, later analysis the **high-compliance venous blood vessels** YW p. 472.e2.
- **Respiratory component.** Arises from fluctuations in arterial blood pressure and cerebral venous outflow across the respiratory cycle, generated by thoracic and abdominal pressure changes. **During inspiration arterial blood pressure falls and the cerebral vein-to-central venous pressure gradient increases; venous return therefore increases on**

inspiration with a concomitant drop in total CBV YW p. 472.e2.

- **Five peaks, three constant.** At higher resolution "the waveform of highest frequency can be seen to consist of as many as **five smaller peaks**. Three of these are relatively constant — the **percussion wave (W1)**, the **tidal wave (W2)** and the **dicrotic wave (W3)**." **The percussion wave, the most constant in amplitude, derives from pulsations in large intracranial arteries. The tidal wave has a more variable shape and is thought to arise from brain elastance. The tidal and dicrotic waves are separated by the dicrotic notch, which corresponds to the dicrotic notch in the arterial pulse waveform** YW p. 472.e2.
- **Why the pulsatile components matter clinically.** "Changes in these pulsatile components can be **one of the earliest signs that the ICP is beginning to rise**, as a reflection of the increased conductance of pressure waves through a 'tightening' brain" YW p. 472.e2.

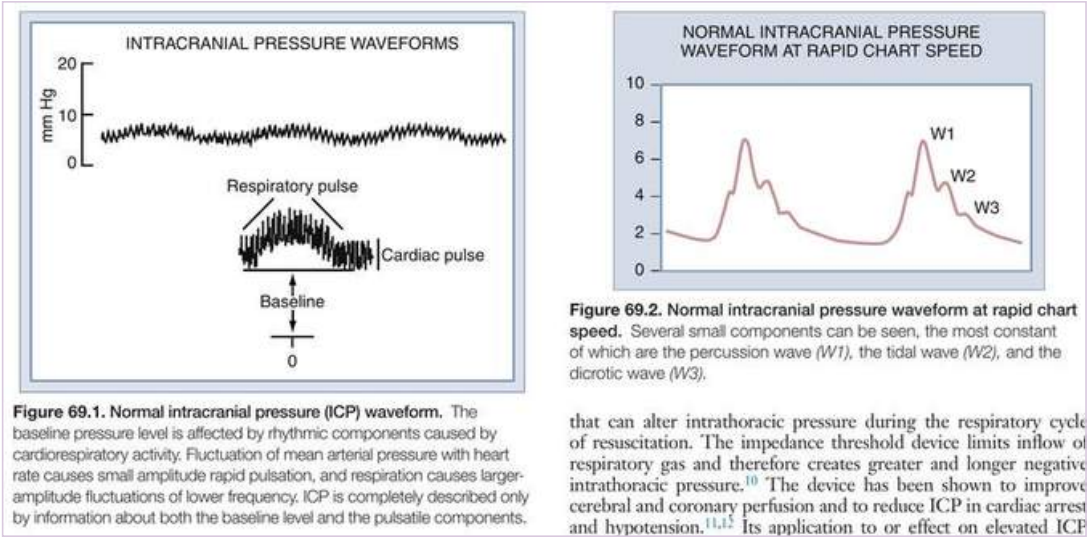


Figure 69.1. Normal intracranial pressure (ICP) waveform. The baseline pressure level is affected by rhythmic components caused by cardiorespiratory activity. Fluctuation of mean arterial pressure with heart rate causes small amplitude rapid pulsation, and respiration causes larger-amplitude fluctuations of lower frequency. ICP is completely described only by information about both the baseline level and the pulsatile components.

Figure 69.2. Normal intracranial pressure waveform at rapid chart speed. Several small components can be seen, the most constant of which are the percussion wave *(W1)*, the tidal wave *(W2)*, and the dicrotic wave *(W3)*.

that can alter intrathoracic pressure during the respiratory cycle of resuscitation. The impedance threshold device limits inflow of respiratory gas and therefore creates greater and longer negative intrathoracic pressure.[10] The device has been shown to improve cerebral and coronary perfusion and to reduce ICP in cardiac arrest and hypotension.[11,12] Its application to or effect on elevated ICP

*Reproduced from Youmans & Winn 8e, Fig. 69.1, p. 472.e2 — Label when you reproduce it: the ICP trace with the y-axis in mm Hg (0-20); mark the **baseline** level, the small-amplitude rapid **cardiac pulse** and the larger-amplitude lower-frequency **respiratory pulse**. State that ICP is completely described only by information about both the baseline level and the pulsatile components.*

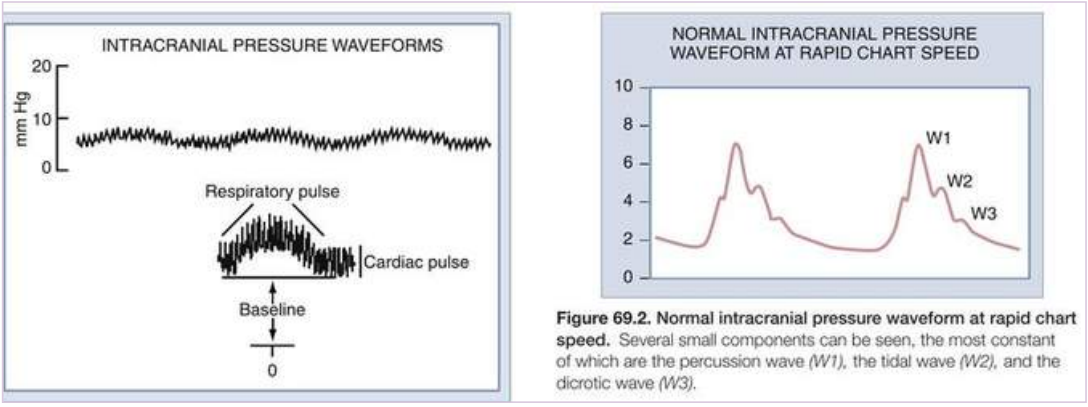


Figure 69.2. Normal intracranial pressure waveform at rapid chart speed. Several small components can be seen, the most constant of which are the percussion wave *(W1)*, the tidal wave *(W2)*, and the dicrotic wave *(W3)*.

*Reproduced from Youmans & Winn 8e, Fig. 69.2, p. 472.e2 — Label when you reproduce it: the same waveform at rapid chart speed, y-axis 0-10 mm Hg; mark **W1 the percussion wave** (from large intracranial artery pulsation, most constant in amplitude), **W2 the tidal wave** (from brain elastance, variable shape), the **dicrotic notch**, and **W3 the dicrotic wave**.*

10. Lundberg's pathological waves — A, B and C

- **Origin of the classification.** Lundberg published results from a large series of patients in which he described "several of the fundamental concepts used today in clinical ICP monitoring, including the **Lundberg A, B, and C waves**" YW p. 472.e1. Youmans is careful to add that **these waves "do not represent part of steady-state ICP dynamics" and "their pathologic significance remains to be defined"** YW p. 472.e7.

- **A waves (plateau waves).** "Characterised by increases in ICP that are **sustained for several minutes** and then **return spontaneously to a new baseline, which is usually slightly higher than the preceding one**." Lundberg postulated they result from an increase in CBV caused by vasodilation. **Rosner** postulated that plateau waves are a **normal compensatory response to decreases in CPP** and that effective management therefore involves **vasopressors**. Rosner's **four phases**: the **drift phase** (a decline in CPP triggers vasodilation), the **plateau phase** (vasodilation has raised ICP to the plateau level), the **ischaemic response phase** (the sudden CPP reduction causes enough cerebral ischaemia to trigger brainstem vasomotor centres to mount a **Cushing response**), and the **resolution phase** (CPP is restored) YW p. 472.e7.
- **B waves.** "**Short elevations of a modest nature (10 to 20 mm Hg) that occur at a frequency of 0.5 to 2 Hz** and are thought to relate to vasodilation secondary to respiratory fluctuations in PaCO₂. However, they are seen in ventilated patients, who in theory should have a constant PaCO₂." Transcranial Doppler studies in humans show that **B waves occur secondary to intracranial vasomotor waves causing variations in CBF**; the physiological basis of the cyclical change in vasomotor tone is not clear. B waves "are believed to reflect increased ICP in a **qualitative** manner" YW p. 472.e7.
- **C waves.** "**More rapid sinusoidal fluctuations occurring approximately every 10 seconds and corresponding to Traube-Hering-Mayer fluctuations in arterial pressure**"; like B waves they reflect raised ICP only qualitatively YW p. 472.e7.

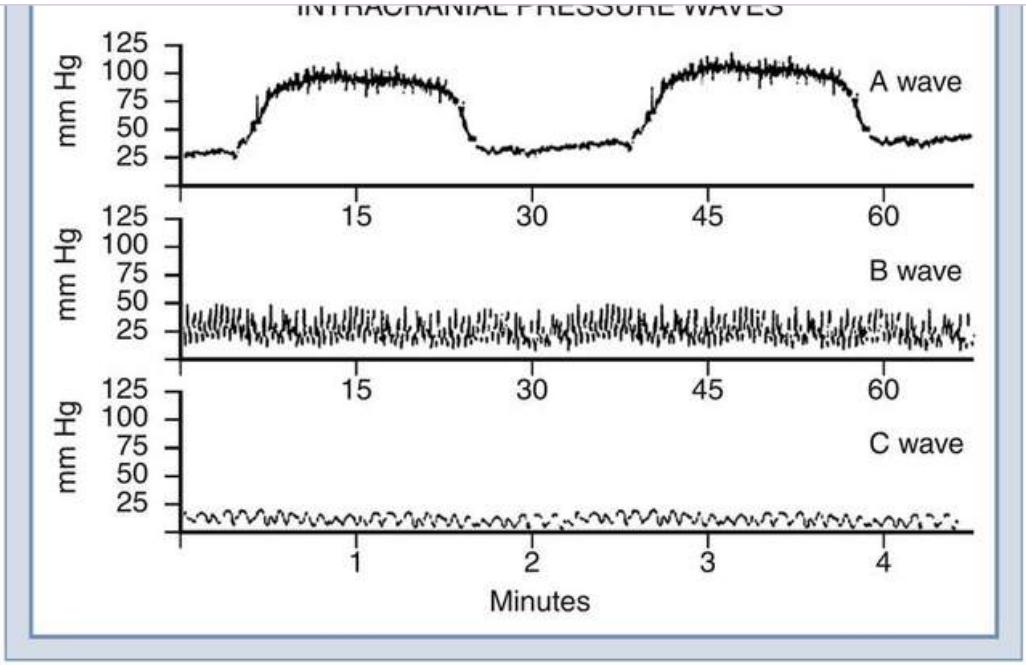


Figure 69.8. Lundberg's classification of intracranial pressure (ICP) waves. A waves, or plateau waves, are prolonged stable increases in ICP that spontaneously recover to a new higher baseline. B waves are short, modest elevations in ICP, and C waves are rapid sinusoidal fluctuations. It is important to note that these waves do not represent part of steady-state ICP dynamics. Their pathologic significance remains to be defined.

*Reproduced from Youmans & Winn 8e, Fig. 69.8, p. 472.e7 — Label when you reproduce it: three stacked traces, all y-axis 25-125 mm Hg. Top — **A wave (plateau wave)**, x-axis in minutes to 60, showing prolonged stable rises that recover spontaneously to a new, higher baseline. Middle — **B wave**, same time base, short modest elevations. Bottom — **C wave**, x-axis 1-4 minutes, rapid low-amplitude sinusoidal fluctuations. Annotate A-wave phases: drift, plateau, ischaemic response (Cushing), resolution.*

Table 3 · Intracranial pressure waves at a glance — from Youmans & Winn 8e, Ch. 69 pp. 472.e1-472.e2 and 472.e6-472.e7 (Figs. 69.1, 69.2 and 69.8).

Wave	Period / frequency	Amplitude	Mechanism	Significance
Baseline (mean ICP)	—	7-15 mm Hg supine; upper limit of normal 15-20	Steady-state balance of CSF formation, storage and absorption	Treat when persistently >22 mm Hg (BTF)
Respiratory pulse	Respiratory rate	Larger amplitude, lower frequency than cardiac	Arterial pressure and cerebral venous outflow change with thoracoabdominal pressure; venous return rises on inspiration	Altered by mechanical ventilation and intrathoracic disease
Cardiac pulse	Heart rate	Small amplitude, rapid	Left ventricular contraction → cyclical CBV change; probably transmitted by high-compliance veins	Its **amplitude** rises as compliance falls
W1 percussion	Within one cardiac cycle	Most constant	Pulsation in large intracranial arteries	Reference peak
W2 tidal	Within one cardiac cycle	Variable	**Brain elastance**	The compliance-sensitive peak
W3 dicrotic	After the dicrotic notch	Small	Corresponds to the arterial dicrotic notch	—
Lundberg **A** (plateau)	Several minutes	Rises to 50-100 mm Hg	Vasodilation raising CBV after a fall in CPP; Rosner's drift → plateau → ischaemic response (Cushing) → resolution	Ominous; recovers to a **new higher baseline**
Lundberg **B**	0.5-2 Hz	10-20 mm Hg	Intracranial vasomotor waves altering CBF (TCD evidence); classically PaCO₂ fluctuation, but seen in ventilated patients	Qualitative marker of raised ICP
Lundberg **C**	~every 10 s	Small, sinusoidal	Traube-Hering-Mayer fluctuations in arterial pressure	Qualitative marker of raised ICP

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **The BBB is a neurovascular unit of six components** — microvascular endothelium, basement membrane, neurons, astrocytes, pericytes and microglia (plus the extracellular matrix) — **not simply a layer of tight junctions**.
- **Three ultrastructural differences from peripheral endothelium: no fenestrations with low pinocytotic activity; ubiquitous tight junctions; a much higher mitochondrial concentration.**
- **Tight junctions = occludin + claudins (3, 5, 12) + JAMs, scaffolded by ZO-1/2/3; adherens junctions = VE-cadherin + catenins + vinculin + actinin.**
- **The BBB excludes most molecules >180 Da that are hydrophilic or charged**; gases, small lipophiles (methanol, ethanol) and nutrients (glucose, ascorbate) cross freely.
- **Four transport mechanisms: paracellular aqueous, transcellular lipophilic, adsorptive transcytosis (the route HIV-1 takes), and saturable transport (receptor-mediated and channel-mediated).**
- **The enzymatic barrier is examinable: γ-glutamyl transpeptidase, alkaline phosphatase and aromatic L-amino acid decarboxylase**, plus CYP enzymes — which is why carbamazepine can be biotransformed into a proconvulsant metabolite.
- **GLUT1 is abluminal (3-4× the luminal level); P-glycoprotein/MDR1 is luminal** — polarity, not just permeability, decides what reaches the neuron.
- **>99% of brain capillaries have a BBB; the exceptions are the circumventricular organs — median eminence, pituitary, choroid plexus, subfornical organ, lamina terminalis and area postrema — which exist for peripheral chemosensing.**
- **The blood-CSF barrier sits at choroid plexus *epithelium*, not endothelium, and its surface area is ~1000-fold smaller than the BBB's** — which is why it contributes little to drug entry into parenchyma.

- **Autoregulation works at the precapillary arteriole in response to transmural pressure over a MAP of 60-150 mm Hg** — and is right-shifted and linearised after TBI.
- **1 torr of PaCO₂ = 3% change in CBF**; CO₂ works through perivascular H⁺, not through molecular CO₂.
- **ICP has three components — baseline, cardiac pulse, respiratory pulse — and at rapid chart speed W1 percussion, W2 tidal (brain elastance), W3 dicrotic.** Rising pulse amplitude is an *early* sign of a tightening brain.
- **Lundberg A = plateau waves over minutes recovering to a new higher baseline (Rosner: drift, plateau, ischaemic response/Cushing, resolution); B = 10-20 mm Hg at 0.5-2 Hz from vasomotor waves; C = every ~10 s, Traube-Hering-Mayer.**
- **Youmans' caveat is worth a mark: A, B and C waves are not part of steady-state ICP dynamics and their pathological significance "remains to be defined."**

Pages read for this answer — Youmans & Winn 8e: 471.e1, 471.e2, 471.e3, 471.e5, 471.e6, 471.e8, 471.e10, 472.e1, 472.e2, 472.e5, 472.e7, 472.e10, 473.e1, 473.e2, 972, 2978, 3207.e11, 3207.e12, 3207.e13, 3207.e14, 3207.e15, 3207.e16

a) Draw a diagram of blood brain barrier. [4]
b) Monro Kellie doctrine. [3]
c) Lund hypothesis for cerebral perfusion pressure management. [3]

LONG | MAY 2024 · Paper I · Q7 | 10 marks

Also asked as: Neurophysiology — also asked as OCT 2023 · Paper I · Q1 (a: Blood brain barrier [5]; b: Regulation of cerebral blood flow [3]; c: Intracranial pressure waves [2]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 68 *The Blood-Brain Barrier*, §Functional Anatomy of the Blood-Brain Barrier and §Transport Across the Blood-Brain Barrier, pp. 471.e1-471.e6, 471.e8, 471.e10 (Figs. 68.1, 68.5, pp. 471.e2, 471.e8; Box 68.1, p. 471.e2; Table 68.1, p. 471.e5). Supplementary: Ch. 70 *Cerebral Edema*, §Monroe-Kellie Doctrine, §Blood-Brain Barrier and §Glymphatic System, pp. 473, 473.e1-473.e2 (Figs. 70.1, 70.4, pp. 473.e2, 473.e6; Table 70.1, p. 473.e3); Ch. 69 *Physiology of the CSF and Intracranial Pressure*, §Historical Considerations, §Steady-State ICP and CSF Dynamics, §VBLOOD and §VBRAIN, pp. 472, 472.e1, 472.e3-472.e5, 472.e9-472.e11 (Table 69.2, p. 472.e9); Ch. 388 *Invasive Physiologic Monitoring for TBI*, pp. 3028, 3031 (Fig. 388.1, p. 3028); Ch. 384 *Clinical Pathophysiology of TBI*, pp. 2978-2979 (Figs. 384.4-384.5, pp. 2977-2978); Ch. 387 *Management of Severe Traumatic Brain Injury*, §Lund therapy, p. 3010; Ch. 71 *Extracellular Fluid Movement and Clearance in the Brain*, p. 474.e4 (Fig. 71.3, p. 474.e4); Ch. 37 *Intracranial Pressure Monitoring*, p. 288.

(a) Draw a diagram of the blood-brain barrier [4]

1. What to draw — the neurovascular unit, with every cell named

- **Youmans' definition dictates the diagram.** "The blood-brain barrier (BBB) is a '**neurovascular unit**' composed of **microvascular endothelium, basement membrane, neurons, and neuroglial structures: astrocytes, pericytes, and microglia**" YW p. 471.e1. Draw the capillary in cross-section or longitudinal section and put all six elements on it; a diagram of endothelium plus tight junctions alone will lose marks.
- **What sits where.** "The anatomic BBB is formed by a **monolayer of microvascular endothelial cells that line the intraluminal space of brain capillaries and are supported by astrocyte end-feet**. The low permeability that characterizes the BBB is conferred in part by **tight packing of ECs and formation of TJs and adherens junctions**. The EC layer has a **luminal** (inside the vessel) and **abluminal** membrane separated by **300 to 500 nm of cytoplasm** between the blood and brain. The luminal surface is in contact with the blood supply, whereas on the abluminal surface **ECs are enveloped in a basement membrane and separated into regions associated with a pericyte**" YW p. 471.e1.
- **The Ch. 70 version, stated for the diagram.** "The blood-brain barrier is composed of a **basement membrane, closely apposed astrocytic foot processes, pericytes, and vascular endothelial cells**. Under normal conditions the tight junctions between endothelial cells restrict the passage of most **large (greater than 180 Da), hydrophilic, and/or charged molecules** by restricting paracellular movement." A **perivascular space filled with small amounts of cerebrospinal fluid is found between these layers** — draw it, because it is the entry to the glymphatic pathway [YW pp. 473.e1, 473.e2].

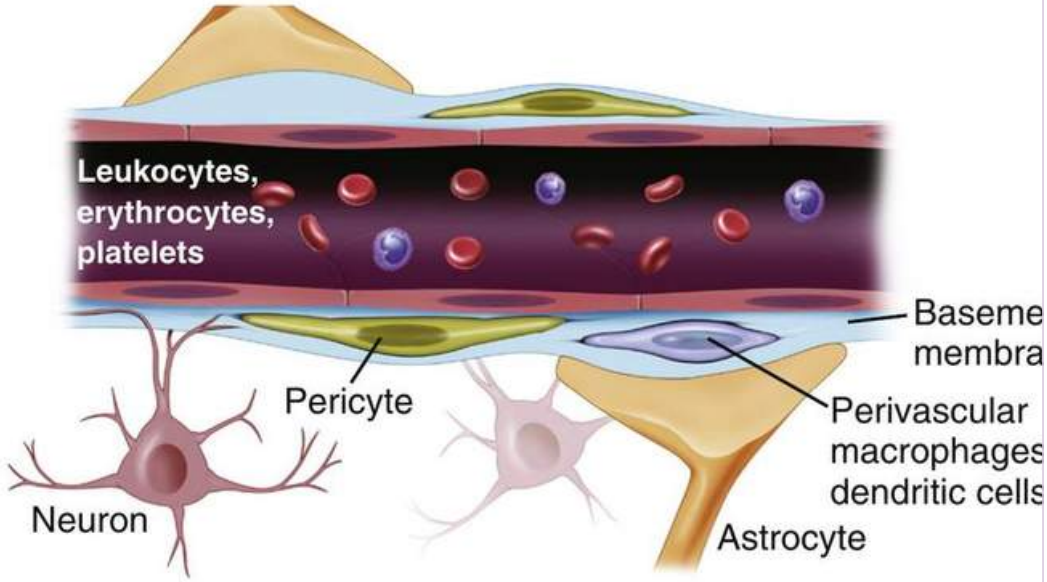


Figure 68.1. Schematic of a "neurovascular unit," which consists of endothelial cells, astrocytes, pericytes, macrophages, microglia, neurons, the basement membrane, and the extracellular matrix.

*Reproduced from Youmans & Winn 8e, Fig. 68.1, p. 471.e2 — Label when you reproduce it: this is the diagram to reproduce. Label the lumen with **leukocytes, erythrocytes and platelets**; the **endothelial cell** monolayer; the **basement membrane**; the **pericyte** embedded in that basement membrane; **perivascular macrophages and dendritic cells**; the **astrocyte** with its end-foot apposed to the vessel; the **neuron**; and — from the caption — **microglia** and the **extracellular matrix**. Add the **tight junction** between adjacent endothelial cells and the **perivascular (CSF-containing) space**.*

2. The eight things to write on the diagram as annotations

- **Tight junction composition.** TJs regulate paracellular transport and consist of **occludin, claudin and junctional adhesion molecules**. The detailed schematic names **claudin-3, -5 and -12** as the backbone (claudins form dimers and bind homotypically to claudins on adjacent cells to produce the primary seal), **occludin** as the dynamic regulatory protein whose presence correlates with increased transendothelial electrical resistance and decreased paracellular permeability, **JAMs** (which with **PECAM** regulate leukocyte migration), and the accessory scaffolds **ZO-1, ZO-2, ZO-3, cingulin and 7H6** [YW pp. 471.e1, 471.e8].
- **Adherens junction composition.** AJs "mediate cell spacing and transmit cytoskeletal signals and include **cadherin, catenins, vinculin, and actinin**"; **VE-cadherin** sits at the adherens junction near the basolateral side and is **not specific for cerebral endothelial junctions** [YW pp. 471.e2, 471.e8].
- **No fenestrations, rare pinocytosis, abundant mitochondria.** "The cytoplasm of brain microvascular ECs has **rare pinocyte vesicles**… These ECs also contain a **greater concentration of mitochondria**, presumably to generate the greater energy needed to actively transport nutrients" YW p. 471.e2. Youmans lists the three differences from peripheral endothelium as **(1) no fenestrations with low pinocytotic activity, (2) ubiquitous tight junctions, (3) much higher mitochondrial concentration** YW p. 471.e5.
- **Astrocyte end-feet cover >90%.** "Astrocytes have end-feet that border the basement membrane of parenchymal vessels and **densely surround TJs, reducing the size of the gap between ECs**… **More than 90% of astrocyte foot processes surround ECs**" YW p. 471.e2. Draw **aquaporin-4** on the end-foot: "BBB polarity is additionally maintained by astrocytes, in which distribution of **aquaporin-4** plays a significant role in water absorption and potentially in edema formation" YW p. 471.e2.
- **Pericyte coverage 20-30%.** Pericyte cellular projections "penetrate the basal lamina and cover **20% to 30% of the microvascular circumference**"; they are most abundant on venules, share a common basement membrane with brain ECs, act as a **secondary BBB** by monitoring the perivascular space and phagocytosing unwanted substances, synthesise

laminin and fibronectin, and express **PDGFR** YW p. 471.e3.

- **The polarity arrows.** Mark **GLUT1 abluminal** (three to four times higher than luminal) and **P-glycoprotein (MDR1) luminal**; **Na⁺,K⁺-ATPase, Na⁺/H⁺ exchanger and Na⁺-amino acid transporter abluminal**; **alkaline phosphatase and γ-glutamyl transpeptidase luminal** YW p. 471.e2.
- **The enzymatic barrier.** Write in the box: **"three main catalytic agents — γ-glutamyl transpeptidase, alkaline phosphatase, aromatic L-amino acid decarboxylase — concentrated in cerebral vessels,"** plus CYP enzymes (CYP3A4, CYP2D6, CYP2E1, CYP2C9, CYP2C19) performing phase I oxidation, phase II conjugation (UGT, SULT, GST) and phase III elimination through multidrug transporters, regulated by **PXR and RXR** YW p. 471.e2.
- **Extracellular matrix.** Label **laminin, collagen type IV and integrins** as the anchoring proteins that mediate polarity at the EC-astrocyte interface and **upregulate TJ protein expression** YW p. 471.e3.

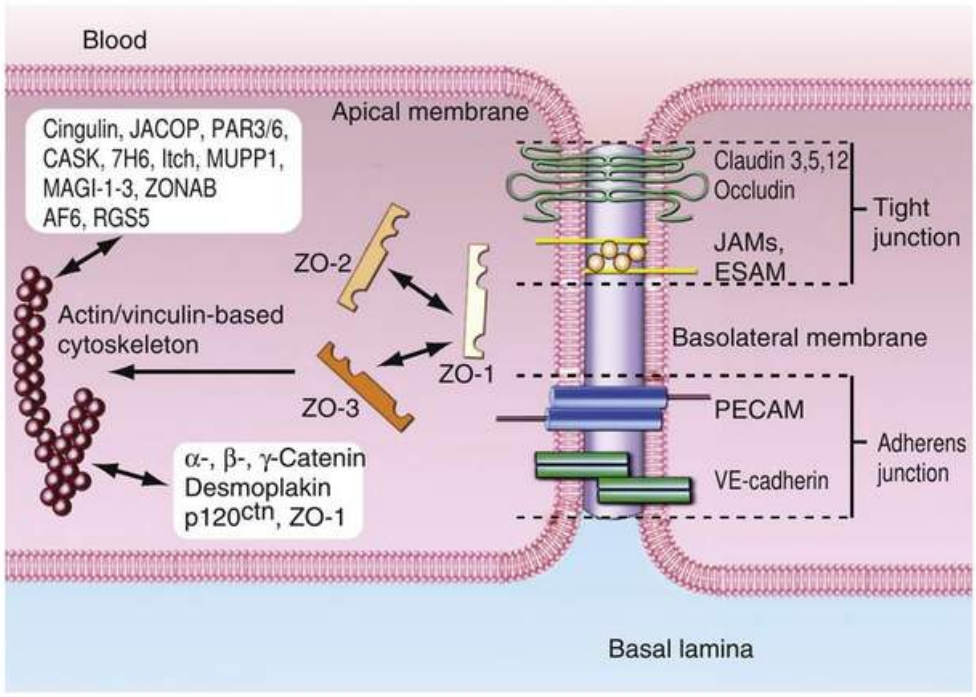


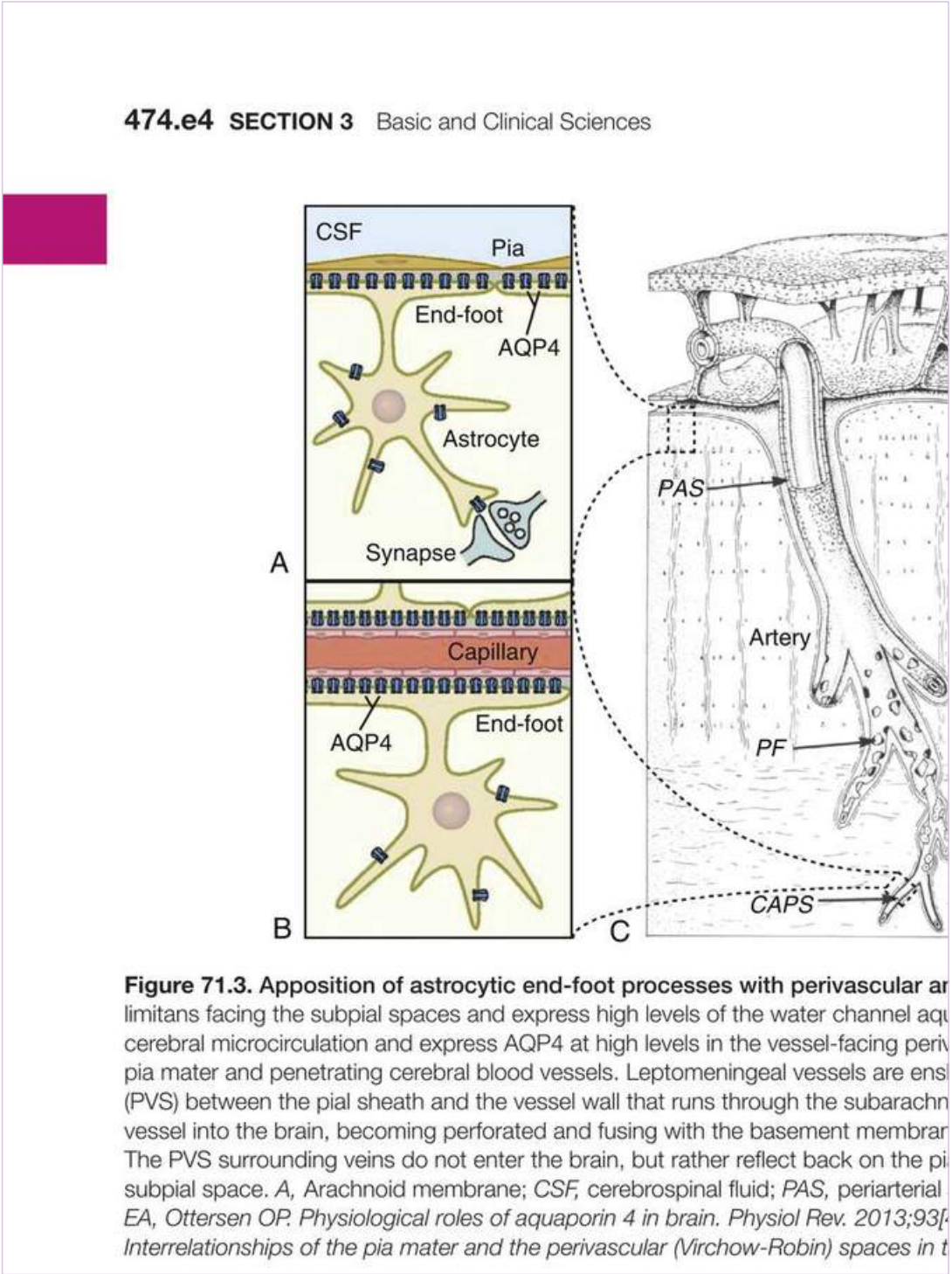
Figure 68.5. Schematic of a tight junction at the blood-brain barrier (BBB). Claudins make up the backbone of the tight junction strands, form dimers, and bind homotypically to claudins on adjacent cells to produce the primary seal of the tight junction. Occludin functions as a dynamic regulatory protein the presence of which at the BBB is correlated with increased transendothelial electrical resistance and decreased paracellular permeability. Junctional adhesion molecules (JAMs) are localized at the tight junction and, in association with platelet endothelial cellular adhesion molecule-1 (PECAM), regulate leukocyte migration across the BBB. Several accessory proteins also contribute to its structural support, such as zona occludens-1 (ZO-1) through ZO-3, cingulin, and 7H6. Adherens junctions are located near the basolateral side of the endothelial cells and are not specific for cerebral endothelial junctions. *ESAM,* Endothelial cell–selective adhesion molecule; *VE,* vascular endothelial.

*Reproduced from Youmans & Winn 8e, Fig. 68.5, p. 471.e8 — Label when you reproduce it: the molecular blow-up of one tight junction — lumen (Blood) above the **apical membrane**; **claudin 3, 5, 12** and **occludin** spanning the intercellular cleft as the **tight junction**; **JAMs** and **ESAM**; the cytoplasmic scaffold (**ZO-1, ZO-2, ZO-3, cingulin, 7H6, MAGI-1-3, MUPP1, PAR3/6, CASK, AF6**) linking to the **actin/vinculin cytoskeleton**; then the **basolateral membrane** with **PECAM** and **VE-cadherin** at the **adherens junction** with **α-, β-, γ-catenin, desmoplakin, p120^{ctn}**; and the **basal lamina** beneath.*

3. Add the numbers, then add the exits

- **Geometry.** Brain microvasculature total surface area **20 m²**; cerebral capillary endothelial surface area **100 cm²/g tissue**; total length **650 km**; inner capillary lumen **6 µm**; cortical capillaries **20 µm apart** YW p. 471.e5. Ch. 70 gives capillary network total area **12-20 m²** and mean intercapillary distance **~40 microns**, with the brain consuming **~20% of the total circulating blood volume** while being only **2%-3% of total body mass** YW p. 473.e1.
- **Where the barrier is absent — put these outside your diagram and name them.** "**More than 99% of brain**

capillaries have a BBB, with the exception of the circumventricular organs. Circumventricular organs are important for **peripheral chemosensing** and include the **median eminence, pituitary gland, choroid plexus, subfornical organ, lamina terminalis, and area postrema**" YW p. 471.e5.



*Reproduced from Youmans & Winn 8e, Fig. 71.3, p. 474.e4 — Label when you reproduce it: (A) the subpial level — **CSF**, **pia**, an astrocyte **end-foot** expressing **AQP4** at high density on the vessel-facing surface, and a **synapse**; (B) the capillary level — **AQP4** on the end-feet flanking the capillary; (C) the **perivascular (Virchow-Robin) space** between the pial sheath and the penetrating artery, becoming perforated and fusing with the basement membrane before the terminal capillary bed, with the **perivenous** return route. This is the efflux limb that complements the BBB's influx.*

- **Add the efflux limb — glymphatics.** "Whereas the blood-brain barrier represents a fluid **input** pathway to brain interstitial tissue, the glymphatic system represents a fluid pathway for **eliminating** excess brain fluid and solutes." CSF is driven along **periarterial (Virchow-Robin) spaces** by arterial pulsation, a pressure gradient, respirations and

vasomotor motility; it enters the parenchyma **through aquaporin-4 water channels on astrocyte foot processes**, moves **by convection to the perivenous spaces of the deep cerebral veins**, and drains via **cervical lymphatics, arachnoid granulations and the perineural space of cranial nerves** [YW pp. 473.e1, 473.e2].

Table 1 · Components of the blood-brain barrier and what each contributes — from Youmans & Winn 8e, Ch. 68 pp. 471.e1-471.e5 and Ch. 70 pp. 473.e1-473.e2.

Component	Structural contribution	Functional contribution	Number to quote
Microvascular endothelium	Monolayer lining brain capillaries; luminal and abluminal membranes 300-500 nm apart; no fenestrations	Physical barrier; charge and transporter polarity; enzymatic barrier	Excludes most hydrophilic/charged molecules >180 Da
Tight junctions	Occludin + claudin-3/-5/-12 + JAMs, scaffolded by ZO-1/2/3, cingulin, 7H6	Restrict paracellular transport of large or hydrophobic molecules	Occludin presence ↑ transendothelial electrical resistance
Adherens junctions	VE-cadherin, α/β/γ-catenins, vinculin, actinin, desmoplakin, p120^{ctn}	Cell spacing; transmit cytoskeletal signals	Not specific to cerebral endothelium
Basement membrane	Envelops abluminal endothelium; shared with pericyte	Mechanical support	—
Pericytes	In the endothelial basement membrane; commonest on venules	Secondary BBB, phagocytosis of the perivascular space; CBF regulation; no-reflow phenomenon; PDGFR-expressing	Projections cover **20-30%** of microvascular circumference
Astrocytes	End-feet on the parenchymal vessel basement membrane, densely surrounding tight junctions	Induce *and* maintain barrier properties; AQP4-mediated water handling; adrenergic, cholinergic, peptidergic contacts	**>90%** of astrocyte foot processes surround ECs
Microglia	Perivascular resident macrophages	Immunosurveillance; antigen presentation to T cells; cytokine secretion	Central in MS, stroke, trauma, Alzheimer amyloid clearance
Neurons	Contact astrocytes and their ECs	Predominantly **enzymatic** modulation; noradrenergic, serotoninergic, cholinergic, GABAergic innervation	—
Extracellular matrix	Laminin, collagen IV, integrins	Physical stability; polarity at the EC-astrocyte interface; upregulates TJ proteins	Its disruption impairs BBB integrity
Mitochondria	Concentrated in brain ECs	Energy for active transport	Much higher than peripheral endothelium

(b) Monro-Kellie doctrine [3]

4. The doctrine in the original words, then in the equation

- **Monro (Edinburgh, turn of the 19th century).** "For, as the substance of the brain, like that of other solids of our body, is nearly incompressible, **the quantity of blood within the head must be the same, or very nearly the same at all times**, whether in health or disease, in life or after death, those cases only excepted in which water or other matter is effused, or secreted from the blood vessels; for in these a quantity of blood, equal in bulk to the effused matter, will be pressed out of the cranium" YW p. 472.e1.
- **Kellie (Medico-Chirurgical Society of Edinburgh).** "If these premises be true, it does not then appear very conceivable how any portion of the circulating fluid can ever be **withdrawn from within the cranium, without its place being simultaneously occupied by some equivalent**; or how anything new or exuberant can be intruded **without an equivalent displacement**." "These ideas, which were formalized physiologically later, became known as the

Monro-Kellie doctrine" YW p. 472.e1.

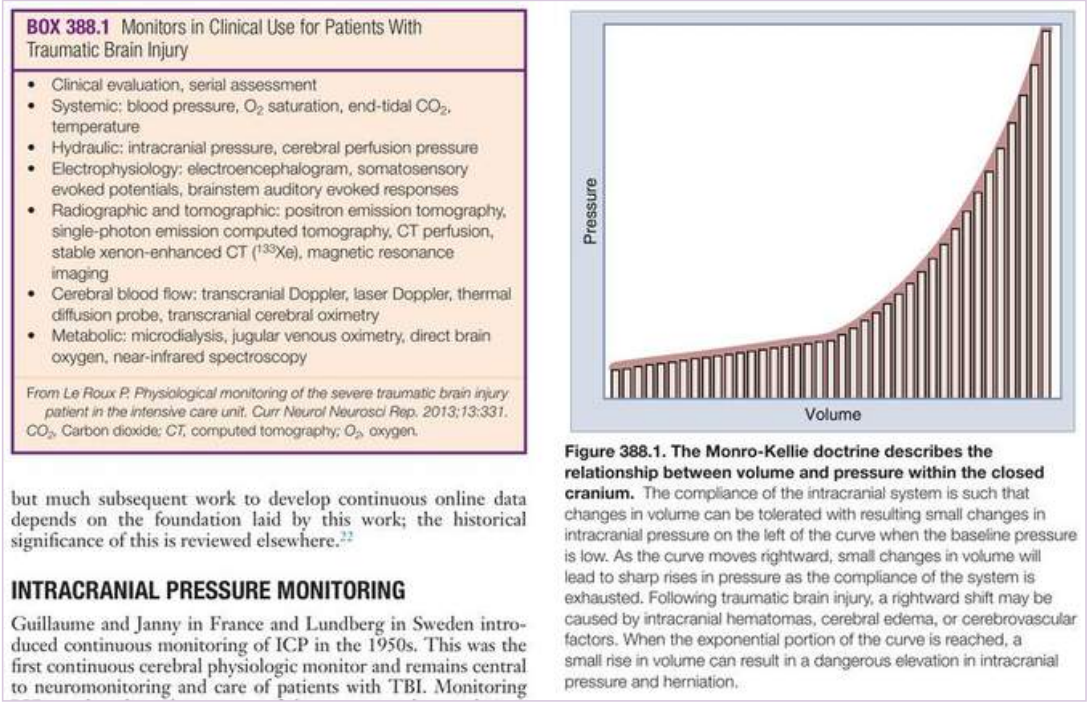
- **Youmans' equation — learn it in this form.**
  - **V1_{CSF} + V1_{BLOOD} + V1_{BRAIN} + V1_{OTHER} = V_{INTRACRANIAL SPACE} = V2_{CSF} + V2_{BLOOD} + V2_{BRAIN} + V2_{OTHER}** where V_{OTHER} is "any abnormal component, such as a tumor" [YW pp. 472, 472.e4].
  - **"This volume must be constant for a given individual"** YW p. 472.e1.
  - **"The ability of the dural coverings to distend is very limited, so any change in volume of one of the three intracranial components must occur at the expense of the other two if ICP is to be maintained"** YW p. 472.e4.
- **The three-part formulation from Ch. 37.** The Monro-Kellie doctrine states that **(1) the brain is housed in the non-expandable skull; (2) brain parenchyma is fairly non-compressible; and (3) the volume of blood is relatively constant, and outflow of venous blood is necessary for the inflow of arterial blood.** "Later, CSF was recognized as a component of brain volume in addition to brain parenchyma and blood, and it was incorporated into the doctrine" YW p. 288.
- **The Ch. 70 restatement.** "This doctrine defines the cranial vault (calvaria) as a **fixed-volume structure**… Per the Monroe-Kellie doctrine, **increases in any of the three components results in a corresponding decrease in the other components**" YW p. 473.e1.
- **Ch. 388 adds compliance.** "The Monro-Kellie doctrine describes the relationship between volume and pressure within the closed cranium… **The compliance of the intracranial system is such that** changes in volume can be tolerated with resulting small changes in intracranial pressure on the left of the curve when the baseline pressure is low. As the curve moves rightward, small changes in volume will lead to **sharp rises in pressure as the compliance of the system is exhausted**" YW p. 3028.

5. Volumes, the pressure-volume consequence, and the exceptions

- **Volumes to quote.** Of the typically **1500 mL** intracranial space in the adult, **approximately 87% is brain, 9% compartmental CSF (ventricles, cisterns and subarachnoid space) and 4% blood** YW p. 472.e3. Ch. 70 gives absolute figures: **brain parenchyma 1250-1500 mL, CSF 125-150 mL, blood 125-150 mL** YW p. 473.e1. The extracellular space is in direct contact with the CSF and forms **approximately 15% of the total brain volume**; total CSF includes compartmental CSF plus the extracellular space. Measured **cranial CSF volume in humans: mean 164.5 mL, range 62.2-267 mL**; **ventricular volume mean 31.9 mL, range 7.49-70.5 mL** YW p. 472.e3.
- **Non-linearity is the doctrine's direct corollary.** "The relationship between intracranial volume and ICP is **not linear** … In the normal adult, this relationship describes a **hyperbolic** curve" with a flat **period of spatial compensation** and a steep **period of spatial decompensation**; above **50 mm Hg** and as ICP approaches MAP the curve flattens again, "thus the complete curve is not hyperbolic but rather **sigmoid**" YW p. 472.e5.
- **Which compartment buffers, and how fast.** "Although the **brain occupies 80% of the intracranial space**, this volume is effectively available for compensation **when increases in V_{OTHER} occur slowly**. With more rapid changes, the brain shifts and **herniations** are more likely to occur. Although blood and CSF occupy less of the intracranial space, **their total volume can be reduced more rapidly, and therefore they usually change first** in the compensation" YW p. 472.e6.
- **The steady-state equation that follows. ICP = (I_f × R_o) + P_d** — steady-state ICP is proportional to the rate of CSF formation, the resistance to CSF absorption and the dural sinus pressure. **(I_f × R_o) contributes only about 10% of total ICP**, the remainder being dural sinus pressure — which is why outflow resistance must increase markedly to raise ICP significantly, while **much smaller elevations of sagittal sinus pressure from venous sinus obstruction are transmitted directly to the CSF system** [YW pp. 472.e4, 472.e5].
- **Where the doctrine breaks down.** "**Craniectomy essentially nullifies the Monroe-Kellie doctrine** that governs" intracranial volume-pressure relations YW p. 3105.e1. Youmans' practical use of that fact: "Based on the Monroe-Kellie doctrine, **craniectomy to expand overall cranial volume can be performed to maintain blood flow and prevent herniation and patient death**" YW p. 473.e10. It also explains why **PRx becomes unreliable after decompressive**

craniectomy, since CBF and CBV changes no longer translate into ICP changes once cranial compliance is altered YW p. 3031.

- **The physiological state is dynamic, not static.** "It is important to note that **even the physiologic state is far from static; it is rather a dynamic equilibrium**. Constant changes induced by the heartbeat, systemic blood pressure, fluid status, and intrathoracic pressure invoke transient changes within the intracranial compartment that are considered part of the steady state" YW p. 472.e4.



BOX 388.1 Monitors in Clinical Use for Patients With Traumatic Brain Injury

- Clinical evaluation, serial assessment
- Systemic: blood pressure, O_2 saturation, end-tidal CO_2, temperature
- Hydraulic: intracranial pressure, cerebral perfusion pressure
- Electrophysiology: electroencephalogram, somatosensory evoked potentials, brainstem auditory evoked responses
- Radiographic and tomographic: positron emission tomography, single-photon emission computed tomography, CT perfusion, stable xenon-enhanced CT (^{133}Xe), magnetic resonance imaging
- Cerebral blood flow: transcranial Doppler, laser Doppler, thermal diffusion probe, transcranial cerebral oximetry
- Metabolic: microdialysis, jugular venous oximetry, direct brain oxygen, near-infrared spectroscopy

From Le Roux P. Physiological monitoring of the severe traumatic brain injury patient in the intensive care unit. Curr Neurol Neurosci Rep. 2013;13:331.
CO_2, Carbon dioxide; CT, computed tomography; O_2, oxygen.

but much subsequent work to develop continuous online data depends on the foundation laid by this work; the historical significance of this is reviewed elsewhere.[22]

INTRACRANIAL PRESSURE MONITORING

Guillaume and Janny in France and Lundberg in Sweden introduced continuous monitoring of ICP in the 1950s. This was the first continuous cerebral physiologic monitor and remains central to neuromonitoring and care of patients with TBI. Monitoring

Figure 388.1. The Monro-Kellie doctrine describes the relationship between volume and pressure within the closed cranium. The compliance of the intracranial system is such that changes in volume can be tolerated with resulting small changes in intracranial pressure on the left of the curve when the baseline pressure is low. As the curve moves rightward, small changes in volume will lead to sharp rises in pressure as the compliance of the system is exhausted. Following traumatic brain injury, a rightward shift may be caused by intracranial hematomas, cerebral edema, or cerebrovascular factors. When the exponential portion of the curve is reached, a small rise in volume can result in a dangerous elevation in intracranial pressure and herniation.

Reproduced from Youmans & Winn 8e, Fig. 388.1, p. 3028 — Label when you reproduce it: pressure (y-axis) against volume (x-axis); the flat left-hand limb where compliance absorbs added volume with only small ICP change, the knee, and the exponential right-hand limb where a small volume increment produces a dangerous ICP rise and herniation. Annotate that after TBI the whole curve shifts rightward because of intracranial haematoma, cerebral oedema or cerebrovascular factors.

Table 2 · Therapeutic modalities for compartmental reduction of intracranial pressure — reproduced in full from Youmans & Winn 8e, Table 69.2, p. 472.e9. This is the Monro-Kellie doctrine used as a treatment algorithm.

Compartment	Modalities
V_{CSF}	Acetazolamide; furosemide; corticosteroids; external drainage; internal drainage
V_{BLOOD}	Hyperventilation; head elevation; barbiturates
V_{BRAIN}	Cerebral perfusion pressure management; **Lund protocol**; antihypertensives; fluid resuscitation; corticosteroids; barbiturates; osmotic agents; diuretics; hypothermia
V_{OTHER}	Surgical evacuation; craniectomy

Youmans' footnote to this table: "Although this table provides a conceptual framework, therapies often have multiple methods of action, not all of which can be shown here. For example, barbiturates reduce the metabolic demand of the brain and therefore lower cerebral blood flow and cerebral blood volume while reducing energy demand and therefore limiting edema (action at V_{BLOOD} and V_{CSF})." YW p. 472.e9

(c) Lund hypothesis for cerebral perfusion pressure management [3]

6. The physiological premise — a Starling, not a perfusion, argument

- **The starting principle.** "An intuitive mechanism by which CBV could be lowered is **reduction of CPP**. This principal, coupled with a **reduction of hydrostatic forces in damaged capillary beds**, underlies the **Lund protocol** for raised

ICP" YW p. 472.e11.

- **Stated as a therapeutic aim.** "Another approach, called '**Lund therapy**,' emphasises **reduction in microvascular pressures to minimise oedema formation in the brain**" YW p. 3010.
- **Why it is heretical.** "This protocol, however, **contrasts starkly with the general principles of CPP management** and with recommendations of the Brain Trauma Foundation, which involve maintenance or elevation of CPP in the range of **60 to 70 mm Hg**" YW p. 472.e11.

7. The three goals and their agents

- **Youmans lists them explicitly** YW p. 3010:
  - **1. Preserve a normal colloid osmotic pressure** — by **infusion of albumin and red blood cells**. The original protocol advocated "maintenance of plasma osmolarity with albumin infusion" YW p. 472.e11.
  - **2. Reduce capillary hydrostatic pressure by reducing systemic blood pressure** — with **metoprolol and clonidine** (β-blockade and central α₂-agonism).
  - **3. Reduce cerebral blood volume by vasoconstricting precapillary resistance vessels** — with **low-dose thiopental and dihydroergotamine**. The original protocol advocated "precapillary vasoconstriction with dihydroergotamine," but **"subsequently, the use of dihydroergotamine has been discontinued"** [YW pp. 3010, 472.e11].
- **What Lund therapy deliberately avoids.** "Treatments that would **favour increasing transcapillary filtration of fluid are avoided**, including **cerebrospinal fluid drainage, high-dose (to burst suppression) barbiturates, osmotic diuretics, and high CPP**. **Decompressive craniectomy**, which can also increase oedema formation, **is reserved for a last resort** after all other treatments have failed" YW p. 3010.

8. The evidence, and the counter-argument the examiner wants

- **Trial evidence.** "Initial clinical trials of this approach yielded **outcomes no poorer than those of more conventional techniques**, but equally, **no good trial to date has demonstrated its clinical superiority**." One review identified **10 studies** examining outcome using the Lund protocol; comparing these with other TBI series, "the investigators concluded that the Lund protocol **tends to have a more favourable outcome**" YW p. 472.e11. A Cochrane review of "the Lund concept for severe traumatic brain injury" is cited in the chapter's reference list YW p. 472.e13.
- **The opposing theory — Rosner's vasodilatory cascade.** "An opposing theory to the Lund concept argues that with **elevation of the CPP with vasopressors**, the blood vessel is **stimulated by the mechanisms of pressure autoregulation to vasoconstriction, consequently reducing CBV and ICP**. This argument **appears to hold only when pressure autoregulation remains intact**" YW p. 472.e11.
- **Rosner's refinement, which reconciles the two camps.** "Rosner also proposed that in many cases in which **loss of pressure autoregulation is seen, the mechanism is not lost but, rather, the curve is shifted to the right**. Vasopressors manipulate the vessel back into a state in which it can autoregulate. If this argument is correct, **the real challenge is in distinguishing those brains that will benefit from this type of therapy**" YW p. 472.e11.
- **The unresolved risk.** "The possible risks associated with pressor therapy to regions of brain where there is **BBB disruption are unresolved**. Several studies have questioned the risk for systemic hypertension in brain injury and have demonstrated ways in which pathology can be worsened by vasopressors" YW p. 472.e11.
- **Albumin is the one clear casualty.** "**Use of albumin is not recommended in traumatic brain injury because it has been linked with worsened outcome**" YW p. 472.e11 — a direct contradiction of Lund's first goal, and the single most examinable criticism.
- **How to resolve it at the bedside — autoregulation-guided therapy.** Youmans' own resolution is not to pick a side but to measure. "It is likely that neither [ICP-targeted nor CPP-targeted] is accurate, but rather ideal treatment will need to address maintenance of appropriately regulated tissue blood flow in the context of disordered ICP, CPP, and autoregulation. However, for this to be used clinically, **a real-time measure of autoregulation must be available**" YW p. 472.e6. Howells' comparison provides the rule: **autoregulation preserved → higher CPP is beneficial; autoregulation impaired → ICP-targeted care with CPP in the 50-60 mm Hg range is preferable** YW p. 3031. The SIBICC tier-2 **MAP challenge** operationalises this: if autoregulation is intact the patient may tolerate a higher CPP; if

impaired, the patient may require CPP in the lower recommended range to avoid ICP elevation [YW pp. 3030, 3031].

Table 3 · Lund concept versus CPP-targeted (Rosner) management — compiled from Youmans & Winn 8e, Ch. 69 pp. 472.e6, 472.e11 and Ch. 387 p. 3010, with the current BTF target from Ch. 388 p. 3031.

	Lund concept	CPP-targeted / Rosner
Governing principle	Starling forces: reduce microvascular pressure to minimise transcapillary filtration and oedema	Perfusion: keep CPP high enough to prevent ischaemia, and let pressure autoregulation vasoconstrict and lower CBV
CPP direction	**Reduce**	**Maintain or elevate** (BTF 4th edition target 60-70 mm Hg)
Colloid osmotic pressure	Preserve with **albumin and red cell** infusion	Not a target; **albumin is not recommended in TBI — linked with worsened outcome**
Systemic blood pressure	Lower it — **metoprolol, clonidine**	Raise it — fluids and **vasopressors**
Cerebral blood volume	Reduce by precapillary vasoconstriction — **low-dose thiopental**, originally **dihydroergotamine** (since discontinued)	Reduce indirectly via autoregulatory vasoconstriction at higher CPP
Deliberately avoided	CSF drainage, high-dose barbiturates to burst suppression, osmotic diuretics, high CPP	—
Decompressive craniectomy	**Last resort only** — it can itself increase oedema formation	A tier-3 option
Prerequisite for it to work	Damaged, leaky capillary bed (BBB disruption)	**Intact pressure autoregulation**, or a right-shifted curve that vasopressors can recruit back
Evidence status	Outcomes no poorer than conventional care; one review of 10 studies suggested a tendency to more favourable outcome; **no trial has shown superiority**	Reduced incidence of cerebral ischaemia but **no outcome benefit and a fivefold rise in pulmonary complications** when CPP was held >70

pt of ICP ? has quate nged with and ? <18 ? was

s an at its ute). g per to 71 owly niron nced ents, lues. oned

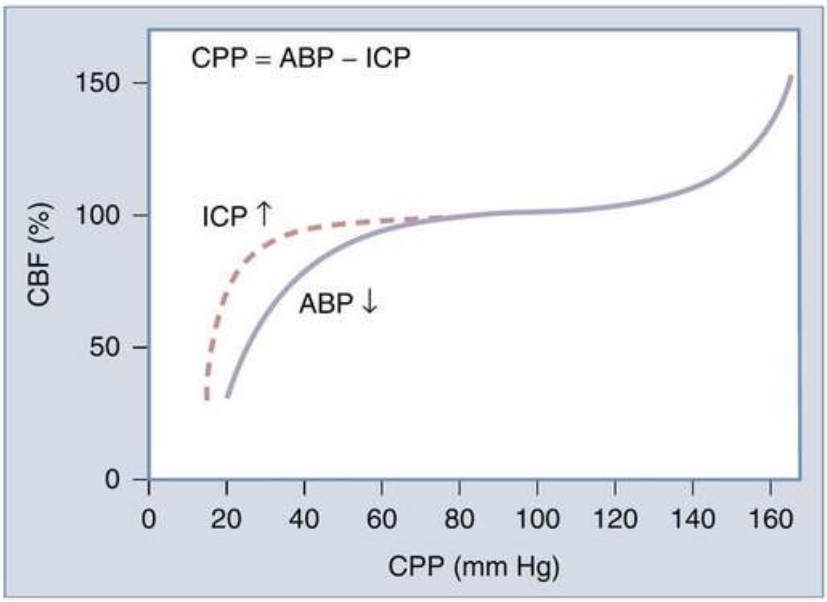


Figure 384.4. Pressure autoregulation in humans. *ABP,* Arterial blood pressure; *CBF,* cerebral blood flow; *CPP,* cerebral perfusion pressure; *ICP,* intracranial pressure.

*Reproduced from Youmans & Winn 8e, Fig. 384.4, p. 2977 — Label when you reproduce it: CBF as % of normal against CPP (mm Hg), with **CPP = ABP − ICP** written in the panel. Draw the solid curve for a CPP fall driven by falling **ABP** and the broken curve for a CPP fall driven by rising **ICP**; the point to make is that the ICP-driven limb breaks away at a higher CPP — which is precisely the situation in which the Lund and CPP-targeted camps give opposite advice.*

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Draw the neurovascular unit, not a tight junction** — endothelium, basement membrane, pericyte, astrocyte end-foot, microglia, neuron, extracellular matrix, plus the perivascular CSF space.
- **Astrocyte end-feet cover >90% of the endothelium; pericyte processes cover 20-30% of the microvascular circumference** — two numbers worth writing on the diagram.
- **Tight junction = occludin + claudin-3/-5/-12 + JAMs + ZO-1/2/3; adherens junction = VE-cadherin + catenins + vinculin + actinin.**
- **Polarity is examinable: GLUT1 abluminal (3-4× luminal), P-glycoprotein luminal, alkaline phosphatase and γ-GT luminal, Na⁺,K⁺-ATPase abluminal.**
- **Monro-Kellie in one line: V_{CSF} + V_{BLOOD} + V_{BRAIN} + V_{OTHER} is constant, because the dura distends only minimally** — quote Monro's "nearly incompressible" and Kellie's "equivalent displacement."
- **1500 mL total: brain 87%, CSF 9%, blood 4%** — or, from Ch. 70, brain 1250-1500 mL, CSF 125-150 mL, blood 125-150 mL.
- **Blood and CSF buffer first because they can be reduced fastest; the brain's 80% is only available if V_{OTHER} grows slowly — otherwise the brain shifts and herniates.**
- **ICP = (I_f × R_o) + P_d, and (I_f × R_o) is only ~10% of ICP** — which is why venous sinus obstruction raises ICP so readily.
- **Craniectomy essentially nullifies the Monro-Kellie doctrine** — and is why PRx becomes unreliable after decompression.
- **Lund = lower microvascular pressure to stop oedema: albumin + red cells for colloid osmotic pressure, metoprolol + clonidine to lower BP, low-dose thiopental (originally dihydroergotamine) for precapillary vasoconstriction.**
- **Lund deliberately avoids CSF drainage, burst-suppression barbiturates, osmotic diuretics and high CPP, and keeps craniectomy as a last resort.**
- **The single best criticism of Lund: Youmans states albumin is not recommended in TBI because it has been**

linked with worsened outcome.

- **Rosner's counter-argument only works if pressure autoregulation is intact — or if the curve is merely right-shifted and can be recruited back by vasopressors.** Distinguishing those brains is the real clinical challenge, which is what the MAP challenge and PRx are for.

Pages read for this answer — Youmans & Winn 8e: 288, 471.e1, 471.e2, 471.e3, 471.e5, 471.e8, 472, 472.e1, 472.e3, 472.e4, 472.e5, 472.e6, 472.e9, 472.e11, 472.e13, 473.e1, 473.e2, 473.e10, 3010, 3028, 3030, 3031, 3105.e1

a) Cerebral autoregulation [5]
b) Pathophysiology of cerebral edema. [5]

LONG | MAY 2024 · Paper I · Q8 | 10 marks

Also asked as: Neurophysiology — also asked as OCT 2025 · Paper I · Q8 (Cerebral edema: a) Classify the types of cerebral edema [3]; b) Explain pathophysiology [4]; c) Management [3]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 403 *Cerebral Blood Flow and Metabolism and Cerebral Ischemia*, §Cerebral Autoregulation, pp. 3207.e12-3207.e14 (Fig. 403.3, p. 3207.e13; Table 403.1, p. 3207.e14). Supplementary: Ch. 69 *Physiology of the CSF and Intracranial Pressure*, §Non-Steady-State Dynamics and §Effects of Elevated Intracranial Pressure, pp. 472.e5-472.e7, 472.e11 (Figs. 69.5-69.7, pp. 472.e6-472.e7); Ch. 388 *Invasive Physiologic Monitoring for TBI*, §Cerebral Perfusion Pressure and §Parameters Derived From ICP, MAP, CPP, pp. 3030-3032 (Figs. 388.2-388.3, pp. 3031-3032); Ch. 384 *Clinical Pathophysiology of TBI*, pp. 2977-2978 (Fig. 384.4, p. 2977; Table 384.11, p. 2978); Ch. 70 *Cerebral Edema*, §Cerebral Fluid Homeostasis, §Pathophysiology of Cerebral Edema, §Imaging of Cerebral Edema and §Management of Cerebral Edema, pp. 473, 473.e1-473.e10 (Table 70.1, p. 473.e3; Figs. 70.1-70.9, pp. 473.e2-473.e10); Ch. 404 *Cerebral Ischemia*, p. 3209 (Fig. 404.1, p. 3209).

(a) Cerebral autoregulation [5]

1. Definition, site of action and limits

- **Definition, verbatim.** "The brain maintains its regional and total blood flow (and therefore perfusion) at a fairly constant rate over a wide range of systemic blood pressure by a vasomotor phenomenon known as **cerebral autoregulation**. Autoregulation involves the **sustained constriction or dilation of cerebral resistance vessels, principally the precapillary arterioles, purely in response to changes in transmural pressure caused by variations in CPP**" YW p. 3207.e13.
- **Two definitions to give.** Ch. 388's phrasing is more clinical: "This phenomenon of a **relatively constant CBF over a broad range of perfusion pressures** is termed cerebral autoregulation" YW p. 3030; and mechanistically, "This regulatory mechanism occurs at the level of the **arterioles, which constrict with increasing pressure** to regulate CBF and maintain flow at a constant rate" YW p. 3032.
- **Why CPP and not MAP. CPP = MAP − ICP**, because in the brain the mean venous pressure closely approximates ICP. "In normal individuals, CPP varies directly with MAP because **ICP is constant**" [YW pp. 3030, 3207.e13].
- **The limits.** "In effect, **the brain is protected from fluctuations in perfusion over a MAP range of 60 to 150 mm Hg** . Beyond these limits, CPP passively follows MAP" YW p. 3207.e13. Ch. 388: "The **lower limit of CAR when it is preserved is estimated to be 50 to 60 mm Hg in adult patients, decreasing in an age-related fashion in the pediatric population**, whereas the **upper limit is 150 mm Hg**" YW p. 3030. Ch. 69 frames the operating envelope of vascular tone as **arterial blood pressure 50 to 160 mm Hg and PaCO₂ 20 to 70 mm Hg**, with **mean normal adult CBF 53 mL/100 g per minute** YW p. 472.e5.
- **What happens outside the limits.** Below the lower limit **"there is vascular collapse, and CBF declines with falling perfusion pressure"** (passive collapse); above the upper limit **CBF rises with increasing perfusion pressure** (autoregulation breakthrough), which increases CBV and can raise ICP [YW pp. 3032, 3030].
- **The limits are not invariable** YW p. 3207.e13:
  - **Right shift** — chronic hypertension (associated with increased sympathetic tone) and states associated with increased renin release.
  - **Left shift** — sleep; "physiologic hypotension" in athletes; "pathologic hypotension" associated with haemorrhage;

angiotensin-converting enzyme inhibitors; prolonged hypoxaemia; hypercapnia.

- **Disturbed** — acute severe hypotension or hypertension.
- **Profoundly impaired or abolished** — severe cerebral ischaemia, arteriovenous malformation beds, TBI, and after aneurysmal SAH.

- **Time course.** "The changes induced by autoregulation are **not instantaneous**; measurements in pial arteries indicate a time course ranging from **5 to 10 seconds**. In vitro evaluations indicate a longer interval of **60 to 120 seconds** between intraluminal pressure change and arteriolar dilation" YW p. 3207.e13.

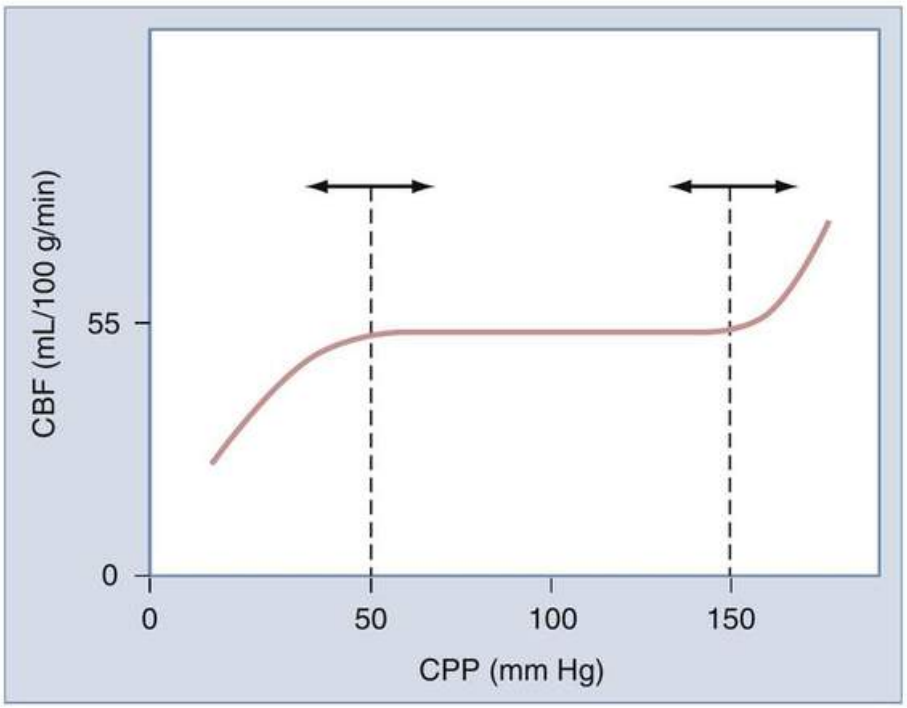


Figure 403.3. Classic cerebral autoregulation curve. Cerebral autoregulation maintains a relatively constant rate of cerebral blood flow (CBF) across a wide range of cerebral perfusion pressure (CPP), as shown (plateau). The normal pressure limits of autoregulation *(vertical broken lines)* may be shifted to the left or right in certain conditions *(arrows)* and impaired or abolished in others (see text for details). Note the respective relatively steep rise and fall in CBF as CPP changes above and below the normal limits of autoregulation.

range
resolu
cours
chang
autor
may
produ
withi
120-s
respo
(i.e.,
still p
wall).
do in
becau
recep
sugge
but pr
Tl
role t
Arter
deper
to inc
to de
that r
influe
contr
entry

*Reproduced from Youmans & Winn 8e, Fig. 403.3, p. 3207.e13 — Label when you reproduce it: CBF (mL/100 g/min) on the y-axis with the plateau at **55**; CPP (mm Hg, 0-150) on the x-axis; the two **vertical broken lines** marking the normal pressure limits of autoregulation; the **horizontal arrows** showing that these limits shift left or right in certain conditions; and the relatively steep rise and fall of CBF beyond the limits.*

2. Mechanisms — the four hypotheses in order of strength

- **Myogenic hypothesis** — Youmans' favoured mechanism. It "accords a key role to the **inherent response of VSM to mechanical stimulation**. Arterioles typically exhibit a state of **partial contraction that is dependent on intraluminal pressure**; an increase in pressure leads to increased contraction, whereas a decrease in pressure leads to decreased contraction. It is clear that this is a phenomenon that resides in the smooth muscle cell and involves the **obligatory influence of Ca²⁺**." The contractile sequence: **depolarisation of VSM cells → Ca²⁺ entry through L-type voltage-gated calcium channels → facilitation of calcium-induced calcium release from the sarcoplasmic reticulum → Ca²⁺-dependent activation of myosin light-chain phosphorylation → actin-myosin-based contraction**. Candidate mechanosensors: **stretch-activated channels** whose deformation depolarises by admitting cations, specifically the TRP superfamily members **TRPC6, TRPV2 and TRPM4** (antisense

downregulation significantly attenuates pressure-induced depolarisation and myogenic constriction; these non-selective cation channels are also important for Ca²⁺ conductance and are synergistic with IP₃ receptors in astrocytic end-foot neurovascular coupling); and **VSM integrins** acting as mechanotransducers at **dense plaques** through physical associations with the extracellular matrix, cytoskeleton and protein tyrosine kinases — the most compelling evidence being that **peptides containing integrin-specific amino acid sequences are potently vasoactive**, and that integrin signalling regulates VSM [Ca²⁺]_i by altering L-type Ca²⁺ current [YW pp. 3207.e13, 3207.e13].

- **Endothelial hypothesis** — "supported by evidence that the endothelium can respond to physical stimuli such as **pulsatile stretch and shear stress**. It is clear that the endothelium is by no means a passive and inert barrier between the blood and VSM but rather has a critical vasomodulatory role through the synthesis, elaboration, and release of **EDRFs such as NO, prostaglandin I₂, and EDHF, as well as endothelium-derived contracting factors (EDCFs) such as ET-1 and thromboxane A₂**. An **increase in flow rate and shear stress without an increase in transmural pressure can induce vasodilation, most likely through the endothelial release of NO**." Endothelium-dependent arteriolar contractions in response to increased transmural pressure have been attributed to depressed EDRF release and/or increased EDCF release — but **"some studies have found that disruption of the endothelium does not impair transmural pressure-induced arteriolar constriction"** [YW pp. 3207.e13, 3207.e14].
- **Neurogenic hypothesis** — attributes cerebrovascular resistance to **neurotransmitter release from perivascular nerve fibres**, which arborise throughout the adventitial layer of cerebral arteries and come from **extrinsic** (remote neurons) or **intrinsic** (local neurons) sources. Supporting evidence: dense innervation; specific receptors for biogenic amines and peptides on endothelial and smooth muscle cells; nerve stimulation studies showing altered vasomotor tone even in mechanically de-endothelialised arteries, with inhibition by specific receptor antagonists; isometric force recordings with acetylcholine, CGRP, an NO donor, noradrenaline, serotonin and substance P; and a time course of transmitter release, binding and action comparable to the rapid time course of autoregulation. **The one clearly attributable function: "The innervation of extracerebral arteries by sympathetic nerve ganglia probably serves to shift the upper limit of the autoregulatory curve to higher pressures. This is believed to be partly mediated by neuropeptide Y and would serve to protect the brain against hypertension secondary to sympathetic activation."** Against it: "although stimulation of the parasympathetic ganglia elicits strong vasodilation via acetylcholine-mediated endothelial-dependent release of NO, **it does not seem to play any role in autoregulation**"; the trigeminovascular CGRP system "**again has no known role in autoregulation**"; and "if there are mechanisms for triggering neurotransmitter release from intrinsic perivascular nerves in the setting of increased transmural pressure, **they have not been determined**" [YW pp. 3207.e14, 3207.e14].
- **Metabolic hypothesis** — Youmans marshals **three arguments against** it for autoregulation specifically YW p. 3207.e13 :
  - **1.** "Microdialysis measurements of the extracellular and perivascular concentrations of **H⁺, K⁺, and adenosine**, key mediators in metabolic vasoregulation, normally **do not change in response to alterations in CPP in the autoregulatory range**." *Counterpoint:* dialysis has poor time resolution, which matters given the 5- to 120-second time course; and **Winn and colleagues did demonstrate adenosine concentration changes within the autoregulatory range**.
  - **2.** "The time course of autoregulation may be **too rapid** to depend on the generation of metabolic products." *Counterpoint:* adenosine has been generated **within seconds** after ischaemia.
  - **3.** "The autoregulatory response has been observed in **isolated, perfused vessels in vitro**" — not subject to neuroglial metabolism, though metabolite production within the vessel wall remains possible.
  - **In favour:** "Experiments in a murine model of autoregulation do indicate a role for metabolic factors, in this case **adenosine**, because **autoregulation was significantly decreased in adenosine receptor knockout mice**."
  - **Youmans' verdict:** "Taken together, these arguments suggest that **metabolic factors may play a role in autoregulation, but probably not the dominant role under physiologic conditions**" YW p. 3207.e13.

Table 1 · Origins of neurovascular innervation — reproduced in full from Youmans & Winn 8e, Table 403.1, p. 3207.e14. Only the sympathetic limb has an established autoregulatory role (right-shifting the upper limit via neuropeptide Y).

Classification	Subdivision	Source	Neurotransmitter	Vasomotor effect
Extrinsic — autonomic ganglionic	Sympathetic	Superior cervical ganglion	Adenosine triphosphate / Neuropeptide Y / Norepinephrine	Vasoconstriction / Vasoconstriction / Vasoconstriction (α)
	Parasympathetic	Pterygopalatine (sphenopalatine) and otic ganglia	Acetylcholine / Nitric oxide / Vasoactive intestinal peptide	Vasodilation / Vasodilation / Vasodilation
Extrinsic — non-autonomic ganglionic peptidergic	Trigeminovascular	Gasserian (trigeminal) ganglion	Calcitonin gene-related peptide / Neurokinin A / Substance P	Vasodilation / Vasodilation / Vasodilation
Extrinsic — nuclear monoaminergic	Catecholaminergic	Locus caeruleus, ventrolateral medulla	Norepinephrine	Vasodilation (β₂)
	Serotoninergic	Raphe nuclei	Serotonin	Vasodilation or vasoconstriction
Intrinsic — local peptidergic	Adventitial local neurons	—	Neuropeptide Y / Vasoactive intestinal peptide	Vasoconstriction / Vasodilation

3. Autoregulation in disease — reserve, pressure passivity and bedside measurement

- **Autoregulatory reserve.** "The autoregulatory reserve may be defined as **the difference between the CPP at a given moment and the lower limit of autoregulation**. Considering that the lower limit of autoregulation is within the range of **50 to 70 mm Hg**, the autoregulatory reserve for a **CPP of 90 mm Hg would be 20 to 40 mm Hg**. Thus, a CPP below the autoregulatory threshold exhausts the autoregulatory reserve" YW p. 472.e6.
- **What a right shift costs.** "In many pathologic cases, autoregulation is disturbed, commonly so that the **response curve is shifted to the right and is more linear**. This change **reduces the autoregulatory reserve for any given CPP**. If the autoregulatory reserve is exhausted, CBF begins to fall, ultimately causing tissue ischaemia. **Ischaemia creates cytotoxic oedema, which in turn contributes to the high ICP and low CPP.** Clearly a **vicious circle of oedema and ICP elevation** can ensue if treatment attempts do not prevent it" YW p. 472.e7.
- **Pressure passivity — the term to use.** "Patients with this disturbance in normal pressure autoregulation are termed **pressure passive** because their CBF will be dependent on CPP. A sharp rise in CPP in these patients can result in elevation of CBF and thus cerebral blood volume, which can result in a **dangerous rise in intracranial pressure**. Conversely, a sharp drop in CPP in a patient who is pressure passive can result in a substantial decrease in CBF that can lead to **inadequate tissue perfusion**" YW p. 3032.
- **Coupling of CPP to compliance.** "When CPP decreases, the **wall tension of reactive brain vessels decreases, thereby increasing the transmission of the arterial pulse wave** to the intracranial contents. Similarly, when a reduction of CPP is caused by increased ICP, **brain compliance decreases**." A decrease in CPP therefore increases **both** blood-pressure and ICP pulsatility — "highly predictive for fatal outcome because **levelling off or decrease in the ICP pulse amplitude implies that cerebral vessels are no longer pressure-reactive**" YW p. 472.e6.
- **PRx — measuring autoregulation at the bedside.** The **pressure reactivity index** is "the correlation coefficient between changes in blood pressure and ICP," calculated as the **moving correlation coefficient between 40 consecutive 5-second averages of ICP and MABP captured at ≥60 Hz** (Czosnyka); Ch. 388 describes it as the running correlation between MAP and ICP over a **3- to 4-minute** interval. **PRx is negative when autoregulation is intact and positive when it is impaired**; **PRx >0.2 for more than 6 hours is associated with increased mortality**. It works best with an intact cranium, since **after decompressive craniectomy cranial compliance is altered** and CBF/CBV changes no longer produce ICP changes. In a fatal terminal rise in ICP from 60 to 90 mm Hg over one hour, PRx rose from low values toward 1.0 and stayed high; in a recovering plateau wave PRx fell back with the ICP [YW pp. 472.e6, 3031, 3032].
- **RAP and RAC. RAP** (correlation between mean ICP wave amplitude and mean ICP) varies from **+1 to −1**: 0 = good compensatory reserve, → +1 = poor reserve, **<0 = reserve exhausted and autoregulation collapsed**. **RAC** relates ICP

pulse amplitude to CPP. CENTER-TBI data show **both PRx and RAC predict 6- and 12-month mortality** in severe TBI [YW pp. 472.e6, 3032].

- **The MAP challenge — the practical test.** SIBICC tier 2. *Prerequisites:* arterial line, ICP monitor, and an additional advanced cerebral monitor (PbtO₂ or Hemedex CBF); patient haemodynamically stable with **ICP controlled and below 22 mm Hg**; not to be performed if respiratorily, haemodynamically or otherwise systemically unstable. *Before:* baseline arterial blood gas and record heart rate, MAP, ICP, CPP, PbtO₂, CBF and ventilation parameters. *Challenge:* vasopressor infusion (noradrenaline if central access, phenylephrine if only peripheral) to **raise MAP by 10-15 mm Hg over 10-20 minutes**, recording every 5 minutes. *STOP if:* **ICP exceeds 25 mm Hg, MAP exceeds 120 mm Hg, desaturation, any respiratory instability, or any other untoward effect.** *Interpretation:* **no substantial increase in PbtO₂ and/or CBF with rising MAP = intact autoregulation**; **a substantial increase = impaired autoregulation**. *Therapeutic implication:* **intact → the patient may tolerate a higher CPP** (less likely to raise ICP, may improve PbtO₂); **impaired → the patient may require CPP in the lower recommended range to avoid ICP elevation** YW p. 3031.
- **Therapeutic consequence — Howells' rule.** "When CAR was **preserved**, a strategy to maintain **higher CPP** was beneficial, whereas in patients with **impaired CAR, ICP-targeted care and a CPP in the 50- to 60-mm Hg range was preferable**." CPP targets have evolved: >70 mm Hg early (abandoned after a **fivefold increase in pulmonary complications** with no outcome benefit), **50-70** in BTF 3rd edition, **60-70** in BTF 4th edition, and now individualised **CPP-opt**, with time spent **below** CPP-opt particularly harmful in impaired autoregulation [YW pp. 3031, 3031].

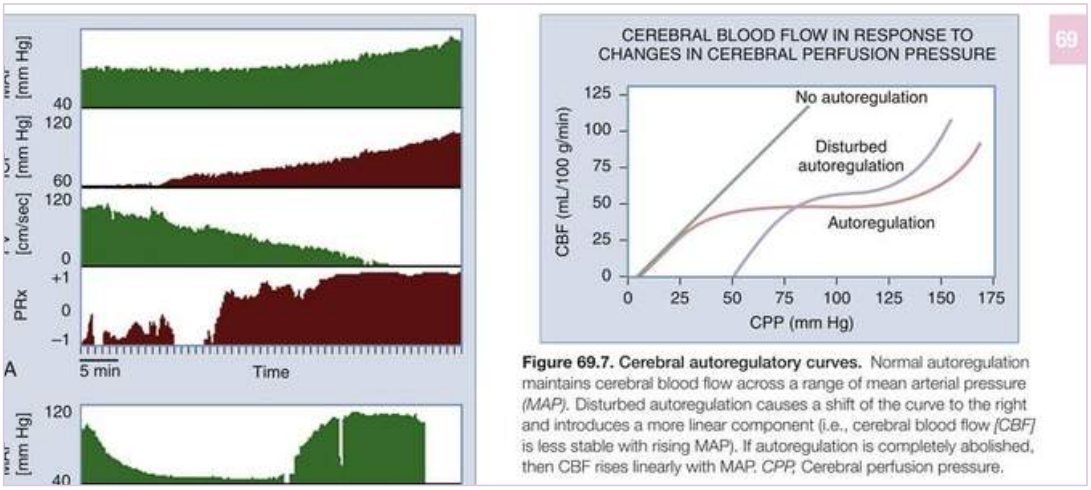


Figure 69.7. Cerebral autoregulatory curves. Normal autoregulation maintains cerebral blood flow across a range of mean arterial pressure *(MAP)*. Disturbed autoregulation causes a shift of the curve to the right and introduces a more linear component (i.e., cerebral blood flow *[CBF]* is less stable with rising MAP). If autoregulation is completely abolished, then CBF rises linearly with MAP. *CPP,* Cerebral perfusion pressure.

*Reproduced from Youmans & Winn 8e, Fig. 69.7, p. 472.e7 — Label when you reproduce it: CBF (mL/100 g/min, 0-125) against CPP (mm Hg, 0-175); three curves — **normal autoregulation** (a flat plateau), **disturbed autoregulation** (right-shifted with a more linear component, so CBF is less stable with rising MAP) and **no autoregulation** (a straight line from the origin, CBF rising linearly with MAP). Write beside it that a right shift reduces autoregulatory reserve for any given CPP.*

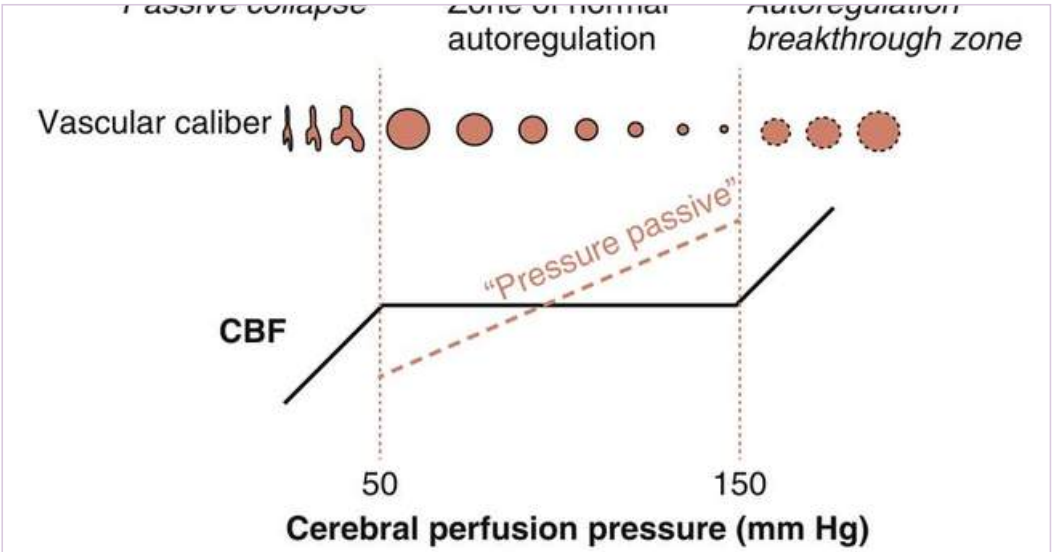


Figure 388.3. Classical cerebral pressure autoregulation curve that describes the relationship between cerebral perfusion pressure (CPP) and cerebral blood flow (CBF). Over a wide range of CPP, CBF remains essentially constant if autoregulation is preserved. This regulatory mechanism occurs at the level of the arterioles, which constrict with increasing pressure to regulate CBF and maintain flow at a constant rate. Below the lower limit of autoregulation (CPP of about 50 mm Hg in adults), there is vascular collapse, and CBF declines with falling perfusion pressure. Above the upper limit of cerebral pressure autoregulation (CPP of about 150 mm Hg in adults), CBF will rise with increasing perfusion pressure. However, normal cerebral pressure autoregulation is impaired in a large percentage of patients with severe traumatic brain injury. When autoregulation is impaired, changes in pressure within the normal autoregulatory range of 50 to 150 mm Hg will lead to changes in CBF. Patients with this disturbance in normal pressure autoregulation are termed *pressure passive* because their CBF will be dependent on CPP. A sharp rise in CPP in these patients can result in elevation of CBF and thus cerebral blood volume, which can result in a dangerous rise in intracranial pressure. Conversely, a sharp drop in CPP in a patient who is pressure passive can result in a substantial decrease in CBF that can lead to inadequate tissue perfusion. Because of these relationships between autoregulation status, CPP, and CBF, the target CPP in patients severe traumatic brain injury can often depend on whether cerebral autoregulation status is preserved or impaired.

*Reproduced from Youmans & Winn 8e, Fig. 388.3, p. 3032 — Label when you reproduce it: the three zones along the CPP axis — **passive collapse** below ~50 mm Hg, **zone of normal autoregulation** 50-150 mm Hg, **autoregulation breakthrough zone** above ~150 mm Hg; the row of arterioles showing progressive constriction of **vascular calibre** across the plateau; the flat **CBF** plateau; and the broken diagonal labelled **"pressure passive"** that replaces the plateau when autoregulation is lost after severe TBI.*

Table 2 · Status of cerebral blood flow, cerebral blood volume and arteriovenous difference of oxygen under various clinical conditions — reproduced in full from Youmans & Winn 8e, Table 384.11, p. 2978. The autoregulation-intact and autoregulation-defective rows are the whole answer to "why does autoregulatory status change my management?"

Feature with primary reduction	CBF	CBV (ICP)	AVDO₂
Decreased CMRO₂ (within physiologic limits)	↓	↓	=
Low CPP (autoregulation intact)	=	↑	=
Low CPP (autoregulation defective)	↓	↓	↑
Lower blood viscosity (autoregulation intact)	=	↓	=
Low blood viscosity (autoregulation defective)	↑	=	↓
Low PaCO₂ (hyperventilation)	↓	↓	↑
Small cerebral artery diameter (cerebral vasospasm)	↓	↑	↑

(b) Pathophysiology of cerebral edema [5]

4. Definition and the four-type classification

- **Definition.** "Cerebral edema is the **pathologic excess of intracellular and/or extracellular fluid in the brain** that can be associated with neurological morbidity and mortality" YW p. 473. Ch. 69's version: "Defined as an **increase in the brain tissue water content**, brain edema therefore can be thought of as contributing to either **V_{OTHER} or V_{BRAIN}**" YW p. 472.e5.
- **The four types.** "Cerebral edema is classified as **vasogenic, cytotoxic, interstitial, or osmotic**. **More than one form of cerebral edema can occur contemporaneously in a disease state.** Dysfunction of the blood-brain barrier, altered cellular metabolism, osmotic homeostasis, and/or the glymphatic system underlies the development and progression of cerebral edema" YW p. 473.
- **Historical lineage.** "At the turn of the century, **Reichardt** reported differences between a **dry swollen brain and a wet edematous brain**. **Klatzo** subsequently paved the way for all future discussions of edema by introducing two terms, **cytotoxic and vasogenic**, to indicate **intracellular and extracellular water accumulation** respectively" YW p. 472.e5. "Based on landmark work by **Klatzo (1967)**, cerebral edema was initially classified into two types… Later, **interstitial and osmotic** cerebral edema were identified" YW p. 473.e2.
- **Youmans' important caveat — the dichotomy is a simplification.** "This division is a **simplification** for two reasons. First, for brain tissue water to rise, **even under cytotoxic conditions, water has to enter the tissue from an external source, the most likely of which is blood vessels. Therefore, even cytotoxic edema has a 'vasogenic' origin.** It is the **pathologic cause** and the **final site of edema accumulation** that must distinguish these phenomena. Furthermore, studies in traumatic brain injury have suggested that the vasogenic component of injury may have been **overemphasised** and that the importance of a disrupted BBB lies in the **provision of a low-resistance pathway for movement of water to cells that are swelling cytotoxically**. Cytotoxic edema and vasogenic edema may not, therefore, be separate entities, and **a classification of edema based on the terms intact barrier and open barrier may have merit**" YW p. 472.e5.
- **Why the Monro-Kellie doctrine makes oedema dangerous.** "Under edematous conditions, increases of intraparenchymal fluid (edema) expand the brain tissue volume that necessarily leads to the reduction in cerebral blood and cerebrospinal fluid volume. Consequently, relative increases in brain volume due to cerebral edema can cause **reduced blood volume (flow) and significant secondary injury from ischemia or brain herniation**" YW p. 473.e1.

Table 3 · Types of cerebral edema and their treatment — reproduced in full from Youmans & Winn 8e, Table 70.1, p. 473.e3. Learn this table; it answers classification, pathophysiology and management in one grid.

Feature	Vasogenic oedema	Cytotoxic oedema	Interstitial oedema	Osmotic oedema

CHAPTER 5

Neuro-Oncology: Gliomas, Intra-axial Tumours & Neuropathology

15
QUESTIONS SOLVED

WHO Classification of Gliomas / Recurrent GBM

7 questions

Recurrent GBM:

a) Diagnosis.

b) Indications for surgery

c) Timozolamide

LONG | JUN 2020 · Paper III · Q9 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 159 *Malignant Gliomas: Anaplastic Astrocytoma, Glioblastoma, Gliosarcoma, and Anaplastic Oligodendroglioma*, §Neuroimaging Studies, §Management, §Radiation Therapy and Chemotherapy and §Patient Outcome and Survival, pp. 1101-1111 (Figs. 159.2-159.3, pp. 1101-1102; Fig. 159.7, p. 1109; Fig. 159.8, p. 1111; **Table 159.1**, p. 1102; **Table 159.5**, p. 1110). Ch. 160 *Radiologic and Clinical Criteria of Treatment Response*, §Findings in the Imaging of Brain Tumors Are Nonspecific, §The RANO Criteria, §Drugs Interfering With Contrast Uptake and §Postsurgical Imaging, pp. 1117-1118.e4 (**Table 160.1** and **Table 160.2**, pp. 1118.e1, 1118.e3). Ch. 144 *Radiologic Features of Central Nervous System Tumors*, §Metabolic Imaging by MRS and §Tumor Progression Versus Radiation Necrosis or Pseudoprogression, pp. 995-996, 1010-1011 (Fig. 144.2, p. 996; Figs. 144.23-144.24, pp. 1010-1011). Ch. 147 *Principles of Chemotherapy*, §Concepts in Chemotherapy, §Mechanisms of Drug Resistance and §Chemotherapeutic Agents, pp. 1029-1032 (Fig. 147.1, p. 1029; **Table 147.1** and **Table 147.2**, p. 1032). Supplementary: Ch. 162 *Local Therapies for Gliomas*, pp. 1132-1137 (Figs. 162.1, 162.4, 162.7); Ch. 157B *Fluorescence-guided Brain Tumor Surgery*, pp. 1090.e2-1090.e4; Ch. 153 *Risks of Intrinsic Brain Tumor Surgery*, p. 1065; Ch. 133, pp. 900-901.

(a) Recurrent glioblastoma — diagnosis [3]

1. First fix the biology: recurrence is the rule, not the exception

- **Recurrence is inevitable and the surgeon must expect it.** Youmans states it plainly: "**despite gross total resection and adjuvant chemotherapy and radiation, glioblastoma will invariably recur, either locally or at a distant site**" YW p.1132. Even after apparently curative resection, **microsatellites of tumour cells are scattered through normal brain** and retain the capacity to proliferate YW p.1103.
- **The infiltration is wider than any image.** Autopsy studies show high-grade gliomas usually extend beyond a single carotid or vertebral territory, spread through CSF pathways and may extend past the 2-cm margin demonstrated by CT or MRI; stereotactic biopsies of T2-hyperintense brain remote from the enhancing tumour contain tumour cells, and biopsies of *radiologically normal* brain grow tumour in vitro YW p.1103. Dandy reported contralateral recurrence **after hemispherectomy** as early as 1928 [YW pp. 1100, 1103].
- **Therefore imaging and histology both underestimate the true extent of disease** YW p.1103. Late recurrence beyond the resection cavity, across the corpus callosum, or as a new distant enhancing nodule is entirely consistent with GBM biology.

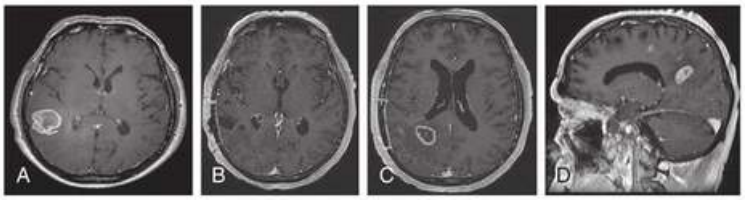


Figure 162.1. Despite gross total resection and adjuvant chemotherapy and radiation, glioblastoma will invariably recur, either locally or at a distant site. (A) Axial T1-weighted postcontrast MRI shows a newly diagnosed glioblastoma multiforme, which was fully resected. Although the 4-month MR image (B) revealed no evidence of recurrence, by 14 months (C and D) multiple new sites of enhancing tumor were noted at varying distances from the original resection cavity. In the future, therapeutic techniques better able to address invasion and distant recurrences may improve outcomes.

Reproduced from Youmans & Winn 8e, Fig. 162.1, p. 1132 — Label when you reproduce it: (A) newly diagnosed GBM on axial T1 post-contrast, fully resected; (B) 4-month scan with no evidence of recurrence; (C and D) at 14 months, multiple new enhancing sites at varying distances from the original resection cavity. Point out that the recurrences are both local (cavity wall) and distant — the radiological proof that GBM is a whole-brain disease.

2. Clinical diagnosis — the triggers that should make you re-image

- **Progressive, relentless headache** is the hallmark symptom; raised intracranial pressure produces headache, nausea and vomiting, blurred or double vision and drowsiness, typically worse in the morning and easing through the day, with extraocular palsies, papilloedema, pupillary abnormality or falling conscious level YW p.1102.
- **New or worsening focal deficit** — focal or global (altered cognition, personality change) according to the site and extent of infiltration YW p.1102.
- **New or increasingly frequent seizures** — up to a third of GBM patients have seizures at some point YW p.1102.
- **Beware the confounders.** Clinical deterioration is *not* synonymous with progression: metabolic derangement, postictal states and drug side effects (phenytoin, valproate) all mimic tumour progression YW p.1118.e3. Conversely early progression may be entirely asymptomatic. Youmans' rule for day-to-day practice: "**only clear and undeniable clinical evidence should be taken as a reason to diagnose progression, and steroid dosage and other confounding factors must be considered**"; if deterioration follows a significant steroid reduction, no conclusion can be drawn and treatment should continue YW p.1118.e4.
- **Steroids cut both ways** — "the start of steroid treatment alone may induce a partial response"; a *reduction* in steroid dose may be followed by an apparent increase in tumour size YW p.1118.e3.

3. The formal radiological criteria — Macdonald, then RANO

Table 1 · Macdonald response criteria for brain tumours — reproduced from Youmans & Winn 8e, Table 160.1, p. 1118.e1.

Category of response	Description
Complete response	Disappearance of enhancement on consecutive imaging ≥1 month apart; off steroids; neurologically stable or improved
Partial response	≥50% reduction in size* of enhancing tumour on consecutive imaging ≥1 month apart; steroids stable or reduced; neurologically stable or improved
Progressive disease	>25% increase in size of enhancing tumour, **or** any new tumour on imaging, **or** neurologically worse, with steroids stable or reduced
Stable disease	All other situations

*Size = largest cross-sectional diameter × largest diameter perpendicular to it YW p.1118.e1.

- **Why Macdonald needed revision.** The criteria were built on the contrast-enhancing area as a surrogate for tumour, and contrast uptake is *non-specific*: it reflects "tumour activity, vascular permeability, radiotherapy-induced pseudoprogression, radiation necrosis, postsurgical ischaemic lesions, or inflammatory responses in patients treated with effective immunotherapy" YW p.1118.e1. Almost by definition the target lesion lies **inside the radiotherapy volume** , or the patient has had a second operation — both of which generate new enhancement YW p.1118.e1.

Table 2 · Basic RANO (Response Assessment in Neuro-Oncology) response criteria — reproduced in full from Youmans & Winn 8e, Table 160.2, p. 1118.e3.

Criterion	Complete response	Partial response	Stable disease	Progressive disease
T1 Gd-enhancing disease (2-dimensional)	None	≥50% decrease	<50% decrease but <25% increase	≥25% increase*
T2/FLAIR disease	Stable or decreased	Stable or decreased	Stable or decreased	Increased*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable†
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse
Requirement for response	All	All	All	Any*

*Progression is established if this criterion is present. †An increase in corticosteroids alone does not qualify as progressive disease YW p.1118.e3.

- **Two extra RANO provisions worth quoting.** (i) Patients with progression of glioblastoma **within 3 months of the end of radiotherapy should not enter trials of novel agents** unless the recurrence is outside the high-dose radiotherapy volume **or is histologically confirmed** — otherwise the apparent success is merely resolution of pseudoprogression YW p.1118.e2. (ii) The **"hindsight" clause** — if suspected progression is unclear, treatment may continue, but if follow-up confirms progression the official date of progression is the date it was **first radiologically suspected** YW p.1118.e2.

4. Pseudoprogression and radiation necrosis — the single most important differential

- **The numbers.** "In up to **40%** of patients, MRI studies performed in the first month after radiotherapy or local chemotherapy may show increased enhancement", and "in **50%** of these cases … the increased enhancement reflects a transient increase in vessel permeability that is a result of radiotherapy, a phenomenon that improves with time and is designated **pseudoprogression**" YW p.1106. Early studies after the introduction of RT + temozolomide showed that **up to 20% of patients** may suffer pseudoprogression at the end of radiotherapy, and it may account for **up to half of all patients with a progressive lesion at that time-point** YW p.1118.e2.
- **Timing.** A transient increase in enhancement, oedema and mass effect "typically occurs between **3 and 12 months** following treatment" YW p.1010. Radiation effects are classified as **acute (within weeks), subacute (within 3-4 months)** and **late (4 months to many years)**; **70% of focal late radiation injuries occur within 2 years** of therapy YW p.1010.
- **On conventional imaging they are indistinguishable.** "On CT and standard MRI sequences, radionecrosis and pseudoprogression are often indistinguishable from tumour, including enlargement or new enhancement, oedema, and mass effect. **Knowing the radiation dose lines can be very helpful because radionecrosis should not occur distant from the treated regions**" YW p.1010.
- **Perfusion (DSC-MRI / rCBV)** improves accuracy: "typically, radionecrosis would not be expected to demonstrate elevated rCBV" YW p.1010. In the illustrated case, the nodular enhancing region had **high diffusivity on the ADC map and low rCBV**, both of which fell over the following 2 months — compatible with radiation necrosis YW p.1010.
- **MRS.** Higher Ch:Cr and Ch:NAA ratios are seen in tumour recurrence than in normal brain or treatment necrosis; a meta-analysis gives the **Ch:NAA ratio a sensitivity of 0.88 and specificity of 0.86** for separating recurrence from radionecrosis, improved further by multivoxel acquisition (chemical shift imaging) YW p.1010.
- **FDG-PET** has a broad and inconsistent range of sensitivity and specificity: recurrent tumour with altered metabolism may show **low** FDG uptake (false negative), while radiation necrosis with inflammation shows **increased** glucose metabolism (false positive) YW p.1010. Amino-acid and amino-acid-analogue tracers give better tumour-to-brain contrast, and **fluorodopa is superior to FDG** in evaluating recurrent low- and high-grade glioma YW p.1106.

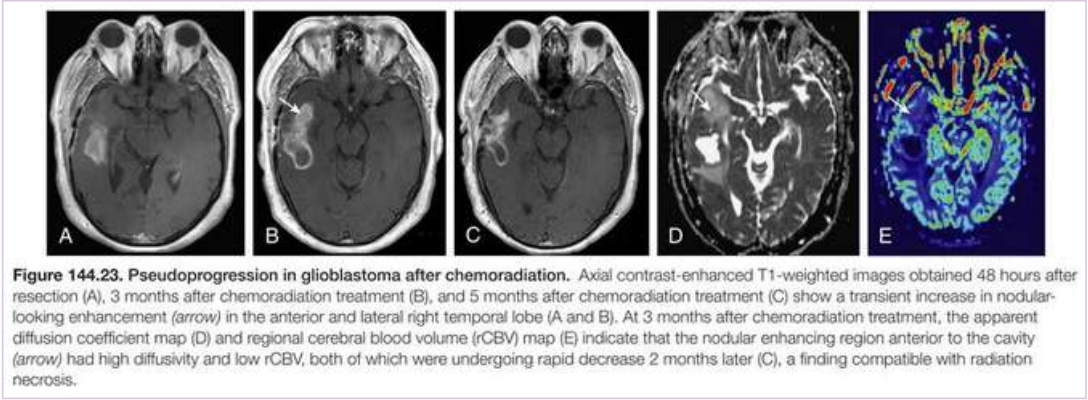


Figure 144.23. Pseudoprogression in glioblastoma after chemoradiation. Axial contrast-enhanced T1-weighted images obtained 48 hours after resection (A), 3 months after chemoradiation treatment (B), and 5 months after chemoradiation treatment (C) show a transient increase in nodular-looking enhancement *(arrow)* in the anterior and lateral right temporal lobe (A and B). At 3 months after chemoradiation treatment, the apparent diffusion coefficient map (D) and regional cerebral blood volume (rCBV) map (E) indicate that the nodular enhancing region anterior to the cavity *(arrow)* had high diffusivity and low rCBV, both of which were undergoing rapid decrease 2 months later (C), a finding compatible with radiation necrosis.

Reproduced from Youmans & Winn 8e, Fig. 144.23, p. 1010 — Label when you reproduce it: (A) axial contrast-enhanced T1 48 hours after resection; (B) 3 months after chemoradiation, transient increase in nodular enhancement (arrow) in the anterior and lateral right temporal lobe; (C) 5 months after chemoradiation with the nodule resolving; (D) ADC map showing high diffusivity in the nodule; (E) rCBV map showing LOW regional cerebral blood volume — the two findings that made the diagnosis radiation necrosis rather than recurrence.

5. Advanced imaging for the recurrent lesion

- **MRS.** The most useful metabolites are **NAA** (neuronal marker, falls with any neuronal damage), **choline** (cell-turnover marker, elevated in neoplasia and in glioblastoma "many times higher than in normal brain"), **creatine, myo-inositol, lactate and lipid** YW p.996. Lipid and lactate are best measured at short TE (32 ms) and rise with grade because of hypoxia and necrosis, and are associated with poor survival YW p.996.
- **An elevated Ch:NAA ratio in the peritumoral region indicates tumour infiltration rather than oedema**; thresholds quoted are **Ch:NAA >2, lactate:NAA >0.25 and the presence of lipid** to demarcate infiltrated parenchyma, and **Ch:NAA >2.1** to identify aggressive phenotype within a glioblastoma for radiosurgical boosting YW p.996. The MRS abnormality was at least **24% larger** than the T2-defined abnormality in one series YW p.996.
- **2-Hydroxyglutarate.** MRS has been optimised to detect IDH1/IDH2-mutant gliomas through the elevated **2-hydroxyglutarate** oncometabolite, allowing preoperative diagnosis, definition of extent and post-treatment monitoring YW p.996; the same principle is used to monitor IDH-mutant tumours, although technical challenges have limited uptake YW p.1118.e3.
- **Perfusion.** rCBV correlates with astrocytic tumour grade, identifies focal regions for biopsy, differentiates glioma from metastasis and distinguishes recurrence/progression from post-therapy radiation necrosis YW p.995.
- **Standard MRI remains the cornerstone** — T1 before and after contrast, T2/FLAIR and diffusion-weighted imaging — and a **standardised brain tumour imaging protocol** is now routine in trials YW p.1118.e3.

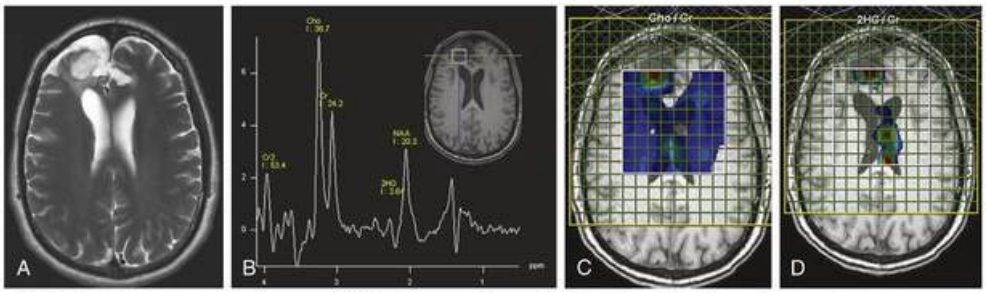


Figure 144.2. Magnetic resonance spectroscopy (MRS) of recurrent glioma. (A) Axial T2-weighted image shows an enlarging mass adjacent to the surgical cavity from previously resected oligoastrocytoma (World Health Organization grade II) with isocitrate dehydrogenase 1 mutation. (B) Single-spectrum MRS with region of interest placed over the mass, obtained at echo time of 97 milliseconds, showed elevated choline *(Cho)* and decreased *N*-acetyl aspartate *(NAA)* levels. There is also a prominent peak at 2.2 consistent with 2-hydroxyglutarate *(2HG)*. (C and D) Color maps from multivoxel MRS imaging (chemical shift imaging) show Cho–creatine *(Cr)* (C) and 2HG:Cr (D) within the mass in comparison with adjacent brain. (*Courtesy Dr. Alexander Lin, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*)

Reproduced from Youmans & Winn 8e, Fig. 144.2, p. 996 — Label when you reproduce it: (A) axial T2 showing an enlarging mass beside the cavity of a previously resected IDH1-mutant grade II oligoastrocytoma; (B) single-voxel MRS at TE 97 ms with elevated choline (Cho), reduced N-acetyl aspartate (NAA) and a prominent peak at 2.2 ppm corresponding to 2-hydroxyglutarate (2HG); (C and D) colour maps from multivoxel chemical shift imaging showing raised Cho:Cr and 2HG:Cr within the mass compared with adjacent brain.

6. Pitfalls specific to the post-operative and post-treatment brain

- **Postoperative enhancement follows a predictable sequence.** Within the first 3 days a **thin linear enhancement** develops around the resection cavity; thereafter it may become **thick and nodular**; dural and meningeal enhancement is more pronounced and lasts longer. Linear enhancement may persist **3-6 months** and meningeal enhancement much longer YW p.1118.e4.
- **Therefore MRI within 24-48 hours of surgery is mandatory** to define residual enhancing tumour; **nodular or mass-like enhancement in an area that was tumour preoperatively on a scan done within 48 hours is highly suggestive of residual tumour** YW p.1118.e4. A scan at 4-6 weeks may falsely suggest tumour growth and disturb radiotherapy planning YW p.1118.e4.
- **DWI should be part of the standard postoperative evaluation** to identify peri-cavity ischaemia that will later enhance and be mistaken for tumour YW p.1118.e4.
- **Pseudoresponse.** Bevacizumab and other anti-VEGF agents reduce abnormal vessel permeability and therefore reduce contrast uptake **without a true antitumour effect** — the RANO criteria consequently give more weight to T2/FLAIR in these patients YW p.1118.e3.
- **Local therapies cause the same trap.** Carmustine wafers, locally delivered targeted toxins, gene constructs and stereotactic radiosurgery all induce inflammatory responses, ischaemic lesions or radiation necrosis that mimic progression YW p.1118.e4.
- **Histological confirmation.** Where the distinction cannot be made and the answer changes management, tissue is the arbiter — and RANO itself permits entry into trials within 3 months of radiotherapy only if the recurrence is **histologically confirmed** YW p.1118.e2. Note the frozen-section caveat: necrotic tissue is "almost impossible to interpret", freezing artefact limits interpretation, and larger fragments are therefore favoured YW p.911.

(b) Indications for surgery in recurrent glioblastoma [3]

7. Who is a candidate — Youmans' explicit statement

- **"Approximately 20% to 30% of patients with recurrent glioblastoma are candidates for a second resection, which is typically considered when the lesions are large, circumscribed, and causing neurological deficits"** YW p.1111. Learn that sentence verbatim; it contains the three anatomical/clinical criteria (large, circumscribed, symptomatic) and the proportion.
- **The four goals of surgery apply equally at recurrence** YW p.1107:
  - **(1) To obtain a tissue diagnosis** — imaging cannot reliably predict tumour type or grade, so tissue is required in

essentially all cases before treatment recommendations and prognostication YW p.1107. At recurrence this additionally resolves recurrence versus radionecrosis and permits re-testing of molecular markers.

- **(2) To decrease mass effect** — relief of mass effect improves signs and symptoms, **lessens steroid dependence** and can prevent early death from progressive mass effect YW p.1107.
- **(3) To reduce the tumour burden** — extensive resection may reduce burden to a point that makes radiotherapy and chemotherapy more effective YW p.1110.
- **(4) To increase survival and quality of life** YW p.1107.

8. The evidence that extent of resection matters at re-operation

- **McGirt's 700-patient series is the key data set.** Both GTR and NTR were **independently** associated with prolonged survival, and this was observed **"for both primary and revision resection of glioblastoma, independent of age, KPS score, subsequent resection, and the two adjuvant therapies proven to influence survival (carmustine-loaded polymer and TMZ)"**; longer survival was seen after GTR than after NTR for **both** primary and revision resection YW p.1108.
- **The revision-resection survival figures to quote** — after revision surgery for recurrent GBM, median survival was **11 months after GTR, 9 months after NTR and 5 months after STR** (compare 13 / 11 / 8 months after primary resection) YW p.1101.
- **Definitions matter in the exam**: GTR = no residual enhancement on MRI; NTR = rim enhancement of the resection cavity; STR = residual **nodular** enhancement YW p.1101.
- **Quantitative thresholds.** Chaichana's volumetric study of 259 newly diagnosed GBMs found the minimum thresholds significantly associated with survival and recurrence were **70% resection and 5 cm³ residual volume**; >70% resection gave median survival **14.4 vs 10.5 months** (P = .0003) and PFS **9.0 vs 7.1 months** (P = .01); residual volume <5 cm³ gave **15.3 vs 11.6 months** (P = .001) and PFS **9.2 vs 7.5 months** (P = .005) YW p.1109. Lacroix's threshold was **98%**, Sanai's **78%**, Grabowski's **98% with a maximum residual volume of 2 cm³** [YW pp. 1109-1110].
- **But not at any price.** Chaichana and colleagues "reported … that **GTR does not have to be achieved at risk of causing an irreversible deficit, inasmuch as poor functional outcome negatively affects survival even when GTR is achieved**" [YW pp. 1109-1110]. Newly acquired postoperative motor and language deficits **reduce overall survival** YW p.1101. The operative principle is therefore **maximal resection with minimal functional impairment**, together with standard chemoradiation YW p.1101.

Table 3 · Variables independently associated with overall survival in glioblastoma (Cox proportional hazards model) — reproduced from Youmans & Winn 8e, Table 159.1, p. 1102.

Variable	Hazard ratio	P value
Age (increasing)	1.023	.001
Karnofsky Performance Scale score (increasing)	0.988	.018
Gross total resection	0.449	.001
Near-total resection	0.614	.002
Gliadel wafers	0.793	.056
Postoperative temozolomide	0.546	.001
Increasing % extent of resection	0.995	.008
>70% resection	0.631	.0006
Increasing residual volume	1.019	.004
<5 cm³ residual volume	0.725	.01

9. Patient-side indications and contraindications

- **Favourable factors that should push you towards re-operation** — the three most significant prognostic factors

overall are **age, KPS score and extent of resection**, and extent of resection is "**the only one that is potentially modifiable**" [YW pp. 1109, 1111]. Other favourable factors are **IDH1 or IDH2 mutation and MGMT promoter methylation** YW p.1111.

- **Adjuvant opportunity.** Re-operation permits **placement of carmustine-loaded biodegradable wafers**, which is the setting in which they were originally licensed (recurrent malignant glioma) [YW pp. 1100, 1110]; it also allows **convection-enhanced delivery catheters**, **direct intracavitary injection of viral vectors or immunotherapy**, and **laser interstitial thermal therapy** as alternatives when the tumour is unresectable [YW pp. 1135-1137].
- **Relative contraindications**:
  - **Recent bevacizumab** — antiangiogenic drugs are "associated with an increased risk of ischemic and hemorrhagic events and the relative contraindication to further surgery after their use" YW p.1111.
  - **Poor KPS, advanced age and eloquent/deep diffuse disease** where GTR is unattainable — biopsy alone or non-surgical salvage is then appropriate [YW pp. 1107, 1110].
  - **Gliomatosis-type multilobar disease** — here "the role of surgery is often restricted to biopsy or decompressive craniectomy, or both, in selected patients in whom intracranial pressure is substantially high" YW p.1112.
- **Operative risks to quote when consenting.** Postoperative haematomas cause neurological deficit in **1% to 5%** of patients and about **12.5% of those needing re-craniotomy die within 30 days** of the first operation YW p.1065; the **"wounded glioma syndrome"** (haemorrhage into incompletely resected vascular tumour) and injury to sylvian vessels during ultrasonic aspiration of a recurrent temporal GBM are the archetypal catastrophes YW p.1065.

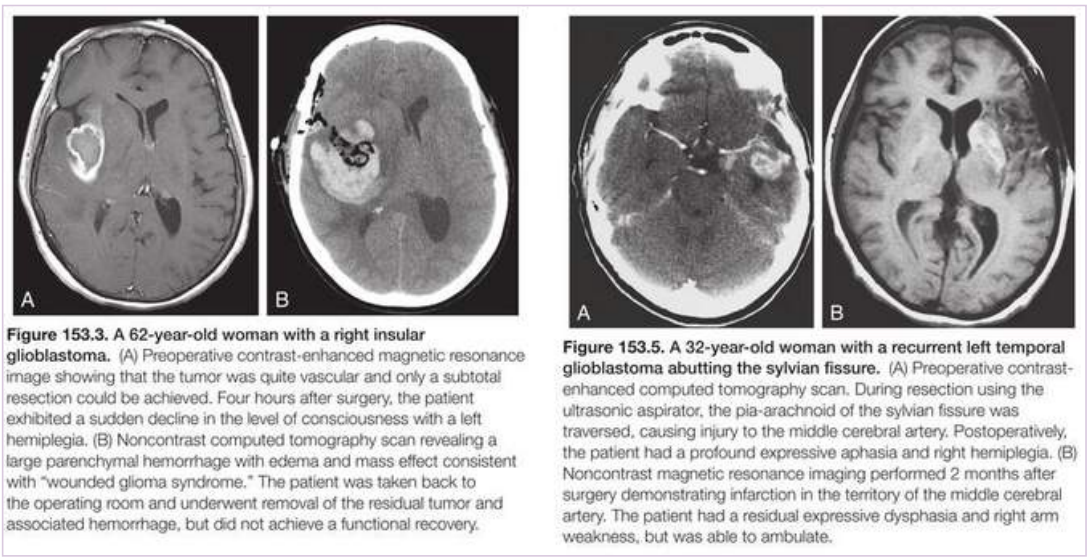


Figure 153.3. A 62-year-old woman with a right insular glioblastoma. (A) Preoperative contrast-enhanced magnetic resonance image showing that the tumor was quite vascular and only a subtotal resection could be achieved. Four hours after surgery, the patient exhibited a sudden decline in the level of consciousness with a left hemiplegia. (B) Noncontrast computed tomography scan revealing a large parenchymal hemorrhage with edema and mass effect consistent with "wounded glioma syndrome." The patient was taken back to the operating room and underwent removal of the residual tumor and associated hemorrhage, but did not achieve a functional recovery.

Figure 153.5. A 32-year-old woman with a recurrent left temporal glioblastoma abutting the sylvian fissure. (A) Preoperative contrast-enhanced computed tomography scan. During resection using the ultrasonic aspirator, the pia-arachnoid of the sylvian fissure was traversed, causing injury to the middle cerebral artery. Postoperatively, the patient had a profound expressive aphasia and right hemiplegia. (B) Noncontrast magnetic resonance imaging performed 2 months after surgery demonstrating infarction in the territory of the middle cerebral artery. The patient had a residual expressive dysphasia and right arm weakness, but was able to ambulate.

Reproduced from Youmans & Winn 8e, Fig. 153.5, p. 1065 — Label when you reproduce it: a 32-year-old woman with a recurrent left temporal glioblastoma abutting the sylvian fissure. (A) Preoperative contrast-enhanced CT. (B) Non-contrast MRI 2 months after surgery showing MCA-territory infarction, because the pia-arachnoid of the sylvian fissure was traversed with the ultrasonic aspirator and the middle cerebral artery injured. Note the outcome: profound expressive aphasia and right hemiplegia, resolving to residual dysphasia and arm weakness.

10. Adjuncts that make a second resection safer and more complete

- **5-ALA fluorescence-guided surgery** is the one agent tested in a large phase 3 randomised trial: it permitted more complete resections of contrast-enhancing tumour (**65% vs 36%**, P > 0.001) and improved 6-month progression-free survival YW p.1090.e2. Dose is **20 mg/kg as an oral solution at least 3 hours before induction**; fluorescence is visible from 3 hours and peaks at 6-8 hours; side effects are hypotension, transient liver-enzyme rise, nausea and transient skin photosensitivity YW p.1090.e2.
- **Specifically in recurrence** — "multiple patient studies suggest a survival benefit after complete resection of contrast-enhancing tumour in recurrent HGGs, making 5-ALA an attractive tool for recurrent gliomas as well. **Higher rates of complete resection and longer overall survival were associated with the use of 5-ALA in patients undergoing repeat surgery**"; the majority of recurrent gliomas fluoresce and fluorescence predicts the presence of

tumour cells (positive predictive value **99.5%** for solid fluorescence in recurrent HGG) [YW pp. 1090.e2]. **Caveat**: sensitivity and specificity may be impaired by post-therapeutic necrosis, vascular hyalinisation and gliosis YW p.1090.e2 .

- **Awake craniotomy and cortical/subcortical mapping, DTI, functional MRI, neuronavigation, intraoperative ultrasound and intraoperative MRI** all increase extent of resection while reducing injury to eloquent cortex; brain shift during resection makes preoperative image-based planning inaccurate, which is the specific argument for intraoperative imaging [YW pp. 1100, 1107].

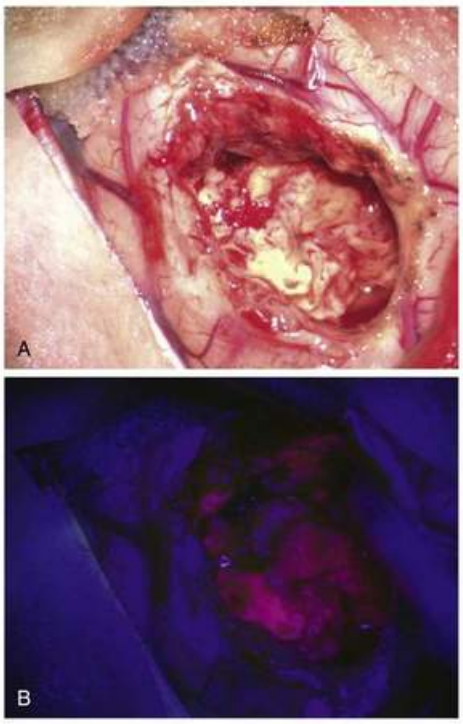


Figure 157B.2. Fluorescence-guided surgery using 5-ALA (20 mg/kg body weight 4 hours before surgery) for resection of a malignant glioma. (A) Tumor cavity under white-light illumination. (B) Tumor cavity under blue-light illumination. The image shows the different qualities of fluorescence: intense, red fluorescence versus pale, pink fluorescence, in solid tumor and the tumor infiltrating zone, respectively. Normal brain tissue does not show any signs of fluorescence and appears blue. 5-ALA accumulates specifically in malignant glioma tissue.



Figure 157B.3. Fluorescence-guided surgery with fluorescein as an off-label use (5 mg/kg body weight at the time of skin incision) for resection of a malignant glioma. (A) Tumor cavity under white-light illumination. (B) Tumor cavity under blue-light illumination. Green-yellow fluorescence can be seen within the tumor; however, as a result of extravasation, normal brain tissue, edematous brain, and the cutting edges are also stained. Fluorescein is not tumor-specific and rather a marker of a disrupted blood-brain barrier.

Fluorescein Fluorescence-guided Surgery for

Reproduced from Youmans & Winn 8e, Fig. 157B.2, p. 1090.e4 — Label when you reproduce it: fluorescence-guided surgery using 5-ALA, 20 mg/kg given 4 hours before surgery, for resection of a malignant glioma. (A) Tumour cavity under white light. (B) The same cavity under blue light — mark the two qualities of fluorescence: intense red fluorescence of solid tumour versus pale pink fluorescence of the infiltrating zone, with non-fluorescent normal brain appearing blue.

(c) Temozolomide [4]

11. What it is and how it works

- **Class.** Temozolomide is an **alkylating agent** — specifically one of the **non-classic alkylators**, grouped with procarbazine, alongside the nitrogen mustards (cyclophosphamide, ifosfamide), aziridines (thiotepa), nitrosoureas (carmustine, lomustine) and platinums (cisplatin, carboplatin) YW p.1031.
- **Mechanism.** Alkylating agents "directly damage the DNA through covalent binding of alkyl groups to cellular molecules"; they are **not cell-cycle specific** and depend on cell proliferation for activity, and their activity is enhanced by **radiation, hyperthermia and inhibition of DNA repair** YW p.1031. Specifically, temozolomide and the nitrosoureas "exert their cytotoxic effect on DNA by **methylating guanine at the O6 position**" YW p.1029.
- **Route and pharmacological advantage.** Temozolomide is given **orally** — an important property in neuro-oncology, because only un-ionised, low-molecular-weight (generally ≤400) lipophilic drugs cross an intact blood-brain barrier by passive diffusion [YW pp. 1030, 1032].

12. Resistance — MGMT, and why it is the marker that matters

- **The repair enzyme.** "The resultant O6-methylguanine can be repaired by the **MGMT** enzyme via removal of the alkyl group; thus **tumours expressing high levels of MGMT are considered resistant to alkylating agents**" YW p.1029. MGMT is "a ubiquitous cellular enzyme largely responsible for resistance to the cytotoxic action of DNA alkylating agents such as temozolomide, carmustine, lomustine, and procarbazine" YW p.901.
- **The prognostic/predictive value.** "To date, **MGMT promoter methylation status is the single most important prognostic marker for predicting benefit from chemotherapy with alkylating agents**" YW p.901. The 2005 phase 3 trial established that patients whose tumours showed MGMT promoter methylation survived longer after treatment than those without YW p.901.
- **The numbers.** MGMT-methylated patients (**45%** of the total) treated with temozolomide survived a median of **21.7 months with a 2-year survival of 46%**; unmethylated patients had a median survival of **12.7 months and 2-year survival of 13.8%** [YW pp. 1110-1111].
- **Other resistance mechanisms.** Drug resistance operates through altered uptake/efflux (transport-mediated), altered DNA repair, altered drug activation/inactivation, altered target-enzyme levels or affinity, and impaired apoptosis; **the first two are particularly important in neuro-oncology** YW p.1029. **MDR1/P-glycoprotein** overexpression is "one of the major factors of failure of chemotherapy against CNS tumours", pumping drug out of cells and acting as a permeability barrier; Pgp is highly expressed at the BBB and blood-CSF barrier and in tumour endothelium YW p.1029. The **base excision repair pathway**, with **PARP-1** as the pivotal enzyme, also renders alkylators ineffective by repairing N7-methylguanine and N3-methyladenine adducts — hence PARP inhibitors (veliparib, olaparib) with RT and/or temozolomide in recurrent GBM phase 1/2 trials YW p.1029.

13. The Stupp regimen and its outcome

- **Concurrent phase**: temozolomide **75 mg/m² daily for 6 weeks, continuous, concurrent with radiotherapy** [YW pp. 1029, 1032].
- **Adjuvant phase**: temozolomide **150-200 mg/m² orally, daily for 5 days every 28 days**, for 6 cycles (Youmans' chemotherapy table gives 6-12 months) [YW pp. 1029, 1032, 1110].
- **Standard of care**: "maximal, safe resection followed by chemoradiation with **Stupp protocol** is standard of care" YW p.1100. Stupp's prospective randomised trial demonstrated a median overall survival of **14.6 months** with resection plus 60 Gy radiotherapy plus temozolomide [YW pp. 1100, 1110]; the regimen "prolongs the median survival to **14.6 months from 12.1 months** with radiotherapy alone" YW p.1029.
- **Multimodality escalation.** Attenello's analysis of survival after GBM resection: radiotherapy alone **9 months** (n = 147); Gliadel + radiotherapy **13 months** (n = 45); radiotherapy + temozolomide **15 months** (n = 52); **Gliadel + radiotherapy + temozolomide 20 months** (n = 32) YW p.1111. The Johns Hopkins group reported a mean survival of **20 months** when carmustine wafers, temozolomide and radiotherapy were all combined after resection YW p.1110.
- **Dose intensification.** "Increasing dose intensity, defined as the amount of drug delivered per unit time, maximizes the cell kill", and "a dose reduction of chemotherapeutic agents by 20% can **lower the cure rate by 50%**" YW p.1029. However, **dose-dense temozolomide during the adjuvant phase did not improve efficacy in newly diagnosed GBM** YW p.1029.

Table 4 · Chemotherapy regimens and doses for malignant glioma — reproduced from Youmans & Winn 8e, Table 147.1 (p. 1032) and Table 159.5 (p. 1110).

Setting	Regimen and dose
Glioblastoma, first line	Temozolomide 75 mg/m² × 6 weeks concurrent with RT; then adjuvant 150-200 mg/m² daily × 5 days every 28 days for 6-12 months
Glioblastoma, first line (alternative)	Lomustine (CCNU) 100 mg/m² day 1 + temozolomide 100 mg/m² days 2-6, during and after RT, every 6 weeks up to 6 cycles
Glioblastoma, salvage	Carmustine (BCNU) 150-200 mg/m² day 1 every 6 weeks
Glioblastoma, salvage	Carboplatin (AUC 4-7 mg/mL/min)

Glioblastoma, salvage	Irinotecan 340 mg/m² (on enzyme-inducing AEDs) or 125 mg/m² (not on EIAEDs) weekly × 4 weeks, then 2 weeks rest, every 6 weeks
Glioblastoma, salvage	Lomustine (CCNU) 90-110 mg/m² every 6 weeks
Glioblastoma, salvage — dose-dense TMZ	50 mg/m² daily for 12 months; **or** 1 week on (120 mg/m²/day)/1 week off; **or** 3 weeks on (75 mg/m²/day)/1 week off
Anaplastic glioma WHO III	RT 60 Gy then PCV (procarbazine 60 mg/m² PO days 8-21, CCNU 110 mg/m² PO day 1, vincristine 1.4 mg/m² IV days 8 and 29) every 6 weeks × 6 cycles; or RT then TMZ 150-200 mg/m² for 12 cycles
Bevacizumab (progression)	10 mg/kg IV every 2 weeks until progression or intolerable adverse effects

14. Temozolomide at recurrence

- **Rechallenge.** "In carefully selected patients with recurrent GBM, **rechallenge with dose-dense temozolomide can be an option, particularly in those with MGMT promoter mutation and patients whose disease has not progressed during the first six cycles of conventional adjuvant temozolomide or who have a treatment-free interval**"; whether standard-dose temozolomide is equally efficacious is unclear YW p.1029.
- **Position among salvage options.** "The main strategies for recurrent glioblastoma after the standard treatment are **nitrosourea-based regimens (carmustine, lomustine), alternate-day dosing regimens of TMZ, and bevacizumab (Avastin)**" YW p.1111. EANO's recommendation for progression in GBM under 65-70 years is **revision resection, reirradiation, rechallenge chemotherapy, or bevacizumab** YW p.1110.
- **Dual alkylator combination.** The phase 3 **CeTeG/NOA-09** trial randomised 141 newly diagnosed **MGMT-methylated** GBM patients under 70 to temozolomide + CCNU versus temozolomide alone; in the modified intention-to-treat analysis of 129 patients, overall survival was superior with the combination (**43.1 vs 31.4 months; HR 0.60**), at the cost of worse haematological toxicity and nausea. The rationale is synergy through different mechanisms of DNA damage, potentially overcoming temozolomide-induced mismatch-repair mutation; the findings should be interpreted cautiously given the small sample YW p.1030.
- **Elderly patients.** For GBM over 65-70 years Youmans lists **resection or biopsy followed by radiotherapy or temozolomide, with or without radiotherapy, on the basis of MGMT status and performance status** YW p.1110.

15. Toxicity, interactions and practical prescribing

- **Common adverse effects of temozolomide**: **nausea, vomiting and bone-marrow suppression** YW p.1032. Class effects of alkylators include nausea, vomiting, haematopoietic suppression, immunosuppression, gonadal toxicity, teratogenesis, interstitial pneumonitis (carmustine) and renal toxicity (cyclophosphamide); **secondary acute myelogenous leukaemia is a rare complication occurring 4 to 7 years after treatment** YW p.1031.
- **Antiepileptic interaction.** Phenytoin and carbamazepine **induce hepatic cytochrome P-450**, increasing the metabolism of chemotherapeutic agents and diminishing their effectiveness; **non-inducing agents such as levetiracetam are preferred** YW p.1107. Note that irinotecan dosing is doubled (340 vs 125 mg/m²) in patients taking enzyme-inducing AEDs YW p.1032.
- **Steroid co-morbidity.** Prolonged dexamethasone brings Cushing syndrome, steroid myopathy, **uncontrolled hyperglycaemia (independently associated with decreased survival in malignant astrocytoma surgery)**, immunosuppression with risk of *Pneumocystis jirovecii* pneumonitis, osteoporosis and compression fractures; vitamin D, calcium and bisphosphonates should be instituted YW p.1107.
- **Venous thromboembolism** complicates 20-30% of malignant glioma patients; anticoagulation is generally safe after the immediate postoperative period, intratumoral haemorrhage risk is low, LMWH is more effective and safer than warfarin, and **IVC filters carry high complication rates** YW p.1107.
- **Cell-cycle context.** Remember the cell-cycle figure: alkylating agents are **cell-cycle non-specific**, in contrast to methotrexate (G1 and S), vinca alkaloids and podophyllotoxins (M) and camptothecin analogues such as irinotecan (G2) YW p.1029.

TABLE 159.1 Variables Associated With Overall Survival of Glioblastoma Multiforme in Proportional Hazards Regression Analysis (Cox Model)

	Multivariate Analysis	
Variable	**Hazard Ratio**	***P* Value**
Age[a]	1.023	.001
Karnofsky Performance Scale score[a]	0.988	.018
Gross total resection	0.449	.001
Near-total resection	0.614	.002
Gliadel wafers	0.793	.056
Postoperative temozolomide[b]	0.546	.001
Increasing % extent of resection	0.995	.008
>70% of resection	0.631	.0006
Increasing residual volume	1.019	.004
<5-cm^3 residual volume	0.725	.01

Modified from McGirt MJ, Chaichana KL, Gathinji M, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. J Neurosurg. 2009;110:156–162, and Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, et al. Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol. 2014;16(1):113–122.

In a large cohort of patients, decreasing age, increasing Karnofsky Performance Scale score, increasing extent of resection, treatment with Gliadel wafer, and treatment with temozolomide, were independently associated with improved overall survival. Patients who underwent either gross total resection or near-total resection exhibited an independent survival benefit in comparison with patients who underwent subtotal resection, independent of subsequent treatment modalities. Chaichana and colleagues[30] made three-dimensional volumetric tumor measurements and dichotomized percentage of resection and residual tumor volume to find the minimum percentage of resection and maximal residual volume significantly associated with survival.

[a]Increasing variable.

[b]Includes temozolomide administered concomitantly with radiotherapy or as delayed adjuvant treatment.



Figure 159.3. Placement of carmustine-loaded implants (Gliadel wafers). After resection of a malignant glioma, the carmustine-loaded biodegradable polymers were placed within the tumor cavity. As the wafers dissolve, they release carmustine locally and provide direct delivery of chemotherapy to the tumor cavity and the surrounding brain parenchyma, where brain tumor microsatellites may be present. (*From Lesniak MS, Brem H. Targeted therapy for brain tumours. Nat Rev Drug Discov. 2004;3:499–508.*)

of 53 years.[61,62] However, gliosarcoma may also occur in children, and in rare cases, infantile gliosarcoma has been reported.[65] Gliosarcoma occurs in a male-to-female ratio of 1.8:1.[61,62]

Clinical Manifestations

Anaplastic Astrocytoma and Glioblastoma

Reproduced from Youmans & Winn 8e, Fig. 159.3, p. 1102 — Label when you reproduce it: placement of carmustine-loaded biodegradable implants (Gliadel wafers) lining the walls of the cavity after resection of a malignant glioma. In the label note that up to eight wafers may be placed, that BCNU is released over 5 days while the polymer matrix disintegrates over 6-8 weeks, and that peak systemic BCNU levels are less than 1/600 of those after systemic administration and undetectable within 24 hours.

16. Where temozolomide sits among the other local and systemic options

- **Local delivery.** Carmustine-loaded wafers produce high local concentration; a limitation is that drug moves by **diffusion**, penetrating only **2 to 4 mm with a 250- to 100-fold drop in concentration over that distance** YW p.1134. Reported local toxicity includes **increased infection, malignant oedema, seizures, wound breakdown, CSF leakage and intracranial hypertension**; "although clinical trials have demonstrated improved survival in glioma patients receiving BCNU wafers compared with placebo, subsequent trials revealed **superiority of oral temozolomide with concurrent radiation followed by monotherapy with temozolomide in terms of overall survival**" [YW pp. 1031, 1134].
- **Convection-enhanced delivery** uses bulk flow from a small hydrostatic pressure gradient and is therefore independent of molecular weight and diffusivity, distributing small and large molecules over large regions; infusion rates are typically **1-10 µL/min**, and the ratio of volume of distribution to volume of infusion ranges from **3:1 in oedematous brain to 10:1 in the compacted fibres of the brainstem** [YW pp. 1134-1135].
- **Intra-arterial and BBB-disruption strategies** increase delivery 10- to 100-fold with mannitol, but phase 3 trials have not demonstrated improved efficacy over intravenous delivery, and complications include **seizures (6-7%), transient neurological symptoms (2.5-20%) and stroke (4%)** [YW pp. 1030, 1132-1133].
- **Tumour-treating fields.** "The most recent paradigm shift has been the addition of tumour treatment electric fields" — the NovoTTF-100A (Optune) device, approved by the FDA in 2011 for recurrent glioma and in 2015 for newly diagnosed lesions after **EF-14 established improved overall survival by adding 4.9 months** [YW pp. 1100, 1111].
- **Bevacizumab** markedly improves PFS and reduces steroid requirement (improving quality of life) but "the available data do not show an OS benefit"; current data suggest any clinical benefit in glioma is **due to oedema control** [YW pp. 1111, 1118.e3].

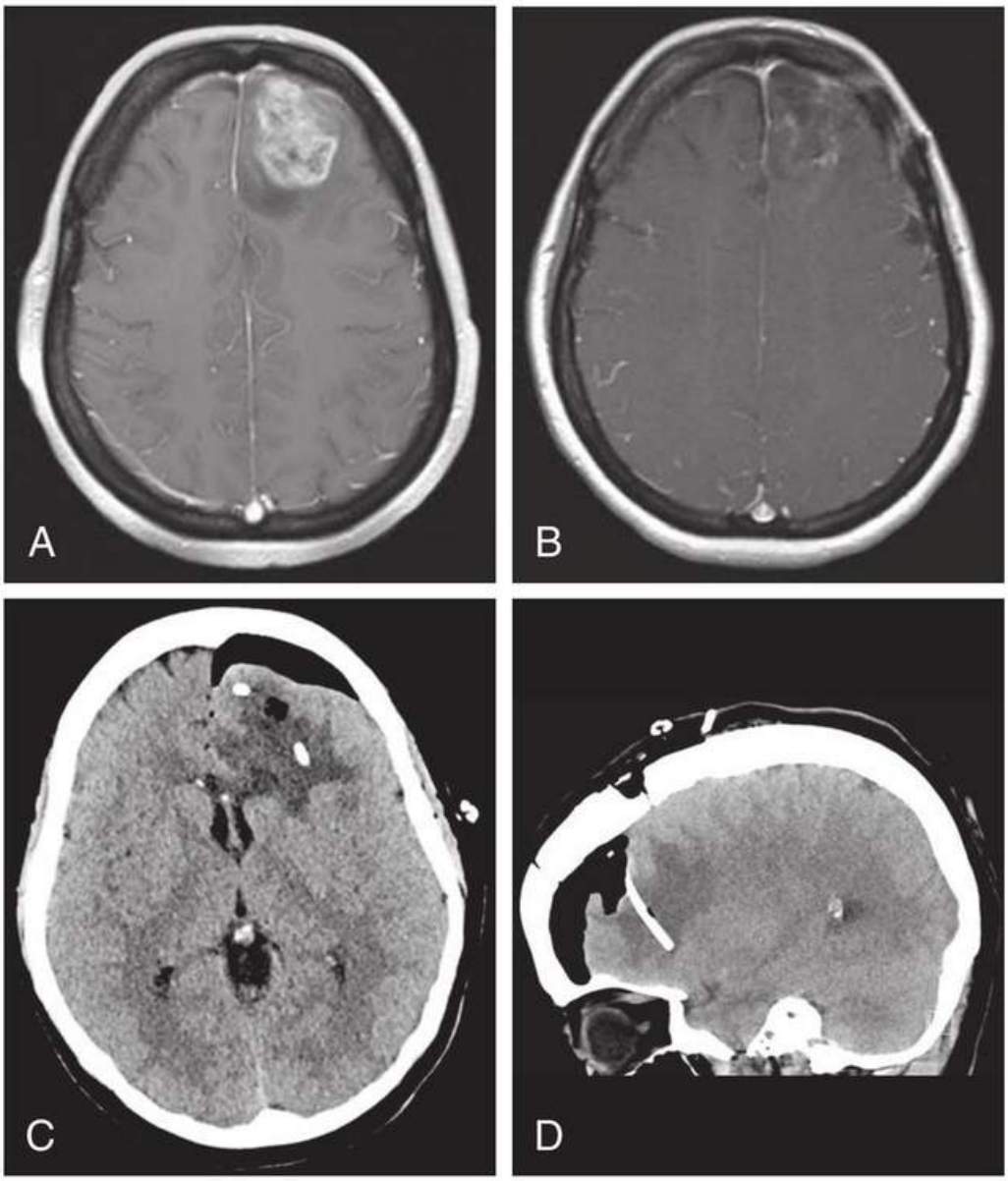


Figure 162.4. Patient with recurrent glioblastoma underwent repeat surgical resection and placement of multiple convection-enhanced delivery catheters for postoperative infusion of carboplatin over 72 hours. Preoperative (A) and postoperative (B) T1-weighted postcontrast MR images demonstrate resection of the left frontal tumor. Axial (C) and sagittal (D) CT scans show infusion catheter placement into the brain around the resection cavity.

Reproduced from Youmans & Winn 8e, Fig. 162.4, p. 1135 — Label when you reproduce it: a patient with recurrent glioblastoma who underwent repeat resection and placement of multiple convection-enhanced delivery catheters for postoperative infusion of carboplatin over 72 hours. (A) Preoperative and (B) postoperative T1 post-contrast MRI showing resection of the left frontal tumour; (C) axial and (D) sagittal CT showing the infusion catheters placed in the brain around the resection cavity.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **"GBM will invariably recur, either locally or at a distant site"** — quote this, then quote Dandy's contralateral recurrence after hemispherectomy (1928).
- **RANO progression = ≥25% increase in the 2D enhancing area, OR increased T2/FLAIR, OR any new lesion, OR clinical deterioration** — *any one* suffices, and a steroid increase alone never qualifies.
- **Up to 40% of scans in the first month after chemoradiation show increased enhancement, and half of these are pseudoprogression.** Pseudoprogression affects up to 20% of newly diagnosed GBM and up to half of those "progressing" at the end of radiotherapy.
- **Radionecrosis does not occur outside the radiation dose lines** — the single most useful bedside discriminator. It shows **high ADC and low rCBV**; recurrence shows the opposite.
- **RANO bans trial entry for progression within 3 months of radiotherapy** unless it is outside the high-dose volume or histologically confirmed.
- **Ch:NAA >2 means infiltrating tumour, not oedema**; Ch:NAA distinguishes recurrence from radionecrosis with sensitivity 0.88 and specificity 0.86; 2-hydroxyglutarate on MRS means IDH mutation.
- **20-30% of recurrent GBMs are candidates for a second resection — large, circumscribed, causing neurological deficit.**
- **Revision resection survival: GTR 11, NTR 9, STR 5 months.** Primary resection: 13 / 11 / 8 months.
- **Thresholds: 70% resection and <5 cm³ residual** (Chaichana) — but never at the price of an irreversible deficit, because poor function negates the survival gain of GTR.
- **Recent bevacizumab is a relative contraindication to re-operation** (wound and haemorrhagic complications).
- **5-ALA 20 mg/kg orally ≥3 h preoperatively**; phase 3 trial gave complete resection in 65% vs 36%; positive predictive value of solid fluorescence in recurrent HGG is 99.5%.
- **Temozolomide = non-classic alkylator, oral, cell-cycle non-specific, methylates guanine at O6.**
- **Stupp: 75 mg/m²/day for 6 weeks with RT, then 150-200 mg/m² days 1-5 of each 28-day cycle × 6.** Median survival 14.6 vs 12.1 months.
- **MGMT promoter methylation is the single most important marker predicting benefit from alkylating chemotherapy**: methylated (45%) 21.7 months and 46% 2-year survival; unmethylated 12.7 months and 13.8%.
- **A 20% dose reduction halves the cure rate** — but dose-dense adjuvant temozolomide did not improve outcome in newly diagnosed GBM.
- **CeTeG/NOA-09: TMZ + CCNU in MGMT-methylated GBM gave 43.1 vs 31.4 months (HR 0.60).**
- **Never combine temozolomide with enzyme-inducing antiepileptics if avoidable** — phenytoin and carbamazepine induce CYP450 and reduce efficacy; use levetiracetam.
- **Multimodality survival ladder: RT alone 9 → Gliadel + RT 13 → RT + TMZ 15 → Gliadel + RT + TMZ 20 months.**

Pages read for this answer — Youmans & Winn 8e: 901, 911, 995, 996, 1010, 1029, 1030, 1031, 1032, 1065, 1090.e2, 1100, 1101, 1102, 1103, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1118.e1, 1118.e2, 1118.e3, 1118.e4, 1132, 1133, 1134, 1135, 1136, 1137

2016 - WHO classification of Glioblastoma multiforme and its full description.

LONG | DEC 2020 · Paper III · Q10 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 133 *Brain Tumors: An Overview of Current Histopathologic and Genetic Classifications*, §Astrocytomas, §Oligodendroglial Tumors and §Intraoperative Consultation, pp. 900-903, 911 (Figs. 133.1-133.4, pp. 900-903; **Table 133.1 — WHO 2016 Classification of Infiltrating Gliomas**, p. 900). Ch. 159 *Malignant Gliomas*, §Epidemiology, §Histopathology and Molecular Biology, §The 2016 World Health Organization CNS Classification, §Neuroimaging Studies, §Management and §Midline Gliomas, pp. 1100-1116 (Figs. 159.1-159.2, p. 1101; Figs. 159.4-159.6, pp. 1103-1106; **Table 159.2 — Grading of Selected CNS Tumors According to the 2016 WHO Classification**, p. 1105; Tables 159.1, 159.3-159.5, pp. 1102, 1108, 1110). Ch. 158 *Low-Grade Gliomas*, §Histologic Features, §Immunohistochemical Assessment and §Molecular Pathogenesis and Integrated Diagnosis, pp. 1092-1096 (Figs. 158.2-158.3, pp. 1093-1094). Supplementary: Ch. 10 *Magnetic Resonance Imaging*, p. 153 (Fig. 10.29); Ch. 296 *Fractionated Radiotherapy for Brain Tumors*, p. 2295 (Fig. 296.2); Ch. 147 *Principles of Chemotherapy*, pp. 1029-1032.

(a) The 2016 WHO classification of glioblastoma [3]

1. The conceptual shift — genotype now outranks phenotype

- **The 2016 revision was the first WHO CNS classification to use molecular parameters.** "The 2016 WHO classification uses **molecular parameters for the first time in addition to histology** to define several brain tumor entities. It presents **major restructuring of the glioma classification** and includes new entities such as glioblastoma, IDH wild-type; glioblastoma, IDH mutant; and diffuse midline gliomas (H3K27M mutated)" YW p.1105.
- **Historical sequence to quote**: the WHO classification of brain tumours was first published in **1979**, modified in **1993, 2000 and 2007**, and updated most recently in **2016** YW p.1105. The 2007 system "was widely criticized for relying on the histologic and morphologic characteristics of these lesions", being a four-tiered schema of pilocytic astrocytoma (grade I), low-grade astrocytoma (grade II), anaplastic astrocytoma (grade III) and glioblastoma (grade IV) YW p.1105.
- **The governing rule in cases of discordance**: "in cases of discordance, **the genotype trumps the histologic findings** (e.g., a tumor that resembles an anaplastic oligodendroglioma histologically but has IDH mutation and lacks 1p19q co-deletion will be considered astrocytic)" YW p.1105.
- **Why the change was necessary.** "Although the histologic grading criteria to distinguish among diffuse astrocytoma WHO grade II, anaplastic astrocytoma WHO grade III, and glioblastoma WHO grade IV are still utilized in the WHO 2016 classification system, **the increased understanding of the molecular alterations that drive astrocytomas challenges the prognostic value of grading on histologic grounds alone**"; "the presence or absence of IDH1/IDH2 mutations in an astrocytoma is a **more powerful predictor of tumor behavior than grading based on histologic features alone**" YW p.900.

2. The four major changes affecting the malignant glioma group

Youmans enumerates them exactly YW p.1105:

- **New entities — IDH wild-type glioblastoma**, **IDH mutant glioblastoma**, **diffuse midline glioma (H3K27M mutant)** and **diffuse leptomeningeal glioneuronal tumour**.
- **New variant** (a subtype of an entity with potential clinical significance) — **epithelioid glioblastoma**.
- **New histologic pattern — glioblastoma with primitive neuronal component (GB/PN)**, a renaming of glioblastoma with PNET-like component (GB-PNET).
- **Deletion — gliomatosis cerebri has been deleted as a distinct entity and is now considered a growth pattern**.
- In addition, **oligoastrocytoma (mixed glioma) was eliminated**, since nearly all morphologically mixed gliomas can be categorised as oligodendroglioma or astrocytoma on molecular features; the residual prior diagnoses of oligoastrocytoma and anaplastic oligoastrocytoma are now designated **NOS** [YW pp. 903, 1112].
- **The NOS ("not otherwise specified") designation** is used "to indicate that the defining molecular alterations … have not been evaluated and the diagnosis is based on histologic grounds alone" — usually because IDH testing is unavailable, "which is rare in modern centres" [YW pp. 903, 1105].

Table 1 · Grading of diffuse astrocytic and oligodendroglial tumours according to the 2016 WHO classification — reproduced in full from Youmans & Winn 8e, Table 159.2, p. 1105.

Entity	Grade
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH mutant	II
Oligodendroglioma, IDH mutant and 1p/19q co-deleted	II
Anaplastic astrocytoma, IDH mutant	III
Anaplastic oligodendroglioma, IDH mutant and 1p/19q co-deleted	III
Glioblastoma, IDH wild-type	**IV**
Glioblastoma, IDH mutant	**IV**

Diffuse midline glioma, H3 K27M mutant	**IV**
Other astrocytic tumours	
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III

3. The three glioblastoma entities of 2016, stated formally

- **Glioblastoma, IDH wild-type (WHO grade IV)** — "within glioblastoma diagnoses, **IDH wild-type is the most common (90% of cases)**. It denotes the lesion as **primary, or de novo, glioblastoma** and predominates in older patients" YW p.1105. Molecularly it carries **TERT promoter mutation, combined whole chromosome 7 gain and whole chromosome 10 loss (+7/−10), EGFR amplification and PTEN mutation/loss** [YW pp. 900, 901].
- **Glioblastoma, IDH mutant (WHO grade IV)** — "IDH mutant indicates the lesion as a **secondary glioblastoma**, having transformed from a lower grade astrocytoma, and is typically found in younger adults" YW p.1105. "In molecular terms, **IDH-wildtype GBM is the equivalent of primary GBM and IDH-mutant GBM is the equivalent of secondary GBM**", although rarely IDH-mutant GBM presents de novo YW p.901.
- **Glioblastoma, NOS** — used when IDH status has not been assessed YW p.1105.
- **Diffuse midline glioma, H3 K27M-mutant (WHO grade IV)** is the fourth grade IV diffuse glioma, discussed in §9 below.
- **Note the 2016 threshold for the diagnosis of glioblastoma itself**: "**the presence of necrosis is not required for a diagnosis of GBM; vascular proliferation, in conjunction with pleomorphism and increased mitotic activity, is sufficient according to WHO 2016 criteria**" YW p.900.
- **And the molecularly-defined escape clause**: "it is possible to make a diagnosis of '**diffuse astrocytoma with molecular alterations of glioblastoma**' in a patient with an infiltrating astrocytoma **without** the presence of vascular proliferation or necrosis, if the critical genetic alterations (**TERT promoter mutation, EGFR amplification, or +7/−10**) can be demonstrated" YW p.901. cIMPACT-NOW subsequently recommended a grade IV designation for this group — "**diffuse astrocytic glioma, IDH wild-type, with molecular features of glioblastoma**" — because such tumours "often follow a clinical course more typical of IDH wild-type glioblastoma than that of a low-grade glioma" YW p.1096.

Table 2 · WHO 2016 classification of infiltrating gliomas — reproduced in full from Youmans & Winn 8e, Table 133.1, p. 900.

Diagnosis	Common mutations	Additional characteristics
Astrocytomas		
Diffuse astrocytoma, IDH-mutant (grade II) Anaplastic astrocytoma, IDH-mutant (grade III) **Glioblastoma, IDH-mutant (grade IV)**	IDH1/IDH2; ATRX; TP53	Usually younger patients (40-50 years); present as lower-grade gliomas; **most glioblastomas in this group are secondary**
Diffuse astrocytoma, IDH-wildtype (grade II) Anaplastic astrocytoma, IDH-wildtype (grade III) **Glioblastoma, IDH-wildtype (grade IV)**	TERT promoter; EGFR amplification; +7/−10; PTEN mutation/loss	Usually older patients (>55 years); present as high-grade gliomas; **most glioblastomas in this group are primary**
Diffuse midline glioma, H3-K27M-mutant	H3.3 p.K27M	Midline location, infiltrating on histology, H3.3 p.K27M mutation
Oligodendrogliomas		
Oligodendroglioma, IDH-mutant, 1p/19q codeleted (grade II) Anaplastic oligodendroglioma, IDH-mutant, 1p/19q codeleted (grade III)	IDH1/IDH2; 1p/19q codeletion	ATRX is wild-type (ATRX mutation and 1p/19q codeletion are mutually exclusive); strong correlation with perinuclear clearing on histology

(b) Full description of glioblastoma [7]

4. Epidemiology — the numbers examiners ask for

- **GBM is "unfortunately both the most common glioma and the most malignant primary brain tumour arising in adults"** YW p.900. Malignant astrocytomas are the most common primary brain tumour in adults YW p.1101.
- **Incidence data** YW p.1101:
  - Primary malignant CNS tumours account for about **2% of all cancers** but a disproportionate share of cancer morbidity and mortality.
  - An estimated **43,800 new benign and malignant brain tumours** are diagnosed annually in the United States; approximately **12,760** of those patients die.
  - The incidence of brain tumours is **14.8 per 100,000 person-years**, about half histologically malignant.
  - There are approximately **11,000 new high-grade gliomas each year in the USA, of which glioblastoma accounts for 9000**.
  - **The incidence of glioblastoma is approximately 3.19 per 100,000.**
  - Malignant CNS tumours are the **leading cause of death from solid tumours in children** and the **third leading cause of cancer-related death in adolescents and adults aged 15-34 years**.
- **Age and sex** — mean age at onset of anaplastic astrocytoma **≈40 years** (initial diagnosis ≈41 years), of glioblastoma **53 years**, with incidence peaking between **65 and 74 years**; GBM is more common in men, **M:F 1.5:1** [YW pp. 900, 1101].
- **Site and pattern.** "Most commonly GBMs are solitary tumours of the cerebral hemispheres, but they may develop at almost any site within the neuraxis, including the cerebellum and the spinal cord. In many cases they infiltrate across the corpus callosum or arise directly within it, with bilateral extension (**butterfly tumour**). **Multifocal tumours are observed in about 2% of patients** and are often mistaken for metastatic disease on preoperative neuroimaging" YW p.900.

5. Gross and microscopic pathology

- **Gross.** "The necrotic tumour mass may be partially delineated on gross examination, but infiltrating glioma cells can easily be identified microscopically **well beyond the apparent gross tumour boundaries**" YW p.900.
- **Cytology.** "The cellular morphology of GBM cells is highly variable, with the spectrum ranging from **small, tightly packed, round or elongated cells to giant bizarre and multinucleated forms**, all of which are frequently encountered within a single tumour" YW p.900.
- **The two histologic hallmarks.** "**Microvascular proliferation and foci of necrosis are histologic hallmarks of GBM** " YW p.900.
  - **Vascular proliferation** "is defined as the presence of blood vessels with **multilayered vessel walls (more than two cell layers thick)**. So-called **glomeruloid vascular proliferation** constitutes the most obvious and characteristic example of the florid microvascular proliferation seen in GBM" YW p.900.
  - **Necrosis** — "large areas of necrosis are typical of GBMs, which also frequently exhibit **multiple small serpiginous zones of necrosis surrounded by densely crowded tumour cells in a pseudopalisading pattern**" YW p.900.
- **The VEGF loop that explains the ring enhancement.** "**The hypoxic perinecrotic apoptotic cells strongly express vascular endothelial growth factor, which in turn induces the characteristically prominent vascular proliferation** ", and "the typical peripheral, ring-like zone of contrast enhancement seen on CT and MRI corresponds to the **highly vascularised peripheral area** of the neoplasm" YW p.900.
- **Proliferation indices.** "Mitotic figures are typically readily identified, and corresponding proliferation marker indices, such as the **Ki-67 antigen**, show elevated levels" YW p.900. Quantitatively: **anaplastic astrocytoma (grade III) has a MIB-1/Ki-67 labelling index of 5% to 10%**, while **glioblastoma shows a mean labelling index generally between 10% and 20%** with extensive intratumoral heterogeneity YW p.1105.
- **Immunophenotype.** "**Positive immunostaining for GFAP is characteristic but highly variable, and can be absent**

in some instances" YW p.900. Diffuse gliomas are positive for **GFAP and OLIG2**; neurofilament protein staining highlights entrapped axons and thereby confirms an infiltrative growth pattern [YW pp. 1092-1093].

- **Secondary structures of Scherer** — perineuronal satellitosis, perivascular aggregation and subpial condensation — are the common patterns of infiltrative growth in diffuse gliomas YW p.1092.

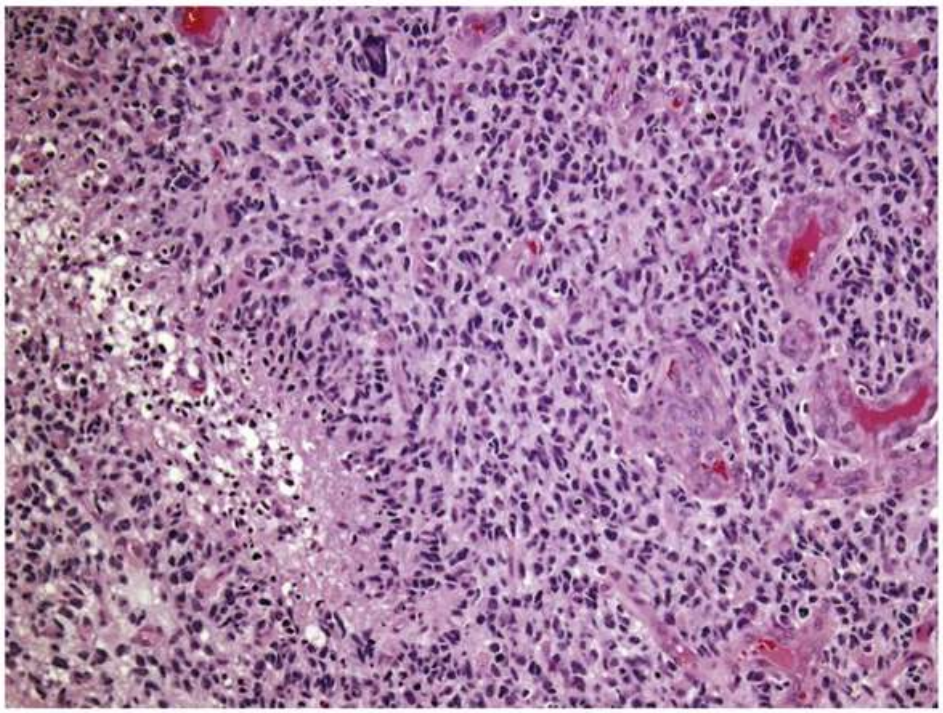


Figure 133.1. Glioblastoma. The most malignant form of diffuse glioma, glioblastoma is also the most common primary brain tumor. Diagnostic histopathologic features, as shown here, include tumor necrosis with surrounding pseudopalisading tumor cells (referred to as *pseudopalisading necrosis*) and hyperplasia of adjacent blood vessels (vascular proliferation) in response to the hypoxic conditions. Based on clinical, morphologic, and molecular characteristics, glioblastomas can be further subclassified into a number of subtypes with prognostic significance (see text for details).

Reproduced from Youmans & Winn 8e, Fig. 133.1, p. 900 — Label when you reproduce it: glioblastoma histopathology — identify (i) the zone of tumour necrosis, (ii) the surrounding rim of densely crowded tumour cells arranged as PSEUDOPALISADING NECROSIS, and (iii) the hyperplastic, multilayered adjacent blood vessels (vascular/microvascular proliferation) formed in response to hypoxia. State that these two features — pseudopalisading necrosis and vascular proliferation — are the diagnostic histopathologic hallmarks of glioblastoma.

6. Molecular biology — primary versus secondary glioblastoma

- **The two subsets, defined clinically and genetically** YW p.900:
  - **Primary GBM** "arises de novo (i.e., without evidence of a preexisting lower grade astrocytoma), typically in patients in the **sixth decade of life and beyond**".
  - **Secondary GBM** "tends to develop in **younger adults (<45 years old)** by malignant progression from a diffuse astrocytoma of WHO grade II or III".
  - They are "**morphologically indistinguishable and respond similarly to conventional therapy**. However, they differ biologically and genetically and thus may respond differently to targeted molecular therapies" YW p.1103.
- **IDH1 — the discovery that reorganised the field.** In 2008 Yan and colleagues sequenced more than 20,000

protein-coding genes in 22 human glioblastoma samples and found a new mutated gene, **isocitrate dehydrogenase 1 (IDH1)**, shared by many patients with secondary glioblastoma YW p.1103. **A specific IDH1 mutation was present in 70% of WHO grade II and III astrocytomas and oligodendrogliomas, as well as in glioblastomas that developed from these lower-grade lesions** [YW pp. 1103-1104].

- **The most common IDH mutation is IDH1 p.R132H, present in approximately 95% of IDH-mutant tumours**, and there is a mutation-specific antibody in routine clinical use YW p.901. The antibody detects only p.R132H (~90% of IDH-mutant diffuse gliomas) and **does not** recognise the less common IDH1 variants (p.R132S, p.R132C, p.R132G) or the **IDH2 p.R172** mutant protein — so IDH-wild-type status must be proven by sequencing, "not simply negative by immunohistochemistry" [YW pp. 1093, 1096].
- **IDH-mutant signature.** "IDH1 or IDH2 mutations in astrocytomas frequently coexist with mutations in **TP53 and ATRX**. Therefore, the molecular signature of low-grade astrocytomas, which have better prognosis, is **IDH1 or IDH2 mutant, TP53 mutant, and ATRX mutant**" YW p.900. IDH-mutant astrocytomas occur in younger patients and typically present as grade II or III with later progression to GBM YW p.901.
- **IDH-wild-type signature.** "IDH-wildtype astrocytomas have worse prognosis and frequently have mutations in the **promoter of the TERT gene, EGFR amplification, and PTEN mutations**", and present later in life, frequently as grade IV tumours [YW pp. 900-901]. Molecular alterations of GBM include **TERT promoter mutations, +7/−10 and EGFR amplification** YW p.901.
- **ATRX and 1p/19q are mutually exclusive.** "Large-scale genomic studies have shown that ATRX mutations and 1p/19q co-deletion are mutually exclusive events. Therefore the presence of an ATRX mutation or loss of ATRX expression, demonstrated by immunohistochemistry in a diffuse glioma, **essentially excludes the diagnosis of oligodendroglioma**" YW p.901.
- **The classical growth-factor and tumour-suppressor pathways** [YW pp. 1103-1104]:
  - **Primary GBM**: EGFR amplification and mutation, loss of heterozygosity of chromosome 10q, PTEN deletion, p16 deletion.
  - **Secondary GBM**: TP53 mutation, PDGFR overexpression, p16 and retinoblastoma (Rb) pathway abnormalities, LOH 10q.
  - **PTEN**, which negatively regulates the PI3K pathway, "is inactivated in **40% to 50%** of patients with glioblastoma"; PTEN mutations are rare in lower-grade astrocytic tumours YW p.1104.
  - **TP53** mutations "are the first detectable genetic mutations in **two-thirds** of precursor low-grade diffuse astrocytomas"; they also occur in primary GBM but in **<30%** of cases YW p.1104.
  - **EGFR** amplification or mutation "occurs almost exclusively in primary glioblastoma and is observed in approximately **40% to 50%**"; "about half of tumours with EGFR amplification express a constitutively autophosphorylated variant known as **EGFRvIII** that lacks the extracellular ligand-binding domain" — an important target for kinase inhibitors, immunotoxins and peptide vaccines YW p.1104.
  - Many of these pathways converge on **upregulation of VEGF, which promotes angiogenesis** YW p.1104.
- **MGMT.** "MGMT is an important repair enzyme that contributes to resistance of tumours to alkylating agents such as carmustine or TMZ"; **MGMT promoter methylation status is the single most important prognostic marker for predicting benefit from chemotherapy with alkylating agents** [YW pp. 901, 1110].
- **Cancer stem cells.** "There is now increasing evidence that … **neural stem cells, or related progenitor cells, can transform into brain tumour stem cells** and give rise to malignant gliomas by escaping the mechanisms that control proliferation, programmed differentiation, and apoptosis"; they are identified by **CD133 (prominin 1) and nestin**, they produce VEGF and promote angiogenesis, and **they require a vascular niche for optimal function** — the rationale for antiangiogenic therapy YW p.1105. GBM's therapeutic resistance is attributed to its invasive properties, this stem-cell-like population, and **retention of abundant DNA repair mechanisms** YW p.901.

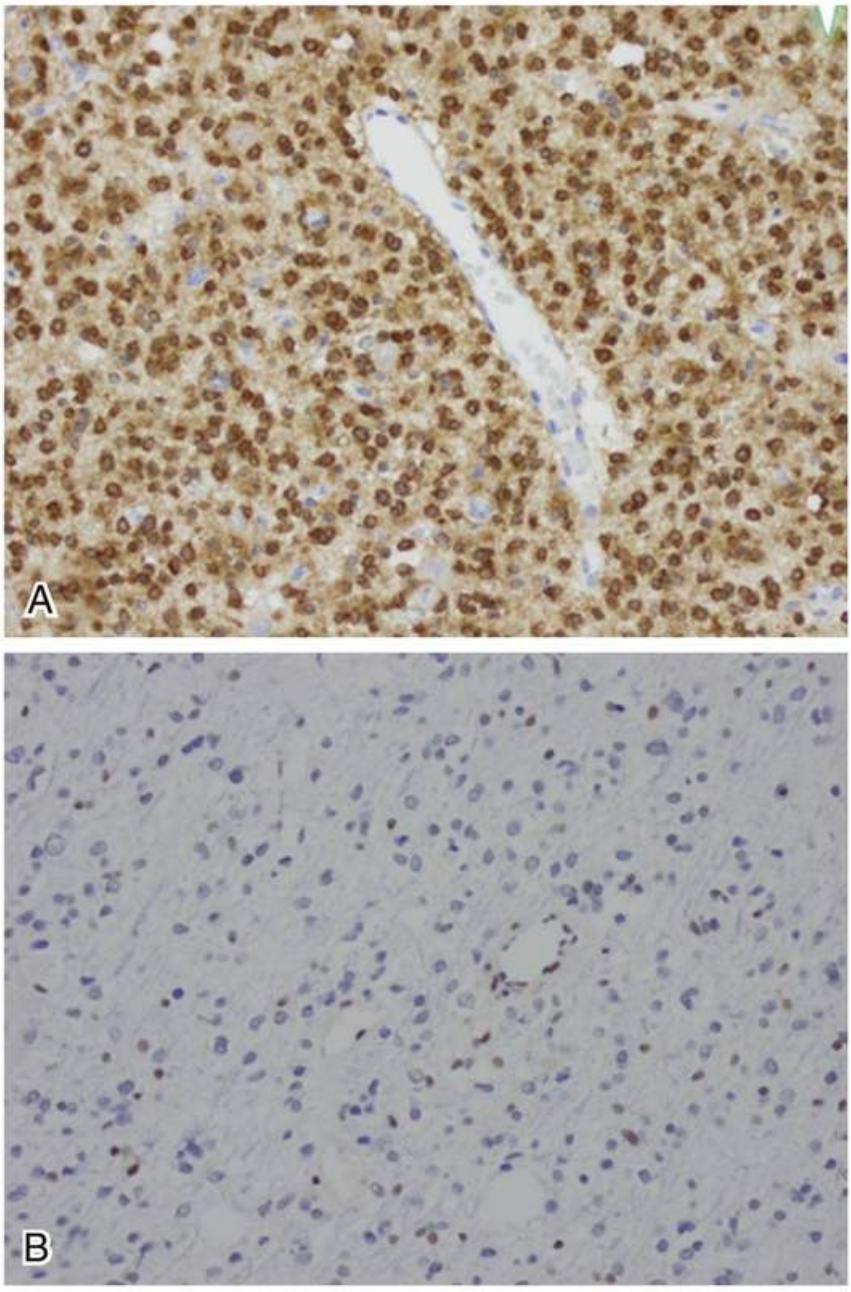


Figure 133.2. Astrocytoma. (A) IDH-mutant astrocytoma demonstrated by expression of IDH1 p.R132H mutant protein in tumor cells (*brown staining*). Note that endothelial cells in the blood vessel in the center of the image are negative and do not express the mutant protein. (B) Loss of ATRX expression in an infiltrating astrocytoma due to an *ATRX* mutation. Note that normal endothelial cells and entrapped normal glial cells retain wild-type expression of the ATRX protein.

Reproduced from Youmans & Winn 8e, Fig. 133.2, p. 901 — Label when you reproduce it: (A) IDH-mutant astrocytoma demonstrated by brown nuclear/cytoplasmic expression of IDH1 p.R132H mutant protein in tumour cells — note that endothelial cells in the central blood vessel are NEGATIVE, which is the internal control. (B) Loss of ATRX expression in an infiltrating astrocytoma due to an ATRX mutation, with normal endothelial cells and entrapped normal glial cells retaining wild-type ATRX expression. State that IDH1 R132H positivity plus ATRX loss plus p53 overexpression is the astrocytic triad, and that ATRX loss excludes oligodendroglioma.

Table 3 · Primary (IDH wild-type) versus secondary (IDH mutant) glioblastoma — compiled from Youmans & Winn 8e, Ch. 133 pp. 900-901 and Ch. 159 pp. 1103-1105.

Feature	Primary GBM = **glioblastoma, IDH wild-type**	Secondary GBM = **glioblastoma, IDH mutant**
Proportion of all GBM	**~90%**	~10%
Origin	De novo, no preexisting lower-grade lesion	Malignant progression from WHO grade II/III astrocytoma
Typical age	≥6th decade; usually >55 years	Younger adults, **<45 years**
Presentation	As a high-grade glioma	As a lower-grade glioma first
IDH1/IDH2	Wild-type	Mutant (IDH1 p.R132H in ~95%)
Companion mutations	TERT promoter, EGFR amplification (40-50%), +7/−10, PTEN loss (40-50%), p16 deletion, LOH 10q	TP53 (two-thirds of precursor grade II lesions), ATRX, PDGFR overexpression, p16/Rb, LOH 10q
EGFRvIII	~50% of EGFR-amplified tumours	Rare
Prognosis	Worse	Better (IDH mutation is a favourable prognostic factor)
Morphology	Indistinguishable from the other	Indistinguishable from the other

7. Variants and patterns of glioblastoma in the 2016 scheme

- **Epithelioid glioblastoma** — "a newly identified subset of the IDH wild-type group … typical of younger adults, showcasing a **more superficial location and sharper demarcation**. Histologically, there are **large epithelioid cells with prominent nucleoli (like melanoma cells), vesicular chromatin, and abundant eosinophilic cytoplasm**. They are often **BRAF V600E positive** and can have lower grade components and rhabdoid cells" YW p.1105. **BRAF p.V600E can be seen in approximately 50% of GBMs with epithelioid morphology** YW p.902.
- **Glioblastoma with primitive neuronal component (GB/PN)** — a renaming of GB-PNET, with "a **biphasic** histologic pattern that includes both glial and primitive components"; the PNET subgroup shows increased CSF dissemination and metastases **in up to 40% of cases**, "and therefore **should prompt spinal imaging when GB/PN is diagnosed**" YW p.1105.
- **Gliosarcoma** — "a rare glioblastoma variant characterised by a **biphasic tissue pattern with glial and mesenchymal components**" YW p.1105.
  - **Histology**: the glial portion is most commonly astrocytic with nuclear atypia and mitoses; the sarcomatous portion consists of neoplastic mesenchymal spindle cells with **reticulin** formation, nuclear atypia, increased mitotic activity and necrosis YW p.1105.
  - **Immunohistochemistry is the key**: "**GFAP is present in glial regions but found in very low quantities in sarcomatous regions**"; "strong staining for **vimentin**, which is a marker for mesenchymal cells, occurs mostly in sarcomatous areas"; and **there is no reticulin staining in glial regions, except around blood vessels, but sarcomatous regions are rich in reticulin** [YW pp. 1105-1106].
  - **Clinical distinctives**: mean age **53 years**, **M:F 1.8:1**, "**a tough, well-circumscribed lobular mass often attached to the dura** that at surgery may outwardly resemble a meningioma"; marked tendency to **dural invasion** with mixed dural and pial supply in nearly half of cases; **extracranial metastases in 15% to 30%** (thyroid, liver, lung, pleura, adrenal, pancreas, spleen, lymph nodes, scalp, oral mucosa, spinal cord); median survival **6.6 months** from surgery [YW pp. 1102-1103, 1111-1112].
- **Gliomatosis cerebri** — "the presence of a histologically confirmed glioma with **widespread, diffuse involvement of three or more cerebral lobes**"; in 2016 it is a **growth pattern**, not an entity, and can be seen with any of the diffuse glioma subtypes including oligodendroglioma; it may correspond to grade II, III or IV; poor prognostic factors are **age >65, KPS <70, high-grade tumour, number of regions involved, bilateralism, focal deficits or contrast enhancement at diagnosis, and high Ki-67**; median overall survival is **10 to 30 months** with treatment failure at about 8 months [YW pp. 901, 1112].

8. Neuroimaging

- **MRI is the preferred study.** "Standard T1- and T2-weighted MRI studies with and without contrast agent are able to reveal brain tumours with high sensitivity with regard to size and localisation. They can also reveal mass effect, oedema, haemorrhage, necrosis, and signs of increased intracranial pressure" YW p.1106.
- **The classical appearance** — "high-grade glioma normally appears as an **irregular hypodense lesion on T1-weighted MRI with various degrees of contrast enhancement and oedema. The presence of ring-like enhancement surrounding irregularly shaped areas of presumed necrosis is suggestive of glioblastoma**" YW p.1106.
- **The traps**: "anaplastic astrocytomas can appear as **nonenhancing** tumours, and even glioblastomas may initially manifest as nonenhancing lesions, **especially in older patients**"; conversely "low-grade gliomas occasionally demonstrate contrast enhancement" YW p.1106. CT is used acutely to exclude haemorrhage or large infarction YW p.1106 .
- **Imaging features by category** [YW pp. 994-995]: GBM is on the differential for **necrosis** (with metastasis), **high cellularity** (with lymphoma, PNET, metastasis) and **high vascularity** (with haemangioblastoma and metastasis) among intra-axial tumours. **Vasogenic oedema does not cross the grey-white junction**, unlike cytotoxic oedema; tumour cellularity correlates with CT hyperdensity and with **reduced ADC**; **rCBV correlates with astrocytic grade** and identifies biopsy targets [YW pp. 994-995].
- **Functional and metabolic imaging.** Functional MRI defines eloquent cortex (motor cortex, Broca and Wernicke areas, visual cortex); MRS differentiates tumour from stroke, old trauma, radionecrosis, infection and multiple sclerosis; **FDG-PET demonstrates hypermetabolism in high-grade tumours, has prognostic value, and high uptake in a previously low-grade tumour establishes the diagnosis of anaplastic transformation**; amino-acid tracers give better tumour-to-brain contrast, and **fluorodopa is superior to FDG** for recurrent glioma YW p.1106.
- **Pseudoprogression.** "In up to **40%** of patients, MRI studies performed in the first month after radiotherapy or local chemotherapy may show increased enhancement", and in **50%** of these the enhancement reflects a transient increase in vessel permeability — **pseudoprogression** YW p.1106.

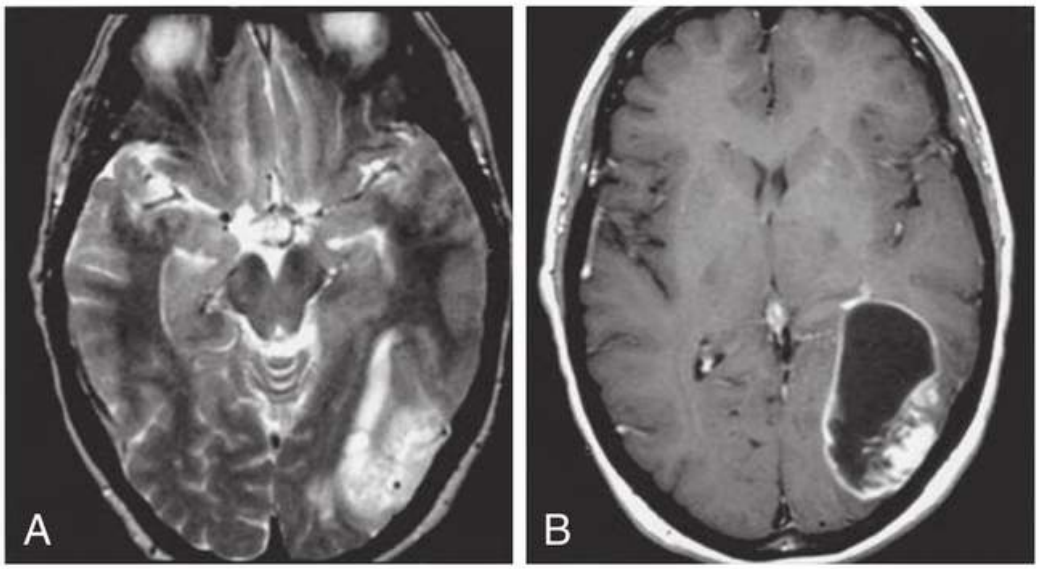


Figure 10.29. Glioblastoma multiforme. (A) Fast spin echo, T2-weighted axial image demonstrating a heterogeneously hyperintense mass in the left temporal and occipital lobes. (B) Spin echo, T1-weighted, contrast-enhanced axial image demonstrating a large cystic anterior component with thin peripheral enhancement and a heterogeneously enhancing solid component along the posterolateral aspect of the mass.

Reproduced from Youmans & Winn 8e, Fig. 10.29, p. 153 — Label when you reproduce it: glioblastoma multiforme by MRI sequence. (A) Fast spin echo T2-weighted image showing the heterogeneous, hyperintense mass with surrounding oedema; then the T1-weighted pre- and post-gadolinium images showing the thick, irregular ring of enhancement surrounding central necrosis. Label the enhancing rim, the necrotic core, the peritumoral T2/FLAIR signal (infiltrating tumour plus oedema) and any mass effect or midline shift.

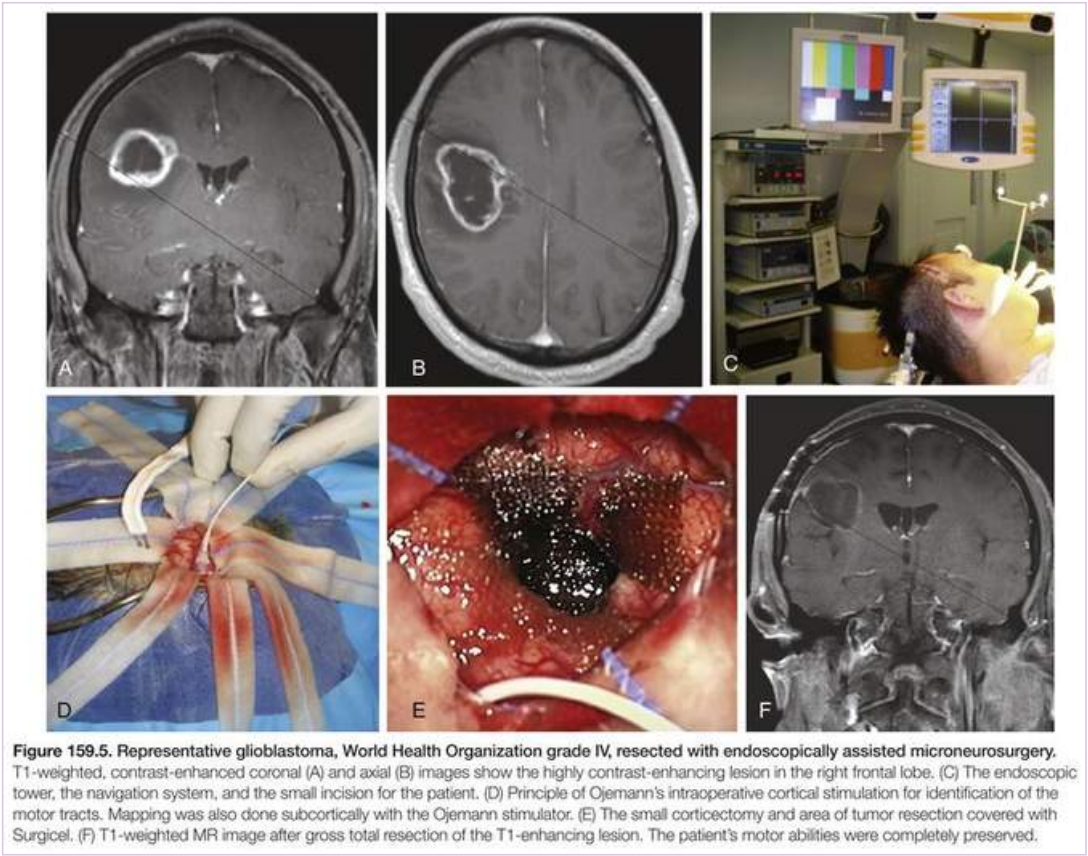


Figure 159.5. Representative glioblastoma, World Health Organization grade IV, resected with endoscopically assisted microneurosurgery. T1-weighted, contrast-enhanced coronal (A) and axial (B) images show the highly contrast-enhancing lesion in the right frontal lobe. (C) The endoscopic tower, the navigation system, and the small incision for the patient. (D) Principle of Ojemann's intraoperative cortical stimulation for identification of the motor tracts. Mapping was also done subcortically with the Ojemann stimulator. (E) The small corticectomy and area of tumor resection covered with Surgicel. (F) T1-weighted MR image after gross total resection of the T1-enhancing lesion. The patient's motor abilities were completely preserved.

Reproduced from Youmans & Winn 8e, Fig. 159.5, p. 1104 — Label when you reproduce it: representative glioblastoma, WHO grade IV, resected with endoscopically assisted microneurosurgery. (A and B) T1 contrast-enhanced coronal and axial images showing the highly enhancing right frontal lesion. (C) The endoscopic tower, navigation system and small incision. (D) Ojemann intraoperative cortical (and subcortical) stimulation to identify the motor tracts. (E) The small corticectomy and resection bed covered with Surgicel. (F) Postoperative T1 confirming gross total resection of the enhancing lesion with motor function preserved.

9. Diffuse midline glioma, H3 K27M-mutant — the other new grade IV entity

- **Definition.** "The '**diffuse midline glioma, H3 K27M-mutant**' (DMG-K27M) is a newly recognised entity defined in the WHO 2016 classification system as a **highly malignant infiltrative midline glioma with a K27M mutation in either H3F3A or HIST1H3B/C genes**" YW p.901. The mutation is "a substitution of **lysine to methionine at codon 27 in H3F3A**, which is the histone H3 gene" (also, less frequently, HIST1H3B) YW p.1115.
- **Distribution.** "The H3 K27M mutation is found in **the majority of diffuse intrinsic pontine gliomas and nearly half of diffuse gliomas arising at any other midline location of the CNS (mostly the thalamus, brainstem, and spinal cord)**" and is most common in children but can occur at any age YW p.901. Quantitatively: **30% of paediatric glioblastoma, 80% of DIPG and 15-50% of adult midline gliomas** carry the mutation; NIH estimates a prevalence of 6000 with 791 new cases/year in the USA (447 in adults) YW p.1115.
- **Grading rule.** "Any diffuse gliomas located within midline structures of the CNS harbouring a histone H3 K27M mutation are assigned as **WHO grade IV irrespective of having high-grade histologic features** such as elevated mitotic activity, necrosis, and microvascular proliferation, given the poor prognosis" YW p.1096. Hence a bland, hypocellular biopsy with low-grade features is still grade IV if K27M-mutant YW p.901.
- **Diagnostic caveat.** "Although K27M mutations have also been described in the context of other histologies such as pilocytic astrocytoma, ganglioglioma, and ependymoma and in tumours away from the midline, … **only the midline infiltrative gliomas bearing the K27M mutation qualify for the DMG-K27M diagnosis**" YW p.901. Detection is "readily demonstrated by immunohistochemistry with antibodies targeting the mutant protein", and "it is increasingly common practice that **every diffuse midline glioma, regardless of histology, patient age, and anatomic location, be assessed by immunohistochemistry for this mutation**" [YW pp. 901, 1115].
- **Companion alterations**: mutually exclusive **TP53 or PPM1D** mutations, hotspot **FGFR1** kinase-domain mutations

(p.N546, p.K656), **PDGFRA** amplification/mutation, and inactivation of **NF1 and ATRX**; DMGs uniformly lack IDH1/IDH2 mutation and do not typically carry TERT promoter mutation or EGFR amplification YW p.1096.

- **Imaging and outcome** — heterogeneous, T1 hypointense, T2 hyperintense, **not avidly enhancing** unless previously irradiated, with normal diffusion; median survival **9.1 to 19.6 months**, which is paradoxically **better** than IDH-wild-type high-grade tumours in one comparison (17.6 vs 7.7 months) [YW pp. 1115-1116]. **H3F3A G34R/V** mutation defines a separate group of **hemispheric** high-grade gliomas of children and young adults YW p.901.

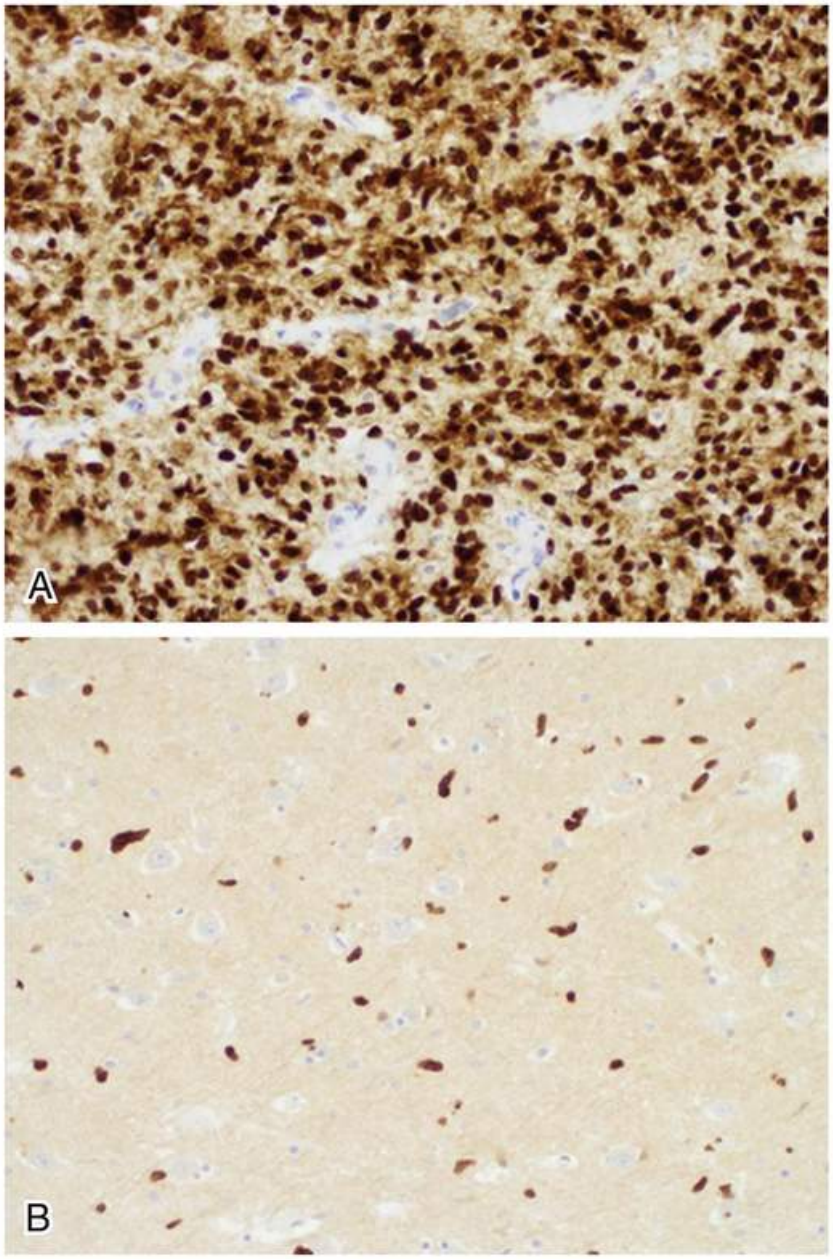


Figure 133.3. Diffuse midline glioma, H3-K27M mutant. (A) Note *brown staining* demonstrating expression of the histone H3.3 mutant protein with a lysin-to-methionine mutation in amino acid 27 (K27M). This is a somatic mutation only present in tumor cells; the endothelial cells do not have the mutation, as demonstrated by negative H3.3 p.K27M staining. (B) An area with lower density of tumor cells infiltrating brain parenchyma. Note the large neurons in the background that do not express the mutant protein.

Reproduced from Youmans & Winn 8e, Fig. 133.3, p. 902 — Label when you reproduce it: diffuse midline glioma, H3-K27M mutant. (A) Brown nuclear staining demonstrating expression of the histone H3.3 K27M mutant protein — emphasise that this is a somatic mutation present only in tumour cells, so the endothelial cells are negative (internal control). (B) An area of lower tumour-cell density infiltrating brain parenchyma, with large background neurons that do not express the mutant protein. Note that a bland, hypocellular biopsy like this is still WHO grade IV if K27M-mutant.

10. Clinical features

- **Raised intracranial pressure** — headache, nausea and vomiting, blurred or double vision, drowsiness, with

extraocular palsies, papilloedema, pupillary abnormalities or reduced conscious level; "typically more prominent in the morning and improve over the course of the day. **Relentless progressive headaches are a hallmark symptom**" YW p.1102.

- **Seizures** in up to a third of patients with glioblastoma YW p.1102.
- **Neurological deficits** are common and vary with location and extent of infiltration; they may be focal or global (altered cognition, personality change) YW p.1102.
- **Site of recurrence** — AA and GBM "tend to recur locally, often at the margins of the tumour resection and **even when GTR has been performed radiographically**" YW p.1102.

11. Management in outline

- **Surgery — the four goals**: obtain a tissue diagnosis, decrease mass effect, reduce tumour burden, and increase survival and quality of life YW p.1107.
- **Extent of resection matters, and is the only modifiable prognostic factor** YW p.1109. After primary GBM resection median survival was **13 months (GTR), 11 (NTR) and 8 (STR)**; after revision surgery **11, 9 and 5 months** YW p.1101. Volumetric thresholds: **98%** (Lacroix), **78%** (Sanai), **70% resection and 5 cm³ residual** (Chaichana), **98% with ≤2 cm³ residual** (Grabowski) [YW pp. 1109-1110].
- **Standard of care** — "maximal, safe resection followed by chemoradiation with **Stupp protocol**": 60 Gy radiotherapy with concurrent temozolomide **75 mg/m²/day for 6 weeks**, then adjuvant temozolomide **150-200 mg/m² days 1-5 of each 28-day cycle**, median overall survival **14.6 months** [YW pp. 1100, 1110, 1032].
- **Radiotherapy volumes.** The high-dose volume is defined by outlining the contrast-enhancing volume and adding a **1.5- to 2.0-cm anatomically constrained margin** for the clinical target volume plus a small margin for the planning target volume; the low-dose volume is defined the same way from the **FLAIR** volume YW p.2295. Conformal (IMRT) techniques have **level I evidence** for superior cognitive, intellectual and endocrine preservation YW p.2295.
- **Local therapy** — **carmustine-loaded biodegradable wafers (Gliadel)**: up to **eight** wafers in the cavity, BCNU released over **5 days**, polymer dissolving over **6-8 weeks**, peak systemic levels **<1/600** of systemic dosing and undetectable at 24 hours; recurrent malignant glioma survival **23 → 31 weeks**; initial therapy **58.1 vs 39.9 weeks** (Valtonen) and **13.8 vs 11.6 months** (Westphal) [YW pp. 1100, 1110, 1134].
- **Tumour-treating fields** — NovoTTF-100A/Optune; FDA approval 2011 for recurrent and 2015 for newly diagnosed GBM after **EF-14 added 4.9 months** of overall survival [YW pp. 1100, 1111].
- **Recurrence** — "approximately **20% to 30%** of patients with recurrent glioblastoma are candidates for a second resection, which is typically considered when the lesions are **large, circumscribed, and causing neurological deficits** "; the main strategies are **nitrosourea-based regimens, alternate-day temozolomide and bevacizumab**, and the role of reirradiation is uncertain YW p.1111.
- **Multimodality survival ladder** (Attenello): radiotherapy alone **9 months**; Gliadel + RT **13 months**; RT + temozolomide **15 months**; Gliadel + RT + temozolomide **20 months** YW p.1111.

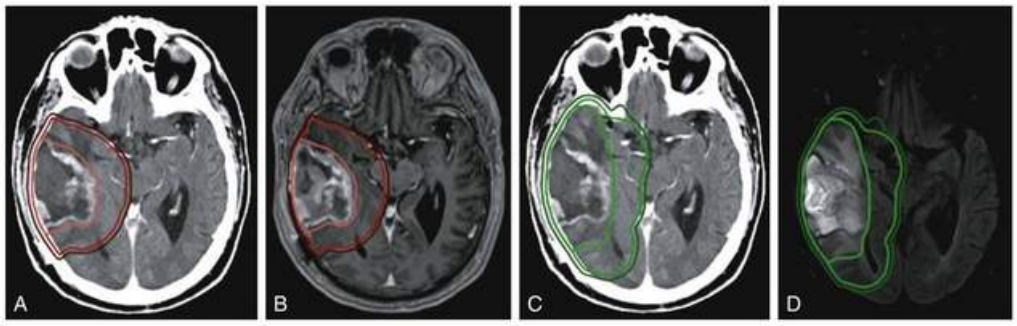


Figure 296.2. Target volume delineation for a patient with a right temporal glioblastoma to be treated with fractionated external beam radiotherapy is performed with fusion of the axial postcontrast magnetic resonance imaging (MRI) and fluid-attenuated inversion recovery (FLAIR) sequences with the treatment planning computed tomography (CT) scan. (A and B) The high-dose region is delineated on the treatment planning CT scan (A) by outlining the contrast-enhanced volume on MRI (B) and adding a 1.5- to 2.0-cm anatomically constrained margin to account for the clinical target volume (CTV) and a 0.3-mm margin for the planning target volume (PTV; *light red*, *red*, and *dark red*). (C and D) The low-dose region is delineated on the treatment planning CT scan (C) by outlining the FLAIR volume on MRI (D) and adding a 1.5- to 2.0-cm anatomically constrained margin to account for the CTV and a 0.3-mm margin for the PTV (*light green*, *green*, and *dark green*).

Reproduced from Youmans & Winn 8e, Fig. 296.2, p. 2295 — Label when you reproduce it: target volume delineation for a right temporal glioblastoma. (A) The high-dose region on the planning CT, drawn from (B) the contrast-enhancing volume on MRI plus a 1.5-2.0 cm anatomically constrained CTV margin and a small PTV margin (light red / red / dark red). (C) The low-dose region on the planning CT, drawn from (D) the FLAIR volume plus the same margins (light green / green / dark green). Label GTV, CTV and PTV explicitly.

12. Outcome and prognostic factors

- **"Median length of survival for glioblastoma is less than 2 years despite advances in surgical technology, radiotherapy, and chemotherapy, and 2 to 5 years for patients with anaplastic glioma"** [YW pp. 1100, 1111].
- **"Latest 5-year survival for glioblastoma has been reported to be 6%"** [YW pp. 1100, 1111].
- **"Currently, age, KPS score and extent of resection are the most significant prognostic factors. Other favourable prognostic factors are IDH1 or IDH2 mutation and MGMT promoter methylation"** YW p.1111.
- **MGMT numbers**: methylated (45%) — median **21.7 months**, 2-year survival **46%**; unmethylated — median **12.7 months**, 2-year survival **13.8%** [YW pp. 1110-1111].
- **In the predominantly elderly population of patients with malignant glioma, "there is no major difference in prognosis between anaplastic astrocytoma and glioblastoma"** YW p.1111.
- **Gliosarcoma** has a slightly but statistically significantly worse prognosis than glioblastoma in the SEER analysis; reported median survival **6 to 14.8 months**, and **6.6 months** from surgery in a 14-year single-centre series, improving to **14 months (46% 1-year)** with radiotherapy and **30 months (77% 1-year)** with combined radiation and chemotherapy [YW pp. 1111-1112].
- **Individual patient survival is heterogeneous, with some long-term survivors**; other proposed prognostic factors include tumour size, tumour location and even **marital status** YW p.1111.

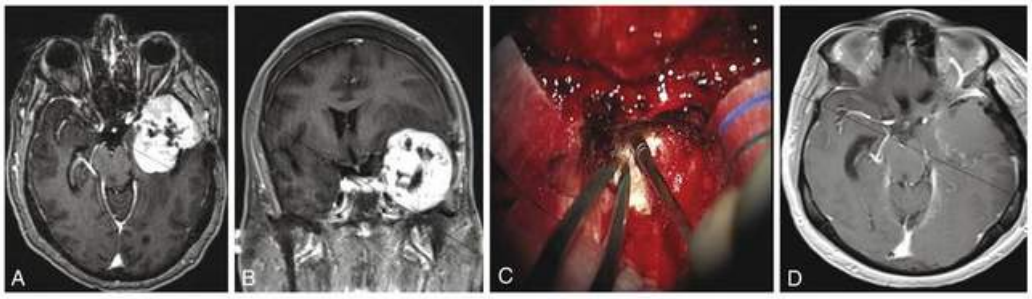


Figure 159.6. Images in a patient with a gliosarcoma. (A and B) Axial and coronal preoperative T1-weighted, contrast-enhanced MR images, respectively, demonstrating a well-circumscribed lesion with a mass effect and surrounding edema. (C) Intraoperative photograph of a tenacious lesion, which was firm and rubbery. (D) T1-weighted contrast-enhanced MR image after gross total resection of the lesion.

Reproduced from Youmans & Winn 8e, Fig. 159.6, p. 1106 — Label when you reproduce it: gliosarcoma. (A and B) Axial and coronal preoperative T1 contrast-enhanced MR images showing a well-circumscribed, dural-based-looking lesion with mass effect and surrounding oedema — the meningioma mimic. (C) Intraoperative photograph of the tenacious, firm, rubbery lesion. (D) Postoperative T1 contrast-enhanced image after gross total resection. In the label record that gliosarcoma is GFAP-positive in glial areas, vimentin- and reticulin-rich in sarcomatous areas, and metastasises extracranially in 15-30%.

13. Frozen-section and intraoperative diagnosis — a 2016-era limitation

- **Sampling is the surgeon's responsibility.** "An important part of a successful intraoperative consultation, which relies on the neurosurgeon, is **selecting the optimal tissue sample** to submit for analysis. Sampling bias can have great impact on the preliminary diagnosis … therefore **larger tissue fragments are favoured**" YW p.911.
- **Necrotic tissue is "almost impossible to interpret" on histologic examination** (other than to recognise necrosis), and freezing artefact limits interpretation YW p.911.
- **"The distinction between astrocytoma and oligodendroglioma is not feasible at the time of intraoperative consultation"** — the perinuclear clearing of oligodendroglioma "is an artefact of permanent processing that is not seen in frozen tissue sections" YW p.911.
- **Molecular diagnosis cannot be delivered intraoperatively**; "as a result, a diagnosis of **infiltrating glioma, with or without high-grade features**, is a reasonable preliminary diagnosis issued during intraoperative consultation" YW p.911.
- **Intraoperative cytologic smears** do allow the two lineages to be told apart morphologically in experienced hands — elongate, irregular hyperchromatic nuclei with fibrillar processes for astrocytoma, monotonous round-to-ovoid nuclei with delicate chromatin for oligodendroglioma YW p.1097.

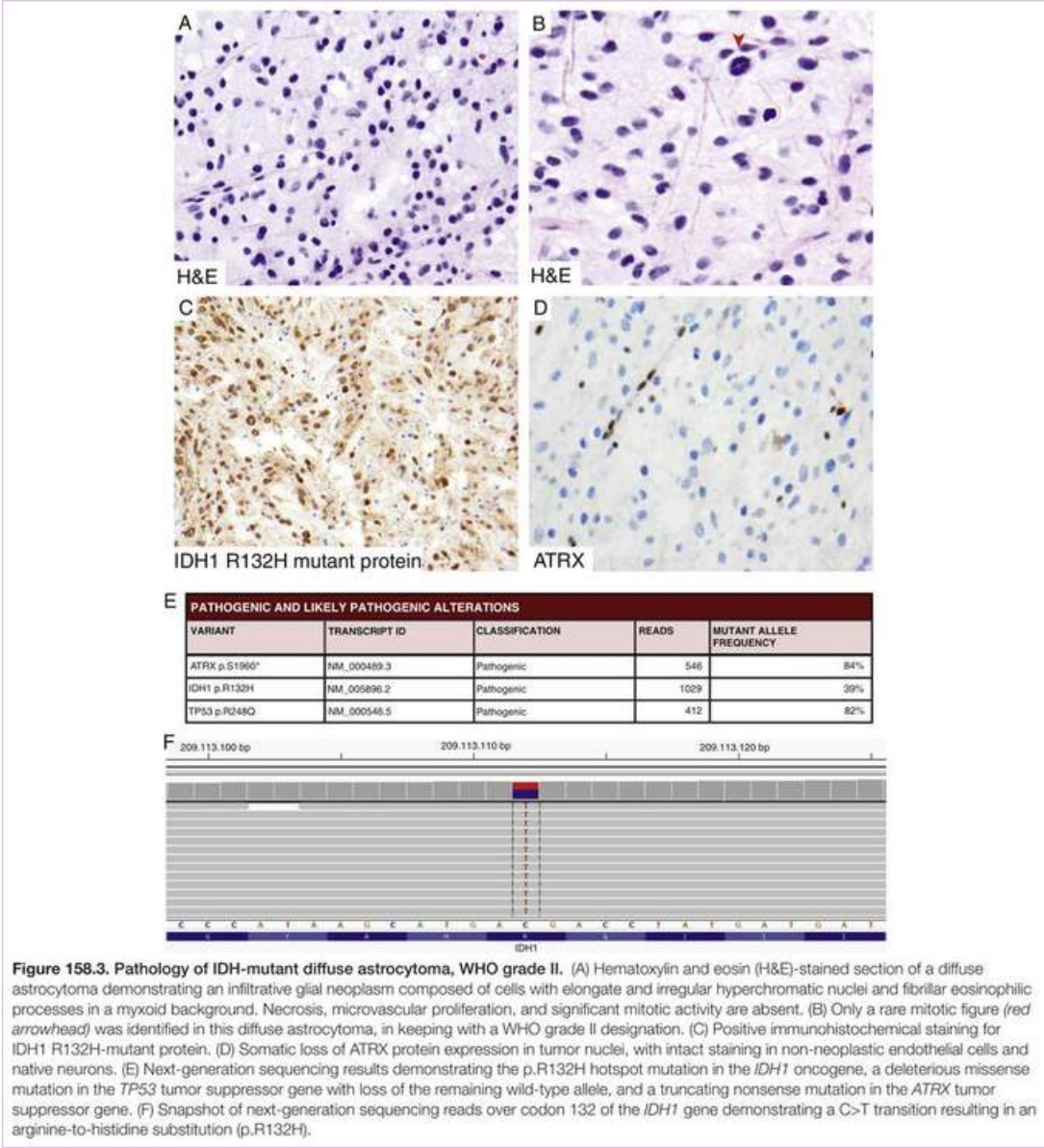


Figure 158.3. Pathology of IDH-mutant diffuse astrocytoma, WHO grade II. (A) Hematoxylin and eosin (H&E)-stained section of a diffuse astrocytoma demonstrating an infiltrative glial neoplasm composed of cells with elongate and irregular hyperchromatic nuclei and fibrillar eosinophilic processes in a myxoid background. Necrosis, microvascular proliferation, and significant mitotic activity are absent. (B) Only a rare mitotic figure *(red arrowhead)* was identified in this diffuse astrocytoma, in keeping with a WHO grade II designation. (C) Positive immunohistochemical staining for IDH1 R132H-mutant protein. (D) Somatic loss of ATRX protein expression in tumor nuclei, with intact staining in non-neoplastic endothelial cells and native neurons. (E) Next-generation sequencing results demonstrating the p.R132H hotspot mutation in the *IDH1* oncogene, a deleterious missense mutation in the *TP53* tumor suppressor gene with loss of the remaining wild-type allele, and a truncating nonsense mutation in the *ATRX* tumor suppressor gene. (F) Snapshot of next-generation sequencing reads over codon 132 of the *IDH1* gene demonstrating a C>T transition resulting in an arginine-to-histidine substitution (p.R132H).

Reproduced from Youmans & Winn 8e, Fig. 158.3, p. 1094 — Label when you reproduce it: pathology of IDH-mutant diffuse astrocytoma, WHO grade II — the precursor lesion of secondary (IDH-mutant) glioblastoma. (A) H&E showing an infiltrative glial neoplasm with elongate, irregular hyperchromatic nuclei and fibrillar eosinophilic processes in a myxoid background, with NO necrosis, vascular proliferation or significant mitotic activity. (B) A rare mitotic figure (red arrowhead) keeping it grade II. (C) Positive IDH1 R132H immunostaining. (D) Somatic loss of ATRX in tumour nuclei with intact staining in endothelial cells and native neurons. (E and F) Next-generation sequencing showing IDH1 p.R132H, TP53 p.R248Q and the truncating ATRX p.S1960 mutation — the complete IDH-mutant astrocytic triad.*

GUIDELINE UPDATE

WHO CNS5, 2021 — The book's account stops at the 2016 revision (its fullest statements are Table 133.1, p. 900 and Table 159.2, p. 1105), and it cites cIMPACT-NOW only in passing YW p.1096; the question as set in 2020 asks for the 2016 scheme, but candidates should know that the 5th edition (2021) went further: the term "glioblastoma" is now reserved for **IDH-wild-type adult-type diffuse glioma, CNS WHO grade 4**, diagnosed by necrosis or microvascular proliferation **or** any one of TERT promoter mutation, EGFR amplification or +7/−10 (exactly the criteria Youmans anticipates on p. 901); "glioblastoma, IDH-mutant" is abolished and reclassified as **astrocytoma, IDH-mutant, CNS WHO grade 4**, graded 4 by necrosis/microvascular proliferation or homozygous CDKN2A/B deletion; grading became within-type using Arabic numerals; and paediatric-type diffuse gliomas (including diffuse midline glioma, H3 K27-altered and diffuse hemispheric glioma, H3 G34-mutant) were separated from adult-type tumours.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **2016 was the first WHO CNS classification to use molecular parameters**, and the governing rule is that **genotype trumps histology** in any discordance.
- **Necrosis is not required for a diagnosis of GBM** — vascular proliferation with pleomorphism and increased mitoses suffices.
- **Vascular proliferation = vessel walls more than two cell layers thick**; glomeruloid proliferation is its florid form; pseudopalisading necrosis is the other hallmark.
- **The enhancing ring is the hypervascular periphery**, driven by VEGF from hypoxic perinecrotic apoptotic cells.
- **Three GBM entities in 2016: IDH wild-type (90%, = primary), IDH mutant (= secondary), and NOS.** Plus diffuse midline glioma H3 K27M-mutant as a separate grade IV.
- **New entities 2016**: IDH-wt GBM, IDH-mut GBM, diffuse midline glioma H3K27M, diffuse leptomeningeal glioneuronal tumour. **New variant**: epithelioid GBM. **New pattern**: GB/PN. **Deleted**: gliomatosis cerebri (now a growth pattern) and oligoastrocytoma.
- **IDH1 p.R132H accounts for ~95% of IDH-mutant tumours** and has a specific antibody; a negative antibody does NOT prove IDH wild-type — you must sequence.
- **Astrocytic triad: IDH mutant + TP53 mutant + ATRX loss.** ATRX loss and 1p/19q codeletion are mutually exclusive; ATRX loss excludes oligodendroglioma.
- **1p/19q codeletion by FISH without IDH mutation is probably a glioblastoma** — partial deletions mimic true codeletion on FISH.
- **GB/PN mandates spinal imaging** — CSF dissemination in up to 40%.
- **Ki-67/MIB-1: anaplastic astrocytoma 5-10%, glioblastoma 10-20%.**
- **Epithelioid GBM is BRAF V600E-positive in ~50%** — a targetable mutation in a grade IV tumour.
- **Gliosarcoma: dural-based meningioma mimic, GFAP in glial areas, vimentin and reticulin in sarcomatous areas, extracranial metastasis in 15-30%, median survival 6.6 months.**
- **A K27M-mutant midline diffuse glioma is grade IV even if the histology looks low grade.**
- **GBM incidence 3.19/100,000; 9000 of the 11,000 annual US high-grade gliomas; mean age 53 years; M:F 1.5:1; multifocal in 2%.**
- **Prognosis: median <2 years, 5-year survival 6%.** The three key prognostic factors are age, KPS and extent of resection — and only extent of resection is modifiable.
- **Radiotherapy CTV = enhancing volume + 1.5-2.0 cm** for the high-dose volume, and the FLAIR volume + the same margin for the low-dose volume.
- **The frozen section cannot separate astrocytoma from oligodendroglioma** — report "infiltrating glioma, with or without high-grade features".

Pages read for this answer — Youmans & Winn 8e: 900, 901, 902, 903, 911, 994, 995, 1032, 1092, 1093, 1096, 1097, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1109, 1110, 1111, 1112, 1115, 1116, 1134, 2295

a) Chemotherapy of Glioblastoma multiforme. [3]
b) Management of CSF leaks. [4]
c) Treatment options for unruptured intracranial aneurysms/AVMs. [3]

LONG | JUN 2021 · Paper II · Q8 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 147 *Principles of Chemotherapy*, §Concepts in Chemotherapy, §Delivery of Chemotherapy to the Brain and §Chemotherapeutic Agents in CNS Tumors, pp. 1029-1032 (Fig. 147.1, p. 1029; **Table 147.1** and **Table 147.2**, p. 1032). Ch. 159 *Malignant Gliomas*, §Radiation Therapy and Chemotherapy for Anaplastic Astrocytoma and Glioblastoma and §Patient Outcome, pp. 1110-1111 (Fig. 159.3, p. 1102; Fig. 159.8, p. 1111; **Table 159.5**, p. 1110). Ch. 162 *Local Therapies for Gliomas*, §Drug-Impregnated Biopolymers, §Convection-Enhanced Delivery and §Direct Injection, pp. 1132-1137 (Figs. 162.3-162.4, pp. 1134-1135; Tables 162.1-162.3). Ch. 400 *Traumatic Cerebrospinal Fluid Fistulas*, §Pathophysiology, §Diagnostic Tests, §Medical Management, §Surgical Management and §Endoscopic Repair, pp. 3163-3169 (Fig. 400.1, p. 3164; **Table 400.1** and **Table 400.2**, pp. 3165-3166). Ch. 427 *Surgical Decision Making for the Treatment of Intracranial Aneurysms*, §The Unruptured Aneurysm, §Surgical Risk and §Which Patient Should Be Treated, pp. 3429-3432 (**Box 427.1**, p. 3429; Fig. 427.1, p. 3431; **Table 427.1**, p. 3430). Ch. 430 *Endovascular Approaches to Intracranial Aneurysms*, pp. 3488-3492 (**Table 430.1** and **Table 430.2**, p. 3490). Ch. 452 *Therapeutic Decision Making in the Management of Arteriovenous Malformations of the Brain*, pp. 3677.e2-3677.e5 (**Table 452.1**, p. 3677.e2). Supplementary: Ch. 145, p. 1019 (Fig. 145.6); Ch. 456, p. 3719 (Fig. 456.8); Ch. 213, p. 1630 (Fig. 213.15).

(a) Chemotherapy of glioblastoma multiforme [3]

1. Why chemotherapy is hard in the brain — the three barriers

- **The blood-brain barrier.** "The normal BBB is composed of **nonfenestrated endothelial cells characterised by tight junctions** that impede the movement of unwanted substances such as drugs into the CNS" YW p.1030. Additional contributors to low permeability are low pinocytotic activity, interaction of astrocytic processes and pericytes with endothelium, **ATP-binding cassette transporters, insulin receptors, multidrug-resistance-associated proteins and transferrin receptors**, and the absence of lymphatic drainage and of major histocompatibility complex YW p.1030.
- **"Only un-ionised, low-molecular-weight (generally 400 or less), lipophilic drugs can pass through the BBB by passive diffusion; these are best exemplified by nitrosoureas, which are frequently used for CNS tumours"** YW p.1030.
- **The blood-tumour barrier.** Tumour-derived VEGF drives angiogenesis; the new vessels are "anatomically and functionally abnormal, having **thin endothelial cells, open tight junctions, gap junctions, fenestrations, and numerous intracellular vesicles with aberrant basement membrane**", producing the contrast enhancement and peritumoral oedema seen on imaging YW p.1030. Crucially, **permeability varies through the tumour**: it is altered centrally while "the permeability in the proliferating tumour periphery remains intact" — so **water-soluble agents reach the growing edge in lower concentration, contributing to local failure**; lipid-soluble drug concentration stays relatively constant across all regions YW p.1030.
- **Regional blood flow.** There are "significant differences in regional blood flow within the tumour, with **the lowest rate in the central necrotic area**. Because of this variation, even highly lipophilic agents are less able to reach the areas with low blood flow" YW p.1030.
- **Drug resistance.** Resistance operates through altered uptake/efflux, altered DNA repair, altered activation/inactivation, altered target enzymes and impaired apoptosis; **the first two dominate in neuro-oncology** YW p.1029. **MDR1/P-glycoprotein** overexpression is "one of the major factors of failure of chemotherapy against CNS tumours" and is highly expressed at the BBB, the blood-CSF barrier and in tumour endothelium YW p.1029. **MGMT** removes the alkyl group from O6-methylguanine, so "**tumours expressing high levels of MGMT are considered resistant to alkylating agents**"; the **base excision repair pathway with PARP-1** repairs N7-methylguanine and N3-methyladenine adducts and is itself a therapeutic target (veliparib, olaparib with RT and/or temozolomide in recurrent GBM) YW p.1029.

2. The Stupp regimen — first-line standard of care

- **Concurrent chemoradiation.** "A 6-week regimen of **continuous daily temozolomide at 75 mg/m² with RT** improved the outcome compared with RT alone in newly diagnosed GBM" YW p.1029.

- **Adjuvant phase.** "In the standard treatment for GBM, the alkylating agent temozolomide is given alone for **six cycles** following concurrent radiotherapy and temozolomide. **This regimen prolongs the median survival to 14.6 months from 12.1 months with radiotherapy alone**" YW p.1029. The adjuvant dose is **150-200 mg/m² orally daily for 5 days every 28 days** YW p.1032.
- **Mechanism.** Temozolomide is a **non-classic alkylating agent**, given orally, **cell-cycle non-specific**, acting by **methylating guanine at the O6 position**; alkylator activity is enhanced by radiation, hyperthermia and inhibition of DNA repair [YW pp. 1029, 1031].
- **MGMT is the predictive marker.** "A greater survival benefit was observed in GBM patients with **methylated MGMT promoter** treated with temozolomide and radiotherapy compared to patients who lacked MGMT promoter methylation" YW p.1029. The figures: methylated (45% of patients) median survival **21.7 months**, 2-year survival **46%**; unmethylated median **12.7 months**, 2-year survival **13.8%** [YW pp. 1110-1111]. MGMT promoter methylation status is "**the single most important prognostic marker for predicting benefit from chemotherapy with alkylating agents** " YW p.901.
- **Dose intensity.** "Increasing dose intensity, defined as the amount of drug delivered per unit time, maximizes the cell kill" and "**a dose reduction of chemotherapeutic agents by 20% can lower the cure rate by 50%**"; but **dose-dense temozolomide during the adjuvant phase did not improve efficacy in newly diagnosed GBM** YW p.1029.

Table 1 · Chemotherapy regimens and doses used for glioblastoma and anaplastic glioma — reproduced from Youmans & Winn 8e, Table 147.1, p. 1032 and Table 159.5, p. 1110.

Setting	Drug / regimen and dose
GBM, first line (Stupp)	Temozolomide **75 mg/m²/day × 6 weeks concurrent with 60 Gy RT**, then adjuvant **150-200 mg/m² days 1-5 every 28 days × 6-12 months**
GBM, first line alternative (CeTeG/NOA-09)	Lomustine (CCNU) 100 mg/m² day 1 + temozolomide 100 mg/m² days 2-6, during and after RT, every 6 weeks up to 6 cycles
GBM, salvage	Carmustine (BCNU) 150-200 mg/m² day 1 every 6 weeks
GBM, salvage	Carboplatin, AUC 4-7 mg/mL/min
GBM, salvage	Irinotecan 340 mg/m² (on enzyme-inducing AEDs) or 125 mg/m² (not on EIAEDs), weekly × 4 weeks then 2 weeks rest, every 6 weeks
GBM, salvage	Lomustine (CCNU) 90-110 mg/m² every 6 weeks
GBM, salvage — dose-dense TMZ	50 mg/m² daily × 12 months; **or** 1 week on (120 mg/m²/day)/1 week off; **or** 3 weeks on (75 mg/m²/day)/1 week off
GBM >65-70 years	Resection or biopsy, then radiotherapy **or** temozolomide, with or without radiotherapy, **on the basis of MGMT status and performance status**
Anaplastic glioma WHO III	RT 60 Gy then **PCV** — procarbazine 60 mg/m² PO days 8-21, CCNU 110 mg/m² PO day 1, vincristine 1.4 mg/m² IV days 8 and 29 — every 6 weeks × 6 cycles; or RT then TMZ 150-200 mg/m² × 12 cycles
Progression, antiangiogenic	Bevacizumab 10 mg/kg IV every 2 weeks until progression or intolerable adverse effects

3. Combination and second-line systemic chemotherapy

- **Principles of combination chemotherapy** YW p.1030 — use drugs with **non-overlapping toxicities** so each can be given at near-maximal dose; combine agents with **different mechanisms and minimal cross-resistance**; use drugs with **single-agent efficacy**; treat **early with minimal treatment interval** while allowing recovery of sensitive tissues.
- **The dual-alkylator regimen (CeTeG/NOA-09).** 141 newly diagnosed **MGMT-methylated** GBM patients <70 years randomised to temozolomide + CCNU versus temozolomide alone during and after RT; in the modified intention-to-treat analysis of 129 patients, **overall survival was superior with combination therapy (43.1 vs 31.4 months; HR 0.60)**, with worse haematological toxicity and nausea. Rationale: "synergistic effects through different mechanisms of DNA damage, potentially overcoming temozolomide-induced mismatch repair mutation" YW p.1030.

- **Recurrence.** "The main strategies for recurrent glioblastoma after the standard treatment are **nitrosourea-based regimens (carmustine, lomustine), alternate-day dosing regimens of TMZ, and bevacizumab (Avastin)**" YW p.1111. **Rechallenge with dose-dense temozolomide** is an option in selected patients, "particularly in those with MGMT promoter mutation and patients whose disease has not progressed during the first six cycles of conventional adjuvant temozolomide or who have a treatment-free interval" YW p.1029.
- **Bevacizumab.** FDA-approved for malignant glioma and "commonly reserved for glioblastoma recurrence. Although bevacizumab markedly improves progression-free survival and decreases the need for steroids (thereby improving quality of life), **the available data do not show an OS benefit**. In addition, antiangiogenic drugs are associated with an **increased risk of ischemic and haemorrhagic events and the relative contraindication to further surgery after their use**" YW p.1111.
- **Neoadjuvant chemotherapy** is being explored: neoadjuvant temozolomide 2-3 weeks after surgery followed by hypofractionated accelerated RT with concurrent and adjuvant temozolomide improved survival in newly diagnosed GBM, **especially in MGMT-methylated patients**, in a phase 2 study YW p.1029.
- **Class-based agents and their toxicities**: alkylators (nausea, vomiting, marrow suppression, immunosuppression, gonadal toxicity, teratogenesis, interstitial pneumonitis with carmustine, and **secondary acute myelogenous leukaemia 4-7 years later**); antimetabolites (S-phase, hypersensitivity, marrow suppression, mucositis, hepato- and nephrotoxicity); topoisomerase inhibitors (irinotecan — early cholinergic diarrhoea treated with atropine, late diarrhoea with loperamide; etoposide — second AML risk); vinca alkaloids (peripheral neuropathy is the dose-limiting toxicity of vincristine, SIADH, constipation) [YW pp. 1031-1032].

Table 2 · Frequently used chemotherapeutic agents for CNS tumours — route and common adverse effects. Reproduced from Youmans & Winn 8e, Table 147.2, p. 1032.

Class	Drug	Route	Common adverse effects
Alkylating	Temozolomide	Oral	Nausea, vomiting, bone-marrow suppression
Alkylating	CCNU (lomustine)	Oral	Nausea, vomiting, BM suppression, renal and pulmonary toxicity
Alkylating	BCNU (carmustine)	IV	Nausea, vomiting, BM suppression, renal and pulmonary toxicity, **secondary acute leukaemias**
Alkylating	Cyclophosphamide	IV	Nausea, vomiting, BM suppression, cystitis
Alkylating	Carboplatin	IV	Nausea, vomiting, BM suppression, hepatotoxicity, renal toxicity at high dose
Alkylating	Procarbazine	Oral	Nausea, vomiting, BM suppression, hypersensitivity; **avoid with SSRIs and tyramine-rich food**
Antimetabolite	Methotrexate	IV	BM suppression, mucositis, renal toxicity, hepatotoxicity
Antimetabolite	Cytarabine (Ara-C)	IV	Nausea, vomiting, BM suppression, conjunctivitis, keratitis, neurotoxicity
Topoisomerase I inhibitor	Irinotecan	IV	BM suppression, diarrhoea and cholinergic toxicity
Topoisomerase II inhibitor	Etoposide	IV	Nausea, vomiting, BM suppression, allergy, hepatotoxicity
Antimitotic	Vincristine	IV	**Peripheral neuropathy**, SIADH, rash, constipation

4. Local and BBB-circumventing delivery — the neurosurgeon's contribution

- **Carmustine-impregnated wafers (Gliadel).** Up to **eight** BCNU-loaded wafers are applied to the resection cavity immediately after resection; the polymer supports gradual release and protects undelivered drug; **systemic BCNU peaks at <1/600 of the level after systemic administration and is undetectable within 24 hours**; BCNU is released over **5 days** and the polymer disintegrates completely over **6-8 weeks** YW p.1134. Trial data: recurrent malignant glioma **23 → 31 weeks** after revision resection (Brem); as initial therapy **58.1 vs 39.9 weeks** (Valtonen), with GBM specifically **53.3 vs 39.9 weeks**; and **13.8 vs 11.6 months** in the multicentre long-term study (Westphal) [YW pp. 1110, 1116]. Placebo-controlled studies show a **2.2-month** prolongation of survival with a **6-month survival rate of 56%**

versus 36% YW p.1031.

- **Limitations of wafers** — the drug moves by **diffusion**, so penetration is only **2 to 4 mm with a 250- to 100-fold fall in concentration** across that distance; reported toxicity includes **increased infection, malignant oedema, seizures, wound breakdown, CSF leakage and intracranial hypertension**; and subsequent trials showed the superiority of oral temozolomide with concurrent radiation [YW pp. 1031, 1134].
- **Convection-enhanced delivery (CED).** Uses **bulk flow** driven by a small hydrostatic pressure gradient, "largely independent of the molecular weight, concentration gradient, or diffusivity of a substance", so both small and large molecules can be distributed over large regions; typical infusion rates **1-10 µL/min**; ratio of volume of distribution to volume of infusion **3:1 in oedematous brain to 10:1 in the compacted fibres of the brainstem**; co-infusion of gadolinium permits real-time monitoring [YW pp. 1134-1135]. Limitations: **backflow at high infusion rates** (mitigated by step-design cannulas), intraparenchymal air from stylet removal, poor distribution of agents >50-100 nm (viruses, nanoparticles) because the extracellular space is ~100 nm, extracellular binding, **leakage into CSF spaces**, and futility for drugs that cross the BBB because they leak back into the circulation [YW pp. 1135-1136].
- **Direct intracavitary injection.** Repeated puncture of the cavity walls with a blunt side-opening needle, injecting **1 to 2 cm deep to the surface to minimise backflow**; a phase 1/2 trial of stereotactic MRI-guided BCNU found a maximum tolerated dose of **5 mL and 240 mg** with median overall survival **55 weeks** [YW pp. 1136-1137]. Viral vectors injected into the cavity walls (e.g., replicating retroviral vector encoding cytosine deaminase with systemic 5-fluorocytosine) gave **durable complete responses in 21.7%** of the phase 3-eligible subgroup YW p.1137.
- **Intra-arterial and BBB-disruption strategies.** Hypertonic mannitol causes osmotic shock in endothelial cells and **increases drug delivery by 10- to 100-fold**, but requires transfemoral angiography and general anaesthesia and carries stroke and seizure risk; **RMP-7 (a bradykinin analogue) was abandoned** after trials showed no survival benefit; MR-guided focused ultrasound with microbubbles is in phase 1 trials; and **intra-arterial carmustine "is neither safe nor effective in prolonging survival in patients with malignant gliomas"**, with reported leukoencephalopathy and blindness [YW pp. 1030-1031]. Complications of BBB disruption/intra-arterial chemotherapy: **seizures 6-7%, transient neurological symptoms 2.5-20%, stroke 4%**; phase 3 trials of intra-arterial ACNU ± carboplatin showed no benefit [YW pp. 1132-1133].
- **Intrathecal/intraventricular delivery** — reserved for leptomeningeal disease; **drug concentration in brain parenchyma is only 1% to 2% of the CSF concentration at 1-2 mm from the surface**, penetration limited to 2-4 mm, with catheter complications (haemorrhage, malposition, infection 1-7%; access-related infection 1-3%; up to 6% requiring surgery for repositioning or removal) [YW pp. 1031, 1133].
- **The multimodality survival ladder** (Attenello): radiotherapy alone **9 months**; Gliadel + RT **13 months**; RT + temozolomide **15 months**; **Gliadel + RT + temozolomide 20 months** YW p.1111.

TABLE 159.1 Variables Associated With Overall Survival of Glioblastoma Multiforme in Proportional Hazards Regression Analysis (Cox Model)

	Multivariate Analysis	
Variable	**Hazard Ratio**	***P* Value**
Age[a]	1.023	.001
Karnofsky Performance Scale score[a]	0.988	.018
Gross total resection	0.449	.001
Near-total resection	0.614	.002
Gliadel wafers	0.793	.056
Postoperative temozolomide[b]	0.546	.001
Increasing % extent of resection	0.995	.008
>70% of resection	0.631	.0006
Increasing residual volume	1.019	.004
<5-cm^3 residual volume	0.725	.01

Modified from McGirt MJ, Chaichana KL, Gathinji M, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. J Neurosurg. 2009;110:156–162, and Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, et al. Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol. 2014;16(1):113–122.

In a large cohort of patients, decreasing age, increasing Karnofsky Performance Scale score, increasing extent of resection, treatment with Gliadel wafer, and treatment with temozolomide, were independently associated with improved overall survival. Patients who underwent either gross total resection or near-total resection exhibited an independent survival benefit in comparison with patients who underwent subtotal resection, independent of subsequent treatment modalities. Chaichana and colleagues[30] made three-dimensional volumetric tumor measurements and dichotomized percentage of resection and residual tumor volume to find the minimum percentage of resection and maximal residual volume significantly associated with survival.

[a]Increasing variable.

[b]Includes temozolomide administered concomitantly with radiotherapy or as delayed adjuvant treatment.



Figure 159.3. Placement of carmustine-loaded implants (Gliadel wafers). After resection of a malignant glioma, the carmustine-loaded biodegradable polymers were placed within the tumor cavity. As the wafers dissolve, they release carmustine locally and provide direct delivery of chemotherapy to the tumor cavity and the surrounding brain parenchyma, where brain tumor microsatellites may be present. (*From Lesniak MS, Brem H. Targeted therapy for brain tumours. Nat Rev Drug Discov. 2004;3:499–508.*)

of 53 years.[61,62] However, gliosarcoma may also occur in children, and in rare cases, infantile gliosarcoma has been reported.[65] Gliosarcoma occurs in a male-to-female ratio of 1.8:1.[61,62]

Clinical Manifestations

Anaplastic Astrocytoma and Glioblastoma

Reproduced from Youmans & Winn 8e, Fig. 159.3, p. 1102 — Label when you reproduce it: placement of carmustine-loaded biodegradable implants (Gliadel wafers) lining the walls of a malignant glioma resection cavity. Note in the label: up to eight wafers, BCNU released over 5 days, polymer dissolved by 6-8 weeks, peak systemic BCNU <1/600 of systemic dosing and undetectable at 24 hours, penetration only 2-4 mm by diffusion.

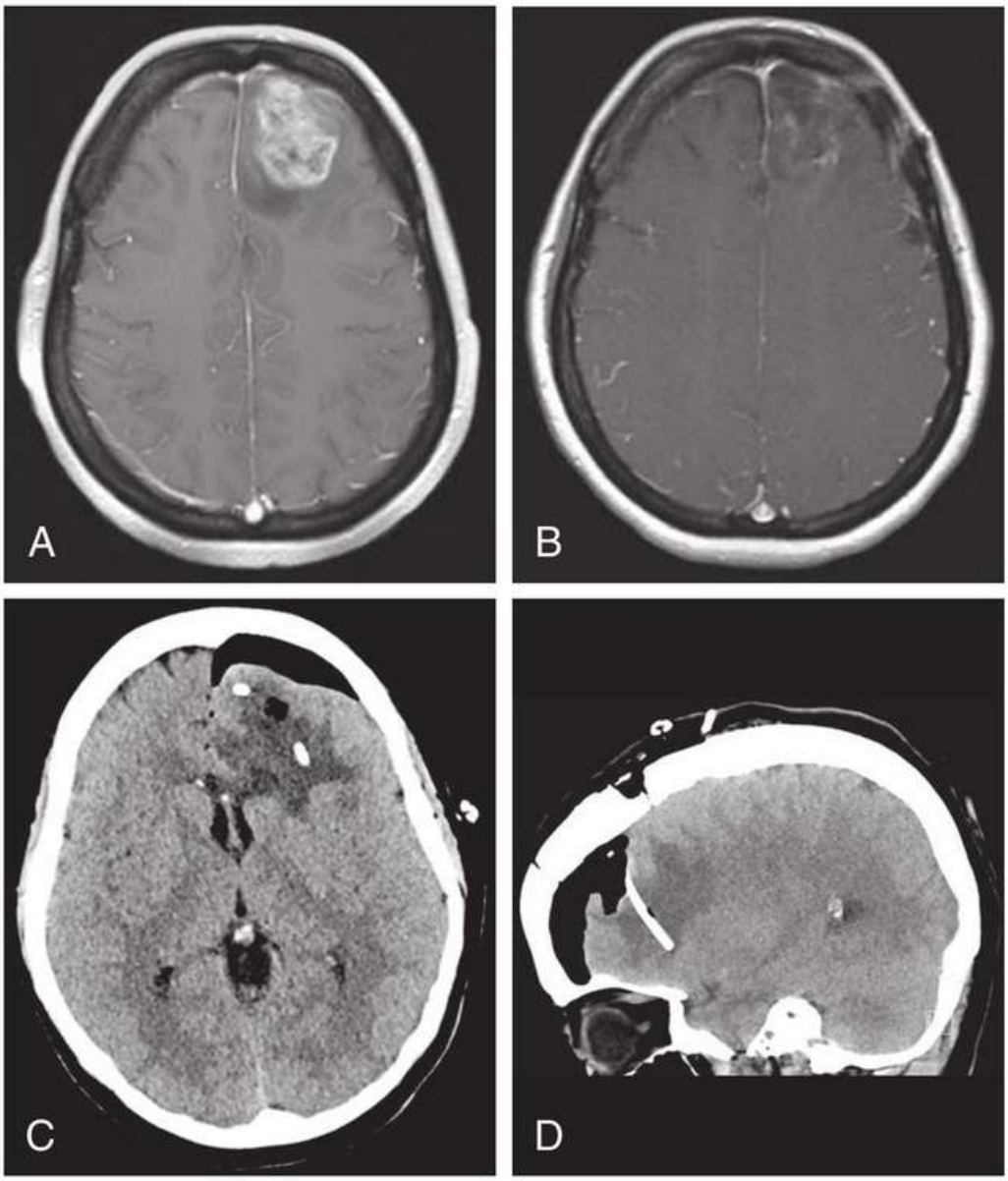


Figure 162.4. Patient with recurrent glioblastoma underwent repeat surgical resection and placement of multiple convection-enhanced delivery catheters for postoperative infusion of carboplatin over 72 hours. Preoperative (A) and postoperative (B) T1-weighted postcontrast MR images demonstrate resection of the left frontal tumor. Axial (C) and sagittal (D) CT scans show infusion catheter placement into the brain around the resection cavity.

Reproduced from Youmans & Winn 8e, Fig. 162.4, p. 1135 — Label when you reproduce it: convection-enhanced delivery in a patient with recurrent glioblastoma who underwent repeat resection and placement of multiple CED catheters for postoperative infusion of carboplatin over 72 hours. (A) Preoperative and (B) postoperative T1 post-contrast MRI showing resection of the left frontal tumour; (C) axial and (D) sagittal CT showing the infusion catheters sited in the brain around the resection cavity. In the label record the infusion rate of 1-10 µL/min and the volume-of-distribution to volume-of-infusion ratio of 3:1 in oedematous brain and 10:1 in the brainstem.

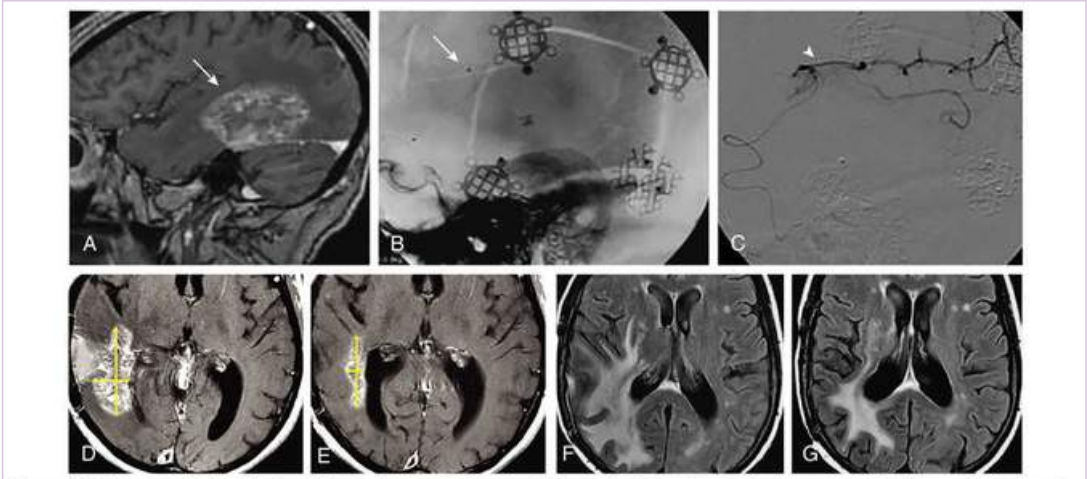


Figure 145.6. Superselective infusion of chemotherapy for recurrent high-grade glioma. Superselective endovascular delivery of bevacizumab for recurrent glioblastoma multiforme (GBM) has been shown to be technically feasible and safe, resulting in a radiographic response with decrease in fluid-attenuated inversion recovery (FLAIR) signal and decreased enhancement on gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI). (A and B) In this patient with recurrent right posterior temporal GBM shown on gadolinium-enhanced T1-weighted MRI in sagittal view (A, denoted by *arrow*), a microcatheter was navigated into the tumor feeding the middle cerebral artery (MCA) branch (B, microcatheter tip denoted by *arrow*) on an unsubtracted digital subtraction angiography. (C) Superselective contrast infusion into the tumor feeding the distal branch of the right MCA under digital subtraction angiography demonstrates the distribution of intra-arterial infusion of mannitol and bevacizumab (delineated by *arrowhead*). (D–G) Contiguous gadolinium-enhanced T1-weighted MRI in axial view demonstrates a marked interval decrease in the size of the enhancing component (D and E), and the marked interval decrease of the associated FLAIR signal on T2-weighted MRI in axial view (F and G) at 1 month. (*Reprinted with permission from Boockvar JA, Tsiouris AJ, Hofstetter CP, et al. Safety and maximum tolerated dose of superselective intraarterial cerebral infusion of bevacizumab after osmotic blood-brain barrier disruption for recurrent malignant glioma. Clinical article. J Neurosurg. 2011;114(3):624–632.*)

Reproduced from Youmans & Winn 8e, Fig. 145.6, p. 1019 — Label when you reproduce it: superselective intra-arterial infusion of chemotherapy for recurrent high-grade glioma — superselective endovascular delivery of bevacizumab. Label the guide catheter position, the microcatheter in the tumour-feeding branch, and the tumour blush. In the label state that mannitol BBB disruption increases delivery 10- to 100-fold but that phase 3 trials have shown no survival advantage over intravenous delivery, with seizures in 6-7%, transient deficits in 2.5-20% and stroke in 4%.

(b) Management of CSF leaks [4]

5. Definition, aetiology and natural history

- **Mechanism.** "Head injuries associated with craniofacial fractures cause **80% of traumatic CSF leaks** when a skull fracture has an associated durotomy that leaks CSF into the nasal cavity, paranasal sinuses, or middle ear" YW p.3163.
- **Incidence.** The incidence of skull base fracture rises with injury severity, and **"CSF leak developing in 11%-45% of skull fractures"**; the reported incidence of skull base fracture in blunt head injury is **7% to 24%**, and of associated CSF fistula **2% to 20.8%**; **one-third of patients with basilar skull fractures may develop a subsequent CSF leak** YW p.3163.
- **Timing.** "After trauma, **50% of CSF leaks are apparent within the first 48 hours and 70% present within the first week**. Some fistulas may appear as late as **2-3 months** after the initial trauma" YW p.3163. Delayed meningitis without a history of rhinorrhoea has been reported **up to 48 years** after the original injury YW p.3165.
- **Site.** Rhinorrhoea is most often caused by fracture of the **frontal bones (30%), sphenoid bones (30%) and ethmoid bones/cribriform plate (23%)**. "The dura is firmly adherent to the thin bone of the anterior fossa floor and is readily torn by fractured bone edges. **The cribriform-ethmoid junction is particularly weak because the anterior ethmoidal artery penetrates the skull base along the lateral margin of the cribriform plate, creating a natural weakness in the bone**" YW p.3163.
- **Otorrhoea/otorhinorrhoea. 70-90% of temporal bone fractures are longitudinal** (parallel to the petrous ridge), damaging the ossicles (conductive deafness) and CN VII, usually with a torn tympanic membrane; **transverse fractures (10-30%)** are associated with CN VIII deficits, sensorineural hearing loss and facial palsy, usually with an intact drum so that CSF leaks via the eustachian tube into the nasopharynx YW p.3163.
- **"The side of rhinorrhoea cannot be relied on to locate the fistula. Although usually ipsilateral to the fracture site, it is frequently contralateral or bilateral"** YW p.3165.

- **Which fistulas will not heal** — "the fistula is unlikely to heal spontaneously if: the bone defect is large with wide separation of the fractures and the torn dural margins **or the dura is penetrated by bony spikes**; there is **inadequate support for the dura** because of extensive loss of bone; **tissue healing is impaired by metabolic disease**; **ICP is raised**" YW p.3165.
- **Delayed onset or recurrence** occurs because of shrinking of blood clot or swollen brain that was plugging the tear, **maturation and shrinkage of the dural scar**, and devascularisation/necrosis of bone and soft tissue YW p.3165. Very-late leaks or infection occur from **age-related brain shrinkage**, an unreliable cerebral-dural scar, or a **growing fracture of the ethmoid forming a herniated encephalocele that stretches and ruptures** YW p.3165.
- **Complications. Pneumocephalus, meningitis and brain abscess** YW p.3163. Intracranial air is present in **20-30%** of post-traumatic CSF fistulas and "alone, it carries the same risk for meningitis as a CSF leak does" YW p.3164. The commonest organisms are ***Streptococcus pneumoniae* and *Haemophilus influenzae***; pneumococcal meningitis may be rapidly fatal and polymicrobial infection including anaerobes is common; **there is a 2.6 times greater rate of intracranial infection with basal skull fractures when a ventricular catheter is used** YW p.3164.

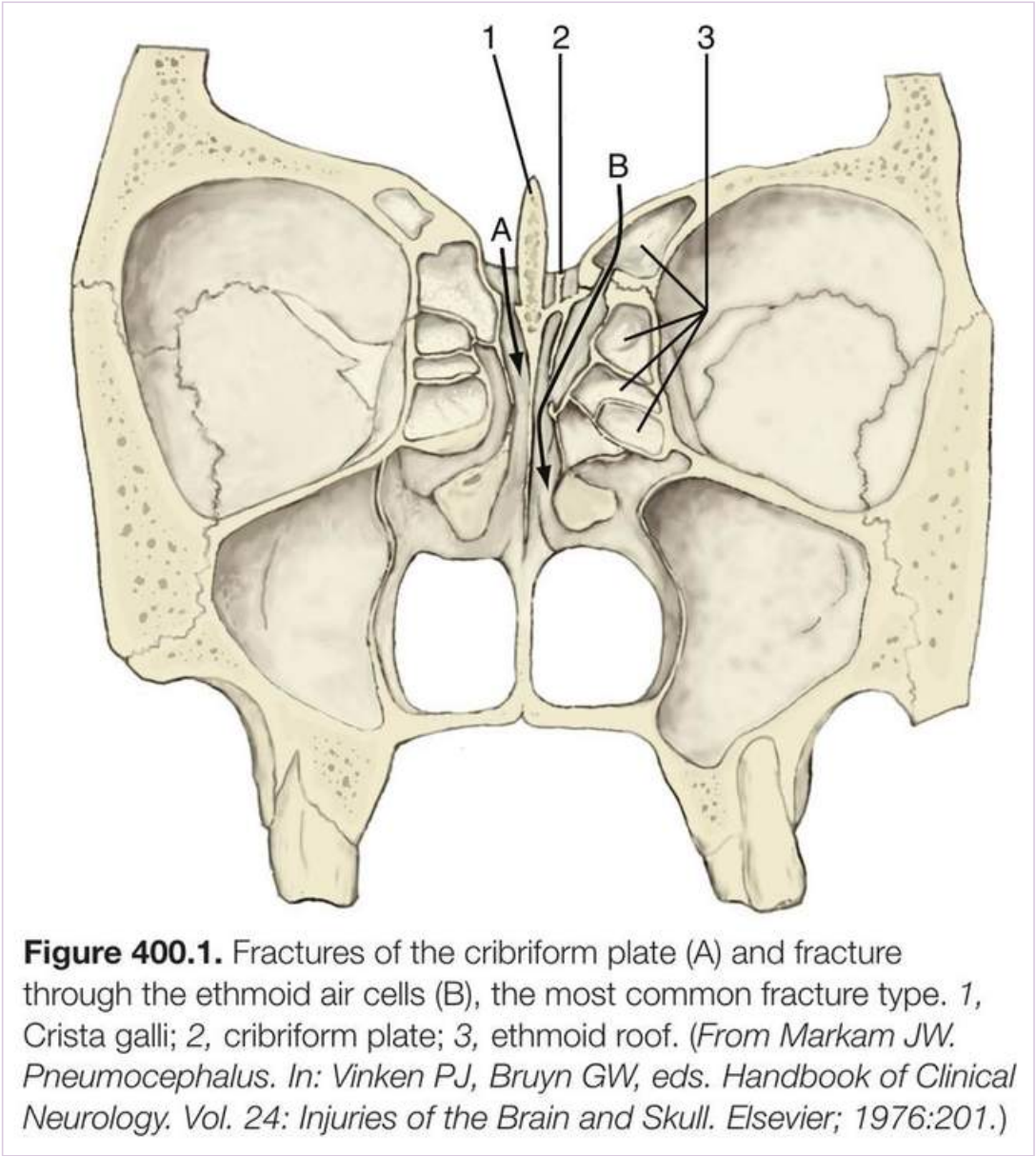


Figure 400.1. Fractures of the cribriform plate (A) and fracture through the ethmoid air cells (B), the most common fracture type. *1,* Crista galli; *2,* cribriform plate; *3,* ethmoid roof. (*From Markam JW. Pneumocephalus. In: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology. Vol. 24: Injuries of the Brain and Skull. Elsevier; 1976:201.*)

Reproduced from Youmans & Winn 8e, Fig. 400.1, p. 3164 — Label when you reproduce it: fractures of the cribriform plate (A) and the fracture patterns that produce CSF rhinorrhoea. Label the cribriform plate, the ethmoid roof, the lateral lamella beside the entry of the anterior ethmoidal artery (the natural weak point), the planum sphenoidale, the posterior wall of the frontal sinus and the frontal recess. Mark the site percentages: frontal 30%, sphenoid 30%, ethmoid/cribriform 23%.

6. Diagnosis — confirm that it is CSF, then localise it

Table 3 · Laboratory tests for identifying cerebrospinal fluid — reproduced in full from Youmans & Winn 8e, Table 400.1, p. 3165.

Test	Detail
Halo (target) sign	On absorbent cloth or filter paper CSF migrates further than blood or nasal discharge and forms a ring-like target/halo pattern
Glucose oxidase test strips	Positive if glucose >20 mg/100 mL. A **negative** strip eliminates the likelihood of a CSF leak, but **a positive result cannot be interpreted** because nasal secretions contain reducing substances; cannot be used on bloody discharge because blood contains glucose
β2-transferrin	Found only in **CSF, perilymph and vitreous humour**; accounts for **15% of total CSF transferrin**; needs **<1 mL**; sensitivity **87-100%**, specificity **71-100%**
β-trace protein (prostaglandin D2 synthase)	High concentration in CSF; nephelometry-based assay is easier, faster and cheaper than β2-transferrin immunoelectrophoresis; sensitivity **91-100%**, specificity **86-100%**; limited utility in bacterial meningitis or renal impairment; not available in the USA
Glucose concentration	Fluid is likely CSF if glucose is **0.5-0.67 of serum** glucose; needs only 0.5-1 mL
Chloride concentration	Concentration **>110 mEq/L** suggests CSF

Table 4 · Radiographic tests to localise a CSF leak — reproduced in full from Youmans & Winn 8e, Table 400.2, p. 3166.

Modality	Key points
Plain radiographs	Limited value; may show fluid in paranasal sinuses or pneumocephalus
CT (fine-cut bone windows, 0.6-1.0 mm)	**Most useful scan; identifies the site of fistula in more than 70% of cases; 91% specificity.** Axial views best show the frontal sinus walls; coronal views show the ethmoid complex, sphenoid sinus roof and tegmen of the middle ear; soft-tissue windows show sinus fluid, intracranial air or soft-tissue dehiscence. Brain swelling influences the timing of surgical exploration
MRI	Distinguishes CSF rhinorrhoea from inflammatory sinus disease — CSF is white on T2 whereas perimucosal discharge and nasal disease are darker; mucosal disease may enhance; may show brain/arachnoid herniation through the bone defect, CSF signal in the sinuses, CSF pooling, dural injury and associated brain injury
Intrathecal fluorescein	**Not FDA-approved; requires full informed consent.** 0.1 mL of 10% fluorescein mixed with 10 mL of the patient's own CSF, injected over 5 minutes, allowed to circulate 1-2 hours. Detected on cottonoid pledgets or by direct endoscopy as **bright yellow-green** staining. Risks: seizures, headache, cranial nerve deficits, especially at higher concentrations — irrigate with saline if an adverse reaction occurs. Radionuclide tracers are no longer used
CT cisternography	Detects the fistula in **76-100%** of active leaks; baseline scan, then 6-7 mL metrizamide or iopamidol via lateral C1-C2 or lumbar puncture, Trendelenburg positioning, repeat coronal scan; leak indicated by bone dehiscence, contrast in the adjacent sinus and distortion of the subarachnoid space
MRI cisternography	Similar technique; reported to have **higher localisation success**

7. Medical and conservative management

- **Antibiotic prophylaxis is genuinely contentious.** "At present, there seems to be **no compelling evidence of either benefit or harm** from the use of prophylactic antibiotics" YW p.3165. One meta-analysis recorded **2.5% infection with antibiotics and 10% without**, and the Mayo Clinic experience found infection halved; but the most recent (2015) and other analyses found **no significant difference** in meningitis, meningitis-related mortality or all-cause mortality YW p.3165.

- **The three arguments against prophylaxis** YW p.3165: (1) the antibiotics commonly used **penetrate CSF poorly**; (2) the **period of risk, and hence the duration of prophylaxis beyond cessation of the leak, is uncertain**; (3) antibiotics may **promote resistant nasopharyngeal strains** and lead to infection with resistant or unusual organisms.
- **What is recommended** — "**pneumococcal vaccination is recommended in patients who have CSF leaks** given that *S. pneumoniae* is the most common pathogen"; because the principal source is the nasopharynx, prophylaxis aims to sterilise it. The authors' institutional practice is **ceftriaxone or cefepime for perioperative prophylaxis** (vancomycin or aztreonam in penicillin allergy), continued **for the duration of nasal packing** and **not continued postoperatively** thereafter [YW pp. 3165-3167].
- **Conservative treatment is indicated when CT shows non-displaced, linear fractures**, because spontaneous healing is likely YW p.3166. Spontaneous resolution of anterior CSF leaks is **47% to 68% within the first 48 hours, reaching 85% within the first week**; **lateral skull base leaks resolve in 95-100%** with conservative management; 60-70% of small-defect cases cease within 1 week [YW pp. 3165-3166].
- **The conservative regimen, in Youmans' own three numbered steps** YW p.3166:
  - **(1) Bed rest with the head elevated moderately (e.g., 30 degrees).**
  - **(2) Avoidance of actions that might cause a sudden increase in ICP** — nose blowing, straining at stool, coughing, sneezing; place the patient on a bowel regimen with laxatives and stool softeners.
  - **(3) CSF drainage with external ventricular drain or lumbar drain.** "If the leak does not cease within **3 days**, intermittent or continuous drainage of lumbar fluid may be considered."
- **Lumbar drainage — the balance.** Success rates of **84-94%** compared with bed rest are quoted; the **risk of infection is lower with lumbar than with ventricular drainage**; but "continuous CSF drainage is potentially hazardous and should be used with caution. **Overdrainage can lead to intracranial aeroceles, severe brain displacement, and coma** and require emergency drainage of the aerocele"; lumbar drainage may promote entry of bacteria through the fistula; and although lumbar drains shorten the duration of rhinorrhoea, **they have not been shown to reduce meningitis risk** YW p.3166.
- **High-pressure leaks.** "In most instances, persistent fistulas are not associated with increased ICP. High-pressure leaks are more common with **spontaneous, non-traumatic** CSF leakage; however, if the leak is accompanied by **post-traumatic hydrocephalus**, it may be maintained by the high CSF pressure, and **the hydrocephalus should be managed by insertion of a lumbar peritoneal shunt as the initial treatment**" YW p.3165. CSF shunting is otherwise rarely definitive YW p.3168.

8. Surgical management — timing

- **Indications for early surgery** YW p.3166:
  - **1. Penetrating injury, including gunshot wounds.**
  - **2. Anterior fossa surgery indicated for another reason** (intracranial haematoma, reconstruction of compound facial fractures) — repair accessible dural tears at the same time.
  - **3. Meningitis (once treated).**
  - **4. A large intracranial aerocele, particularly if intracerebral.**
  - **5. Herniation of brain tissue through the nose.**
  - **6. Radiological appearances indicating a low probability of natural dural repair** — (a) widely comminuted or separated anterior fossa fractures communicating with the nose or paranasal sinuses; (b) displaced bony fragments and spikes of bone; (c) fractures with soft tissue between the bony edges.
- **Indications for delayed surgery** [YW pp. 3166-3167]:
  - **1. Failed conservative management — a CSF leak persisting beyond 10 days.**
  - **2. Recurrent or delayed CSF leakage after 10 days.**
  - **3. Recurrent aerocele after 10 days.**
  - **4. Meningitis or abscess at any time after injury.**

9. Surgical technique — open repair

- **When to go open.** "Open cranial repair is indicated for **large cranial base fractures, open or comminuted fractures, extensive bony defects, and concurrent intracranial haematomas or infections**" YW p.3167.
- **The four goals of any repair**: identification of the leak, preparation of the site, performing the repair primarily or with a graft, and promotion of healing YW p.3167.
- **Intradural versus extradural.** "In general, **intradural exploration allows clearer delineation of the dural tear, does not risk the creation of false tears, and permits more definitive repair**" YW p.3167.
- **Positioning.** Head elevated relative to the heart to reduce venous pressure; cranial fixation and fixed retraction for an intradural approach; **20% mannitol 1 g/kg before scalp incision** for brain relaxation, combined with CSF drainage; supine with the head extended for frontal sinus or anterior fossa leaks; **bicoronal incision behind the hairline**, scalp reflected to the superior orbital margin, craniotomy taken inferiorly across the frontal sinuses and laterally to the temporal crest YW p.3167.
- **Key anterior fossa intraoperative points, verbatim** YW p.3167:
  - **Preserve the draining veins of the superior sagittal sinus.**
  - **Preserve at least one olfactory nerve.**
  - The site of the fistula may be indicated by **brain and arachnoid adherence**.
  - **Primary suture is difficult and rarely successful** — graft using **temporalis fascia or fascia lata**.
  - A **small bony defect can be plugged with muscle or fat**; a **large bony defect filled with bone graft (split calvarium)**.
  - **Cranialise or obliterate the frontal sinus and strip all mucosa**; plug the frontonasal duct with muscle and/or fat (or morselised bone graft).
  - Turn a **pericranial or galeal flap** over the frontal sinus and suture it to the dura.
  - **If no fistula is found, it is not advised to avulse the olfactory nerves and cover the anterior fossa floor with fascia.**
- **Middle fossa points** — avoid opening mastoid air cells or seal them with bone wax; **preserve the vein of Labbé**; the fistula is likely over the **tegmen tympani**. For longitudinal petrous fractures a **square lateral flap with subtemporal craniotomy** is used; for transverse fractures the approach depends on hearing — **translabyrinthine if hearing is lost**, otherwise intracranially via the posterior fossa YW p.3167.
- **Postoperative care** — "**antibiotics are not continued postoperatively. Postoperative CSF drainage is not performed unless the quality of the repair is in doubt.** If an early leak recurs, a period of lumbar drainage may be undertaken" YW p.3167.

10. Endoscopic endonasal repair — now the default for small fistulas

- **The paradigm shift.** "Wigand described the first successful CSF leak repair using endoscopy in **1981**. Since then, the technique has been largely popularised and refined, resulting in **a paradigm shift from open repair to endonasal endoscopic repair of CSF rhinorrhoea**" YW p.3167. Youmans' key concept states it as a **>90% success rate** YW p.3163 .
- **The numbers.** "Successful leak closure ranges from **70% to 100% with the first endoscopic attempt and from 86% to 100% with a second endoscopic repair**. Complication rates are as low as **0.03% for meningitis, haematoma, and abscess** or **1%-2.5% for all morbidities**" YW p.3167.
- **Advantages** — cosmetic preservation, minimisation of trauma to the olfactory region, reduced surgical morbidity, and the ability to repair the frontal sinus **while keeping it patent, thus preventing postoperative mucocele** YW p.3167. Success is higher when the leak site is accurately identified and defects are more medially based around the frontal recess YW p.3167.
- **Causes of endoscopic failure** — "**inaccurate localisation of the defect(s), large (greater than 1.5 cm) or multiple defects, poor graft positioning and adherence, and/or postoperative infection**" YW p.3167.
- **Approach by site** [YW pp. 3167-3168]:
  - **Cribriform plate/anterior skull base** — anterior and posterior ethmoidectomy; remove the middle turbinate only to improve visualisation or postoperative patency.

  - **Central sphenoid/posterior ethmoid** — transethmoid approach; larger leaks may need a transseptal approach with elevation of the septal mucoperichondrial flap and removal of the bony septum to see both sphenoid ostia; sinus obliteration with complete mucosal removal and muscle/fat is an alternative.
  - **Lateral sphenoid sinus** — the **transpterygoid approach** (removal of the uncinate process, anterior and posterior ethmoidectomy, wide sphenoidotomy) is the strategy of choice; elevate and replace a medial mucosal flap off the maxillary posterior wall to preserve mucociliary clearance; **displace the internal maxillary artery, V2, the vidian nerve and the sphenopalatine ganglion laterally before removing the anterior pterygoid process**.
  - **Frontal sinus** — endoscopic modified Lothrop procedure for posterior-table defects; lateral or superior frontal leaks may need a combined "above and below" technique with an osteoplastic flap and obliteration, or a combined endoscopic approach with frontal trephination.
- **Site preparation and grafts** YW p.3168:
  - **Approximately 5 mm of clearance of mucosa off the bone around the fistula is a critical step for graft adherence.** In traumatic leaks, avoid enlarging the fracture; a rotating burr may be used to stimulate osteogenesis.
  - **Autologous graft** (fascia lata, abdominal fat, turbinate mucosa) offers innate growth factors and rapid healing without foreign-body reaction, at the cost of donor-site morbidity and harvest time.
  - **The pedicled nasoseptal flap (NSF)**, based on the **posterior septal branch of the sphenopalatine artery**, is the workhorse vascularised reconstruction; it correlates with **higher success in large defects and "high-flow" leaks**, fewer postoperative leaks and less crusting. Technical keys: **avoid torsion of the pedicle and place the mucosal surface toward the nasal cavity**. Complications of NSF harvest: anosmia, prolonged crusting, septal perforation, epistaxis, mucocele, flap necrosis.
  - **Multilayer repair** is generally used for defects **>1.0 cm** (some authors use 0.5 cm as the threshold); **mucosa must never be used as a primary underlay** because of the risk of intracranial mucocele.
  - **Free fat grafts** suffice for small (<0.5 cm) frontal and sphenoid defects; fat is resistant to infection and adheres strongly to bone.
  - **The "bath-plug" technique** (Wormald and McDonogh, 1997) — autologous fat positioned intracranially against the dura and sutured to seat it, then an overlay mucosal graft, fibrin glue and Gelfoam — has a reported **94% primary and 100% secondary closure rate** for defects from 2 × 1 mm to 12 × 10 mm YW p.3168.
- **Bony grafts** are harvested from the middle/inferior turbinate, nasal septum or nasal floor; **the inferior turbinate offers greater volume than the middle turbinate** YW p.3168.
- **Paediatric leaks** are uncommon because of the flexible cartilaginous skull and underdeveloped sinuses; endoscopic reconstruction is more difficult because of variable sinus pneumatisation, small nasal cavities and difficulty ensuring compliance with sinus precautions, bed rest and nasal examination [YW pp. 3163, 3168].

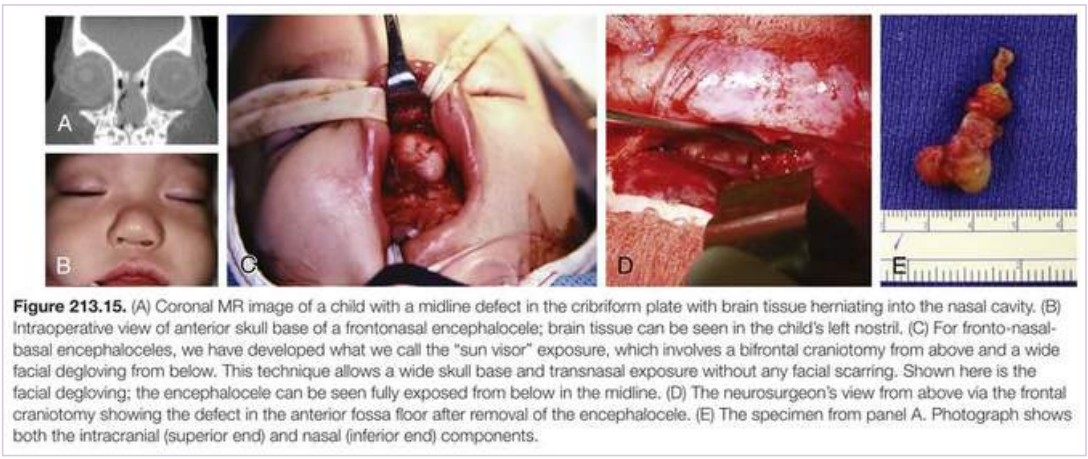


Figure 213.15. (A) Coronal MR image of a child with a midline defect in the cribriform plate with brain tissue herniating into the nasal cavity. (B) Intraoperative view of anterior skull base of a frontonasal encephalocele; brain tissue can be seen in the child's left nostril. (C) For fronto-nasal-basal encephaloceles, we have developed what we call the "sun visor" exposure, which involves a bifrontal craniotomy from above and a wide facial degloving from below. This technique allows a wide skull base and transnasal exposure without any facial scarring. Shown here is the facial degloving; the encephalocele can be seen fully exposed from below in the midline. (D) The neurosurgeon's view from above via the frontal craniotomy showing the defect in the anterior fossa floor after removal of the encephalocele. (E) The specimen from panel A. Photograph shows both the intracranial (superior end) and nasal (inferior end) components.

Reproduced from Youmans & Winn 8e, Fig. 213.15, p. 1630 — Label when you reproduce it: (A) coronal MR image of a child with a midline defect in the cribriform plate with brain tissue herniating through it. Label the bony defect, the herniated brain/meninges, and the nasal cavity below. Use it to illustrate the "growing fracture of the ethmoid leading to a herniated encephalocele that stretches and ruptures" mechanism of very-late-onset CSF rhinorrhoea, and note that herniation of brain tissue through the nose is an indication for early surgery.

(c) Treatment options for unruptured intracranial aneurysms and AVMs [3]

11. Unruptured intracranial aneurysm — quantify the natural history first

- **The framing question.** "Finding an incidental UIA poses a dilemma for physicians and patients because **aneurysm rupture is potentially devastating but preventive repair is not without risks, particularly in older patients**"; it is estimated that **1 in 200-400 will rupture**, and "aneurysms that rupture may not be the same as the ones found incidentally" YW p.3429.
- **The four things to analyse before treatment** YW p.3429: (1) **patient age and comorbid conditions**; (2) **aneurysm morphology, size and attendant risk**; (3) **endovascular versus microsurgical accessibility/suitability and long-term angiographic outcome**; (4) **expected recovery duration and required long-term follow-up**. "Taken together, **the natural history of the patient and the natural history of the particular aneurysm must be considered** "; exclusive focus on either is not optimal.
- **ISUIA.** The retrospective arm gave an annual SAH risk of **0.05%** for lesions <10 mm in patients with no previous SAH, rising **11-fold** for aneurysms >10 mm; the prospective arm of 4060 patients found **size (>7 mm) and location (posterior > anterior circulation)** associated with rupture YW p.3430.
- **Other natural history data.** Korja followed 118 patients to death or SAH: **29% had a SAH; annual rupture rate 1.6% (range 0-6.5%)**, with female sex, current smoking and size ≥7 mm as lifetime risk factors YW p.3430. The Japanese UCAS study of 6697 aneurysms in 5720 patients found an **annual rupture rate of 0.95%**, with increasing size, location (posterior and anterior communicating arteries) and **irregular shape or daughter sac** increasing risk YW p.3430. A systematic review of 12,609 ruptured aneurysms found **the overall mean size of a ruptured aneurysm was 7.0 mm** — "size, while a useful guide, is an oversimplification when used alone" YW p.3430.
- **Aspirin.** "Data are accumulating that **aspirin use may reduce the rate of aneurysm growth and rupture, with an inverse dose-response relationship** among aspirin users" YW p.3430.

Table 5 · Five-year cumulative rupture rates by size and location of unruptured aneurysm (ISUIA) — reproduced from Youmans & Winn 8e, Table 430.1, p. 3490; and the PHASES score — Table 430.2, p. 3490.

Location	<7 mm (no prior SAH)	7–12 mm (prior SAH)	7–12 mm	13–24 mm	≥25 mm
Cavernous carotid artery (n = 210)	0	0	0	3.0%	6.4%
ACoA/ACA, MCA, ICA (n = 1037)	0	1.5%	2.6%	14.5%	40%
Posterior circulation / PComA (n = 445)	2.5%	3.4%	14.5%	18.4%	50%

PHASES component	Points
(P) Population — North American/European (non-Finnish) 0; **Japanese 3; Finnish 5**	0 / 3 / 5
(H) Hypertension — no 0; yes 1	0 / 1
(A) Age — <70 years 0; ≥70 years 1	0 / 1
(S) Size — <7.0 mm 0; 7.0-9.9 mm 3; 10.0-19.9 mm 6; **≥20.0 mm 10**	0 / 3 / 6 / 10
(E) Earlier SAH from another aneurysm — no 0; yes 1	0 / 1
(S) Site — ICA 0; MCA 2; **ACA/posterior circulation 4**	0 / 2 / 4

Interpretation: "an increase in the PHASES score predicts a greater 5-year rupture risk: **3 points or less, 0.7%; 5 points, 1.3%; and 10 points, 5.3%**"; "a **PHASES score ≤3 can be considered to have a low (but not negligible) risk** of aneurysm rupture" YW p.3430.

12. The treatment options for an unruptured aneurysm

- **Observation with serial imaging and risk-factor modification.** "In elderly patients, observation with serial imaging may be appropriate; however, **closer surveillance is required in patients with multiple aneurysms or an aneurysm with irregular morphology**" YW p.3432. "Aneurysm growth on serial imaging may be considered a **surrogate marker**

for increased rupture risk" YW p.3430. Note that quality of life is compromised in patients living with an untreated UIA, and headache-related quality of life can improve after surgery YW p.3432.

- **Microsurgical clip occlusion.** ">90% of aneurysms undergoing surgical clip occlusion are completely obliterated, although this success rate depends on many variables and in particular aneurysm size, with greater success in smaller aneurysms" YW p.3430. Even when the surgeon believes the result is satisfactory, **vessel occlusion or aneurysm remnants are found on 5% of postoperative angiograms** — hence the case for intraoperative or postoperative angiography or 4D CTA YW p.3430.
- **Surgical risk figures to quote** YW p.3431: most case series put morbidity and mortality at **about 5%**; ISUIA suggested combined morbidity and mortality approaching **15% at 1 year**, with ISUIA II in-hospital mortality **1.8%** and adverse outcomes in **8.9%** of survivors; administrative discharge data give mortality **2.5-3%** with adverse events in **21.3-22.4%** ; meta-analyses give combined morbidity and mortality of **3-7%** with a complication risk of about **10%** (King: 4.1% disabled, 1% died; Raaymakers: morbidity 10.9%, mortality 2.6%; Kotowski: mortality 1.7%, unfavourable outcome including death 6.7%).
- **Risk rises with size and with posterior location** YW p.3431: operative morbidity complicated **2% of UIAs <5 mm, 7% of those 6-15 mm and 14% of those >16 mm**; favourable outcome in **83%** of giant UIAs versus **99%** of UIAs <10 mm; clip occlusion achieved in **85% of lesions >10 mm, 93% of lesions <10 mm, but <60% of giant aneurysms** . Giant unruptured basilar aneurysms carried **50% surgical morbidity and mortality** versus **13%** for giant anterior circulation UIAs, and posterior circulation lesions carry a **nearly 10-fold increase in risk** compared with similar-sized anterior circulation lesions. In the anterior circulation, **anterior communicating artery and ICA bifurcation lesions carry the greatest risk**.
- **Long-term durability of clipping** YW p.3430: aneurysm recurrence **0.7% per year** over a mean 14 years; risk of SAH after clipping **0.01% to 0.085% per year**; cumulative 10-year risk of re-treatment or rupture **3.0%**; **no growth or recurrence occurs if the aneurysm is completely occluded**, including giant aneurysms, but the annual haemorrhage rate is **1.9%** where occlusion is incomplete. DSA or high-quality non-invasive imaging **3-5 years after clipping** is advisable, particularly in the elderly in whom DSA stroke risk is higher.
- **Endovascular treatment.** "Advanced age does not appear to increase risk in patients who undergo endovascular procedures for UIA; therefore **older patients may be better treated using endovascular techniques**" YW p.3432. "When managing unruptured aneurysms, **the luxury of time provides increased leeway regarding anticoagulation as well as flow diversion**" YW p.3490 — in contrast to ruptured aneurysms where immediate occlusion is paramount, which limits flow diversion (no immediate occlusion) and stent-assisted coiling (needs dual antiplatelet therapy). In carefully selected patients **flow-diverting stents may be used for complex aneurysms that recur after surgery** YW p.3430.
- **Deconstructive and revascularisation options.** "Rather than direct occlusion, **bypass with vessel occlusion using surgical or endovascular techniques may be a better option**" for heavily calcified or complex aneurysms YW p.3432.
- **Guidelines and consensus.** The 2015 AHA guidelines, in the absence of RCTs, recommend **occlusion of UIAs >5-7 mm among patients with acceptable surgical and medical risk** YW p.3432. A 39-panellist Delphi consensus (the **UIATS — unruptured intracranial aneurysm treatment score**) quantified the key decision factors; "the UIATS is neither prognostic nor predictive; instead, it attempts to congregate the expert" opinion, and "it remains a good screening tool but does not obviate the need for individualised treatment recommendations based on consultation with a cerebrovascular specialist" [YW pp. 3432, 3489, 3492].
- **Youmans' own recommendation, quotable verbatim** YW p.3432: "we recommend that the following UIA patients should be treated: those with **(1) SAH from another aneurysm, (2) a symptomatic aneurysm, (3) aneurysms >7-10 mm in nearly all patients with a life expectancy of 12 or more years, and (4) aneurysms >5 mm if the patient is young or middle-aged**. These recommendations depend on collaboration among a highly experienced cerebrovascular team of microneurosurgeons and endovascular neurosurgeons."
- **Patient-related factors increasing surgical risk** — advanced age (after size and location, age is the next most important risk factor for poor outcome), ischaemic cerebrovascular disease, diabetes mellitus, severe cardiac or pulmonary disease (anaesthetic risk) and advanced malignancy (reduced life expectancy negates benefit) YW p.3432. **Khanna's UIA grading scale** gave a poor outcome incidence rising from **0% in grade 0 to 66% in grade IV** YW

p.3432. A modelling review of 10,545 patients found that **small basilar and supraclinoid aneurysms (5 mm) had operative benefit only in young patients (≈40 years)**, larger aneurysms (10-15 mm) over a wider age range, and **no age/size combination gave an operative benefit for cavernous aneurysms** YW p.3432.

Table 6 · Factors thought to be associated with aneurysm rupture — reproduced in full from Youmans & Winn 8e, Box 427.1, p. 3429.

Category	Factors
Aneurysm-specific	Increased size (>7 mm); irregular shape (non-spherical, multilobed); posterior circulation; anterior communicating artery location; flow straight into the aneurysm; symptomatic aneurysm; association with arteriovenous malformations; aneurysms that increase in size on follow-up imaging; **high aspect ratio — dome-to-neck ratio >1.6**; previous SAH from another aneurysm; circumferential aneurysmal wall enhancement; wall shear stress
Patient-specific	Female sex; increased age; previous and present cigarette smoking; hypertension; binge alcohol drinking; sympathomimetic drugs; family history of SAH
Other	Elevated or increasing atmospheric pressure; seasonal variation (peak in winter)
Scoring systems	**PHASES score ≥3**

13. Unruptured brain AVM — natural history and grading

- **Natural history.** Gross and Du's meta-analysis concluded that "the annual rate of future haemorrhage was **2.2% (95% CI 1.7%-2.7%) for unruptured bAVM and 4.5% (95% CI 3.7%-5.5%) for ruptured bAVM**", and the rate of first haemorrhage for unruptured bAVM "is the same as that reported in **ARUBA** for the prospective untreated group" YW p.3677.e2. Kim's series of >2500 untreated bAVMs reported a lower annual first-haemorrhage rate of **1.3% (1.0-1.7%)** with a similar next-haemorrhage rate of **4.8% (3.9-5.9%)** for ruptured lesions YW p.3677.e3.
- **Risk factors for haemorrhage.** "Previous haemorrhage, deep location, exclusively deep venous drainage, and associated aneurysm" were statistically significant YW p.3677.e2. Youmans' own summary: "**factors that increase the likelihood of rupture of unruptured bAVMs include the presence of aneurysms, deep location (or exclusively deep venous drainage), and age (possibly). Size should not be considered a risk factor**" YW p.3677.e3.
- **Consequence of a bleed.** Pooled data give a **mortality from future haemorrhage of 17-19%** and combined **mortality and morbidity of 34-45%** across the majority of studies YW p.3677.e5.
- **Epidemiology.** bAVM is diagnosed in **no more than 1.5 per 100,000 persons annually** YW p.3677.e2.

Table 7 · Spetzler-Martin grading system for arteriovenous malformations, and the Spetzler-Ponce classification — reproduced from Youmans & Winn 8e, Table 452.1, p. 3677.e2 and Table 456.1, p. 3719.

Graded feature	Points assigned
AVM size (diameter) — small (<3 cm)	1
Medium (3-6 cm)	2
Large (>6 cm)	3
Eloquence of adjacent brain — non-eloquent	0
Eloquent	1
Pattern of venous drainage — superficial only	0
Deep	1
Grade = size + eloquence + venous drainage (I-V)	
Spetzler-Ponce class A = Spetzler-Martin grades I and II	
Spetzler-Ponce class B = Spetzler-Martin grade III	
Spetzler-Ponce class C = Spetzler-Martin grades IV and V	

Definitions to quote: "eloquent location (**sensorimotor, language, and visual cortex; hypothalamus and thalamus;**

internal capsule; brainstem; cerebellar peduncle; deep cerebellar nuclei)" and "deep venous drainage (any drainage into **internal cerebral, basal vein, or precentral cerebellar veins**)" YW p.3677.e2.

14. The four management pathways for an unruptured AVM

- **(1) Conservative management.** "For the conservative management pathway, the risks are the same as for the natural history of bAVM" YW p.3677.e2. The decision model superimposes the 95% CI of the natural-history haemorrhage risk onto the risk of surgery by Spetzler-Ponce class and Lawton-Young grade, so that the cross-over year can be read off [YW pp. 3677.e3, 3677.e5]. For large AVMs treated with focused irradiation, "embarking on treatment … should be done only after consideration of alternative management pathways (**including conservative management**)" YW p.3677.e5.
- **(2) Microsurgical resection.** The Spetzler-Ponce condensation exists precisely to allow honest outcome reporting: for surgeons without a large personal denominator "**it is best to be a member of an experienced team**", and "ensuring that the **SPC class A** bAVM (i.e., Spetzler-Martin grades I and II) resections fall within the 95% CI reported in the literature is important before proceeding to more complex cases" YW p.3677.e2. Early-career cerebrovascular neurosurgeons can achieve SPC class A outcomes comparable to experienced surgeons after a cerebrovascular fellowship in a high-volume academic setting, benchmarked using **CUSUM** methodology against an "unacceptable" boundary complication rate of **3.3%** YW p.3677.e2. Isolated surgeons should "exercise greater conservatism toward more complex cases", considering **alternative management pathways or referral to a specialised neurovascular centre** YW p.3677.e2.
- **(3) Stereotactic radiosurgery / focused irradiation.** "Spetzler-Martin grade III bAVMs can be successfully treated by focused irradiation with an **obliteration rate of around 50% at 3 years and 70% at 5 years** (including those undergoing repeat radiosurgery)"; "the **best obliteration rate is in small bAVMs (<3 cm) with no prior embolization** "; "**the presence of aneurysms increases the likelihood of haemorrhage during the latency period**"; and "the natural history is unchanged until obliteration has occurred" YW p.3677.e5. For larger lesions, repeat irradiation gives **35% and 68% obliteration at 3 and 4 years** after the repeat, and planned staged volumetric reduction gives **no better than 20% at 4 years** with a similar percentage dying of haemorrhage YW p.3677.e5. Outcome can be communicated using the **Virginia Radiosurgery AVM Scale (VRAS)** — 1 point for volume 2-4 cm^3 (0 if smaller, 2 if larger), plus 1 point each for prior haemorrhage and eloquent location: favourable outcome at a mean of 7 years was **81%, 75%, 66%, 47% and 41% for VRAS scores 1 to 5** YW p.3677.e5.
- **(4) Endovascular embolisation.** Used as an adjuvant (Ch. 453) or, in selected lesions, for cure (Ch. 454); note that **prior embolisation reduces the radiosurgical obliteration rate** YW p.3677.e5.
- **ARUBA — the trial to name.** "A later randomized controlled trial comparing medical treatment with interventional therapy for unruptured brain AVMs (**A Randomized Trial of Unruptured Brain Arteriovenous Malformations [ARUBA]**) demonstrated a spontaneous haemorrhage rate of **2.2%** for all AVMs but **included only 18 patients with grade IV AVMs** who were managed with observation. Because of this small number, natural history data on rupture rates for high-grade AVMs cannot be accurately gleaned from this study's data" YW p.3719. ARUBA has "not settled" the management strategy for patients with unruptured AVM YW p.3716.
- **High-grade (Spetzler-Martin IV and V) AVMs.** Barrow's 61-patient series found the **annual pretreatment haemorrhage rate for all high-grade AVMs was 10.4%, falling to 6.1% after initiation of treatment but before complete obliteration**, with the greatest reduction in those presenting with haemorrhage (**13.9% → 5.6%**) — establishing a role for treatment of selected grade IV and V AVMs YW p.3719. Fleetwood reported **9.8% per year** before any treatment; Laakso's Helsinki series reported an annual rupture rate of **3.3%**, with **6%** in patients presenting with haemorrhage YW p.3719. Large AVMs may cause transient and progressive neurological dysfunction through **cerebrovascular steal** as well as headache, seizures and haemorrhage YW p.3719.
- **The honesty principle that ties the section together.** "When comparing treatments for a patient, **it is not enough to compare results from case series without knowing whether the population from which the patients have been selected for each treatment are comparable** … and whether the results from those proposed to perform the treatment have demonstrated that they can replicate the results of others"; the surgeon should be able to say "**I am 95% sure the risk is less than x, but I am 95% sure it is greater than y**", which requires rigorously maintained continuous audit YW p.3677.e2.

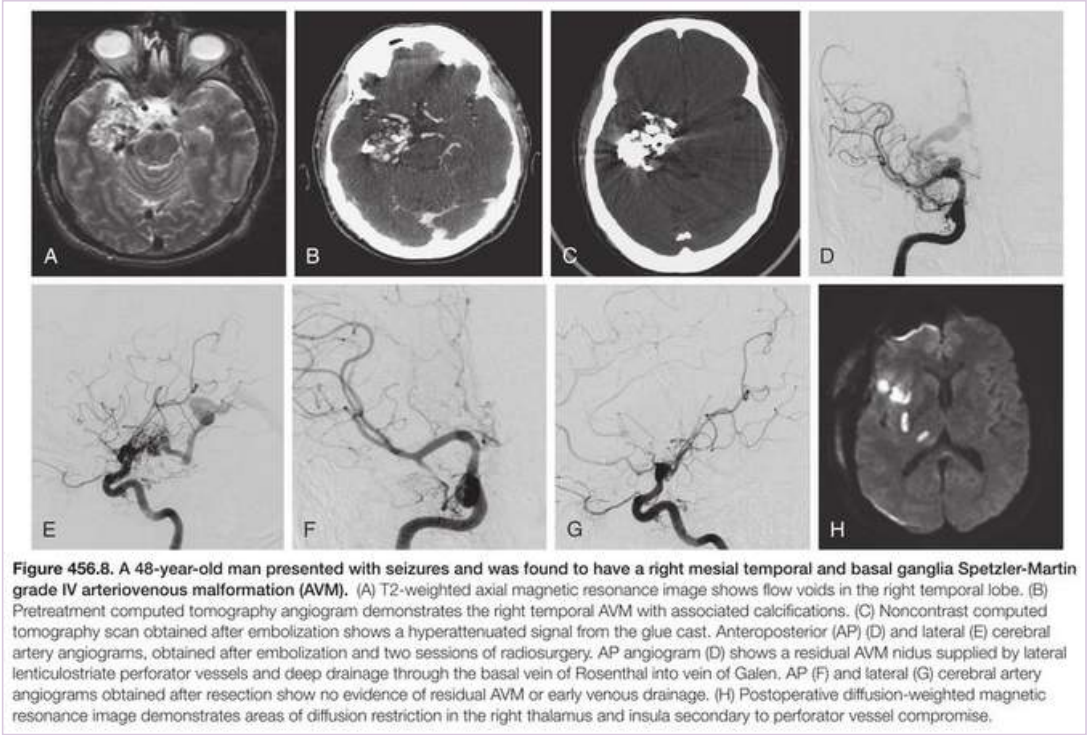


Figure 456.8. A 48-year-old man presented with seizures and was found to have a right mesial temporal and basal ganglia Spetzler-Martin grade IV arteriovenous malformation (AVM). (A) T2-weighted axial magnetic resonance image shows flow voids in the right temporal lobe. (B) Pretreatment computed tomography angiogram demonstrates the right temporal AVM with associated calcifications. (C) Noncontrast computed tomography scan obtained after embolization shows a hyperattenuated signal from the glue cast. Anteroposterior (AP) (D) and lateral (E) cerebral artery angiograms, obtained after embolization and two sessions of radiosurgery. AP angiogram (D) shows a residual AVM nidus supplied by lateral lenticulostriate perforator vessels and deep drainage through the basal vein of Rosenthal into vein of Galen. AP (F) and lateral (G) cerebral artery angiograms obtained after resection show no evidence of residual AVM or early venous drainage. (H) Postoperative diffusion-weighted magnetic resonance image demonstrates areas of diffusion restriction in the right thalamus and insula secondary to perforator vessel compromise.

Reproduced from Youmans & Winn 8e, Fig. 456.8, p. 3731 — Label when you reproduce it: a 48-year-old man with seizures and a right mesial temporal and basal ganglia Spetzler-Martin high-grade AVM. Label the nidus, the deep (basal ganglia) location, the eloquent adjacent structures and the deep venous drainage, then score it: size + eloquence + deep drainage. Use it to illustrate Spetzler-Ponce class C and the cerebrovascular-steal presentation of large AVMs.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Only un-ionised, lipophilic drugs with molecular weight ≤400 cross the intact BBB** — which is why nitrosoureas dominate neuro-oncology.
- **The proliferating rim of a glioma has an intact blood-tumour barrier** — water-soluble drug reaches it poorly, and that is where local failure occurs.
- **Stupp: TMZ 75 mg/m²/day × 6 weeks with 60 Gy, then 150-200 mg/m² days 1-5 of each 28-day cycle × 6.** Median survival 14.6 vs 12.1 months.
- **A 20% dose reduction halves the cure rate**; dose-dense adjuvant TMZ did not help in newly diagnosed GBM.
- **CeTeG/NOA-09: TMZ + CCNU in MGMT-methylated GBM under 70 gave 43.1 vs 31.4 months (HR 0.60).**
- **Bevacizumab improves PFS and steroid requirement but not overall survival**, and is a relative contraindication to further surgery.
- **Gliadel: up to eight wafers, BCNU over 5 days, polymer gone by 6-8 weeks, systemic levels <1/600, diffusion only 2-4 mm.** Survival gain 2.2 months; 6-month survival 56% vs 36%.
- **CED distributes by bulk flow, so molecular weight does not matter**; Vd:Vi ratio 3:1 in oedematous brain and 10:1 in the brainstem.
- **80% of traumatic CSF leaks follow craniofacial fracture**; 50% appear within 48 hours and 70% within a week; a third of basal skull fractures leak.
- **The side of the rhinorrhoea does not localise the fistula.**
- **β2-transferrin is found only in CSF, perilymph and vitreous**, needs <1 mL, sensitivity 87-100%. A negative glucose strip excludes CSF; a positive one means nothing.
- **Fine-cut CT localises the fistula in >70% and is 91% specific** — the single most useful investigation. Intrathecal fluorescein is off-label and can cause seizures.
- **Conservative management: bed rest at 30 degrees, avoid Valsalva, bowel regimen; if no cessation by 3 days consider lumbar drainage.** 85% of anterior leaks stop within a week; lateral skull base leaks stop in 95-100%.
- **Lumbar drains shorten the leak but have NOT been shown to reduce meningitis**, and overdrainage causes aeroceles, brain displacement and coma.

- **Antibiotic prophylaxis: no compelling evidence of benefit or harm — but give pneumococcal vaccination.**
- **Operate late if the leak persists beyond 10 days**; operate early for penetrating injury, another indication for craniotomy, treated meningitis, a large aerocele, brain herniating through the nose, or a fracture that cannot heal.
- **Endoscopic repair: 70-100% first-attempt and 86-100% second-attempt closure, meningitis 0.03%.** Failure comes from missed defects, defects >1.5 cm, poor graft apposition and infection.
- **Nasoseptal flap = posterior septal branch of the sphenopalatine artery**; never use mucosa as an underlay (intracranial mucocele); multilayer repair for defects >1.0 cm.
- **Preserve at least one olfactory nerve and the veins of the superior sagittal sinus; primary dural suture rarely works — graft it.**
- **ISUIA: <7 mm anterior circulation 5-year rupture risk 0%; posterior/PComA 2.5%; ≥25 mm 40-50%.** Mean size of a ruptured aneurysm is 7.0 mm.
- **PHASES: ≤3 points = 0.7%, 5 points = 1.3%, 10 points = 5.3% five-year rupture risk.** Finnish population alone scores 5.
- **Treat a UIA if: previous SAH from another aneurysm; symptomatic; >7-10 mm with ≥12 years' life expectancy; or >5 mm in a young or middle-aged patient.**
- **Posterior circulation UIA surgery carries a nearly 10-fold risk** compared with the same-size anterior lesion; giant basilar UIAs carried 50% morbidity/mortality.
- **Unruptured AVM bleeds at 2.2%/year and ruptured at 4.5%/year** (Gross and Du); mortality of a bleed is 17-19% and combined morbidity/mortality 34-45%.
- **Spetzler-Martin = size (1-3) + eloquence (0-1) + deep drainage (0-1); Spetzler-Ponce A = I-II, B = III, C = IV-V.** Size is *not* a risk factor for rupture, but it is for surgery.
- **Radiosurgery for grade III AVM: ~50% obliteration at 3 years, 70% at 5 years**; best in lesions <3 cm with no prior embolisation; the natural history is unchanged until obliteration.
- **ARUBA contained only 18 grade IV AVMs** — it cannot be used to argue natural history in high-grade lesions.

Pages read for this answer — Youmans & Winn 8e: 901, 1029, 1030, 1031, 1032, 1110, 1111, 1116, 1132, 1133, 1134, 1135, 1136, 1137, 3163, 3164, 3165, 3166, 3167, 3168, 3429, 3430, 3431, 3432, 3489, 3490, 3492, 3677.e2, 3677.e3, 3677.e5, 3716, 3719

a) Describe the recent WHO classification of diffuse gliomas. [5]
b) Management of a case of recurrent GBM. [3]
c) Gliadel wafer. [2]

LONG | APR 2023 · Paper I · Q10 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 158 *Low-Grade Gliomas: Diffuse Astrocytoma and Oligodendroglioma*, §Histologic Features, §Immunohistochemical Assessment of Diffuse Low-Grade Gliomas and §Molecular Pathogenesis and Integrated Diagnosis, pp. 1092-1097 (Fig. 158.2 — the integrated-diagnosis flow diagram, p. 1093; Figs. 158.3-158.5, pp. 1094-1097). Ch. 133 *Brain Tumors: An Overview of Current Histopathologic and Genetic Classifications*, §Astrocytomas, §Oligodendroglial Tumors and §Ependymal Tumors, pp. 900-904 (Figs. 133.1-133.5; **Table 133.1**, p. 900). Ch. 159 *Malignant Gliomas*, §The 2016 WHO CNS Classification, §Management, §Radiation Therapy and Chemotherapy and §Patient Outcome, pp. 1101-1112 (Fig. 159.3, p. 1102; Fig. 159.7, p. 1109; Fig. 159.8, p. 1111; **Table 159.2**, p. 1105; **Table 159.5**, p. 1110; Table 159.1, p. 1102). Ch. 162 *Local Therapies for Gliomas*, §Drug-Impregnated Biopolymers, pp. 1132-1135 (Figs. 162.1, 162.3-162.4; **Table 162.1**, p. 1134). Supplementary: Ch. 147 *Principles of Chemotherapy*, pp. 1029-1032; Ch. 144, p. 1010 (Fig. 144.23); Ch. 160, pp. 1118.e1-1118.e3; Ch. 157B, pp. 1090.e2-1090.e4.

(a) The recent WHO classification of diffuse gliomas [5]

1. The principle — an "integrated diagnosis"

- **Diffuse gliomas are now defined by genotype plus phenotype.** "**Diffuse gliomas are now classified and graded based on a combination of both histologic and molecular criteria**" YW p.1092. "The classification of diffuse gliomas has changed dramatically over the past decade, driven by genomic analyses that have identified characteristic molecular alterations that **enable more accurate subtyping and prognostic classification compared with conventional histologic analysis alone**" YW p.1094.

- **The 2016 revision was the first to do so.** "The 2016 WHO classification uses **molecular parameters for the first time** in addition to histology to define several brain tumour entities. It presents **major restructuring of the glioma classification**" YW p.1105. The lineage of the classification is 1979 → 1993 → 2000 → 2007 → **2016** YW p.1105.
- **Genotype beats phenotype.** "In cases of discordance, **the genotype trumps the histologic findings** (e.g., a tumour that resembles an anaplastic oligodendroglioma histologically but has IDH mutation and lacks 1p19q co-deletion will be considered astrocytic)" YW p.1105.
- **Why it matters to the patient.** "Genetic testing to resolve a diffuse low-grade glioma into one of these different tumour entities provides **superior prognostic information** to affected patients and their caregivers" YW p.1094.
- **What "diffuse" means.** "By definition, both diffuse astrocytoma and oligodendroglioma are **diffusely infiltrative gliomas that widely infiltrate into surrounding brain parenchyma**, in contrast with circumscribed gliomas such as ependymomas and pilocytic astrocytomas that have a solid growth pattern with a sharp interface with adjacent brain" YW p.1092. Infiltration is proven by **entrapped normal brain elements** (axons, neuronal cell bodies), highlighted with **neurofilament protein** immunostaining, and by the **secondary structures of Scherer — perineuronal satellitosis, perivascular aggregation and subpial condensation** YW p.1092.

2. The diffuse glioma entities — the list the examiner wants

Table 1 · Diffuse astrocytic and oligodendroglial tumours and their grades — reproduced from Youmans & Winn 8e, Table 159.2, p. 1105, with the entities of Fig. 158.2, p. 1093 and Table 133.1, p. 900 added.

Integrated diagnosis	Defining molecular alterations	Grade
Diffuse astrocytoma, IDH-mutant	IDH1 p.R132 or IDH2 p.R172 + inactivating TP53 mutation/deletion (+ ATRX inactivation in >90% of adults)	II
Anaplastic astrocytoma, IDH-mutant	As above, with anaplastic histology	III
Glioblastoma, IDH-mutant	As above, with grade IV histology (= secondary GBM)	IV
Oligodendroglioma, IDH-mutant and 1p/19q co-deleted	IDH1/IDH2 mutation + whole-arm 1p/19q co-deletion (+ TERT promoter hotspot in >90% of adults; CIC, FUBP1)	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q co-deleted	As above, with anaplastic histology	III
Glioblastoma, IDH wild-type	TERT promoter mutation, EGFR amplification, +7/−10, PTEN loss (= primary GBM; 90% of all GBM)	IV
Diffuse midline glioma, H3 K27M-mutant	H3 K27M in H3F3A, H3F3B, HIST1H3B or HIST1H3C, in a midline location	IV
Diffuse astrocytic glioma, IDH wild-type, with molecular features of glioblastoma	Low-grade histology **but** EGFR amplification, TERT promoter mutation and/or +7/−10	cIMPACT-NOW recommends **IV**
Diffuse glioma, MYB/MYBL1-altered (isomorphic diffuse glioma)	MYB or MYBL1 fusion/rearrangement as the solitary driver; IDH/BRAF/FGFR1 wild-type	No grade designation yet
Diffuse astrocytoma / anaplastic astrocytoma / glioblastoma / oligodendroglioma, **NOS**	Defining molecular alterations not evaluated	II / III / IV

- **Deletions and demotions.** The category of **oligoastrocytoma is "no longer supported based on molecular studies and has been removed"**, since nearly all morphologically mixed gliomas resolve into astrocytoma or oligodendroglioma; residual cases are designated **NOS**, with only rare accounts of true oligoastrocytoma with combined genotypes [YW pp. 903, 1092, 1112]. **Gliomatosis cerebri** was deleted as an entity and is now "**a pattern of exceptionally diffuse involvement of the CNS that can be seen with any of the diffuse glioma subtypes, including oligodendroglioma**" [YW pp. 901, 1112].

- **New in 2016** YW p.1105: entities — **IDH wild-type GBM, IDH-mutant GBM, diffuse midline glioma (H3K27M-mutant)** and **diffuse leptomeningeal glioneuronal tumour**; new **variant** — **epithelioid glioblastoma**; new **histologic pattern** — **glioblastoma with primitive neuronal component (GB/PN)**.
- **NOS defined**: "the **not otherwise specified (NOS)** designation is used to indicate that the defining molecular alterations of oligodendrogliomas have not been evaluated and the diagnosis is based on **histologic grounds alone**" — usually where IDH testing is unavailable, "which is rare in modern centres" [YW pp. 903, 1105].

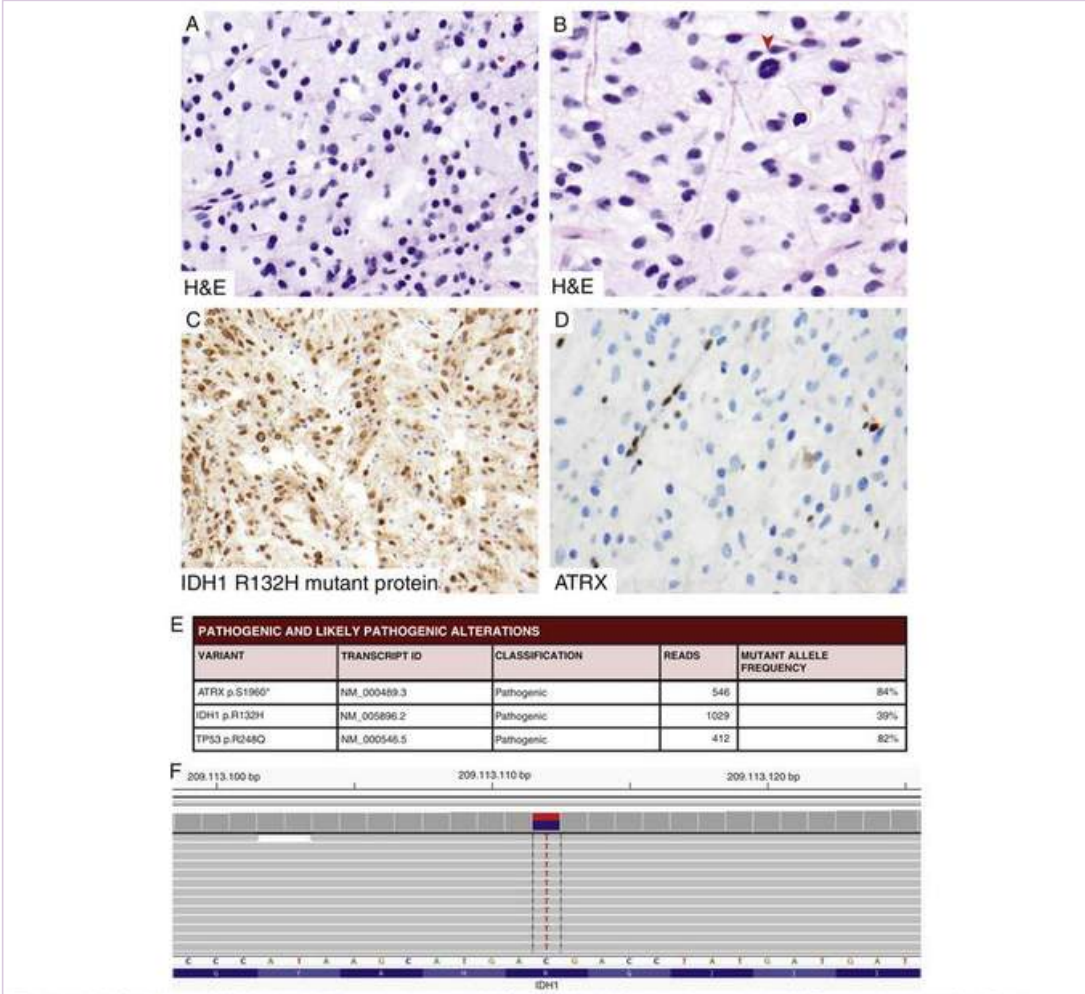


Figure 158.3. Pathology of IDH-mutant diffuse astrocytoma, WHO grade II. (A) Hematoxylin and eosin (H&E)-stained section of a diffuse astrocytoma demonstrating an infiltrative glial neoplasm composed of cells with elongate and irregular hyperchromatic nuclei and fibrillar eosinophilic processes in a myxoid background. Necrosis, microvascular proliferation, and significant mitotic activity are absent. (B) Only a rare mitotic figure *(red arrowhead)* was identified in this diffuse astrocytoma, in keeping with a WHO grade II designation. (C) Positive immunohistochemical staining for IDH1 R132H-mutant protein. (D) Somatic loss of ATRX protein expression in tumor nuclei, with intact staining in non-neoplastic endothelial cells and native neurons. (E) Next-generation sequencing results demonstrating the p.R132H hotspot mutation in the *IDH1* oncogene, a deleterious missense mutation in the *TP53* tumor suppressor gene with loss of the remaining wild-type allele, and a truncating nonsense mutation in the *ATRX* tumor suppressor gene. (F) Snapshot of next-generation sequencing reads over codon 132 of the *IDH1* gene demonstrating a C>T transition resulting in an arginine-to-histidine substitution (p.R132H).

Reproduced from Youmans & Winn 8e, Fig. 158.3, p. 1094 — Label when you reproduce it: pathology of IDH-mutant diffuse astrocytoma, WHO grade II. (A) H&E — infiltrative glial neoplasm with elongate, irregular hyperchromatic nuclei and fibrillar eosinophilic processes in a myxoid background, with NO necrosis, vascular proliferation or significant mitotic activity. (B) A single mitotic figure (red arrowhead), keeping the tumour grade II. (C) Positive immunostaining for IDH1 R132H mutant protein. (D) Somatic loss of ATRX in tumour nuclei with retained staining in non-neoplastic endothelium and native neurons. (E and F) Next-generation sequencing showing IDH1 p.R132H (39% allele frequency), TP53 p.R248Q (82%) and truncating ATRX p.S1960 (84%) — the complete astrocytic molecular triad, and the sequencing snapshot of the C>T transition at IDH1 codon 132.*

3. Each entity in detail — astrocytic line

- **Diffuse astrocytoma, IDH-mutant (grade II)** — "genetically defined by the presence of either an **IDH1 p.R132 or IDH2 p.R172 missense mutation in combination with an inactivating mutation or deletion of the TP53 tumour suppressor gene**. In adults, this combination of IDH1/2 and TP53 mutation is accompanied by inactivating mutations or deletion of the **ATRX** tumour suppressor gene in the vast majority of cases (**>90%**); however, ATRX mutations are

often absent in IDH-mutant diffuse astrocytomas arising during teenage years" YW p.1095.

- **Additional recurrent alterations** — PIK3CA and PIK3R1 (PI3-kinase pathway), SMARCA4 (chromatin remodelling), ZBTB20, and gain of distal 12p including CCND2 (particularly in the **gemistocytic** variant) YW p.1095.
- **Alterations marking malignant progression — CDKN2A homozygous deletion, CDK4 amplification, PDGFRA amplification and MET fusion (often with PTPRZ1)** [YW pp. 1095-1096].
- **What it must lack** — the TERT promoter mutation, 1p/19q co-deletion and CIC/FUBP1 mutations of oligodendroglioma; and the EGFR amplification, TERT promoter mutation and trisomy 7/monosomy 10 of IDH wild-type glioblastoma YW p.1096.
- **Histology** — "ovoid to elongate nuclei with irregular nuclear contours and condensed chromatin", with little or no discernible cytoplasm (**fibrillary variant**) or eccentric bellies of eosinophilic cytoplasm (**gemistocytic variant**), embedded in a dense fibrillary, sometimes myxoid, matrix with mucin-rich microcysts; cellularity low to moderate; significant pleomorphism absent; mitotic activity low or absent "although a strict cut-off is not well established"; **both necrosis and microvascular proliferation must be absent** YW p.1092.

- **Glioblastoma, IDH-mutant (grade IV)** = secondary GBM. "IDH mutant indicates the lesion as a **secondary glioblastoma, having transformed from a lower grade astrocytoma**, and is typically found in younger adults" — "IDH-mutant astrocytomas occur in younger patients and typically present as grade II or III astrocytomas, with later progression to GBM", and although rare, IDH-mutant GBM may present de novo [YW pp. 901, 1105].
- **Glioblastoma, IDH wild-type (grade IV)** = primary GBM, **90% of glioblastomas**, predominating in older patients; molecular alterations are **TERT promoter mutations, +7/−10, EGFR amplification and PTEN mutation/loss** [YW pp. 900-901, 1105].
- **Diffuse astrocytic glioma, IDH wild-type, with molecular features of glioblastoma** — low-grade histology in an older adult, **IDH wild-type by sequencing (not merely negative by immunohistochemistry)**, carrying EGFR amplification, TERT promoter mutation and/or trisomy 7 with monosomy 10; "such … gliomas … **often follow a clinical course more typical of IDH wild-type glioblastoma than that of a low-grade glioma. As such, cIMPACT-NOW has recommended** a grade IV designation" YW p.1096. Youmans elsewhere permits the diagnosis "**diffuse astrocytoma with molecular alterations of glioblastoma**" even without vascular proliferation or necrosis if those genetic changes are demonstrated YW p.901.
- **Diffuse midline glioma, H3 K27M-mutant (grade IV)** — "defined as a diffuse glioma **centred in a midline structure of the CNS (thalamus, brainstem, cerebellum, or spinal cord)** harbouring a recurrent lysine-to-methionine missense mutation (p.K27M) involving **codon 27 in one of the histone H3 genes (H3F3A, H3F3B, HIST1H3B, or HIST1H3C)**" YW p.1096.
  - **The grading rule** — "**any diffuse gliomas located within midline structures … harbouring a histone H3 K27M mutation are assigned as WHO grade IV irrespective of having high-grade histologic features** such as elevated mitotic activity, necrosis, and microvascular proliferation, given the poor prognosis associated with this tumour entity" YW p.1096.
  - **The location rule** — K27M mutations also occur in pilocytic astrocytoma, ganglioglioma and ependymoma and away from the midline, but "**only the midline infiltrative gliomas bearing the K27M mutation qualify for the DMG-K27M diagnosis**" YW p.901.
  - **Frequency** — present in "the majority of diffuse intrinsic pontine gliomas and **nearly half** of diffuse gliomas at any other midline location" YW p.901; quantitatively **30% of paediatric GBM, 80% of DIPG and 15-50% of adult midline gliomas** YW p.1115.
  - **Companion alterations** — mutually exclusive **TP53 or PPM1D**, FGFR1 kinase-domain hotspots (p.N546, p.K656), PDGFRA amplification/mutation, NF1 and ATRX inactivation; **uniformly IDH wild-type**, without TERT promoter mutation or EGFR amplification YW p.1096.
  - **H3F3A G34R/V** defines a separate group of **hemispheric** high-grade gliomas of children and young adults YW p.901.
- **Diffuse glioma, MYB/MYBL1-altered (no grade designation yet)** — "a subtype of low-grade diffuse glioma with

fusion or other rearrangement in the MYB or MYBL1 oncogenes", predominantly in the cerebral hemispheres of children but also in young adults; **isomorphic diffuse glioma** is the nomenclature for the young-adult counterpart; the MYB/MYBL1 rearrangement is the solitary driver, and these tumours "uniformly lack mutations or other alterations in the IDH1, IDH2, BRAF, and FGFR1 genes"; "while not yet a recognised and graded entity by the WHO classification scheme, this emerging tumour entity often follows a **benign or indolent disease course**" YW p.1096.

4. Each entity in detail — oligodendroglial line

- **Oligodendroglioma, IDH-mutant and 1p/19q co-deleted (grade II)** — "genetically defined by the presence of either an **IDH1 p.R132 or IDH2 p.R172 missense mutation in combination with a whole-arm co-deletion of chromosomes 1p and 19q**. In adults, this combination is accompanied by a **hotspot mutation in the promoter region of the TERT gene (either c.-124C>T or c.-146C>T) in the vast majority of cases (>90%)**", though TERT mutations are often absent in teenagers YW p.1096.
  - **Additional recurrent mutations** — PIK3CA/PIK3R1, **CIC, FUBP1, NOTCH1 and TCF12** YW p.1096. Progression markers are less well established but may include NOTCH1 mutation, PIK3CA mutation, TP53 mutation and PDGFRA amplification YW p.1096.
  - **The genetics matter mechanistically** — 1p/19q co-deletion "arises secondary to an initial **translocation** event and constitutes an **independent prognostic marker, with 1p and 19q loss being associated with improved outcome regardless of the specific therapeutic regimen**" YW p.903.
  - **Histology** — "monomorphic round nuclei with delicate chromatin, small pinpoint nucleoli, crisp nuclear membranes, and **clear perinuclear haloes imparting a 'fried-egg' appearance**", with a "rich branching capillary network … often described as resembling **chicken wire**" and frequent **microcalcifications**; "**the perinuclear halo is a diagnostically useful fixation artefact present only in formalin-fixed, paraffin-embedded tumour tissue**"; cellularity low to moderate; mitotic activity low, **with greater than 6 mitotic figures per 10 high-power fields as a generally accepted cut-off for designation of anaplasia**; necrosis and microvascular proliferation absent [YW pp. 903, 1092].
- **Anaplastic oligodendroglioma (grade III)** — high-grade features (increased mitoses, microvascular proliferation, necrosis, or any combination); some show florid vascular proliferation and necrosis mimicking GBM; **mini-gemistocytes** and **gliofibrillary oligodendrocytes** may be present YW p.903.
- **The two critical diagnostic traps** YW p.903:
  - **ATRX loss excludes oligodendroglioma.** "ATRX mutations and 1p/19q co-deletion are mutually exclusive events (with extremely rare exceptions). In the setting of an infiltrating glioma, **loss of ATRX expression, which can be evaluated by immunohistochemistry using an antibody against the ATRX protein, essentially rules out a diagnosis of oligodendroglioma**."
  - **FISH can be fooled.** "A caveat of 1p/19q analysis by fluorescence in situ hybridisation (FISH) is that a small number of GBMs will give an apparent positive result due to **partial deletions** in chromosomes 1p and 19q … **an infiltrating glioma with 1p/19q co-deletion by FISH analysis, but without IDH1 or IDH2 mutations, is most likely an astrocytoma (very likely a GBM)**."
  - Note also that "**paediatric gliomas with an oligodendroglial histologic phenotype very rarely harbour an IDH1/IDH2 mutation or 1p/19q co-deletion**, and their defining molecular alterations remain unknown" YW p.903.

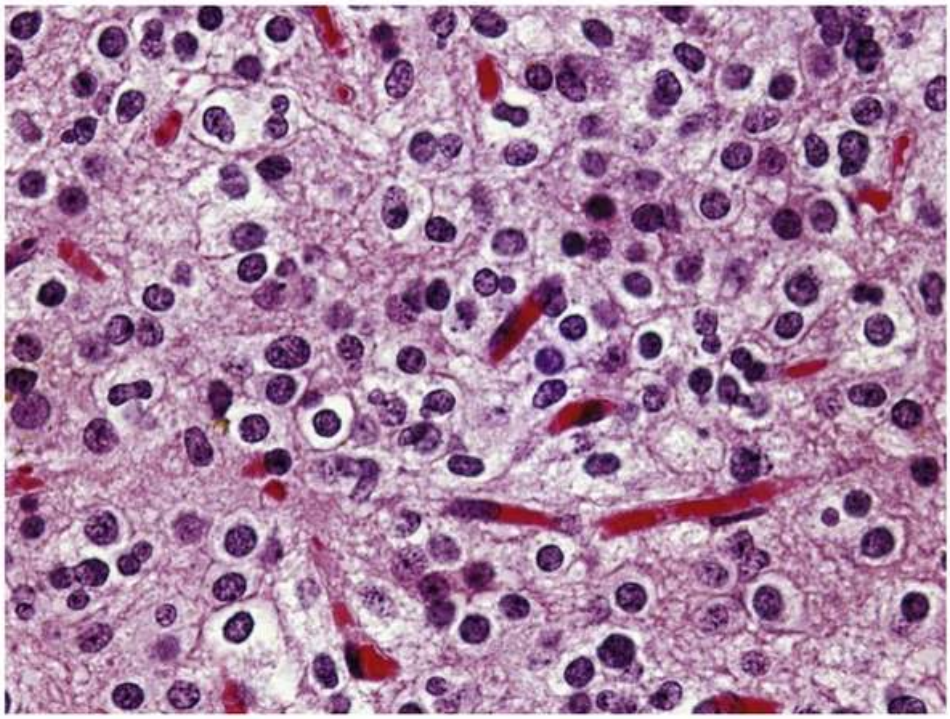


Figure 133.4. Oligodendroglioma. The hallmark morphologic features of oligodendroglioma that separate this diffuse glioma from the astrocytic series are the uniformly round nuclei with surrounding cytoplasmic clearing ("perinuclear halos"). The classic oligodendroglial morphology seen here on hematoxylin-eosin–stained tissue sections correlates highly with the combined deletion of chromosomal arms 1p and 19q.

Reproduced from Youmans & Winn 8e, Fig. 133.4, p. 903 — Label when you reproduce it: oligodendroglioma on H&E — label the uniformly round nuclei with surrounding cytoplasmic clearing ("perinuclear halos", the fried-egg appearance), the delicate branching "chicken-wire" capillary network and any microcalcification. State in the label that the halo is a fixation artefact of paraffin processing — it is NOT seen on frozen section — and that this classic morphology correlates highly with combined 1p/19q deletion.

5. The immunohistochemical toolkit that delivers the integrated diagnosis

- **Lineage markers** — "diffuse low-grade gliomas are glial neoplasms that should be positive for markers of glial differentiation, chiefly **glial fibrillary acidic protein (GFAP) and OLIG2**. GFAP … is uniformly positive in diffuse low-grade gliomas, but it is also present in high-grade gliomas and circumscribed glioma variants such as ependymoma and pilocytic astrocytoma. **OLIG2 is a nuclear transcription factor** most highly expressed in developing and mature oligodendrocytes but also aberrantly expressed in diffuse gliomas" YW p.1093.
- **IDH1 R132H antibody** — "a mutant-specific antibody for IDH1 p.R132H-mutant protein has been developed and entered diagnostic clinical practice", detecting the defining mutation in both astrocytomas and oligodendrogliomas; **it detects only p.R132H (~90% of IDH-mutant diffuse gliomas; ~95% of IDH-mutant tumours in Ch. 133) and does not recognise IDH1 p.R132S/C/G or the IDH2 p.R172-mutant protein** [YW pp. 901, 1093]. Hence IDH wild-type status must be "proven … by sequencing analysis (**not simply negative by immunohistochemistry**)" YW p.1096.
- **p53** — "missense mutations that frequently occur in the TP53 tumour suppressor gene in IDH-mutant diffuse astrocytomas (**but not IDH-mutant and 1p/19q co-deleted oligodendrogliomas**) often lead to stabilisation and overexpression of p53 protein, which can be detected by immunohistochemistry as **strong nuclear positivity in the majority of tumour nuclei**"; but TP53 truncating mutations or gene deletions cause **absence** of p53 expression, so a negative p53 does not exclude an IDH-mutant astrocytoma YW p.1093.

- **ATRX** — "somatic loss of ATRX expression (i.e., **absence in tumour nuclei with intact/retained expression in non-neoplastic endothelial cells and entrapped neurons**) is frequently seen in IDH-mutant diffuse astrocytomas, but not IDH-mutant and 1p/19q co-deleted oligodendrogliomas. However, **only approximately 80% of the inactivating ATRX mutations are truncating** … the remaining 20% are missense variants that disrupt protein function … but do not result in loss of ATRX protein expression by immunohistochemistry" YW p.1093.
- **Histone H3 K27M** — "a mutant-specific antibody for histone H3 p.K27M-mutant protein has been developed and entered diagnostic clinical practice, enabling immunohistochemical detection of this defining mutation in H3 K27M-mutant diffuse gliomas arising in midline structures" [YW pp. 1093-1094]; "it is increasingly common practice that **every diffuse midline glioma, regardless of histology, patient age, and anatomic location, be assessed by immunohistochemistry for this mutation**" YW p.1115.
- **Neurofilament protein** highlights entrapped axons and thereby confirms an infiltrative growth pattern [YW pp. 1092-1093].
- **The limit of intraoperative diagnosis** — "**the distinction between astrocytoma and oligodendroglioma is not feasible at the time of intraoperative consultation**", because the perinuclear clearing is a paraffin artefact not seen on frozen sections, and molecular testing cannot be delivered in that time frame; the correct report is "**infiltrating glioma, with or without high-grade features**" YW p.911. Intraoperative cytologic smears do, however, separate the lineages morphologically YW p.1097.

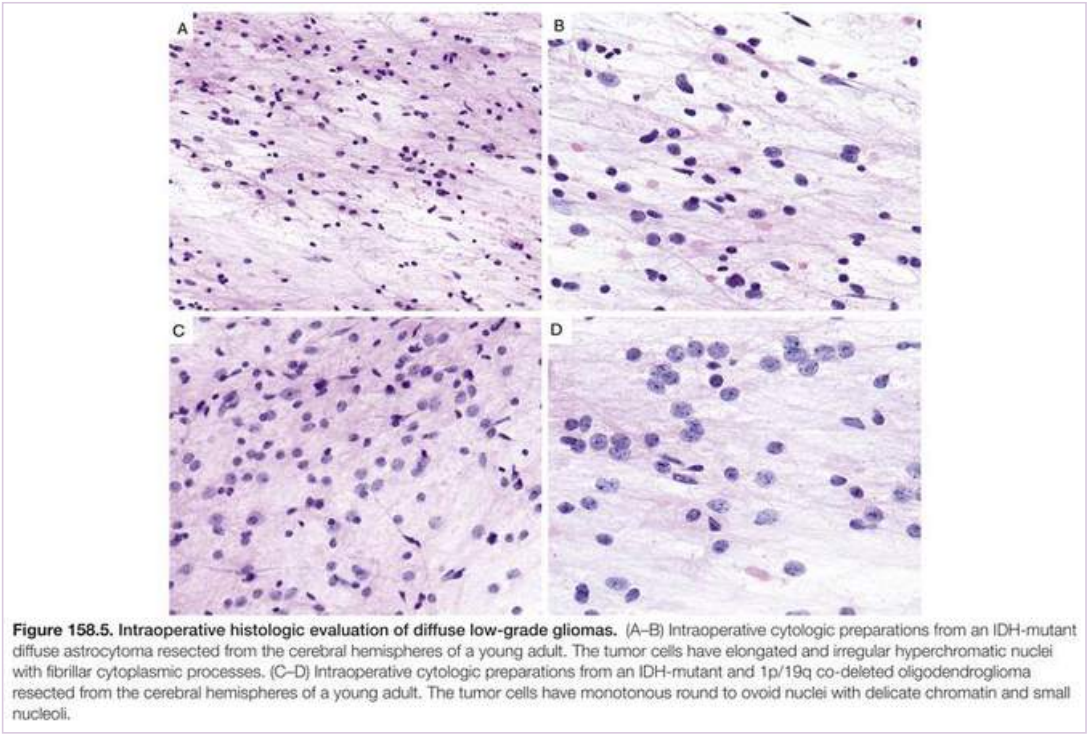


Figure 158.5. Intraoperative histologic evaluation of diffuse low-grade gliomas. (A–B) Intraoperative cytologic preparations from an IDH-mutant diffuse astrocytoma resected from the cerebral hemispheres of a young adult. The tumor cells have elongated and irregular hyperchromatic nuclei with fibrillar cytoplasmic processes. (C–D) Intraoperative cytologic preparations from an IDH-mutant and 1p/19q co-deleted oligodendroglioma resected from the cerebral hemispheres of a young adult. The tumor cells have monotonous round to ovoid nuclei with delicate chromatin and small nucleoli.

Reproduced from Youmans & Winn 8e, Fig. 158.5, p. 1097 — Label when you reproduce it: intraoperative histologic evaluation of diffuse low-grade gliomas. (A-B) Intraoperative cytologic preparations from an IDH-mutant diffuse astrocytoma — elongated, irregular hyperchromatic nuclei with fibrillar cytoplasmic processes. (C-D) Intraoperative cytologic preparations from an IDH-mutant, 1p/19q co-deleted oligodendroglioma — monotonous round-to-ovoid nuclei with delicate chromatin and small nucleoli. Note in the label that the perinuclear halo is absent on smears and frozen sections, so the safe intraoperative diagnosis remains "infiltrating glioma".

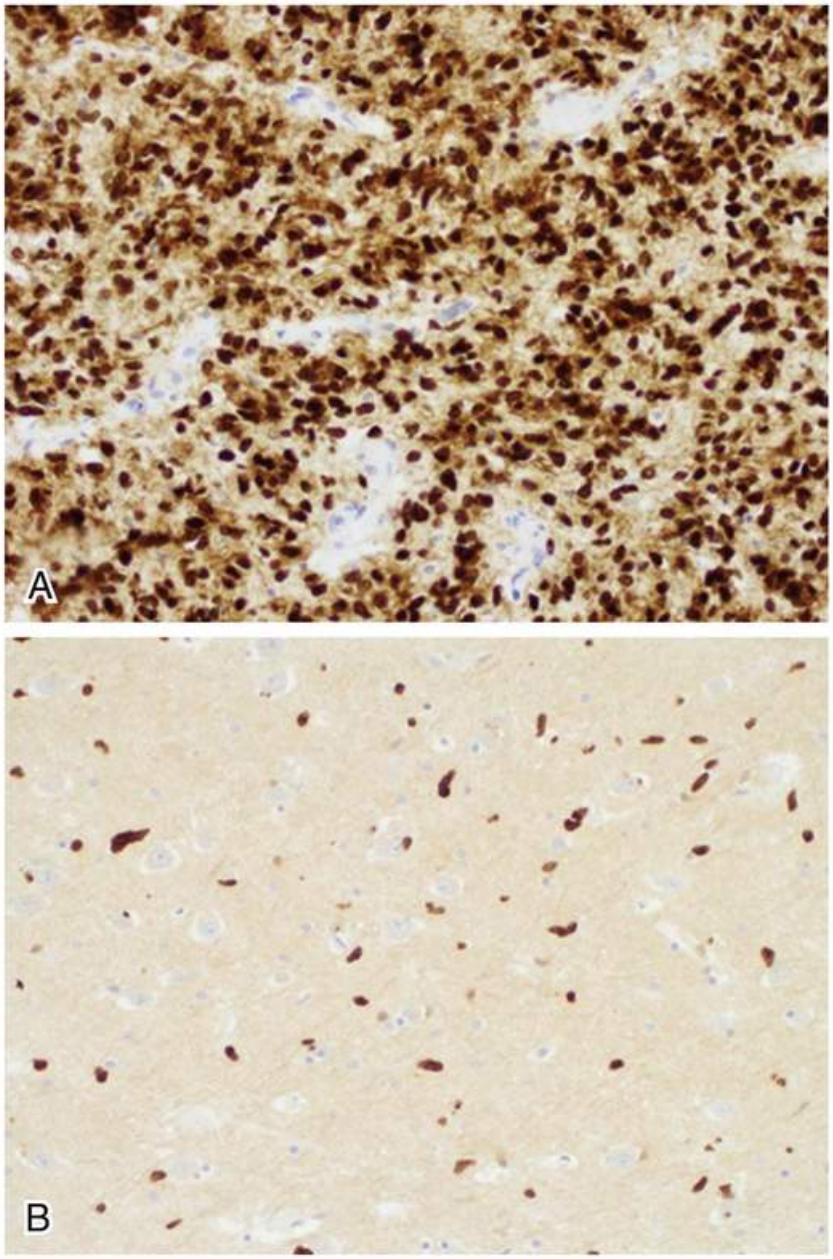


Figure 133.3. Diffuse midline glioma, H3-K27M mutant. (A) Note *brown staining* demonstrating expression of the histone H3.3 mutant protein with a lysin-to-methionine mutation in amino acid 27 (K27M). This is a somatic mutation only present in tumor cells; the endothelial cells do not have the mutation, as demonstrated by negative H3.3 p.K27M staining. (B) An area with lower density of tumor cells infiltrating brain parenchyma. Note the large neurons in the background that do not express the mutant protein.

Reproduced from Youmans & Winn 8e, Fig. 133.3, p. 902 — Label when you reproduce it: diffuse midline glioma, H3-K27M mutant. (A) Brown nuclear staining for the histone H3.3 p.K27M mutant protein, with endothelial cells negative (the somatic-mutation internal control). (B) A hypocellular area of tumour infiltrating parenchyma, with large background neurons that do not express the mutant protein. In the label state the rule: a midline diffuse glioma with K27M is CNS WHO grade IV even when the histology looks low grade.

6. Grading and prognosis under the molecular scheme

- **The histologic features that define higher grade** in a diffuse glioma remain "**significant mitotic activity, increased**

CHAPTER 8

Ventricular, Pineal & Posterior Fossa Lesions

10
QUESTIONS SOLVED

Colloid Cyst of Third Ventricle

3 questions

Colloid cyst of third ventricle:
a) Clinical features. [2]
b) Neuroimaging features. [3]
c) Pathology. [2]
d) Management. [3]

LONG | DEC 2021 · Paper I · Q6 | 10 marks

Also asked as: Ventricular tumours — also asked as DEC 2022 · Paper I · Q3 ("a) Colloid cyst. [3] b) Its Clinical features. [3] c) Colloid cyst management. [4]")

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 171 *Colloid Cysts of the Third Ventricle*, §Introduction, §Histogenesis, §Natural History of Colloid Cysts, §Acute Neurological Decline, §Colloid Cyst Risk Score, §Neuroimaging for Colloid Cysts, §Surgical Decision Making, §Surgical Anatomy, §Surgical Approaches, §Complications and Pitfalls, pp. 1234-1240 (Figs. 171.1, p. 1235; 171.2, p. 1236; 171.3, p. 1237; 171.4, p. 1238; 171.5, p. 1239; Table 171.1, p. 1235). Supplementary: Ch. 228 *Neuroendoscopy*, §Colloid Cysts, pp. 1734-1735 (Figs. 228.4, p. 1734; 228.5, p. 1735). Ch. 170 *Ventricular Tumors*, §Clinical Presentation, §Surgery of the Third Ventricle — Transfrontal and Anterior Interhemispheric Transcallosal Approaches, §Transforaminal, Transchoroidal, Subchoroidal and Interforniceal Techniques, pp. 1203-1204, 1217, 1222-1224 (Figs. 170.15, p. 1222; 170.16, p. 1223; Table 170.1, p. 1204; Table 170.3, pp. 1218-1219).

1. Definition, epidemiology and histogenesis — open with these

1.1 What the lesion is

- **Definition** — "Colloid cysts are rare, benign tumors that arise in the **anterosuperior third ventricle near the foramen of Monro**" YW p.1234. They are **not gliomas and not choroid plexus tumours**; they are epithelium-lined cysts filled with gelatinous mucinous material.
- **Frequency** — they represent **approximately 1% to 2% of all intracranial tumors**, with an estimated incidence of **3.2 per million per year** YW p.1234. Ch. 228 gives the overlapping figure of **0.5% to 1% of all brain tumours** YW p.1734.
- **Why they matter out of proportion to their frequency** — "Although many colloid cysts are asymptomatic, they may cause **obstructive hydrocephalus and, in certain cases, rapid clinical deterioration and death**" YW p.1234. They are the archetypal benign lesion that kills.
- **Youmans' own key-concept list** — colloid cysts are rare tumours of the third ventricle; they often obstruct the foramen of Monro; they may be asymptomatic or cause acute hydrocephalus, neurological deterioration and death; **MRI is the preferred imaging modality**; they may be resected by open microsurgery, endoscopically, or via port-based hybrid approaches; endoscopic surgery carries lower morbidity and shorter stay but possibly higher recurrence; and **the critical structures are the deep veins, the thalamus and the fornix** YW p.1234.

1.2 Embryology and histogenesis — the examiner's favourite opening

- **Normal development** — the neural tube closes in the **fourth week**; during the **fifth week** the prosencephalon divides into telencephalon (cerebral hemispheres) and diencephalon (thalamus, hypothalamus, epithalamus). The cavities of the telencephalon and diencephalon become the **lateral and third ventricles** respectively, and **the foramen of Monro develops at the interface of these two** YW p.1234.
- **First description** — the colloid cyst of the third ventricle was **first described in 1858** YW p.1234.

- **The paraphysis theory (now discarded)** — older studies proposed a neuroectodermal origin from the **paraphysis**, "a neuroectodermally derived structure that temporarily develops at the border of the telencephalon and diencephalon **during week 7 of gestation** and subsequently involutes into choroidal vesicles". The paraphysis arises from the **paraphyseal arch**, which becomes incorporated into the roof of the third ventricle, so persistent remnants were thought to form the cyst YW p.1234.
- **The accepted theory** — "after more intensive study of this topic, it is now widely believed that **cysts arise from ectopic foregut endoderm and not the paraphysis**" YW p.1234.
- **The immunohistochemical argument that settles it** — colloid cysts are "**very similar to Rathke cleft cysts, follicular pituitary gland cysts, and neurenteric cysts**", and crucially "the epithelial lining of colloid cysts **shares few immunohistochemical properties with choroid plexus epithelium**" YW p.1234. All four of those look-alikes are endodermal, which is the argument for a foregut origin.

2. Natural history — what happens if you do nothing

- **Incidental discovery is the rule** — colloid cysts "are frequently asymptomatic and may be discovered only **incidentally** after imaging of the brain for other reasons such as trauma, chronic neurological diseases, or stroke" YW p.1234.
- **Proportion asymptomatic at diagnosis** — "somewhere between **40% and 60%** of patients with a colloid cyst may be asymptomatic when first diagnosed" YW p.1234.
- **Behaviour of the incidental cyst** — "The vast majority of these incidentally discovered tumors will **remain stable in size**, and a small proportion may **spontaneously regress**" YW p.1234.
- **Progression rate** — "it is estimated that **5% to 15% of patients will experience tumor progression within the 5 years after diagnosis**" YW p.1234.
- **Ventriculomegaly is not a sufficient surgical criterion** — Pollock et al. found ventriculomegaly in **72 of 87 (83%) symptomatic** cysts, but also in **21 of 68 (31%) asymptomatic** cysts, "highlighting that the presence of ventriculomegaly should not be the sole criterion for surgery" YW p.1234.
- **Obstructive hydrocephalus among the symptomatic** — Beaumont et al. showed **30 of 65 patients (46.2%)** with symptomatic colloid cysts had confirmed obstructive hydrocephalus [YW pp. 1234-1235].
- **Risk of death once symptomatic** — "One study concluded that the **risk of death in symptomatic patients was 3.1%**" YW p.1235.

(a) Clinical features [2]

3. Symptoms and signs — enumerate them in order of frequency

3.1 The typical symptomatic patient

- **Age** — "Patients with symptomatic cysts tend to be **younger (typically 30-40 years old)** than those with asymptomatic cysts" YW p.1234.
- **Presenting complaints, in the order Youmans lists them** — "patients most often present with **headaches, nausea and/or vomiting, vision changes, dizziness or ataxia, and cognitive impairment**" YW p.1234.
- **Character of the headache** — Ch. 228 adds that colloid cysts "present most commonly with **headache, often of a stuttering nature**, and can result in **rapid clinical deterioration from intracranial hypertension**" YW p.1734. The classically described positional, paroxysmal headache relieved by lying down is the clinical corollary of the ball-valve mechanism.
- **Mechanism of most symptoms** — "In most instances, neurological symptoms are **secondary to hydrocephalus caused by the cyst impeding cerebrospinal fluid (CSF) flow across the foramen of Monro**" YW p.1234.
- **Cognitive/memory symptoms** — cognitive impairment is an established presenting feature YW p.1234, and the fornices that straddle the cyst are the anatomical explanation; forniceal damage causes **persistent short-term memory deficits**

YW p.1240 and even unilateral forniceal injury "has been shown to cause **anterograde amnesia**" YW p.1222.

- **General ventricular-tumour presentation to fall back on** — lesions in the ventricle become symptomatic through **(1) invasion of local structures, (2) raised ICP from tumour mass, (3) hydrocephalus**; adult symptoms are **headache, lethargy, nausea, memory loss, gait disorder, and cognitive or mood changes**; in the infant, **increased head circumference, a bulging fontanelle, distended scalp veins and failure to thrive** YW p.1203.

3.2 Acute neurological decline and sudden death — the marks are here

- **It happens** — "Occasionally, colloid cysts can cause **acute neurological decline or death**" YW p.1235.
- **Mechanism 1 — the ball-valve theory** (the most widely accepted): "the colloid cyst, normally suspended on a pedicle that allows it to only **partially block CSF flow** (e.g., when lying down), may become **dislodged (e.g., by trauma) and fully occlude the foramen of Monro** (or rarely the aqueduct of Sylvius in the posterior third ventricle), leading to acute hydrocephalus" YW p.1235.
- **Mechanism 2 — intracystic haemorrhage** causing acute expansion, or vascular compromise with **ischaemia of the anterior cerebral artery territory** YW p.1235.
- **Mechanism 3 — hypothalamic dysfunction**. Turillazzi et al. reported a **10-year-old boy** with headache and vomiting who lost consciousness and was pronounced dead of cardiac arrest on arrival; autopsy showed a colloid cyst, oedematous brain and ventriculomegaly, plus **coagulative myocytolysis and contraction band necrosis in the myocardium** — attributed to mass effect on the hypothalamus causing **sympathetic overstimulation and catecholamine myotoxicity** YW p.1235.
- **The prodrome — the single most examinable clinical number** — Lagman et al.'s systematic review of fatal colloid cysts found death was "most frequently preceded by symptoms of **headache, nausea and/or vomiting, and decreased consciousness for a mean of 3.3 days** before the patient presented to the hospital" YW p.1235. Beaumont's series concurs: **50% of patients who presented with acute hydrocephalus had new and progressively worsening symptoms over the prior 3 to 4 days** before rapid decline YW p.1237.
- **Autopsy findings in fatal cases — 83.3% ventriculomegaly, 72.2% cerebral oedema, 61.1% cerebral herniation** YW p.1235.
- **Documented precipitants** — "In rare cases, death from colloid cyst was precipitated by **head trauma or air travel**, both of which were hypothesized to have caused acute hydrocephalus" YW p.1235.
- **Risk factors for precipitous decline — younger age, larger cyst size (especially >8 mm), longer duration of symptoms, and hydrocephalus** YW p.1235.

4. Risk stratification — the Colloid Cyst Risk Score (CCRS)

- **Risk factors for a symptomatic cyst — cyst diameter ≥7 mm, cyst volume ≥180 mm³, larger mean Evans ratio, and increased T2/FLAIR hyperintensity** on MRI YW p.1234. The same variables predict hydrocephalus, and "**all but one patient had a colloid cyst within the foramen of Monro at the anterior aspect of the third ventricle**" YW p.1235.
- **The score** — Beaumont et al. created **five binary categories (1 point for yes, 0 for no; maximum 5)**: **age <65 years; headache; axial cyst diameter ≥7 mm; FLAIR hyperintensity; cyst location in an anatomic risk zone** YW p.1235.

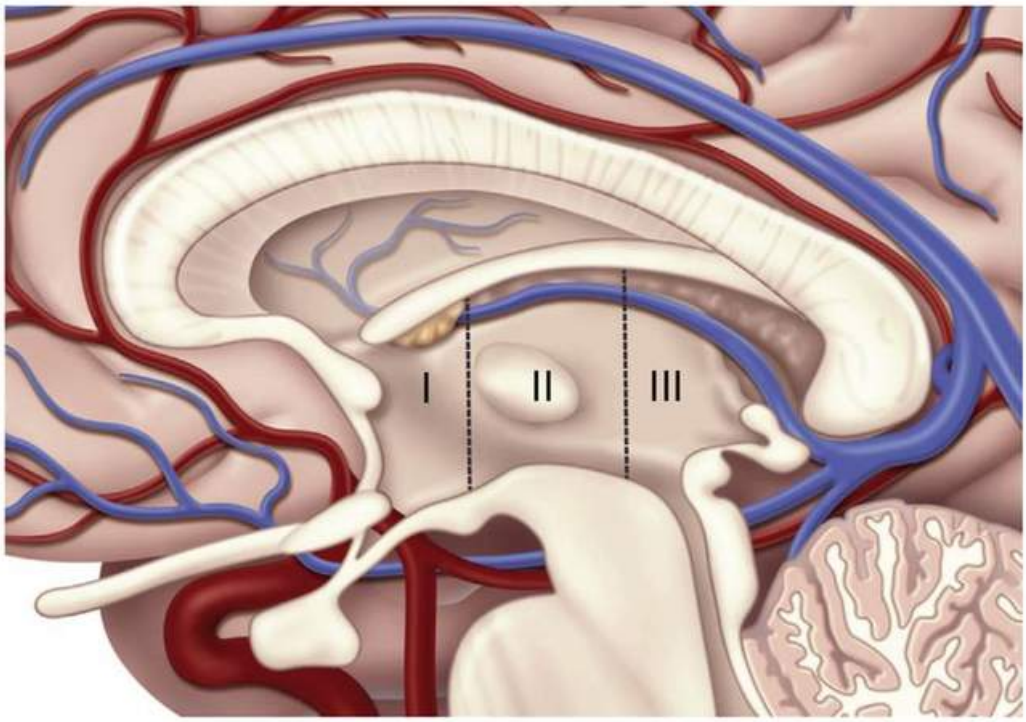


Figure 171.1. Anatomic risk zones for colloid cysts of the third ventricle. The third ventricle was divided into three zones along the sagittal axis. Zone I—from lamina terminalis to a vertical line drawn from the mammillary body and tangential to the massa intermedia; zone II—from the posterior boundary of zone I to the rostral apex of the midbrain tegmentum at the inlet of the cerebral aqueduct; zone III—from the posterior boundary of zone II to the posterior limit of the third ventricle. Zones I and III are referred to collectively as "risk zones." Lesions in zone II can be large and are rarely symptomatic.

Reproduced from Youmans & Winn 8e, Fig. 171.1, p. 1235 — Label when you reproduce it: the sagittal third ventricle divided into zone I (lamina terminalis to a vertical line from the mammillary body tangential to the massa intermedia), zone II (posterior boundary of zone I to the rostral apex of the midbrain tegmentum at the inlet of the cerebral aqueduct) and zone III (posterior boundary of zone II to the posterior limit of the third ventricle). Mark zones I and III as the "risk zones" and note that zone II lesions can be large yet are rarely symptomatic.

Table 1 · Components of the Colloid Cyst Risk Score (CCRS) — reproduced in full from Youmans & Winn 8e, Table 171.1, p. 1235, with the performance data from p. 1235.

Criterion	Yes	No
Age <65 years	1	0
Headache	1	0
Axial diameter ≥7 mm	1	0
FLAIR hyperintensity	1	0
Anatomic risk zone (zone I or zone III)	1	0
Interpretation		
≥4 points	**High risk** for cyst progression and symptoms	
3 points	**Intermediate risk** for cyst progression or symptoms	

≤2 points	**Low risk** for cyst progression or symptoms
Validation figures	Sensitivity **92%**, specificity **93%** for predicting symptomatic cysts; sensitivity **88%**, specificity **82%** for predicting hydrocephalus. **No patient with CCRS ≤1** had a symptomatic cyst or hydrocephalus; **96% with CCRS 5** had symptomatic cysts and **60%** had hydrocephalus; **every patient presenting with hydrocephalus had a CCRS ≥4**

- **Definition of the anatomic risk zones** (Fig. 171.1) — **zone I**: from the lamina terminalis to a vertical line drawn from the mammillary body tangential to the massa intermedia; **zone II**: from the posterior boundary of zone I to the rostral apex of the midbrain tegmentum at the inlet of the cerebral aqueduct; **zone III**: from the posterior boundary of zone II to the posterior limit of the third ventricle. **Zones I and III are collectively the "risk zones"; lesions in zone II can be large and are rarely symptomatic** YW p.1235.
- **External validation** — the CCRS "has subsequently been validated as a useful tool for risk stratification and clinical decision making, and it has been shown to have acceptable **intrarater and interrater reliability** across different patient samples" [YW pp. 1235-1236].

(b) Neuroimaging features [3]

5. Location — the single most discriminating imaging feature

- **The >99% rule** — "Perhaps the most notable imaging feature is that **>99% of colloid cysts are centered near the foramen of Monro, often lodged in the foramen itself**" YW p.1236.
- **Attachment** — "They are most commonly connected to the **anterosuperior aspect of the roof of the third ventricle** and cause the **posterior aspect of the frontal horns of the lateral ventricles to be pushed laterally**. The cysts are **surrounded on either side by the pillars of the fornix**" YW p.1236.
- **Mobility** — cysts may be attached to the third ventricle via a **mobile pedicle** — the anatomical basis of the ball-valve phenomenon [YW pp. 1235-1236].
- **Ectopic sites** — "They are **very rarely located in other areas of the brain, such as the lateral ventricles or cerebellum**" YW p.1236.
- **Size** — "The mean diameter for colloid cysts has been reported in some studies to be as large as **15 mm**" YW p.1236.
- **Morphology** — "cysts are **well-defined, smooth, spherical or ovoid masses**" YW p.1236.
- **Contents that generate the signal** — "They are filled with **gelatinous, mucinous fluid** that results from the internal secretory epithelium and epithelial breakdown and **consists of CSF, blood products, and cholesterol or lipids**" YW p.1236.

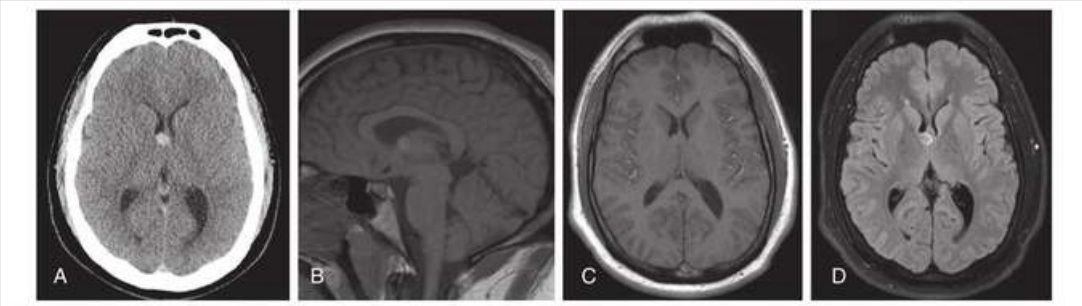


Figure 171.2. Neuroimaging of colloid cyst of the third ventricle. Most colloid cysts are hyperdense on CT (A) and isointense to hyperintense on T1-weighted MRI (B) and exhibit minimal or no peripheral enhancement on postcontrast sequences (C). More than half of colloid cysts demonstrate fluid-attenuated inversion recovery (FLAIR) hyperintensity, and this is significantly correlated with symptomatic lesions and with the development of hydrocephalus (D).[2]

Reproduced from Youmans & Winn 8e, Fig. 171.2, p. 1236 — Label when you reproduce it: (A) axial CT showing the characteristic hyperdense round mass at the foramen of Monro; (B) T1-weighted MRI showing iso- to hyperintensity; (C) post-contrast T1 showing minimal/no peripheral (rim) enhancement only; (D) FLAIR showing hyperintensity — the component that correlates with symptomatic lesions and with the development of hydrocephalus. Also point out the resulting dilatation of both frontal horns.

6. Signal characteristics by modality — and the physical rule behind them

6.1 CT

- **Most are hyperdense** — "**Most cysts will be hyperdense when assessed via CT**. This hyperdensity is **inversely correlated to the intracystic water content**, as cysts with more viscous contents are more hyperdense" YW p.1236.
- **The exception** — "Cysts containing more aqueous content may be **hypodense or isodense** compared with surrounding brain" YW p.1236.
- **Enhancement on CT** — "Cysts will **inconsistently demonstrate a thin rim of enhancement** after administration of iodinated contrast material, which likely represents the **cyst capsule**" YW p.1236.
- **Calcification / haemorrhage** — "Cyst **calcifications or hemorrhage may be rarely observed**" YW p.1236. Calcification therefore argues *against* the diagnosis.

6.2 MRI — the preferred modality

- **Why MRI** — "**MRI is the preferred method for assessing colloid cysts**, although cysts may have more variable appearances on MRI compared with CT" YW p.1236.
- **T1** — "About **two-thirds of cysts will be T1 hyperintense**, but they may appear **isointense or even hypointense**" YW p.1236.
- **T2 and FLAIR** — "**Most cysts will be isointense or hypointense on T2-weighted and FLAIR images**"; note the practical warning that "**cysts that are T2 hypointense may be challenging to identify on FLAIR images**" YW p.1236. Conversely, **more than half of colloid cysts demonstrate FLAIR hyperintensity**, and this is significantly correlated with symptomatic lesions and the development of hydrocephalus YW p.1236.
- **The governing rule — state it as a single sentence** — "the appearance of cysts on MR images is related to the **viscosity of intracystic contents**. Cysts with more viscous contents will appear **hyperintense on T1** and **hypointense on T2 and FLAIR**. Thus for **heavily cholesterol-filled cysts, CT will be hyperdense, T1 hyperintense, and T2/FLAIR hypointense. The converse is true for cysts with high water content**" YW p.1236.
- **The surgical corollary** — "A cyst that is **bright on CT and T1 but darker on T2/FLAIR will be more viscous and difficult to aspirate**, as the intracystic contents may be **firm and keratin-like**" YW p.1236. Fig. 171.3 uses exactly this: **T2 hypointense = firm, non-fluidic** YW p.1237.
- **Gadolinium enhancement** — "Cysts commonly exhibit **slight rim enhancement**... but **intense, homogeneous contrast enhancement strongly suggests a different diagnosis**" YW p.1236.
- **Diffusion** — "Cysts **do not usually exhibit diffusion restriction** on diffusion-weighted imaging" YW p.1236.
- **The "dot sign"** — "Occasionally, cysts may demonstrate an **intracystic nodule that is T1 hyperintense, T2 and FLAIR hypointense, and susceptibility-weighted imaging (SWI) isointense or hypointense — referred to as the 'dot sign'** — although this is **not a consistent finding and should not be expected in all cysts**. The contents of this nodule have not been characterized for colloid cysts, although similar nodules found in **Rathke cleft cysts are composed of mucinous material**" YW p.1236.

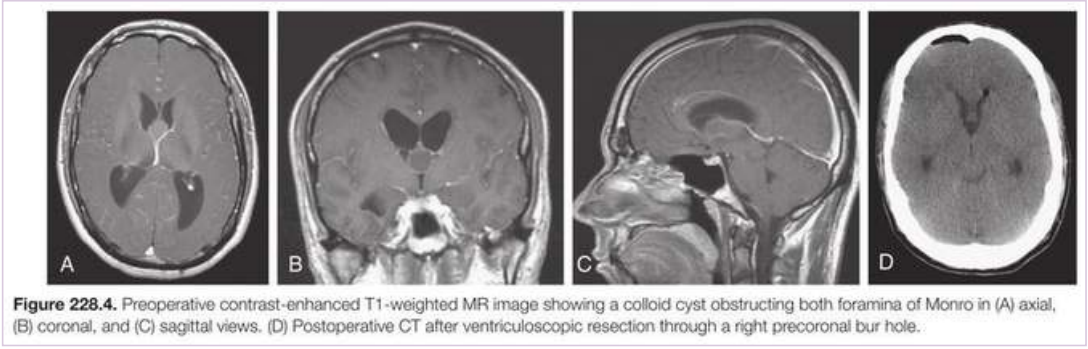


Figure 228.4. Preoperative contrast-enhanced T1-weighted MR image showing a colloid cyst obstructing both foramina of Monro in (A) axial, (B) coronal, and (C) sagittal views. (D) Postoperative CT after ventriculoscopic resection through a right precoronal bur hole.

*Reproduced from Youmans & Winn 8e, Fig. 228.4, p. 1734 — Label when you reproduce it: (A) axial, (B) coronal and (C) sagittal contrast-enhanced T1-weighted MR images of a colloid cyst obstructing *both* foramina of Monro with bifrontal-horn dilatation; (D) the postoperative CT after ventriculoscopic resection through a right precoronal bur hole. Point out that bilateral foraminal obstruction is what produces biventricular (not triventricular) hydrocephalus.*

7. The imaging differential diagnosis — the list Youmans gives

- **Youmans' own list for a lesion at the foramen of Monro** — "the differential diagnosis of a colloid cyst of the third ventricle should include **meningioma, glioma (e.g., pilocytic astrocytoma), choroid plexus papilloma, ependymoma/subependymoma, third ventricular craniopharyngioma, blood products around the foramen of Monro, or CSF flow artifact (MRI pseudocyst) caused by turbulent flow near the foramen of Monro**" YW p.1236.
- **Do not forget the aneurysm** — "**Cerebral aneurysms can also occur in the region of the foramen of Monro** and should be suspected when a spheroid lesion extends inferiorly into the third ventricle" YW p.1236.
- **The three discriminators to quote** YW p.1236:
  - "**Well-circumscribed, round, fluid-filled lesions that extend from the third ventricle into the foramen of Monro are most likely to be colloid cysts.**"
  - "On CT scan, the presence of **calcifications makes the diagnosis of colloid cyst less likely** and may point more toward **meningioma, ependymoma, or calcified aneurysm**."
  - "**Avid contrast enhancement** similarly reduces the likelihood of a colloid cyst and increases the likelihood of **meningioma, ependymoma, craniopharyngioma, or choroid plexus papilloma**."
- **A caution** — "**FLAIR hyperintensities may also be more frequently found with other diagnoses**" YW p.1236, so FLAIR bright signal is a risk marker, not a diagnostic marker.

Table 2 · Imaging signature of a colloid cyst against its differential diagnosis at the foramen of Monro — assembled from Youmans & Winn 8e, Ch. 171 §Neuroimaging and §Diagnostic Algorithm, p. 1236; Ch. 170 §Intraventricular Tumor Pathology, pp. 1230-1232; Table 170.1, p. 1204.

Lesion	Typical CT	T1	T2/FLAIR	Enhancement	Discriminator
Colloid cyst	Hyperdense (viscous) or iso/hypodense (aqueous); calcification rare	~2/3 hyperintense	Usually iso/hypointense; >50% FLAIR bright	**Thin rim only**; no diffusion restriction	>99% at foramen of Monro, round, fluid-filled, fornices straddle it
Meningioma	Iso/hyperdense; **calcified in ~50%** of intraventricular examples	Iso/hypointense	Iso/hyperintense	**Avid, homogeneous**; spoke-wheel	Atrium (usually left) of lateral ventricle; vascular, choroidal feeders
Ependymoma / subependymoma	Iso/hyperdense; calcification, haemorrhage	Hypo/isointense	Hyperintense	Heterogeneous (ependymoma); **subependymoma does not enhance**	Fourth > lateral ventricle; subependymoma is a non-enhancing nodule on the ependymal lining

Choroid plexus papilloma	Well-defined, lobulated, isodense; punctate calcification in ~25%	Isointense to white matter	Slightly hyperintense	**Marked, "frond-like"**	Atrium in children, fourth ventricle in adults; enlarged choroidal feeder
Central neurocytoma	Slightly hyperdense/isodense; **punctate calcification in >50%**	Isointense to grey matter	Hyperintense, **"soap-bubble"**	Mild to moderate	Frontal horn, attached to **septum pellucidum**; young adult
Craniopharyngioma	Mixed density, calcified, cystic	Solid nodule hyperintense	Cyst hyperintense, calcification hypointense	Nodular/rim	Suprasellar, extends up through the floor of the third ventricle
Aneurysm	Spheroid, may calcify	Flow-related signal	Flow void	Depends on thrombus	Extends **inferiorly** into the third ventricle; check CTA/DSA
CSF flow artefact ("MRI pseudocyst")	Normal CT	Variable	Variable	None	Disappears on repeat/alternative sequences; turbulent flow at the foramen

(c) Pathology [2]

8. Gross, microscopic and immunohistochemical pathology

8.1 Gross

- **Site** — a **unilocular cyst wedged in or projecting through the foramen of Monro**, attached to the **anterosuperior roof of the third ventricle**, frequently on a **mobile pedicle**, straddled by the **columns of the fornix**, sometimes growing **above the roof of the third ventricle** between the crura [YW pp. 1236-1237].
- **Contents** — **gelatinous, mucinous fluid** derived from the internal secretory epithelium and from epithelial breakdown, composed of **CSF, blood products and cholesterol/lipids**; the viscosity ranges from **aqueous and easily aspirated to firm and keratin-like** YW p.1236.
- **Relation to choroid plexus** — "**The cyst is commonly invested with choroid plexus** and intimately associated with the fornix, **although nonadherent**" YW p.1238.

8.2 Microscopic

- **Lining epithelium** — "The cysts may be lined with a variety of **pseudostratified, columnar, or cuboidal epithelial cells** in addition to **ciliated columnar epithelium and goblet cells**" YW p.1234. The presence of **cilia and mucin-secreting goblet cells** is the classic respiratory/enteric (foregut) phenotype.
- **Capsule** — "**The cyst capsule is formed by fibroblasts, collagen, and arachnoid cells**" YW p.1234 — the layer that must be removed to prevent recurrence and the layer that adheres to the deep veins.

8.3 Immunohistochemistry and the lesions it separates the cyst from

- **The positive comparison** — "Immunohistochemically, colloid cysts are **very similar to Rathke cleft cysts, follicular pituitary gland cysts, and neurenteric cysts**" YW p.1234.
- **The negative comparison — this is the discriminator** — "The epithelial lining of colloid cysts **shares few immunohistochemical properties with choroid plexus epithelium**" YW p.1234. A colloid cyst is therefore **not** a choroid plexus derivative despite its intimate investment by choroid plexus.
- **Origin statement to write** — ectopic **foregut endoderm**, not the paraphysis YW p.1234.
- **Behaviour** — benign; the entity is grouped in Youmans' classification of ventricular pathology under "**Other lesions and cysts — Colloid cyst — third ventricle**", alongside Rathke cyst (suprasellar), epidermoid (fourth ventricle),

dermoid (suprasellar, pineal), choroid plexus cyst and arachnoid cyst (lateral ventricles) YW p.1204.

(d) Management [3]

9. Surgical anatomy — know it before you choose the corridor

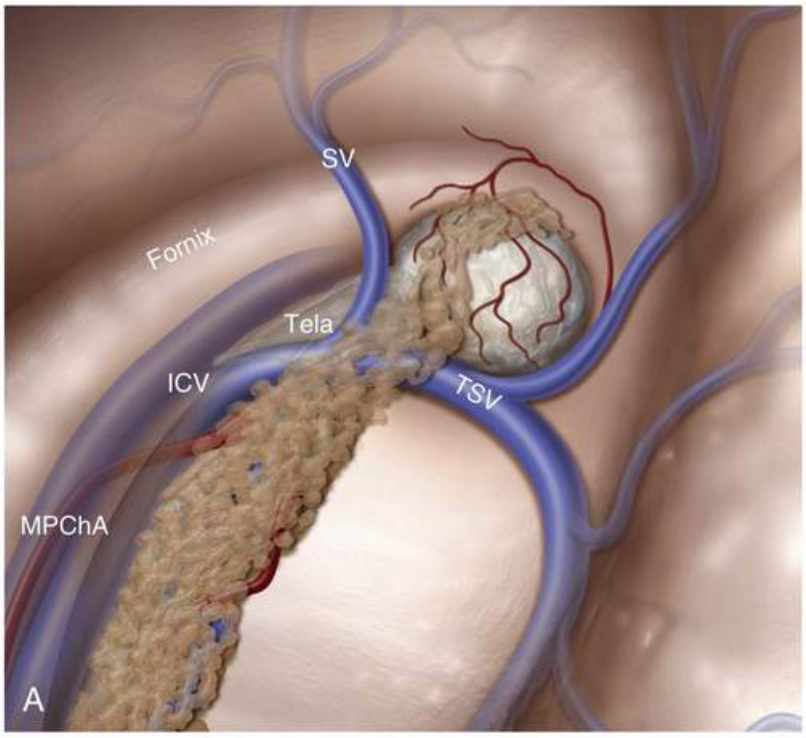


Figure 171.4. Critical neurovascular anatomy and potential attachment points for colloid cysts of the third ventricle.
(A) Critical structures include the fornix, internal cerebral veins *(ICV)*, septal veins *(SV)*, thalamostriate vein *(TSV)*, tela choroidea *(Tela)*, and choroid plexus. The medial posterior choroidal artery *(MPChA)* extends anteriorly and must be identified, particularly during resection of posteriorly positioned cysts. (B) The cyst is commonly invested with choroid plexus and intimately associated with the fornix, although nonadherent. A small penetrating artery extending from the fornix to the cyst can be present. (C) Cyst attachment points at the velum, deep draining veins, tela, and choroid must be carefully dissected to avoid vascular injury.

Reproduced from Youmans & Winn 8e, Fig. 171.4, p. 1238 — Label when you reproduce it: (A) fornix, internal cerebral veins (ICV), septal veins (SV), thalamostriate vein (TSV), tela choroidea (Tela), choroid plexus and the medial posterior choroidal artery (MPChA) running anteriorly; (B) the cyst invested with choroid plexus and intimately associated with but non-adherent to the fornix, with a small penetrating artery running from fornix to cyst; (C) the cyst's attachment points at the velum interpositum, deep veins, tela and choroid that must be dissected to avoid venous injury.

- **The four structures at risk** — "Key anatomic structures that are at risk during excision of a colloid cyst include the **thalamus, the basal ganglia, cerebral veins, the fornix, and the velum interpositum**" YW p.1237.

- **Veins** — "the **internal cerebral veins are found running in the roof of the third ventricle in the velum interpositum**, located in the medial aspect of the choroidal fissure. **These veins should be located prior to passing through the choroidal fissure**" YW p.1237. The **superior choroidal veins** pass through the choroid plexus of the third ventricle and the **thalamostriate veins** pass through the posterior foramen of Monro in the roof of the third ventricle YW p.1237. **Large cysts that grow above the roof of the third ventricle may become adherent to these veins** YW p.1237.
- **Fornix** — the crura wrap around the posterior thalamus toward the splenium, merge near the atrium-body junction into the body of the fornix, which runs along the superomedial thalamus and **separates the floor of the bodies of the lateral ventricles from the roof of the third ventricle**. "**The area between the two crura before their merger provides space through which a posteriorly located colloid cyst may extend above the roof of the third ventricle**" [YW pp. 1237-1238].
- **The four layers of the roof of the third ventricle** — "The fornix provides **one of four layers of the roof of the third ventricle, the others being the two layers of tela choroidea and the vasculature that runs between them**" YW p.1238.
- **Velum interpositum** — "the potential space that exists **between the two layers of tela choroidea** in the roof of the third ventricle. It lies **medially between the thalami and beneath the body of the fornix**. Within this space run the **internal cerebral veins and medial posterior choroidal arteries**" YW p.1238.
- **The landmark that orients every superior approach** — "For both the transcortical transventricular and interhemispheric transcallosal approaches to the third ventricle, **the foramen of Monro can be located by following the thalamostriate vein and the choroid plexus anteriorly until they join at the foramen**" YW p.1238.
- **The venous angle** — the septal vein anastomoses with the thalamostriate vein to form the internal cerebral vein at the level of the foramen of Monro, creating a "U-shape" known as the **venous angle**, typically **3 to 7 mm posterior to the foramen of Monro**; **immediately deep (lateral) to this anastomosis lies the genu of the internal capsule** [YW pp. 1205-1206].

10. Decision-making — who gets operated on

- **The rule** — "**Symptomatic cysts require surgery, ideally as soon as possible** (and technically feasible) after cyst-related symptoms are identified" YW p.1237.
- **The incidental cyst** — "For incidentally found cysts, **observation with periodic surveillance imaging is often recommended** and no surgery is performed unless the patient develops symptoms or demonstrates ventriculomegaly or concerning cyst progression"; "It is quite **uncommon for untreated incidental colloid cysts to cause acute neurological deterioration or death**" YW p.1237.
- **The counter-argument** — Margetis et al. argued for endoscopic resection of some incidental cysts, "especially in **younger patients or patients with large cysts**, given the long-term cumulative probability of neurological decline"; in their series endoscopic resection of incidentally found cysts was **low risk and associated with a greater rate of gross total resection, lower recurrence, lower postoperative morbidity, shorter hospital stay and reduced need for a postoperative EVD** compared with resection of symptomatic cysts YW p.1237.
- **The CCRS-driven algorithm (Fig. 171.3, p. 1237)** — **CCRS ≤2 (low risk): surveillance imaging**, since obstructive hydrocephalus is not expected. **CCRS 3 (intermediate): observe a reliable patient**, otherwise operate. **CCRS ≥4 (high risk): surgery** — commonly symptomatic, with a **20%-60% risk of developing obstructive hydrocephalus**. Within the surgical group, the modality is steered by the imaging: **small ventricles, T2-dark (firm, non-fluidic) contents and a posterior pedicle** favour **port-based minimally invasive surgery or microsurgery**, whereas **ventriculomegaly, T2-bright contents and an intraforaminal cyst** favour **endoscopic resection, port-based MIS or microsurgery** YW p.1237.
- **Hyperacute management — write this as a protocol** YW p.1237:
  - **Immediate CT head** to evaluate for hydrocephalus or another cause.
  - If acute hydrocephalus, **place bilateral EVDs prior to surgery** — most advisable in emergencies with rapid, severe decline, since **EVD placement can prevent herniation and death**.

- Understand the limits: "**EVD placement may not improve a patient's neurological status to a significant degree and is not sufficient treatment** for symptomatic colloid cysts; it is **merely to help stabilize the patient before surgery**."
- Note why bilateral: the cyst may obstruct **both** foramina of Monro YW p.1734, so a unilateral drain may not decompress the contralateral ventricle.

11. The treatment options in order — advantages, disadvantages, numbers

11.1 Shunting (a rescue, not a cure)

- **Indication** — "hydrocephalus caused by cysts may be treated via insertion of a **ventriculoperitoneal shunt (VPS)**. VPS insertion is a viable option for patients who are **poor candidates for surgical resection**" YW p.1238. It can be a **short-term bridge** or a **long-term option** in those unable or unwilling to undergo resection.
- **Laterality** — "Shunts can be placed **unilaterally** if the cyst is obstructing one foramen of Monro but can be placed **bilaterally** if the cyst obstructs both foramina. Furthermore, a **unilateral VPS can be combined with an endoscopic septostomy** to ensure drainage of both lateral ventricles" YW p.1238.
- **Why it is not definitive** — "**VPS placement does not address the cyst itself**, which may progress in size and cause further impediment to CSF flow **or hypothalamic dysfunction**. Accordingly, **shunting is not a recommended long-term option**" YW p.1238. Add shunt infection, malfunction and later obstruction requiring revisions YW p.1238.
- **The trap it creates for the surgeon** — "Surgical resection of a colloid cyst **after VPS placement is possible, although it may be rendered more difficult by decreased ventricular size** from the shunt. Therefore placement of a **programmable valve, particularly one with a high-pressure setting or 'virtual off,' is helpful**" YW p.1238.

11.2 Stereotactic aspiration — abandoned

- "Stereotactic aspiration of cyst contents was initially developed decades ago... **it is a suboptimal treatment strategy because it does not eliminate any part of the cyst capsule**. As a consequence, there is an **unacceptably high rate of cyst recurrence after aspiration (80%). Cyst aspiration has therefore been abandoned in contemporary neurosurgery and no longer represents an acceptable treatment option**" YW p.1240.
- Ch. 228 gives the same verdict with the older numbers — early stereotactic aspiration attempts "noted a **50% to 80% recurrence rate**", with recurrences "**sometimes after years, demanding long-term follow-up**", plus the technical limitations of **neural and vascular injury, difficulty puncturing small thick-walled lesions, and difficulty aspirating viscous contents** YW p.1734.

11.3 Microsurgical resection — the two classical corridors

- **Interhemispheric transcallosal approach** YW p.1238:
  - Craniotomy **lateral to the superior sagittal sinus**, ideally on the **non-dominant** side, although **asymmetrical venous drainage may force a switch of sides**.
  - Craniotomy is **two-thirds anterior and one-third posterior to the coronal suture** (Ch. 170 adds it "should not need to be located more than **3 to 4 cm posterior of the coronal suture** to avoid injury to the motor cortex", with **two burr holes on either side of the SSS**) [YW pp. 1214, 1238].
  - Dissect the interhemispheric fissure with "**extreme care taken to avoid damage to any large draining veins and the leg motor area posteriorly**".
  - Pass below the free edge of the falx, **separate the cingulate gyri**, protect the **ACAs** with a cottonoid, expose the **glistening white corpus callosum**, and perform the callosotomy — **a 2-cm callosotomy is adequate for most intraventricular pathology** YW p.1214.
  - Enter the ventricle; **find the fornices at the base of the septum pellucidum and avoid them**, along with the **thalamostriate and septal veins**; identify normal choroid plexus.
  - If more exposure of the superior third ventricle is needed, "**it is preferable to open the choroidal fissure through the tenia fornicis**": coagulate the choroid plexus and open the tenia **inferolateral to the body of the fornix and medial to the proximal internal cerebral vein**, so as to **preserve the drainage of the thalamostriate and septal**

veins at the venous confluence.

- **"The surgeon should not section the fornix adjacent to the anterosuperior margin of the foramen."**

- **Transcortical transventricular approach** [YW pp. 1238-1239]:
  - "**More useful in patients with dilated ventricles** because it is challenging to traverse narrow lateral ventricles."
  - Using navigation, choose the cortical incision giving the best angle to the cyst; **paramedian frontal craniotomy two-thirds anterior and one-third posterior to the coronal suture**; a **1.5-cm corticotomy**; enter the ipsilateral frontal horn; **cottonoid and dynamic retraction with suction and bipolar** — no fixed retractors.
  - Thereafter identical to the transcallosal route; **opening the choroidal fissure is optimal as it spares the fornix and gives the best view of the third ventricular roof**.
- **Techniques for entering the third ventricle from above** (Fig. 170.12) — **transforaminal, subchoroidal, transchoroidal and interforniceal** YW p.1217. The transchoroidal route releases the **tenia fornicis medial to the choroid plexus**, splitting between the internal cerebral veins; the subchoroidal route opens the more lateral **tenia choroidea** and risks the **thalamostriate and choroidal veins**, and an anatomical study by Bozkurt et al. showed it gives **more limited exposure** than the transchoroidal dissection YW p.1224.
- **Foraminoplasty** — where the foramen is too small, it can be widened **by sacrificing the anterior septal vein** or **via the transchoroidal approach**; Türe et al. showed the septal-thalamostriate-ICV junction is often **further posterior than the classic description**, permitting **safe foraminoplasty without venous sacrifice**, and advocated **planning the side from preoperative venography** YW p.1224.

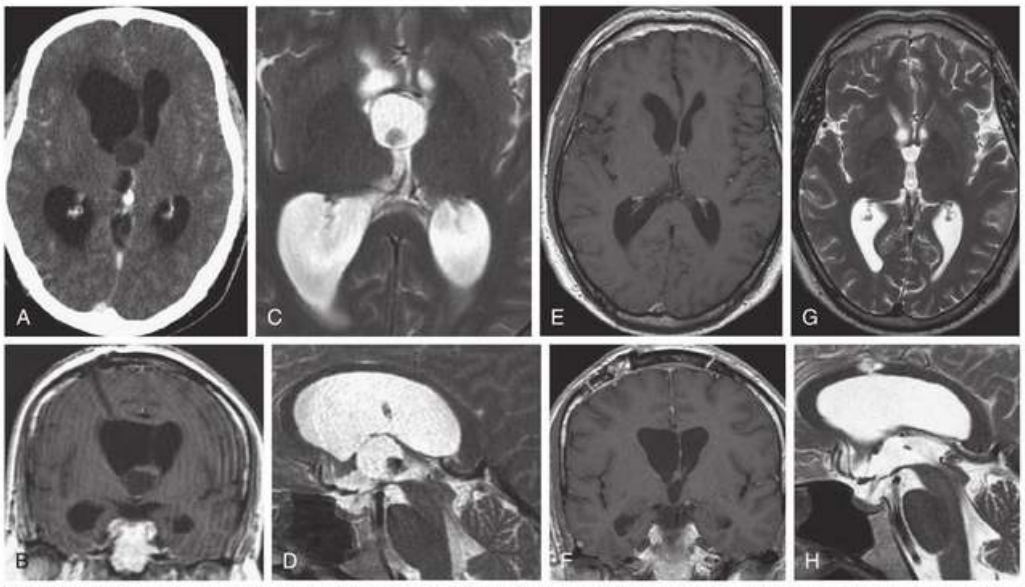


Figure 170.16. A 51-year-old male patient was admitted on an emergency basis for obstructive hydrocephalus, as seen on preoperative CT scans (A–B). Initially, an external ventricular drain was placed to release the raised intraventricular pressure. Preoperative T2-weighted MR images in the axial plane (C) and sagittal plane (D) show a large colloid cyst within the third ventricle obstructing the foramen of Monro. Complete removal of the colloid cyst was achieved microsurgically via the right frontal interhemispheric transcallosal approach and confirmed on postoperative T1-weighted MR images (E–F) and T2-weighted MR images (G–H). The patient's postoperative course was entirely uneventful.

Reproduced from Youmans & Winn 8e, Fig. 170.16, p. 1223 — Label when you reproduce it: (A-B) emergency preoperative CT showing obstructive hydrocephalus (an EVD was placed first); (C) axial and (D) sagittal T2-weighted MRI showing a large colloid cyst in the third ventricle obstructing the foramen of Monro; (E-F) postoperative T1 and (G-H) postoperative T2 images confirming complete microsurgical removal via a right frontal interhemispheric transcallosal approach.

11.4 Endoscopic resection — now the workhorse

- **Why it grew** — "**minimally invasive nature, low rates of morbidity and mortality**, and the more widespread adoption of intraventricular endoscopic approaches" YW p.1239.
- **Demonstrated advantages** — "**significantly reduced rate of complications** compared with conventional microsurgical resection and... **shorter operative times, shorter lengths of hospital stay, reduced overall costs, and increased patient comfort**" YW p.1239. Shunt dependency rates are **similar or lower** than microsurgery YW p.1239.
- **The trade-off** — "there is a **significantly increased rate of residual cyst wall after endoscopic resection** that may be

associated with **increased cyst recurrence on long-term follow-up**" YW p.1239; endoscopic resections "have been associated with **significantly fewer gross total resections and greater residual cyst**", and greater residual is associated with **higher rates of cyst recurrence and reoperations, although recurrences may remain asymptomatic** YW p.1239.

- **Scope choice — rigid endoscopes give superior optics and field of view, are easier to orient, come in 0-, 30- and 70-degree angles, and some have multiple working channels for bimanual technique**; **flexible endoscopes** bend along all three axes and navigate the ventricular system better but have **inferior optical clarity and more limited instrumentation**, and "retracting a bent scope may cause damage to surrounding structures" YW p.1239.
- **Entry points — memorise the two** YW p.1239:
  - **Transforaminal approach: bur hole ~4 cm lateral to midline and 4 cm anterior to the coronal suture.**
  - **Transseptal approach: bur hole ~6 cm lateral to midline and 4 cm anterior to the coronal suture.**
  - Fig. 171.5 gives the alternative single-bur-hole description: **~4 cm lateral to midline, 5 cm anterior to the coronal suture, ≈8 cm posterior to the nasion**, finally optimised with intraoperative neuronavigation YW p.1239.
  - The final position is chosen to **avoid the head of the caudate nucleus** and to reach the anterior horn; **frameless stereotactic neuronavigation is essential** YW p.1239.
- **Which approach for which cyst** — "The **transforaminal approach is generally used for cysts that obviously protrude through the foramen of Monro**... The **transseptal approach can be used when the cyst occludes the foramen of Monro and prevents the surgeon from accessing the cyst via the transforaminal approach**... the cyst must be approached **through the septum pellucidum**. **Larger cysts typically necessitate the transseptal approach**" YW p.1239.
- **Technique — en bloc removal is possible but often difficult**; otherwise **coagulate and fenestrate the cyst wall, remove the contents by suction with a large-bore cannula or endoscopic suction-morcellation device, then dissect the capsule with sharp bimanual dissection, piecemeal, with extreme care not to injure the confluence of internal cerebral, thalamostriate and septal veins**. If a portion of the wall is **relentlessly adherent to the deep veins or the roof of the third ventricle, it is thoroughly coagulated** YW p.1239.
- **Ch. 228's practical points** — the bur hole should be **more lateral and anterior than a standard shunt bur hole** to give a **face-on view of the cyst in the foramen**; **shrink the wall by coagulation first**, then excise; **avoid excessive traction on the capsule** because bleeding from partially avulsed vessels in the roof of the third ventricle is hard to control and quickly obscures the view, and **traction on the fornices may confer significant morbidity**; use **continuous warm irrigation** for oozing and **focal bipolar or laser coagulation** for brisk bleeding; **fenestrate the septum pellucidum** to ensure free communication between the ventricles YW p.1734.

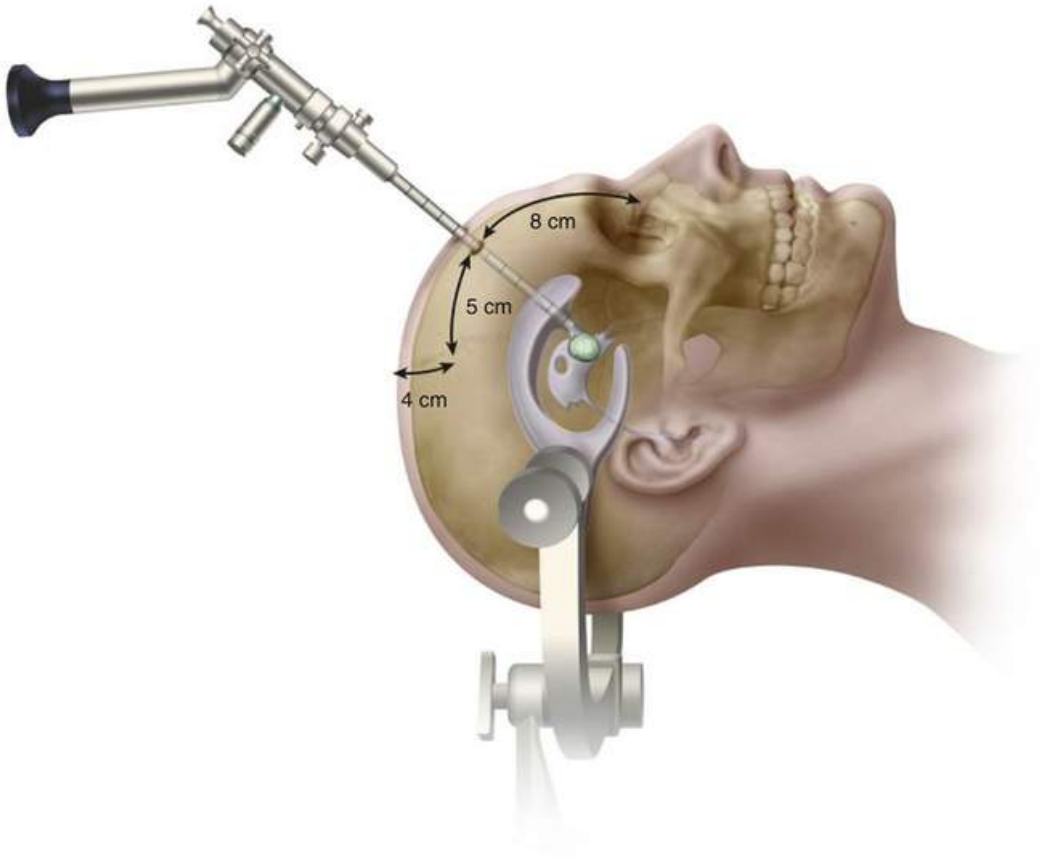


Figure 171.5. Head position and entry point for single bur hole for endoscopic approach. Patient is positioned supine with the head in pin fixation. The bur hole is approximately 4 cm lateral to midline and 5 cm anterior to coronal suture. This is approximately 8 cm posterior to the nasion.[44,74] Final entry point is optimized using intraoperative neuronavigation.

Reproduced from Youmans & Winn 8e, Fig. 171.5, p. 1239 — Label when you reproduce it: supine position with the head in pin fixation; the bur hole ~4 cm lateral to the midline and ~5 cm anterior to the coronal suture, ≈8 cm posterior to the nasion. State that the final entry point is optimised with intraoperative neuronavigation to clear the head of the caudate and align with the foramen of Monro.

11.5 Port-based (stereotactically guided endoscopic port) surgery

- **Rationale** — microsurgical resection sometimes needs "an especially **wide operative corridor** to obtain an adequate view of the lesion with the operative microscope" YW p.1240.
- **Origin** — **stereotactically guided endoscopic port surgery (SEP)**, first used in **2004** with a repurposed **thoracic tubular port**, modified instruments and a stereotactic frame, viewing the ventricles through a mounted endoscope YW p.1240.
- **Result** — "In that initial study, **12 of 12 patients with colloid cysts experienced gross total resection with SEP without postoperative complications**" YW p.1240. It "provided the **dexterity of traditional open surgery while preserving the minimally invasive nature of endoscopic surgery**".

11.6 Conversion from endoscopic to open

- "In one series of **35 endoscopic colloid cyst excisions, six cases were converted to open resection because of cyst adhesion to the fornix**" YW p.1239.
- Osorio et al.: "for the purely endoscopic cases, **0% of patients had their cyst capsule completely removed** compared

with **78% of patients who underwent conversion from endoscopic to open surgery**. There were **no significant differences in postoperative complications** between the two groups" — and an **open transcortical transventricular approach functioned well as a salvage procedure** [YW pp. 1239-1240].

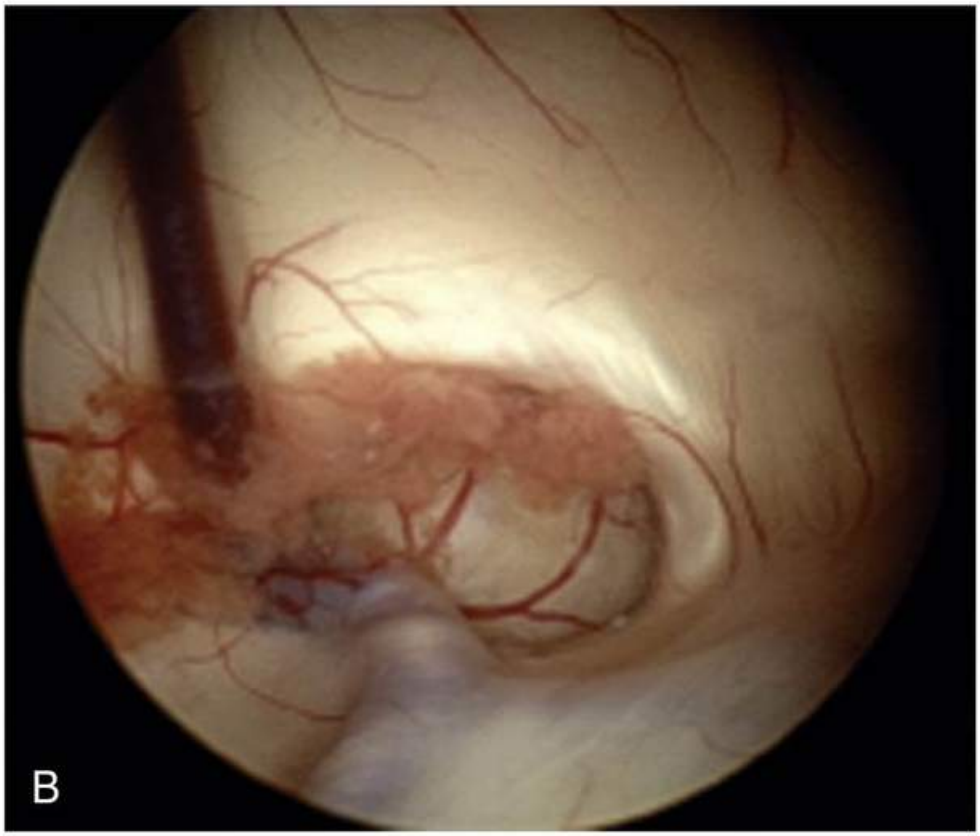


Figure 228.5. (A) Illustration of ventriculoscopic resection of colloid cyst. (B) Cyst visible through the right foramen of Monro.

Reproduced from Youmans & Winn 8e, Fig. 228.5, p. 1735 — Label when you reproduce it: (A) the illustration of ventriculoscopic resection of a colloid cyst — grasping forceps in one channel, laser/coagulating fibre in the other; (B) the endoscopic view of the cyst presenting through the right foramen of Monro, with the choroid plexus, thalamostriate vein and fornix as the surrounding landmarks.

Table 3 · Treatment options for a third-ventricular colloid cyst — indication, advantage, disadvantage. Compiled from Youmans & Winn 8e, Ch. 171 pp. 1237-1240 and Ch. 228 pp. 1734-1735.

Option	When used	Advantage	Disadvantage / risk
Surveillance imaging	CCRS ≤2; reliable CCRS 3 patient	No operative risk; most incidental cysts stay stable and a few regress	5%-15% progress within 5 years; requires reliable follow-up
EVD (bilateral)	Acute decompensation with hydrocephalus	Prevents herniation and death; stabilises before definitive surgery	Not definitive; may not restore neurological status
VP shunt (± septostomy)	Poor surgical candidate; bridge; very large or haemorrhagic cyst	Treats hydrocephalus reliably	Does not treat the cyst; hypothalamic dysfunction may progress; infection, malfunction, revisions; shrinks ventricles and makes later resection harder — use a programmable/"virtual off" valve
Stereotactic aspiration	Historical only	Technically simple	**80% recurrence**; capsule not removed; **abandoned**

Endoscopic (transforaminal / transseptal)	Ventriculomegaly, T2-bright fluid contents, intraforaminal cyst	Lowest morbidity and mortality, shortest operation and stay, lower cost	Significantly more residual capsule, lower GTR, higher recurrence; conversion to open for forniceal adhesion
Microsurgical interhemispheric transcallosal	Small ventricles; large or adherent cyst; salvage	Highest GTR; no corticotomy; best access to the third ventricular roof through the choroidal fissure	SSS/cortical vein injury and venous infarction; SMA syndrome; pericallosal artery injury; disconnection if genu/splenium cut
Microsurgical transcortical transventricular	Dilated ventricles; endoscopic salvage	Wide corridor, direct angle to the foramen	Cortical transgression; contested higher seizure risk; caudate injury
Port-based MIS (SEP)	Firm, T2-dark, posteriorly pedicled cysts; need for bimanual microsurgery	12/12 GTR without complication in the original series; microsurgical dexterity through a minimally invasive corridor	Requires port system and stereotaxy; limited long-term data

12. Complications and pitfalls — and how to avoid each

- **General statement** — "surgery for resection of third ventricular colloid cysts is a **safe and effective procedure**, but it may be associated with some complications" YW p.1240.
- **The list to enumerate** — "**seizures, memory deficits, hemorrhage or hematoma, infarction, meningitis, CSF leak, or motor deficits**" YW p.1240. Ch. 228 adds **memory dysfunction, venous infarction, IVH, hemiparesis, meningitis, seizures, and even death**, plus **aseptic meningitis from release of cyst contents** YW p.1735.
- **Seizures** — "Some surgeons have contended that the risk of seizures after **transcortical** approaches to the ventricle is **higher** than with interhemispheric approaches, **but this is controversial**" YW p.1240.
- **Memory** — "**Damage to the fornix** while obtaining access to the cyst within the foramen of Monro may lead to **persistent short-term memory deficits**" YW p.1240; even unilateral forniceal injury can cause **anterograde amnesia** YW p.1222.
- **Venous infarction** — "the **internal cerebral veins and thalamostriate veins** are at risk of being damaged during surgery, which in rare instances may lead to **thalamic infarction**" YW p.1240.
- **Interhemispheric-specific** — the **superior sagittal sinus or cortical veins** may be damaged during interhemispheric dissection causing **venous infarction**; retraction of the **supplementary motor and/or leg motor areas** can cause **SMA syndrome or isolated contralateral monoparesis**; the **pericallosal branch of the ACA** may be damaged when exposing the corpus callosum YW p.1240.
- **Endoscopic-specific** — "the proper **trajectory is paramount** to avoiding structural damage to the **fornix and caudate nucleus**"; **frameless neuronavigation is a modern standard** for the anterolateral trajectory over the head of the caudate; with older **single-working-channel** scopes bimanual dissection may be impossible, so "the surgeon should **avoid blunt dissection and aggressive traction on the cyst capsule**, both of which may cause damage to the fornix and injury to the deep veins" YW p.1240.
- **Haemostasis in the ventricle** — remember that in the ventricle "there is **no tissue turgor to tamponade** minor bleeding" YW p.1152; this is the physical reason intraventricular bleeding is dangerous.
- **Evidence comparing the two** — critical review over two decades suggests "the two strategies result in **similar rates of shunt dependency**, with a **trend toward a lower morbidity rate in endoscopic cases**"; "a microscopic **transcallosal** approach may result in **lower neurological complications** than a transcortical endoscopic approach, with similar cyst resection rates"; and "**microsurgical techniques are associated with significantly higher rates of gross total resection and decreased recurrence** compared with endoscopic resection" YW p.1735.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **1%-2% of intracranial tumours; incidence 3.2 per million per year; >99% sit at the foramen of Monro** — location alone almost makes the diagnosis.
- **Origin is ectopic foregut endoderm, not the paraphysis.** Immunohistochemically like Rathke cleft, follicular pituitary and neurenteric cysts, and **unlike choroid plexus epithelium**.
- **Lining: pseudostratified/columnar/cuboidal epithelium with ciliated columnar cells and goblet cells; capsule of fibroblasts, collagen and arachnoid cells.**
- **40%-60% are asymptomatic at diagnosis; 5%-15% progress within 5 years; the risk of death once symptomatic is 3.1%.**
- **Ball-valve obstruction on a mobile pedicle** is the accepted mechanism of sudden deterioration; other mechanisms are **intracystic haemorrhage** and **hypothalamic/catecholamine myotoxicity**.
- **The fatal cyst gives a 3.3-day prodrome** of headache, vomiting and reduced consciousness — never send such a patient home.
- **CCRS: age <65, headache, axial diameter ≥7 mm, FLAIR hyperintensity, risk zone. ≥4 = high risk (operate), 3 = intermediate, ≤2 = low (observe).** Every patient who presented with hydrocephalus had CCRS ≥4.
- **Viscosity rule**: viscous/cholesterol-rich = **CT hyperdense, T1 bright, T2/FLAIR dark, hard to aspirate**; aqueous = the converse.
- **Only a thin rim enhances.** Avid homogeneous enhancement or calcification means think meningioma, ependymoma, craniopharyngioma, CPP or aneurysm instead.
- **Ventriculomegaly alone is not an indication for surgery** — 31% of asymptomatic cysts have it.
- **Bilateral EVDs, not unilateral**, for the acutely decompensating patient, because the cyst can block both foramina.
- **Aspiration is dead: 80% recurrence.** Shunting treats the hydrocephalus, not the cyst, and shrinks the ventricles you will later need.
- **Endoscopic bur holes: 4 cm lateral / 4 cm anterior for transforaminal; 6 cm lateral / 4 cm anterior for transseptal** (Fig. 171.5 gives 4 cm lateral / 5 cm anterior / 8 cm behind nasion for a single bur hole).
- **Enter the third ventricle through the choroidal fissure via the tenia fornicis** — medial to the choroid plexus, lateral to the fornix, medial to the ICV — it spares the fornix and preserves the venous confluence.
- **Never section the fornix at the anterosuperior margin of the foramen of Monro.**
- **Endoscopy: lower morbidity, more residual capsule, more recurrence. Microsurgery: higher GTR, less recurrence.** Six of 35 endoscopic cases converted to open for forniceal adhesion; conversion raised complete capsule removal from 0% to 78%.

Pages read for this answer — Youmans & Winn 8e: 1152, 1203, 1204, 1205, 1206, 1214, 1217, 1222, 1224, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1734, 1735

a) Colloid cyst. [3]
b) Its Clinical features. [3]
c) Colloid cyst management. [4]

LONG | DEC 2022 · Paper I · Q3 | 10 marks

Also asked as: Ventricular tumours — also asked as DEC 2021 · Paper I · Q6 ("Colloid cyst of third ventricle: a) Clinical features. [2] b) Neuroimaging features. [3] c) Pathology. [2] d) Management. [3]")

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 171 *Colloid Cysts of the Third Ventricle*, §Introduction, §Histogenesis, §Natural History, §Acute Neurological Decline, §Colloid Cyst Risk Score, §Neuroimaging, §Surgical Decision Making, §Surgical Anatomy, §Surgical Approaches (Shunting, Microsurgical Resection, Endoscopic Resection, Conversion, Port-Based Resection, Cyst Aspiration), §Complications and Pitfalls, pp. 1234-1240 (Figs. 171.1, p. 1235; 171.2, p. 1236; 171.3, p. 1237; 171.4, p. 1238; 171.5, p. 1239; Table 171.1, p. 1235). Supplementary: Ch. 170 *Ventricular Tumors*, §Surgical Anatomy — Lateral Ventricle, §Surgery of the Third Ventricle, §Transforaminal/Transchoroidal/Subchoroidal/Interforniceal Techniques, pp. 1205-1206, 1214, 1216-1219, 1222-1224 (Figs. 170.12, p. 1217; 170.15, p. 1222; Table 170.3, pp. 1218-1219). Ch. 228 *Neuroendoscopy*, §Colloid Cysts, pp. 1734-1735 (Figs. 228.4, p. 1734; 228.5, p. 1735).

(a) Colloid cyst — what it is [3]

1. Definition and one-line answer

- **A colloid cyst is a rare, benign, epithelium-lined cyst arising in the anterosuperior third ventricle near the foramen of Monro**, filled with gelatinous mucinous material, which is clinically important because it obstructs the foramen of Monro and can cause acute hydrocephalus, neurological deterioration and death YW p.1234.
- **Incidence and share** — **1% to 2% of all intracranial tumours**, incidence **3.2 per million per year** YW p.1234; Ch. 228 quotes **0.5% to 1% of all brain tumours** YW p.1734.
- **Youmans' key concepts, verbatim in six lines** YW p.1234:
  - Rare tumours of the third ventricle.
  - **Often obstruct the foramen of Monro.**
  - May be asymptomatic **or** cause acute hydrocephalus, neurological deterioration and death.
  - **MRI is the preferred imaging modality.**
  - Resectable by **open microsurgery, endoscopically, or via port-based hybrid approaches**.
  - Endoscopic surgery has **lower morbidity and shorter stay but possibly a higher risk of recurrence**.
  - **Critical structures: the deep veins, the thalamus and the fornix.**

2. Histogenesis — the developmental story

- **The relevant embryology** — the neural tube closes in the **fourth week**; in the **fifth week** the prosencephalon divides into telencephalon and diencephalon, whose cavities become the **lateral and third ventricles**, and "**the foramen of Monro develops at the interface of these ventricles**" YW p.1234.
- **First description 1858** YW p.1234.
- **The discarded paraphysis theory** — the **paraphysis** is "a neuroectodermally derived structure that temporarily develops at the border of the telencephalon and diencephalon **during week 7 of gestation** and subsequently involutes into choroidal vesicles"; it arises from the **paraphyseal arch**, which becomes incorporated into the **roof of the third ventricle**, so persistent remnants were thought to form the cyst YW p.1234.
- **The current view** — "it is now widely believed that **cysts arise from ectopic foregut endoderm and not the paraphysis**" YW p.1234.
- **Immunohistochemical evidence** — colloid cysts are "**very similar to Rathke cleft cysts, follicular pituitary gland cysts, and neurenteric cysts**", and "the epithelial lining **shares few immunohistochemical properties with choroid plexus epithelium**" YW p.1234. That single negative is the examinable discriminator.

3. Pathology

- **Gross** — a unilocular, well-defined, smooth, spherical or ovoid cyst, **mean diameter reported up to 15 mm**, wedged at or protruding through the foramen of Monro, attached to the **anterosuperior roof of the third ventricle**, often on a **mobile pedicle**, and **straddled by the columns of the fornix** [YW pp. 1236-1237].
- **Contents** — "**gelatinous, mucinous fluid** that results from the internal secretory epithelium and epithelial breakdown and consists of **CSF, blood products, and cholesterol or lipids**" YW p.1236. Viscosity varies from watery to "**firm and keratin-like**" YW p.1236.
- **Lining** — "**pseudostratified, columnar, or cuboidal epithelial cells** in addition to **ciliated columnar epithelium and goblet cells**" YW p.1234.
- **Capsule** — "**fibroblasts, collagen, and arachnoid cells**" YW p.1234.
- **Relation to choroid plexus** — "commonly **invested with choroid plexus** and intimately associated with the fornix, **although nonadherent**"; a **small penetrating artery extending from the fornix to the cyst can be present**; attachment points at the **velum, deep draining veins, tela and choroid** must be carefully dissected YW p.1238.

- **Classification slot** — Youmans lists the colloid cyst among "**Other lesions and cysts**" of the ventricles, with the third ventricle as its location — alongside Rathke cyst (suprasellar), epidermoid (fourth ventricle), dermoid (suprasellar/pineal), choroid plexus cyst and arachnoid cyst (lateral ventricles) YW p.1204.

4. Imaging in one section (because it defines the lesion)

- **Location** — "**>99% of colloid cysts are centered near the foramen of Monro, often lodged in the foramen itself**"; they push the **posterior aspect of the frontal horns laterally**; they are "**very rarely located in other areas of the brain, such as the lateral ventricles or cerebellum**" YW p.1236.
- **CT** — **most are hyperdense**, and the hyperdensity is **inversely correlated with intracystic water content**; aqueous cysts may be **hypo- or isodense**; a **thin rim of enhancement** is inconstant; **calcification or haemorrhage is rare** YW p.1236.
- **MRI** — "**MRI is the preferred method**"; **about two-thirds are T1 hyperintense**; most are **iso- or hypointense on T2 and FLAIR** (T2-dark cysts may be hard to see on FLAIR); **more than half demonstrate FLAIR hyperintensity**, which correlates with symptomatic lesions and hydrocephalus; enhancement is **slight and rim-like only — intense homogeneous enhancement suggests a different diagnosis**; **no diffusion restriction**; the **"dot sign"** (T1-bright, T2/FLAIR-dark, SWI iso/hypointense intracystic nodule) is inconstant YW p.1236.
- **The viscosity rule** — "**for heavily cholesterol-filled cysts, CT will be hyperdense, T1 hyperintense, and T2/FLAIR hypointense. The converse is true for cysts with high water content**"; a cyst bright on CT and T1 and dark on T2/FLAIR "will be **more viscous and difficult to aspirate**" YW p.1236.

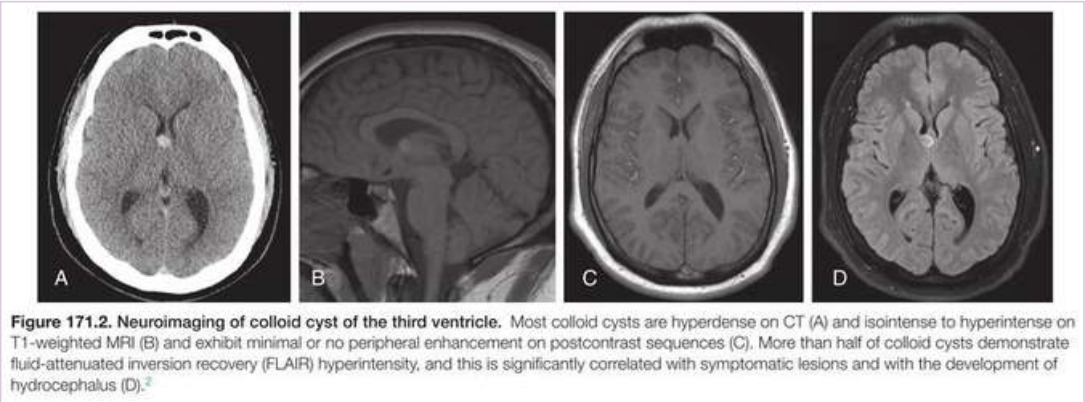


Figure 171.2. Neuroimaging of colloid cyst of the third ventricle. Most colloid cysts are hyperdense on CT (A) and isointense to hyperintense on T1-weighted MRI (B) and exhibit minimal or no peripheral enhancement on postcontrast sequences (C). More than half of colloid cysts demonstrate fluid-attenuated inversion recovery (FLAIR) hyperintensity, and this is significantly correlated with symptomatic lesions and with the development of hydrocephalus (D).[2]

Reproduced from Youmans & Winn 8e, Fig. 171.2, p. 1236 — Label when you reproduce it: (A) axial CT — hyperdense round mass at the foramen of Monro; (B) T1 — iso- to hyperintense; (C) post-contrast T1 — minimal or no peripheral enhancement; (D) FLAIR — hyperintensity, the feature correlated with symptomatic lesions and hydrocephalus. Note the dilated frontal horns pushed laterally.

- **Differential to name — meningioma, glioma (e.g. pilocytic astrocytoma), choroid plexus papilloma, ependymoma/subependymoma, third ventricular craniopharyngioma, blood products around the foramen of Monro, CSF flow artefact (MRI pseudocyst)**, and **aneurysm** when a spheroid lesion extends inferiorly into the third ventricle YW p.1236. **Calcification or avid enhancement argues against a colloid cyst** YW p.1236.

(b) Clinical features [3]

5. The natural history that generates the clinical picture

- **40% to 60% are asymptomatic at first diagnosis** YW p.1234.
- "The **vast majority** of incidentally discovered tumours **remain stable in size**, and a small proportion may **spontaneously regress**" YW p.1234.
- "**5% to 15% of patients will experience tumor progression within the 5 years after diagnosis**" YW p.1234.
- **46.2% (30/65) of symptomatic cysts had confirmed obstructive hydrocephalus** [YW pp. 1234-1235]; ventriculomegaly was present in **83% of symptomatic** but also **31% of asymptomatic** patients — "**the presence of**

ventriculomegaly should not be the sole criterion for surgery" YW p.1234.

- "The **risk of death in symptomatic patients was 3.1%**" YW p.1235.

6. Symptoms and signs

- **Who** — symptomatic patients are **younger, typically 30-40 years old**, than those found incidentally YW p.1234.
- **The list in Youmans' order** — "**headaches, nausea and/or vomiting, vision changes, dizziness or ataxia, and cognitive impairment**" YW p.1234.
- **Headache character** — "most commonly with **headache, often of a stuttering nature**", capable of causing "**rapid clinical deterioration from intracranial hypertension**" YW p.1734. The intermittent, positional nature follows directly from the **ball-valve** behaviour of a pedunculated cyst.
- **Mechanism** — "In most instances, neurological symptoms are **secondary to hydrocephalus caused by the cyst impeding CSF flow across the foramen of Monro**" YW p.1234. If **both foramina** are blocked, hydrocephalus is **biventricular** and both lateral ventricles must be drained [YW pp. 1238, 1734].
- **Memory and cognition** — cognitive impairment is a recognised presenting feature YW p.1234; the fornices flank the cyst, and forniceal injury causes **persistent short-term memory deficit** YW p.1240, with even unilateral injury capable of producing **anterograde amnesia** YW p.1222.
- **Generic intraventricular-mass presentation to fall back on** — symptoms arise from **(1) invasion of local structures, (2) raised ICP from the mass, (3) hydrocephalus**; in adults **headache, lethargy, nausea, memory loss, gait disorder, cognitive or mood changes**; in children, additionally **delayed developmental milestones or retarded growth**; in infants **increased head circumference, bulging fontanelle, distended scalp veins and failure to thrive**; and "**acute deterioration can occur by means of sudden CSF pathway obstruction or intralesional hemorrhage**" YW p.1203.

7. Acute decline and sudden death — three mechanisms and one number

- **Ball-valve theory (most widely accepted)** — a cyst "normally suspended on a pedicle that allows it to only **partially block CSF flow** (e.g., when lying down), may become **dislodged (e.g., by trauma) and fully occlude the foramen of Monro** (or rarely the aqueduct of Sylvius in the posterior third ventricle), leading to acute hydrocephalus" YW p.1235.
- **Intracystic haemorrhage** — acute expansion, or **vascular compromise and ischaemia of the anterior cerebral artery territory** YW p.1235.
- **Hypothalamic dysfunction** — Turillazzi's **10-year-old boy** died of cardiac arrest; autopsy showed the colloid cyst, brain oedema, ventriculomegaly and **coagulative myocytolysis with contraction band necrosis** in the heart, attributed to **sympathetic overstimulation and catecholamine myotoxicity** YW p.1235.
- **The prodrome** — death was "most frequently preceded by symptoms of **headache, nausea and/or vomiting, and decreased consciousness for a mean of 3.3 days**" YW p.1235; and **50% of patients presenting with acute hydrocephalus had new, progressively worsening symptoms over the prior 3 to 4 days** YW p.1237.
- **Autopsy series** — **83.3% ventriculomegaly, 72.2% cerebral oedema, 61.1% cerebral herniation** YW p.1235.
- **Precipitants** — "**head trauma or air travel**" YW p.1235.
- **Risk factors for precipitous decline** — **younger age, larger cyst (especially >8 mm), longer symptom duration, hydrocephalus** YW p.1235.
- **Risk factors for being symptomatic at all** — **cyst diameter ≥7 mm, cyst volume ≥180 mm³, larger Evans ratio, T2/FLAIR hyperintensity**; and **"all but one patient had a colloid cyst within the foramen of Monro at the anterior aspect of the third ventricle"** [YW pp. 1234-1235].

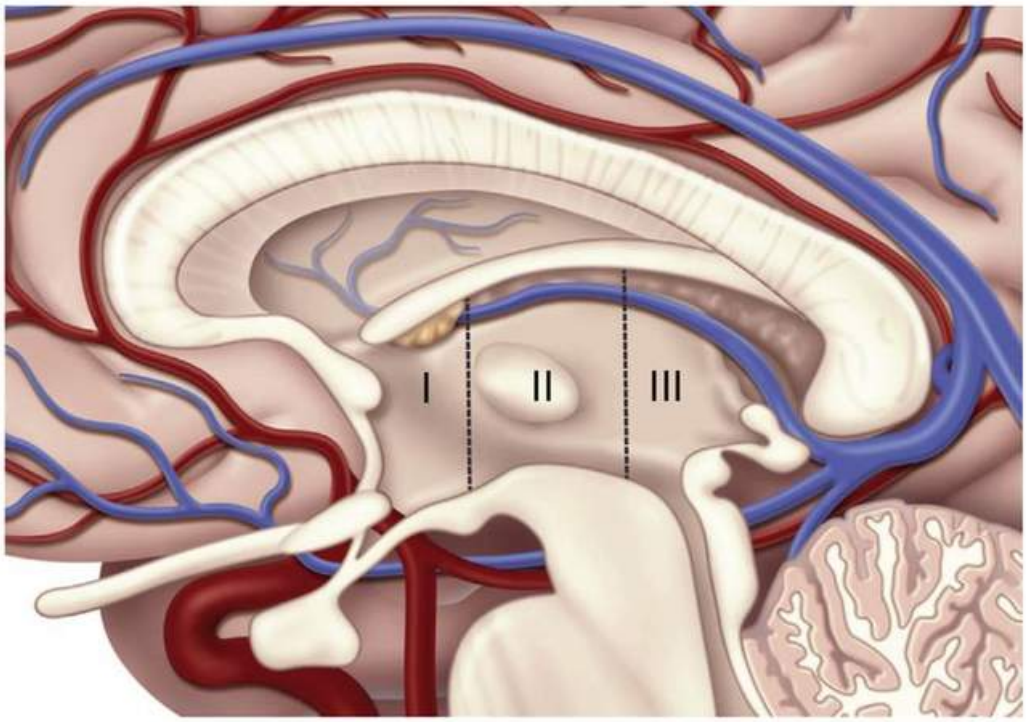


Figure 171.1. Anatomic risk zones for colloid cysts of the third ventricle. The third ventricle was divided into three zones along the sagittal axis. Zone I—from lamina terminalis to a vertical line drawn from the mammillary body and tangential to the massa intermedia; zone II—from the posterior boundary of zone I to the rostral apex of the midbrain tegmentum at the inlet of the cerebral aqueduct; zone III—from the posterior boundary of zone II to the posterior limit of the third ventricle. Zones I and III are referred to collectively as "risk zones." Lesions in zone II can be large and are rarely symptomatic.

Reproduced from Youmans & Winn 8e, Fig. 171.1, p. 1235 — Label when you reproduce it: the three sagittal zones of the third ventricle — zone I (lamina terminalis to a vertical line from the mammillary body tangential to the massa intermedia), zone II (to the rostral apex of the midbrain tegmentum at the aqueductal inlet) and zone III (to the posterior limit of the third ventricle). Mark zones I and III as the "risk zones"; note zone II lesions can be large yet are rarely symptomatic.

Table 1 · Colloid Cyst Risk Score and its performance — reproduced from Youmans & Winn 8e, Table 171.1 and text, p. 1235.

Criterion (1 point each)	Threshold
Age	**<65 years**
Headache	Present
Axial diameter	**≥7 mm**
FLAIR signal	**Hyperintense**
Anatomic risk zone	**Zone I or zone III**
Score ≥4	**High risk** for progression and symptoms — operate (20%-60% risk of obstructive hydrocephalus)
Score 3	**Intermediate** — may be observed in a reliable patient
Score ≤2	**Low risk** — surveillance imaging

Sensitivity / specificity for symptomatic cyst	**92% / 93%**
Sensitivity / specificity for hydrocephalus	**88% / 82%**
CCRS ≤1	**No** symptomatic cysts or hydrocephalus
CCRS 5	**96%** symptomatic, **60%** hydrocephalus
All patients presenting with hydrocephalus	**CCRS ≥4**

(c) Management [4]

8. Surgical anatomy — the five structures you must know before choosing a corridor

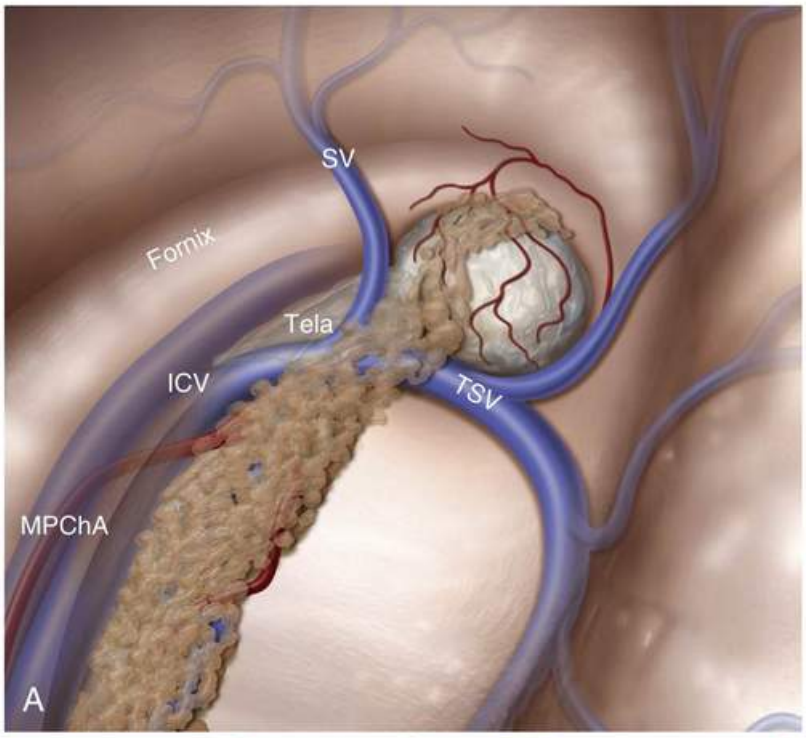


Figure 171.4. Critical neurovascular anatomy and potential attachment points for colloid cysts of the third ventricle.
(A) Critical structures include the fornix, internal cerebral veins *(ICV)*, septal veins *(SV)*, thalamostriate vein *(TSV)*, tela choroidea *(Tela)*, and choroid plexus. The medial posterior choroidal artery *(MPChA)* extends anteriorly and must be identified, particularly during resection of posteriorly positioned cysts. (B) The cyst is commonly invested with choroid plexus and intimately associated with the fornix, although nonadherent. A small penetrating artery extending from the fornix to the cyst can be present. (C) Cyst attachment points at the velum, deep draining veins, tela, and choroid must be carefully dissected to avoid vascular injury.

Reproduced from Youmans & Winn 8e, Fig. 171.4, p. 1238 — Label when you reproduce it: (A) fornix, internal cerebral veins (ICV), septal veins (SV), thalamostriate vein (TSV), tela choroidea, choroid plexus and the medial posterior choroidal artery (MPChA) coursing anteriorly; (B) the cyst invested with choroid plexus, intimately associated with but non-adherent to the fornix, with a small fornix-to-cyst penetrating artery; (C) the attachment points at the velum interpositum, deep draining veins, tela and choroid that must be dissected to avoid vascular injury.

- **The structures at risk** — "the **thalamus, the basal ganglia, cerebral veins, the fornix, and the velum interpositum**" YW p.1237.

- **Roof of the third ventricle has four layers** — "**the fornix, the two layers of tela choroidea, and the vasculature that runs between them**" YW p.1238.
- **Velum interpositum** — the **potential space between the two layers of tela choroidea**, lying **medially between the thalami and beneath the body of the fornix**, containing the **internal cerebral veins and medial posterior choroidal arteries**. "The internal cerebral veins form in the anterior velum at the foramen of Monro from a confluence of the **thalamostriate and anterior septal veins**. They run through the velum and **exit posteriorly above the pineal body into the quadrigeminal cistern**" YW p.1238.
- **The orienting landmark** — "the foramen of Monro can be located by **following the thalamostriate vein and the choroid plexus anteriorly until they join at the foramen**" YW p.1238. In the frontal horn the **septal vein runs medially along the septum pellucidum** toward the foramen; **the septal vein lies medial to the foramen of Monro and the thalamostriate vein lies lateral** [YW pp. 1205, 1214].
- **The venous angle** — the septal-thalamostriate junction forms a **"U-shape"** identifiable on angiogram or CT/MR venography, typically **3 to 7 mm posterior to the foramen of Monro**, with **the genu of the internal capsule immediately deep (lateral) to it** [YW pp. 1205-1206]. **"The septal vein may be safely transected proximal to its junction with the thalamostriate vein to allow for an expanded transforaminal route to the third ventricle"** YW p.1206.
- **Fornix** — crura wrap around the posterior thalamus toward the splenium, merge near the atrium-body junction into the **body of the fornix**, which **separates the floor of the bodies of the lateral ventricles from the roof of the third ventricle**; **the space between the two crura before their merger is the route by which a posterior cyst can extend above the roof of the third ventricle** [YW pp. 1237-1238].
- **During surgery** — "the body of the fornix may be **gently displaced to the contralateral side** to visualize the roof of the third ventricle and open the choroidal fissure in situations in which the foramen of Monro needs to be further opened" [YW pp. 1237-1238].

9. Decision making — the algorithm

- **Symptomatic cyst → surgery as soon as possible** after symptoms are identified YW p.1237.
- **Incidental cyst → surveillance imaging**, unless symptoms develop, ventriculomegaly appears or the cyst progresses YW p.1237.
- **The counter-view** — Margetis et al. argue for endoscopic resection of selected incidental cysts, especially in **younger patients or those with large cysts**, and report that operating on incidental cysts gave **greater GTR, lower recurrence, lower morbidity, shorter stay and less need for postoperative EVD** than operating on symptomatic ones YW p.1237.
- **The CCRS-based decision tree (Fig. 171.3)** YW p.1237:
  - **CCRS <3 → surveillance imaging.**
  - **CCRS 3 → reliable patient? yes → surveillance; no → surgery.**
  - **CCRS >3 → surgery.**
  - Within surgery: **small ventricles, T2-dark (firm, non-fluidic) contents, posterior pedicle → port-based MIS or microsurgery**; **ventriculomegaly, T2-bright contents, intraforaminal cyst → endoscopic, port-based MIS or microsurgery**.
- **Hyperacute management** — **immediate CT**, then, if acute hydrocephalus, **bilateral EVDs prior to surgery**, "most advisable in emergency situations when the patient is undergoing rapid and severe neurological decline, as EVD placement **can prevent herniation and death**"; but "EVD placement **may not improve a patient's neurological status to a significant degree and is not sufficient treatment**" YW p.1237.

10. Shunting — its place and its price

- **Who** — "VPS insertion is a viable option for patients who are **poor candidates for surgical resection**", as a **short-term bridge** or a **long-term** solution in those unwilling or unable to have resection; **particularly large or haemorrhagic cysts may require permanent VPS even after resection** YW p.1238.

- **Laterality** — **unilateral** if one foramen is obstructed; **bilateral** if both; or **unilateral VPS plus endoscopic septostomy** YW p.1238.
- **Why it is not the answer** — "**VPS placement does not address the cyst itself**, which may progress in size and cause further impediment to CSF flow **or hypothalamic dysfunction**. Accordingly, **shunting is not a recommended long-term option**", and it adds **infection, malfunction, later obstruction and revisions** YW p.1238.
- **The technical consequence** — later resection "may be rendered **more difficult by decreased ventricular size** from the shunt. Therefore placement of a **programmable valve, particularly one with a high-pressure setting or 'virtual off,' is helpful**" YW p.1238.

11. Aspiration — why it is no longer an option

- "Stereotactic aspiration... is a **suboptimal treatment strategy because it does not eliminate any part of the cyst capsule**. As a consequence, there is an **unacceptably high rate of cyst recurrence after aspiration (80%)**. Cyst aspiration has therefore been **abandoned in contemporary neurosurgery**" YW p.1240.
- Ch. 228 records the earlier figures — **50% to 80% recurrence**, sometimes **after years**, with technical limits of **neural and vascular injury, difficulty puncturing small thick-walled lesions and difficulty aspirating viscous contents** YW p.1734.

12. Microsurgical resection — steps in order

12.1 Interhemispheric transcallosal approach

- **Craniotomy** — lateral to the SSS, **ideally on the non-dominant side**, though **asymmetrical venous drainage may force a switch**; **two-thirds anterior, one-third posterior to the coronal suture**, and Ch. 170 adds it "should not need to be located more than **3-4 cm posterior of the coronal suture** to avoid injury to the motor cortex", with **two burr holes on either side of the SSS** to expose it fully [YW pp. 1214, 1238].
- **Dural opening** — **C-shaped with the pedicle toward the sinus**; spare bridging veins by **sharp microdissection**; **sutures in the superior falx just below the SSS rotate the sinus away** from the corridor — but avoid excessive tension or occlusion, which risks **sinus thrombosis** YW p.1214.
- **Interhemispheric dissection** — sharp microdissection of arachnoid bands; **cotton balls in the anterior and posterior recesses instead of fixed retractors**; "We **do not use retractors** because of the possibility of direct parenchymal or vascular injury" YW p.1214.
- **Landmarks going down** — the **callosomarginal artery** is met first and must not be mistaken for the deeper **pericallosal artery**; follow it proximally to the **A2 bifurcation**; adherent cinguli can masquerade as the callosum — "**gyri lack the classic white 'sheen' of the corpus callosum**" YW p.1214.
- **Callosotomy** — **posterior to the genu**, midline demarcated by a small callosal artery, confirmed with navigation; "**A 2-cm callosotomy is adequate for most intraventricular pathology**" YW p.1214.
- **Inside the ventricle** — orient on **(1) septal vein, (2) thalamostriate vein, (3) choroid plexus, (4) foramen of Monro**; **fenestrate the septum pellucidum** if more relaxation is needed; take care where **the thalamostriate vein turns medially toward the foramen, because the genu of the internal capsule lies just deep to the ventricular wall there** YW p.1214.
- **Widening the exposure** — "**it is preferable to open the choroidal fissure through the tenia fornicis**"; coagulate the choroid plexus and open the tenia **inferolateral to the body of the fornix and medial to the proximal internal cerebral vein**, preserving the **thalamostriate and septal venous confluence**. **"The surgeon should not section the fornix adjacent to the anterosuperior margin of the foramen."** YW p.1238.
- **Closure** — confirm resection with an **angled endoscope** before closing YW p.1214.

12.2 Transcortical transventricular approach

- **Indication** — "**more useful in patients with dilated ventricles** because it is challenging to traverse narrow lateral ventricles" YW p.1238.

- **Steps** — navigation-selected cortical entry giving the best angle to the cyst; **paramedian frontal craniotomy two-thirds anterior / one-third posterior to the coronal suture**; **1.5-cm corticotomy**; enter the ipsilateral frontal horn; **cottonoid with dynamic retraction using suction and bipolar**; then identical to the transcallosal route; **entering the third ventricle through the choroidal fissure is optimal as it spares the fornix and gives the best view of the third ventricular roof** [YW pp. 1238-1239].
- **Ch. 170's caution on where to enter the cortex** — "The **dominant-sided superior frontal gyrus houses the supplementary motor area and should not be used as a site for corticectomy**"; the commonest complications of the transfrontal approach in order are "**seizure, transient mutism, hemiparesis, short-term memory disturbance, abulia, and attention deficit**" [YW pp. 1215, 1214].

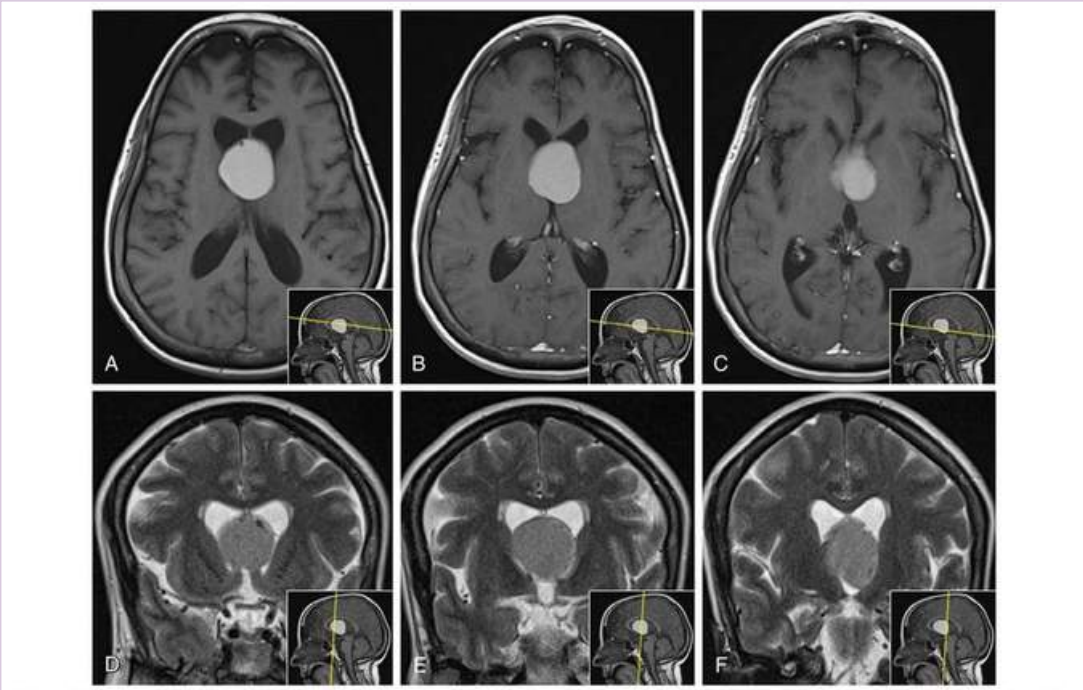


Figure 170.15. A 56-year-old female patient with recurrent episodes of intractable nausea and vomiting underwent a right transfrontal transforaminal approach with foraminoplasty for resection of a third ventricle colloid cyst (A–F).

*Reproduced from Youmans & Winn 8e, Fig. 170.15, p. 1222 — Label when you reproduce it: (A-F) the pre- and postoperative imaging of a 56-year-old woman with recurrent intractable nausea and vomiting who underwent a right transfrontal transforaminal approach **with foraminoplasty** for resection of a third-ventricular colloid cyst. Point out the cyst at the foramen of Monro, the ventriculomegaly, the transcortical trajectory and the postoperative resection cavity.*

12.3 The four techniques for entering the third ventricle from above

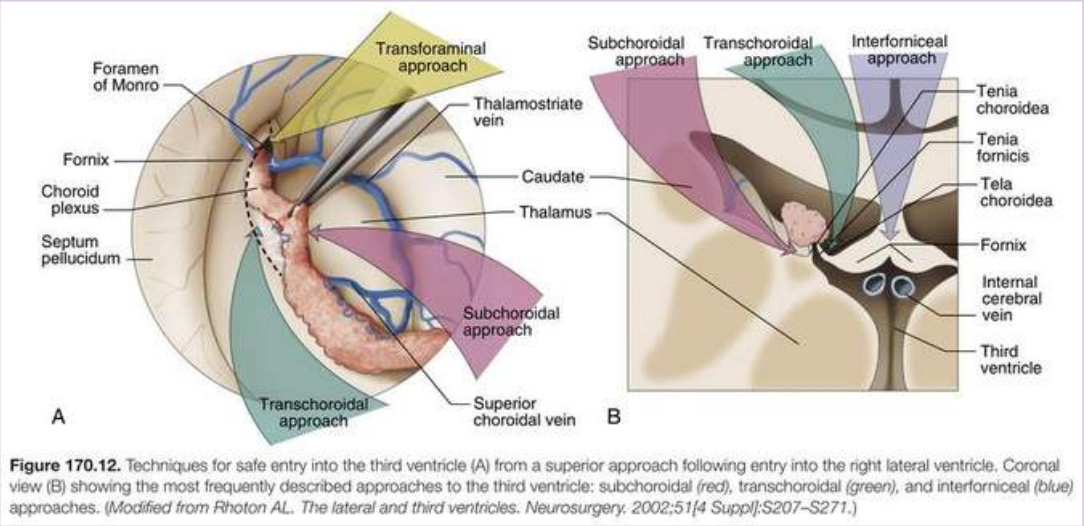


Figure 170.12. Techniques for safe entry into the third ventricle (A) from a superior approach following entry into the right lateral ventricle. Coronal view (B) showing the most frequently described approaches to the third ventricle: subchoroidal *(red)*, transchoroidal *(green)*, and interforniceal *(blue)* approaches. (*Modified from Rhoton AL. The lateral and third ventricles. Neurosurgery. 2002;51[4 Suppl]:S207–S271.*)

*Reproduced from Youmans & Winn 8e, Fig. 170.12, p. 1217 — Label when you reproduce it: (A) the superior view after entering the right lateral ventricle showing the foramen of Monro, thalamostriate vein, fornix, caudate, choroid plexus, thalamus, septum pellucidum and the tenia choroidea/tenia fornicis; (B) the coronal view showing the three routes — **subchoroidal (red), transchoroidal (green) and interforniceal (blue)** — with the internal cerebral vein and superior choroidal vein in the velum interpositum.*

- **Transforaminal** — uses the **widened foramen of Monro**; "the fornix **nearly completely encircles the foramen**, and care must be taken to minimize both traction and direct injury"; **even unilateral injury causes anterograde amnesia**. If wider exposure is needed, **foraminoplasty** is performed by **sacrificing the anterior septal vein** or **via the transchoroidal approach** YW p.1222.
- **Transchoroidal** — opens the **choroidal fissure** through the **tenia fornicis, medial to the choroid plexus**, then dissects **between the internal cerebral veins**. Two reasons to split between the ICVs: it **avoids the thalamostriate and choroidal veins running medially from the thalamus**, and **bridging veins between the two ICVs may be safely ligated without consequence**. The opening can run **from the foramen of Monro to the area immediately anterior to the pineal gland** YW p.1224.
- **Subchoroidal** — opens the **more lateral tenia choroidea**; the **thalamostriate vein, choroidal veins and medial posterior choroidal artery** must be navigated or sacrificed; further from the fornix but with a **theoretical increase in vascular injury**, and Bozkurt et al. showed it gives **more limited exposure** than the transchoroidal dissection YW p.1224.
- **Interforniceal** — described by **Busch in 1944**, based on Dandy and van Wagenen, and **first used successfully on a giant colloid cyst** that had displaced the fornices upward and thinned the median raphe. It gives **wide exposure but risks both forniceal bodies**. A **cavum septi pellucidi** provides the ideal corridor; if the leaves are fused the septum is fenestrated and coagulated down to the **midline raphe**. Starting between the two foramina of Monro, the raphe is opened **posteriorly for 1 to 1.5 cm** — "**further dissection posteriorly risks damaging the forniceal commissure**" YW p.1224.
- **A midline transcallosal route is safer for the fornix than a lateral transcortical one** — "Taking a midline interhemispheric transcallosal approach rather than a lateral transcortical approach provides a **less biased view and working angle to both sides of the ventricle**... thus reducing the risk for forniceal injury" and cognitive/memory loss YW p.1224. Correspondingly, Ch. 170 does "not typically couple [the transfrontal] approach with the interforniceal technique as we believe it **increases the risk for forniceal injury given the lateral-to-medial operative trajectory**" YW p.1222.

Table 2 · The four superior routes into the third ventricle — access, advantage, disadvantage and risk. Reproduced from Youmans & Winn 8e, Table 170.3, pp. 1218-1219, with technical detail from pp. 1222-1224.

Technique	Region reached	Advantage	Disadvantage	Risk

Transforaminal (transcallosal or transfrontal)	Anterior third ventricle	Uses the natural opening; **anterior septal vein can be sacrificed to widen access**	Limited working space through the foramen	**Short-term memory loss from forniceal injury**
Transforaminal transchoroidal	Anterior + posterior	**Extensive access to the third ventricle**; spares the fornix; bridging veins between the ICVs can be ligated	Requires dissection between the internal cerebral veins	Deep venous drainage (especially ICVs) and fornix
Transforaminal subchoroidal	Anterior + posterior	Extensive access; further from the fornix	**Increased risk to the thalamostriate and superior choroidal veins**; more limited exposure than transchoroidal	Thalamostriate, superior choroidal and internal cerebral veins; fornix
Interforniceal (transcallosal)	Anterior + posterior	Extensive midline access; ideal when a cavum septi pellucidi exists or a giant cyst has splayed the fornices	**Increased risk to both fornices** ; raphe may be opened only 1-1.5 cm	Deep venous drainage and **bilateral** forniceal injury

13. Endoscopic resection — the contemporary first choice for the right cyst

- **Why** — **minimally invasive, low morbidity and mortality**, and widespread adoption of intraventricular endoscopy; "**significantly reduced rate of complications** compared with conventional microsurgical resection", with **shorter operative times, shorter hospital stay, reduced overall costs and increased patient comfort**; shunt dependency **similar or lower** than after microsurgery YW p.1239.
- **The price** — "a **significantly increased rate of residual cyst wall** after endoscopic resection that may be associated with **increased cyst recurrence on long-term follow-up**"; endoscopic resections have "significantly **fewer gross total resections and greater residual cyst**", and greater residual drives **recurrence and reoperation**, "although cyst recurrences may remain asymptomatic" YW p.1239.
- **Scope** — **rigid** scopes give superior optics and field of view, are easier to orient, come as **0-, 30- and 70-degree** lenses and may have **multiple working channels for bimanual technique**; **flexible** scopes bend in three axes and navigate better but have **inferior optics and limited instrumentation**, and "retracting a bent scope may cause damage to surrounding structures" YW p.1239.
- **Bur holes — the two numbers** YW p.1239:
  - **Transforaminal: ~4 cm lateral to midline, 4 cm anterior to the coronal suture.**
  - **Transseptal: ~6 cm lateral to midline, 4 cm anterior to the coronal suture.**
  - Fig. 171.5 quotes the single-bur-hole variant: **~4 cm lateral to midline, 5 cm anterior to the coronal suture, ≈8 cm posterior to the nasion**, finalised with neuronavigation.
  - The trajectory must **avoid the head of the caudate nucleus** and reach the anterior horn; "**frameless stereotactic neuronavigation is essential**".
- **Selecting the route** — **transforaminal for cysts obviously protruding through the foramen**; **transseptal when the cyst occludes the foramen and cannot be reached transforaminally — the cyst is then approached through the septum pellucidum**; "**larger cysts typically necessitate the transseptal approach**" YW p.1239.
- **Technique** — **en bloc removal is possible but often not feasible**; otherwise **coagulate and fenestrate the wall, evacuate contents with a large-bore cannula or endoscopic suction-morcellation device, then sharply dissect the capsule bimanually, piecemeal, with extreme care around the confluence of the internal cerebral, thalamostriate and septal veins**; a relentlessly adherent portion is **thoroughly coagulated** rather than avulsed YW p.1239.
- **Ch. 228's practical nuances** — a **more lateral and anterior bur hole than a standard shunt bur hole** gives a **face-on view of the cyst surface in the foramen**; **shrink the wall by coagulation first**; **avoid traction on the capsule** , since bleeding from partially avulsed vessels in the roof of the third ventricle is hard to control and rapidly obscures the view, and **traction on the fornices confers significant morbidity**; **continuous warm irrigation** for oozing, **focal bipolar or laser coagulation** for brisk bleeding; **fenestrate the septum pellucidum** to ensure inter-ventricular

communication YW p.1734.

- **When endoscopy will not reach** — "alternative routes such as the **subfrontal translamina terminalis approach** may be necessary for **posteriorly located lesions obscured by the roof of the third ventricle**", or an **endoscopic transforaminal transchoroidal approach**, which "provides better visualization of the tela choroidea and increases resection of more posteriorly located colloid cysts" YW p.1734. A pragmatic strategy is to **attempt ventriculoscopic resection first and convert the bur hole to a small craniotomy** if it fails YW p.1734.

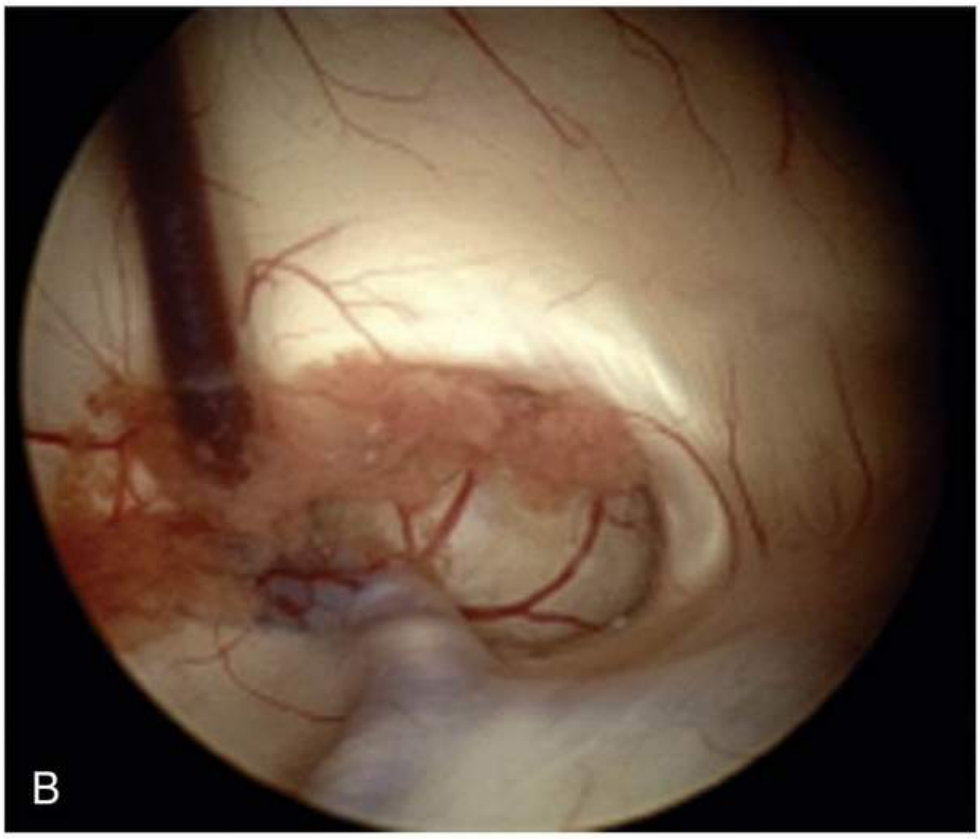


Figure 228.5. (A) Illustration of ventriculoscopic resection of colloid cyst. (B) Cyst visible through the right foramen of Monro.

Reproduced from Youmans & Winn 8e, Fig. 228.5, p. 1735 — Label when you reproduce it: (A) the illustration of ventriculoscopic colloid cyst resection showing grasping forceps in one working channel and the laser/coagulating fibre in the other; (B) the endoscopic view of the cyst presenting through the right foramen of Monro with the choroid plexus, thalamostriate vein and fornix as landmarks.

14. Port-based microsurgery, and conversion

- **Port-based (SEP)** — for cysts needing "an especially **wide operative corridor**" for the microscope. **Stereotactically guided endoscopic port surgery**, first described in **2004** using a repurposed **thoracic tubular port**, modified instruments and a stereotactic frame with a mounted endoscope; it "**provided the dexterity of traditional open surgery while preserving the minimally invasive nature of endoscopic surgery**", and in the original series **12 of 12 colloid cysts had gross total resection without postoperative complications** YW p.1240.
- **Conversion to open** — driven by **adhesion of the cyst to surrounding structures**; "In one series of **35 endoscopic colloid cyst excisions, six cases were converted to open resection because of cyst adhesion to the fornix**" YW p.1239 . Osorio et al. compared purely endoscopic with converted cases: **0% vs 78% complete capsule removal**, with **no significant difference in postoperative complications**, and an **open transcortical transventricular approach functioned well as the salvage procedure** [YW pp. 1239-1240].

15. Complications and how to avoid them

- **Core list** — "**seizures, memory deficits, hemorrhage or hematoma, infarction, meningitis, CSF leak, or motor deficits**" YW p.1240; Ch. 228 adds **venous infarction, IVH, hemiparesis and death**, plus **aseptic meningitis from release of cyst contents** YW p.1735.
- **Fornix** — forniceal damage at the foramen causes **persistent short-term memory deficit** YW p.1240.
- **Deep veins** — ICV and thalamostriate injury may cause **thalamic infarction** YW p.1240.
- **Interhemispheric route** — **SSS or cortical vein injury → venous infarction**; retraction of **SMA / leg motor area → SMA syndrome or isolated contralateral monoparesis**; **pericallosal artery injury** when exposing the callosum YW p.1240.
- **Transcortical route** — a contested but often-quoted **higher seizure rate** YW p.1240.
- **Endoscopic route** — "the proper **trajectory is paramount** to avoiding structural damage to the **fornix and caudate nucleus**"; with single-working-channel scopes, **avoid blunt dissection and aggressive traction on the capsule** YW p.1240.
- **Comparative evidence to quote** — endoscopic vs microscopic give **similar shunt dependency with a trend to lower morbidity for endoscopy**; a **microscopic transcallosal** approach may cause **fewer neurological complications than a transcortical endoscopic** approach with similar resection rates; but **microsurgery achieves significantly higher GTR and lower recurrence** YW p.1735.
- **Follow-up** — recurrence after aspiration or subtotal resection may be **delayed by years**, "**demanding long-term follow-up of these patients**" YW p.1734.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Definition in one line**: a benign, foregut-endoderm-derived, epithelium-lined mucinous cyst of the anterosuperior third ventricle at the foramen of Monro; **1%-2% of intracranial tumours; 3.2 per million per year**.
- **Not from the paraphysis, and not choroid plexus** — immunohistochemically like Rathke cleft, follicular pituitary and neurenteric cysts.
- **Lining: pseudostratified/columnar/cuboidal epithelium with ciliated cells and goblet cells; capsule of fibroblasts, collagen and arachnoid cells.**
- **>99% sit at the foramen of Monro, straddled by the columns of the fornix and invested by choroid plexus but not adherent to the fornix.**
- **Symptomatic patients are 30-40 years old**; headache (often stuttering), nausea/vomiting, visual change, dizziness/ataxia, cognitive impairment.
- **Ball-valve obstruction on a mobile pedicle** explains positional headache and sudden deterioration; trauma and air travel are recorded precipitants.
- **The fatal cyst gives a 3.3-day prodrome**; 83.3% of autopsies show ventriculomegaly, 72.2% oedema, 61.1% herniation; **3.1% mortality once symptomatic**.
- **CCRS ≥4 → operate; 3 → observe only a reliable patient; ≤2 → image and watch.** No patient with CCRS ≤1 had symptoms or hydrocephalus.
- **Roof of the third ventricle = fornix + two layers of tela choroidea + the vessels between them (velum interpositum: ICVs and medial posterior choroidal arteries).**
- **Find the foramen by following the thalamostriate vein and choroid plexus anteriorly to their junction.** Septal vein medial, thalamostriate lateral; venous angle 3-7 mm behind the foramen with the internal capsule genu just deep to it.
- **Foraminoplasty: sacrifice the anterior septal vein, or go transchoroidal** — Türe showed the venous confluence is often further posterior than the classic description, so plan the side from venography.
- **Transchoroidal (tenia fornicis, medial to the plexus) is preferred over subchoroidal (tenia choroidea)** — better exposure and less venous risk.
- **Interforniceal raphe may be split only 1-1.5 cm** before the forniceal commissure is at risk; it was Busch's 1944 answer to a giant colloid cyst.
- **Bur holes: 4 cm lateral / 4 cm anterior = transforaminal; 6 cm lateral / 4 cm anterior = transseptal.** Large cysts

need transseptal.

- **Aspiration has an 80% recurrence rate and is abandoned. Shunting treats the hydrocephalus, not the cyst** — and use a programmable "virtual off" valve if you must shunt before resecting.
- **Endoscopy: lower morbidity, more residual, more recurrence. Microsurgery: higher GTR, less recurrence.** Six of 35 endoscopic cases needed conversion for forniceal adhesion; conversion lifted complete capsule removal from 0% to 78%.

Pages read for this answer — Youmans & Winn 8e: 1203, 1204, 1205, 1206, 1214, 1215, 1222, 1224, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1734, 1735

a) Third ventricular colloid cyst histology. [3]
b) Surgical approaches to colloid cyst. [5]
c) Differential diagnosis of cystic lesions of ventricles. [2]

LONG | OCT 2023 · Paper I · Q3 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 171 *Colloid Cysts of the Third Ventricle*, §Histogenesis, §Neuroimaging for Colloid Cysts (incl. §Diagnostic Algorithm), §Surgical Anatomy, §Surgical Approaches (Shunting, Microsurgical Resection, Endoscopic Resection, Conversion From Endoscopic to Open Resection, Port-Based Microsurgical Resection, Cyst Aspiration), §Complications and Pitfalls, pp. 1234-1240 (Figs. 171.2, p. 1236; 171.4, p. 1238; 171.5, p. 1239). Ch. 170 *Ventricular Tumors*, §General Epidemiology and Classification, §Surgical Anatomy, §Surgery of the Third Ventricle, §Transforaminal/Transchoroidal/Subchoroidal/Interforniceal Techniques, §Intraventricular Tumor Pathology (Epidermoid and Dermoid Cysts), pp. 1203-1206, 1214-1219, 1222-1224, 1230-1232 (Figs. 170.12, p. 1217; 170.16, p. 1223; Table 170.1, p. 1204; Table 170.3, pp. 1218-1219). Supplementary: Ch. 228 *Neuroendoscopy*, §Colloid Cysts and §Arachnoid Cysts, pp. 1734-1735 (Fig. 228.5, p. 1735). Ch. 164 *Pineal Tumors*, §Pathology — benign pineal cysts, p. 1148. Ch. 240 *Cerebellar Astrocytomas*, §Imaging Features, p. 1820. Ch. 59 *Parasitic Infections*, §Neurocysticercosis — Pathology, p. 435.e4.

(a) Third ventricular colloid cyst — histology [3]

1. Histogenesis — where the epithelium comes from

- **Normal development that sets the scene** — the neural tube closes in the **fourth week of gestation**; in the **fifth week** the prosencephalon divides into telencephalon and diencephalon, whose cavities become the **lateral and third ventricles**; "**the foramen of Monro develops at the interface of these ventricles**" YW p.1234. Colloid cysts arise exactly there.
- **The obsolete paraphysis theory** — older work proposed a **neuroectodermal** origin from the **paraphysis**, "a neuroectodermally derived structure that temporarily develops at the border of the telencephalon and diencephalon **during week 7 of gestation** and subsequently involutes into choroidal vesicles". The paraphysis arises from the **paraphyseal arch**, which is incorporated into the **roof of the third ventricle**, so persistent remnants were held to form the cyst YW p.1234.
- **The accepted theory** — "after more intensive study of this topic, it is now widely believed that **cysts arise from ectopic foregut endoderm and not the paraphysis**" YW p.1234. This is why the cyst behaves like a mucus-secreting, ciliated respiratory/enteric-type structure rather than like ependyma.

2. Microscopic appearance — write these four lines

- **Epithelial lining** — "The cysts may be lined with a variety of **pseudostratified, columnar, or cuboidal epithelial cells** in addition to **ciliated columnar epithelium and goblet cells**" YW p.1234. The combination of **cilia plus mucin-secreting goblet cells** is the pathognomonic histological pair.
- **Capsule** — "The cyst capsule is formed by **fibroblasts, collagen, and arachnoid cells**" YW p.1234. This is the layer that has to be excised or thoroughly coagulated to prevent recurrence, and the layer that becomes adherent to the deep veins.

- **Cyst contents** — "**gelatinous, mucinous fluid** that results from the **internal secretory epithelium and epithelial breakdown** and consists of **CSF, blood products, and cholesterol or lipids**" YW p.1236. The cholesterol/lipid fraction determines viscosity, which in turn determines both the imaging signal and whether the lesion can be aspirated — the contents may be **"firm and keratin-like"** YW p.1236.
- **Relations at the light-microscopic/gross interface** — "The cyst is commonly **invested with choroid plexus** and intimately associated with the fornix, **although nonadherent**. A small **penetrating artery extending from the fornix to the cyst can be present**" YW p.1238.

3. Immunohistochemistry — the two comparisons that matter

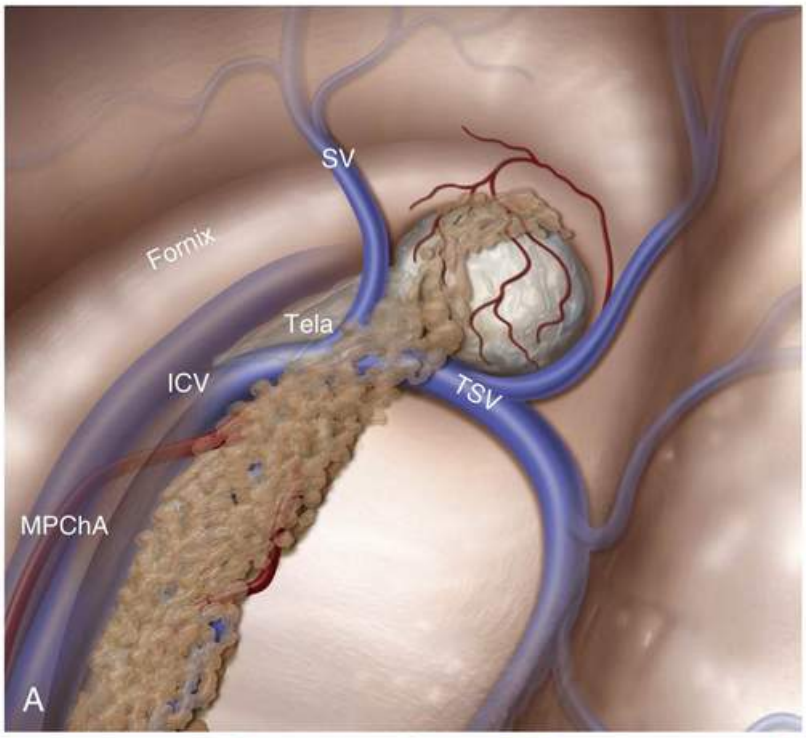
- **Positive comparison** — "Immunohistochemically, colloid cysts are **very similar to Rathke cleft cysts, follicular pituitary gland cysts, and neurenteric cysts**" YW p.1234. All are endodermally derived, mucin-producing, ciliated-epithelium-lined cysts: this is the internal evidence for the foregut hypothesis.
- **Negative comparison — the discriminator** — "The epithelial lining of colloid cysts **shares few immunohistochemical properties with choroid plexus epithelium**" YW p.1234. Despite being wrapped in choroid plexus and lying on the tela choroidea, the colloid cyst is **not** a choroid plexus derivative — which also separates it from choroid plexus cyst and choroid plexus papilloma, both of which express **cytokeratins, vimentin, KIR7.1 and transthyretin** with variable **S100** YW p.1231.
- **Grade and behaviour** — benign; Youmans classifies it under "**Other lesions and cysts**", location **third ventricle**, with no WHO grade assigned YW p.1204.

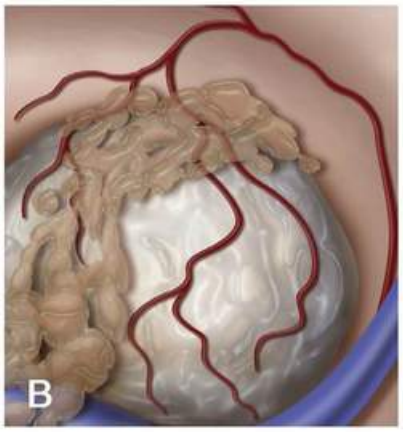
Table 1 · Histology of the colloid cyst against the cysts it is confused with — from Youmans & Winn 8e, Ch. 171 pp. 1234, 1236; Ch. 170 pp. 1231-1232, Table 170.1, p. 1204.

Cyst	Lining	Contents	Immunohistochemistry / key feature
Colloid cyst	Pseudostratified, columnar or cuboidal epithelium; **ciliated columnar cells and goblet cells**; capsule of fibroblasts, collagen, arachnoid cells	Gelatinous mucinous fluid: CSF, blood products, cholesterol/lipids	Like **Rathke cleft, follicular pituitary and neurenteric cysts**; **few shared markers with choroid plexus epithelium**
Rathke cleft cyst	Ciliated cuboidal/columnar epithelium	Mucoid; may contain a T1-bright intracystic nodule of **mucinous material** (the origin of the "dot sign" analogy)	Immunophenotypically similar to colloid cyst; suprasellar location
Epidermoid cyst	**Anucleate squamous epithelium, no skin adnexae or hair**	Creamy, waxy, **pearly-white keratin sheets**	**Keratin and EMA positive**; **restricts diffusion** (arachnoid cyst does not)
Dermoid cyst	Fibrous wall with **keratinising squamous epithelium including skin adnexa**, squamous cells, **hair and sebum**	Greasy pilosebaceous material; **hair shafts seen under polarised light**	Keratin and EMA positive; foreign-body giant-cell reaction if ruptured
Choroid plexus papilloma	Papillary structures with a **delicate fibrovascular core lined by columnar/cuboidal epithelium with vesicular basal nuclei**	Solid tumour, not a cyst	**Cytokeratins, vimentin, KIR7.1, transthyretin**; S100 variable (its presence a favourable prognostic factor)
Arachnoid cyst	Arachnoid membrane (split leaves)	Clear CSF-identical fluid	**No diffusion restriction**; isointense to CSF on every sequence

(b) Surgical approaches to colloid cyst [5]

4. Surgical anatomy — what dictates every approach





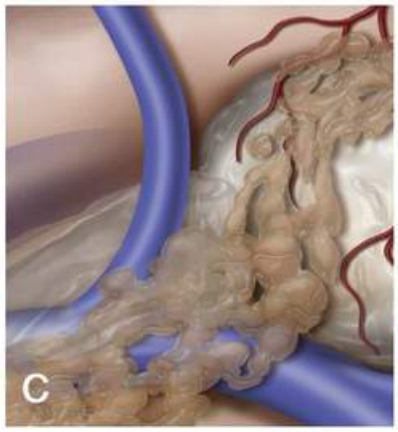


Figure 171.4. Critical neurovascular anatomy and potential attachment points for colloid cysts of the third ventricle. (A) Critical structures include the fornix, internal cerebral veins *(ICV)*, septal veins *(SV)*, thalamostriate vein *(TSV)*, tela choroidea *(Tela)*, and choroid plexus. The medial posterior choroidal artery *(MPChA)* extends anteriorly and must be identified, particularly during resection of posteriorly positioned cysts. (B) The cyst is commonly invested with choroid plexus and intimately associated with the fornix, although nonadherent. A small penetrating artery extending from the fornix to the cyst can be present. (C) Cyst attachment points at the velum, deep draining veins, tela, and choroid must be carefully dissected to avoid vascular injury.

Reproduced from Youmans & Winn 8e, Fig. 171.4, p. 1238 — Label when you reproduce it: (A) fornix, internal cerebral veins (ICV), septal veins (SV), thalamostriate vein (TSV), tela choroidea, choroid plexus, and the medial posterior choroidal artery (MPChA) running anteriorly — the artery that must be identified for posteriorly placed cysts; (B) the cyst invested with choroid plexus and intimately associated with but non-adherent to the fornix, with a small fornix-to-cyst penetrating artery; (C) the attachment points at the velum interpositum, the deep draining veins, the tela and the choroid that must be dissected to avoid vascular injury.

- **Position of the lesion** — "Colloid cysts are usually found in the **anterosuperior aspect of the third ventricle, encroaching on or projecting through the foramen of Monro, straddled by the columns of the fornix**. They can on occasion **grow above the roof of the third ventricle**. **The septum pellucidum sometimes must be traversed to**

access the cyst" YW p.1237.

- **The structures at risk** — "**the thalamus, the basal ganglia, cerebral veins, the fornix, and the velum interpositum** " YW p.1237.
- **The roof of the third ventricle — four layers** — **the fornix, two layers of tela choroidea, and the vasculature between them** YW p.1238.
- **Velum interpositum** — the **potential space between the two layers of tela choroidea**, lying **between the thalami and beneath the body of the fornix**, containing the **internal cerebral veins and the medial posterior choroidal arteries**; the ICVs form in the anterior velum at the foramen of Monro from the **confluence of the thalamostriate and anterior septal veins** and **exit posteriorly above the pineal body into the quadrigeminal cistern** YW p.1238.
- **Venous rules** — "These veins should be **located prior to passing through the choroidal fissure**"; **superior choroidal veins** pass through the choroid plexus of the third ventricle and **thalamostriate veins** pass through the **posterior foramen of Monro** in the roof of the third ventricle; **large cysts growing above the roof may become adherent to these veins** YW p.1237.
- **The venous angle** — septal + thalamostriate = internal cerebral vein, a **"U-shape"** on venography, **3-7 mm posterior to the foramen of Monro**, with the **genu of the internal capsule immediately deep (lateral)** to it; "**the septal vein may be safely transected proximal to its junction with the thalamostriate vein to allow for an expanded transforaminal route**" [YW pp. 1205-1206].
- **Fornix** — the body of the fornix **separates the floor of the bodies of the lateral ventricles from the roof of the third ventricle**; the **interval between the two crura** is how a posterior cyst reaches above the roof; intraoperatively the **body of the fornix may be gently displaced to the contralateral side** to see the third ventricular roof [YW pp. 1237-1238].

5. The full menu of approaches, in order

5.1 CSF diversion alone (not a definitive approach)

- **Bilateral EVDs** before surgery in the acutely decompensating patient — it "**can prevent herniation and death**", but "is **not sufficient treatment** for symptomatic colloid cysts; it is merely to help stabilize the patient before surgery" YW p.1237.
- **VP shunt** for poor surgical candidates, as a bridge, or long-term in those unwilling/unable to have resection; **unilateral if one foramen is obstructed, bilateral if both, or unilateral plus endoscopic septostomy**; large or haemorrhagic cysts may need a permanent shunt even after resection YW p.1238.
- **Why it is not curative** — "**VPS placement does not address the cyst itself**, which may progress in size and cause further impediment to CSF flow or **hypothalamic dysfunction**. Accordingly, **shunting is not a recommended long-term option**" YW p.1238. It also **shrinks the ventricles and makes later resection harder**, hence the advice to use a **programmable valve at a high-pressure setting or "virtual off"** YW p.1238.

5.2 Stereotactic aspiration — historical

- "**it does not eliminate any part of the cyst capsule**. As a consequence, there is an **unacceptably high rate of cyst recurrence after aspiration (80%)**. Cyst aspiration has therefore been **abandoned in contemporary neurosurgery and no longer represents an acceptable treatment option**" YW p.1240. Ch. 228 quotes **50%-80% recurrence**, sometimes **after years**, plus the technical problems of **neural and vascular injury, thick-walled small cysts and viscous contents** YW p.1734.

5.3 Open microsurgery — interhemispheric transcallosal

- **Side and craniotomy** — lateral to the SSS, **ideally non-dominant**, though **asymmetrical venous drainage may force a switch of sides**; **two-thirds anterior and one-third posterior to the coronal suture** YW p.1238; Ch. 170 adds the craniotomy "should not need to be located more than **3 to 4 cm posterior of the coronal suture** to avoid injury to the motor cortex", with **two bur holes either side of the SSS** so the sinus is fully exposed YW p.1214.
- **Dural opening** — **C-shaped with the pedicle toward the sinus**; **sharp microdissection of bridging veins**; **falx sutures below the SSS** rotate the sinus away, but avoid tension that could **thrombose it** YW p.1214.

- **Corridor** — sharp release of arachnoid bands so the hemisphere falls from the falx; **cotton balls in the recesses**, flat patties over the mesial cortex, **no fixed retractors** ("because of the possibility of direct parenchymal or vascular injury and the slightly more restrictive view") YW p.1214.
- **Traps on the way down** — the **callosomarginal artery** appears before the cingulate gyrus and must not be confused with the **pericallosal**; adherent cingulate gyri can be mistaken for the corpus callosum, but "**gyri lack the classic white 'sheen' of the corpus callosum**" YW p.1214.
- **Callosotomy** — **posterior to the genu**, midline marked by a small callosal artery, navigation-confirmed; "**A 2-cm callosotomy is adequate for most intraventricular pathology**" YW p.1214.
- **Orientation inside** — **septal vein, thalamostriate vein, choroid plexus, foramen of Monro**; septal vein **medial**, thalamostriate **lateral**; the **septum pellucidum can be fenestrated** for further relaxation; where the thalamostriate turns medially, the **genu of the internal capsule lies just deep to the ventricular wall** YW p.1214.
- **Enlarging the corridor** — "**it is preferable to open the choroidal fissure through the tenia fornicis**", coagulating choroid plexus and opening the tenia **inferolateral to the body of the fornix and medial to the proximal internal cerebral vein** so as to preserve the **thalamostriate/septal venous confluence**; and "**the surgeon should not section the fornix adjacent to the anterosuperior margin of the foramen**" YW p.1238.
- **Chief risks** — SSS/cortical vein injury with **venous infarction**; **SMA syndrome or isolated contralateral monoparesis** from retraction; **pericallosal artery injury**; **abulia** from cingulate injury; **disconnection syndrome** if the genu or splenium is divided [YW pp. 1211, 1240].

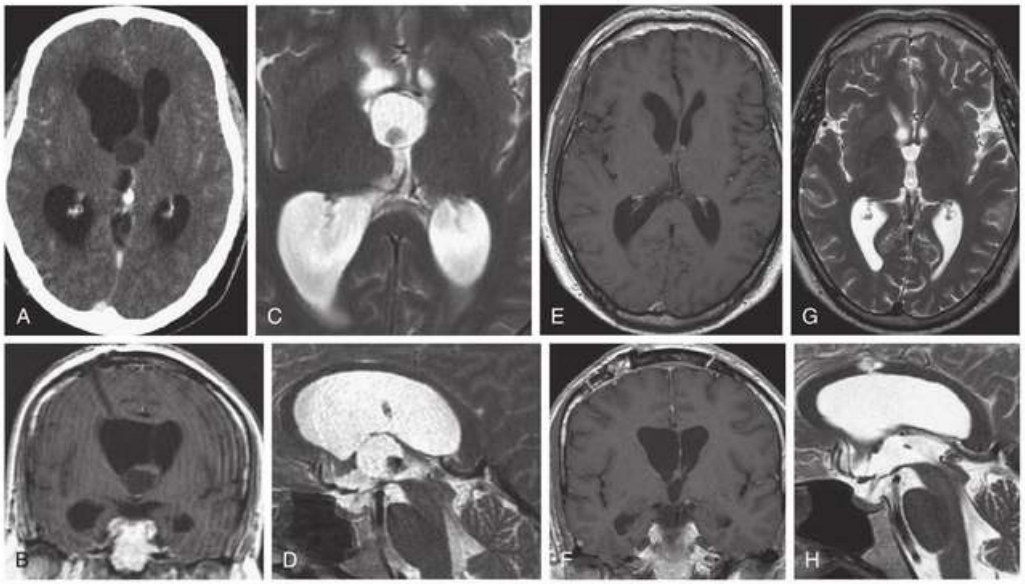


Figure 170.16. A 51-year-old male patient was admitted on an emergency basis for obstructive hydrocephalus, as seen on preoperative CT scans (A–B). Initially, an external ventricular drain was placed to release the raised intraventricular pressure. Preoperative T2-weighted MR images in the axial plane (C) and sagittal plane (D) show a large colloid cyst within the third ventricle obstructing the foramen of Monro. Complete removal of the colloid cyst was achieved microsurgically via the right frontal interhemispheric transcallosal approach and confirmed on postoperative T1-weighted MR images (E–F) and T2-weighted MR images (G–H). The patient's postoperative course was entirely uneventful.

Reproduced from Youmans & Winn 8e, Fig. 170.16, p. 1223 — Label when you reproduce it: (A-B) emergency preoperative CT showing obstructive hydrocephalus (an EVD was placed first to relieve the raised intraventricular pressure); (C) axial and (D) sagittal T2 MRI showing the large colloid cyst obstructing the foramen of Monro; (E-H) postoperative T1 and T2 images after complete microsurgical removal via the right frontal interhemispheric transcallosal approach.

5.4 Open microsurgery — transcortical transventricular

- **Indication** — "**more useful in patients with dilated ventricles** because it is challenging to traverse narrow lateral ventricles" YW p.1238.
- **Steps** — navigation selects the cortical incision giving the best angle to the cyst; **paramedian frontal craniotomy two-thirds anterior / one-third posterior to the coronal suture**; **1.5-cm corticotomy**; enter the ipsilateral frontal horn; **cottonoid plus dynamic retraction with suction and bipolar**; thereafter identical to the transcallosal route, and "**entering the third ventricle through the choroidal fissure is optimal, as it spares the fornix**" and "provides the best

view into the third ventricular roof" [YW pp. 1238-1239].

- **Where not to enter the cortex** — the **dominant superior frontal gyrus houses the supplementary motor area and must not be used** YW p.1215; the commonest complications in order are **seizure, transient mutism, hemiparesis, short-term memory disturbance, abulia, attention deficit** YW p.1215.
- **The unresolved controversy** — "Some surgeons have contended that the risk of seizures after **transcortical** approaches to the ventricle is **higher** than with interhemispheric approaches, **but this is controversial**" YW p.1240.

5.5 The four ways into the third ventricle once you are in the lateral ventricle

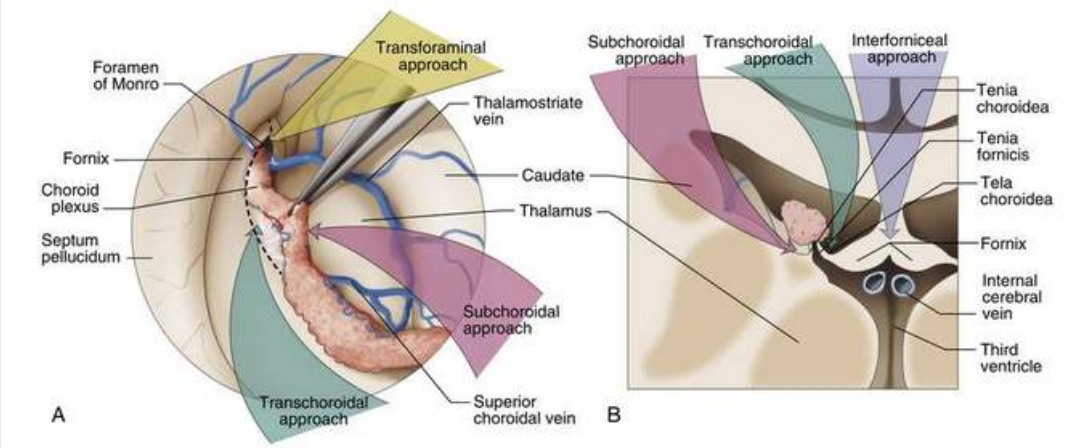


Figure 170.12. Techniques for safe entry into the third ventricle (A) from a superior approach following entry into the right lateral ventricle. Coronal view (B) showing the most frequently described approaches to the third ventricle: subchoroidal *(red)*, transchoroidal *(green)*, and interforniceal *(blue)* approaches. (*Modified from Rhoton AL. The lateral and third ventricles. Neurosurgery. 2002;51[4 Suppl]:S207–S271.*)

*Reproduced from Youmans & Winn 8e, Fig. 170.12, p. 1217 — Label when you reproduce it: (A) the superior view after entering the right lateral ventricle — foramen of Monro, thalamostriate vein, fornix, caudate, choroid plexus, thalamus, septum pellucidum, tenia choroidea and tenia fornicis, with the subchoroidal and transchoroidal routes marked; (B) the coronal view naming the three corridors — **subchoroidal (red), transchoroidal (green) and interforniceal (blue)** — with the internal cerebral vein and superior choroidal vein inside the velum interpositum.*

- **Transforaminal** — exploits a **widened foramen of Monro**; "the **fornix nearly completely encircles the foramen**, and care must be taken to minimize both traction and direct injury to this structure. **Even unilateral injury has been shown to cause anterograde amnesia**". Used for **cysts of the third ventricular roof** and those amenable to **debulking or early fenestration** so the remnant can be delivered through the natural orifice. Where wider exposure is needed, **foraminoplasty**: either **sacrifice the anterior septal vein** or **go transchoroidal** YW p.1222. Türe et al. showed the **septal/thalamostriate/ICV junction is frequently further posterior than the classic description**, allowing **foraminoplasty without venous sacrifice**, and advised **choosing the side from preoperative venography** YW p.1224.
- **Transchoroidal** — described by **Wen et al. in 1998**; uses the **choroidal fissure**, the natural cleft between thalamus and fornix, releasing **medial to the choroid plexus via the tenia fornicis**; then **dissection between the internal cerebral veins**, for two reasons: it **avoids the thalamostriate and choroidal veins** running medially from the thalamus, and **bridging veins between the two ICVs may be safely ligated without consequence**. Dissection continues through the second layer of tela choroidea and the choroid plexus of the third ventricular roof; the opening can extend **from the posterior aspect of the foramen of Monro to immediately anterior to the pineal gland** YW p.1224.
- **Subchoroidal** — opens the **more lateral tenia choroidea**; the **thalamostriate vein, choroidal veins and medial posterior choroidal artery** must be navigated or sacrificed. Further from the fornix, but with a **theoretical increase in vascular injury**; Bozkurt et al. (2018) showed it provides **more limited exposure than the transchoroidal dissection**, and Youmans therefore favours transchoroidal YW p.1224.
- **Interforniceal** — Busch, **1944**, from techniques of Dandy and van Wagenen, and **first used on a giant colloid cyst** that had displaced the fornices upward and thinned the median raphe. Ideal when a **cavum septi pellucidi** exists; otherwise the septum is fenestrated and coagulated down to the **midline raphe**, using the septum-fornix intersection as the guide to the midline. From between the two foramina of Monro the raphe is opened posteriorly **1 to 1.5 cm** — "**further dissection posteriorly risks damaging the forniceal commissure**" YW p.1224.

- **Trajectory matters more than technique** — "Taking a **midline interhemispheric transcallosal** approach rather than a lateral transcortical approach provides a **less biased view and working angle to both sides of the ventricle**. This helps minimize forniceal retraction that often results from the laterally biased cortical entry point, thus **reducing the risk for forniceal injury**" and cognitive/memory loss YW p.1224. Correspondingly, Youmans does "not typically couple [the transfrontal] approach with the interforniceal technique as we believe it **increases the risk for forniceal injury given the lateral-to-medial operative trajectory**" YW p.1222.

5.6 Endoscopic resection

- **Why it has become the default for the right cyst** — "**significantly reduced rate of complications** compared with conventional microsurgical resection... **shorter operative times, shorter lengths of hospital stay, reduced overall costs, and increased patient comfort**", with shunt dependency **similar or lower** YW p.1239.
- **The trade-off** — "there is a **significantly increased rate of residual cyst wall** after endoscopic resection that may be associated with **increased cyst recurrence on long-term follow-up**"; **fewer gross total resections and greater residual cyst**, driving recurrence and reoperation YW p.1239.
- **Instrumentation** — **rigid** scopes: superior optics and field, easier orientation, **0/30/70-degree** lenses, some with **multiple working channels for bimanual technique**. **Flexible** scopes: bendable in three axes, better navigation of the ventricular system, but **inferior optics, limited instruments**, and "retracting a bent scope may cause damage to surrounding structures" YW p.1239.
- **The two bur holes — quote the numbers** YW p.1239:
  - **Transforaminal: ~4 cm lateral to midline, 4 cm anterior to the coronal suture.**
  - **Transseptal: ~6 cm lateral to midline, 4 cm anterior to the coronal suture.**
  - Fig. 171.5 gives the alternative single-bur-hole description: **~4 cm lateral to midline, 5 cm anterior to the coronal suture, about 8 cm posterior to the nasion**, refined by neuronavigation.
  - Final position is chosen "based on optimizing the trajectory to **avoid the head of the caudate nucleus** and access the anterior horn of the lateral ventricle with the use of neuronavigation"; "**frameless stereotactic neuronavigation is essential**".
- **Choosing between them** — "The **transforaminal approach is generally used for cysts that obviously protrude through the foramen of Monro**. This approach removes the cyst beginning with the cyst wall that is extruding through the foramen. The **transseptal approach can be used when the cyst occludes the foramen of Monro and prevents the surgeon from accessing the cyst via the transforaminal approach**... the cyst must be approached **through the septum pellucidum**. **Larger cysts typically necessitate the transseptal approach**" YW p.1239.
- **Technique** — **en bloc removal is possible but often not feasible**; otherwise **coagulate and fenestrate the wall, aspirate contents with a large-bore cannula or an endoscopic suction-morcellation device, then dissect the capsule sharply and bimanually, piecemeal, avoiding the confluence of internal cerebral, thalamostriate and septal veins**. A wall segment **relentlessly adherent to the deep veins or the third ventricular roof is thoroughly coagulated** rather than avulsed YW p.1239.
- **Ch. 228's nuances** — a **more lateral and anterior bur hole than the standard shunt position** gives a **face-on view of the cyst in the foramen**; **shrink the wall by coagulation first**, then excise; **avoid excessive traction** because bleeding from partially avulsed vessels in the roof of the third ventricle "is difficult to control and quickly obscures the operative view", and traction on the fornices "may confer significant morbidity"; **continuous warm irrigation** for oozing, **focal bipolar or laser coagulation** for brisk bleeding; **fenestrate the septum pellucidum** for free communication between the lateral ventricles YW p.1734.
- **When the scope cannot reach** — **posteriorly located cysts obscured by the roof of the third ventricle** may need the **subfrontal translamina terminalis approach**, or an **endoscopic transforaminal transchoroidal approach**, "which provides better visualization of the tela choroidea and increases resection of more posteriorly located colloid cysts"; a pragmatic plan is to **attempt ventriculoscopic resection first and convert the bur hole to a small craniotomy if unsuccessful** YW p.1734.

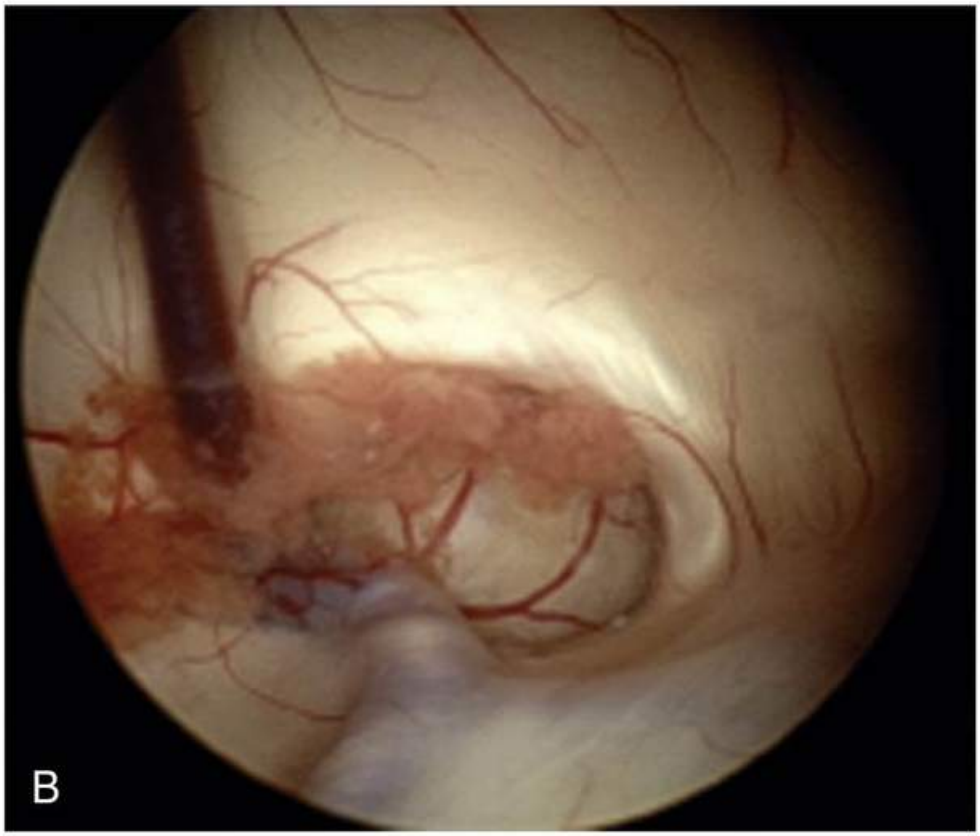


Figure 228.5. (A) Illustration of ventriculoscopic resection of colloid cyst. (B) Cyst visible through the right foramen of Monro.

Reproduced from Youmans & Winn 8e, Fig. 228.5, p. 1735 — Label when you reproduce it: (A) the illustration of ventriculoscopic colloid cyst resection — grasping forceps through one working channel and the laser/coagulating fibre through the other; (B) the endoscopic view of the cyst presenting through the right foramen of Monro, with choroid plexus, thalamostriate vein and fornix as landmarks.

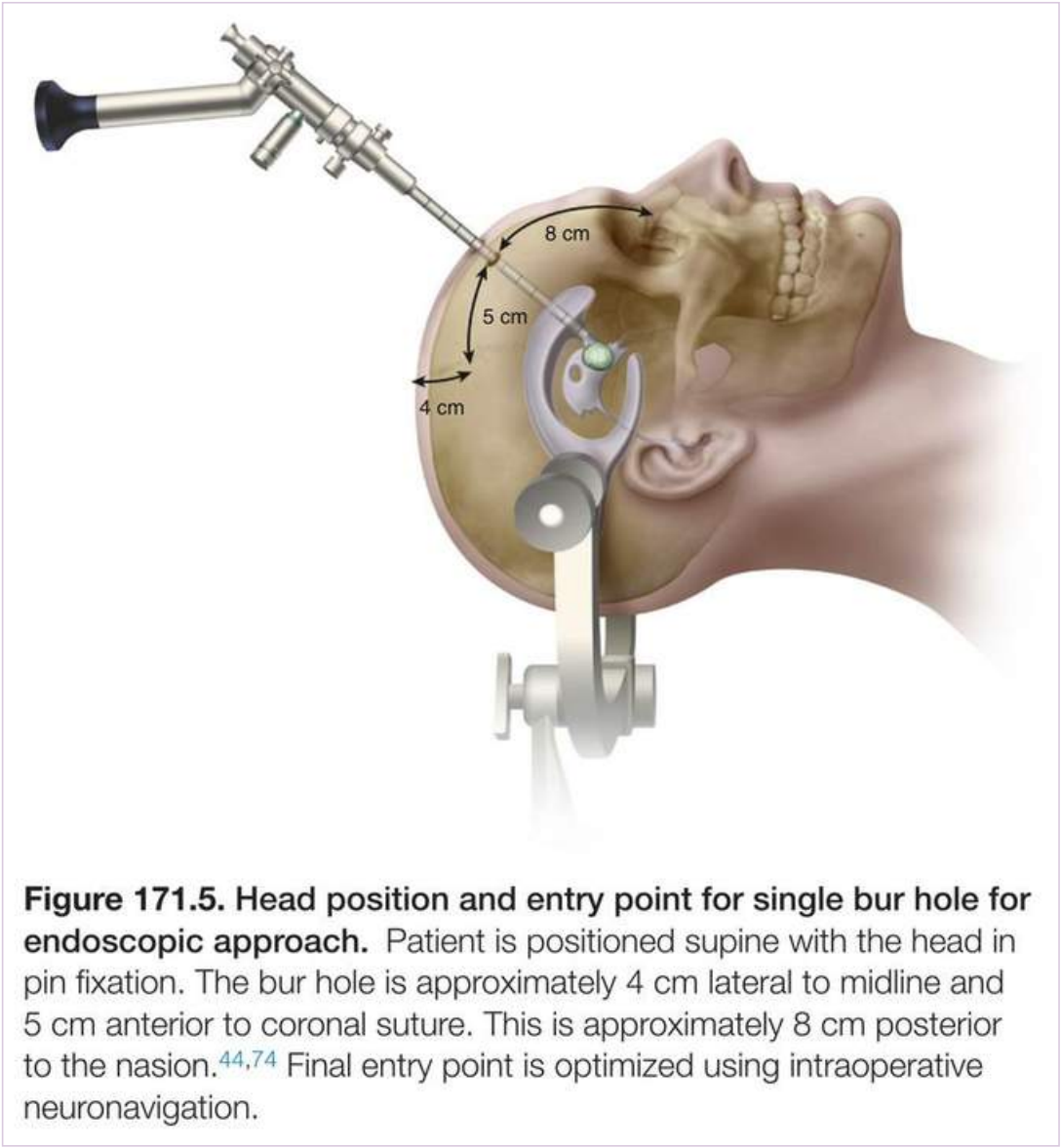


Figure 171.5. Head position and entry point for single bur hole for endoscopic approach. Patient is positioned supine with the head in pin fixation. The bur hole is approximately 4 cm lateral to midline and 5 cm anterior to coronal suture. This is approximately 8 cm posterior to the nasion.[44,74] Final entry point is optimized using intraoperative neuronavigation.

Reproduced from Youmans & Winn 8e, Fig. 171.5, p. 1239 — Label when you reproduce it: supine position with the head in pin fixation; the bur hole ~4 cm lateral to midline and ~5 cm anterior to the coronal suture, about 8 cm posterior to the nasion. Say that the final entry point is optimised with intraoperative neuronavigation so the trajectory clears the head of the caudate nucleus and lines up with the foramen of Monro.

5.7 Port-based (stereotactically guided endoscopic port) microsurgery

- **Rationale** — microsurgical resection sometimes needs "an especially **wide operative corridor** to obtain an adequate view of the lesion with the operative microscope" YW p.1240.
- **History and result** — **SEP** was first used in **2004** with a repurposed **thoracic tubular port**, modified instruments and a stereotactic frame while viewing the ventricle through a mounted endoscope; it "provided the **dexterity of traditional open surgery while preserving the minimally invasive nature of endoscopic surgery**", and in the initial study **12 of 12 patients with colloid cysts achieved gross total resection without postoperative complications** YW p.1240. Later variants use **dual-instrument techniques** or **multiple instruments through one endoscope** YW p.1240.

5.8 Conversion, and salvage

- "In one series of **35 endoscopic colloid cyst excisions, six cases were converted to open resection because of cyst adhesion to the fornix**" YW p.1239.
- Osorio et al.: **0% complete capsule removal in purely endoscopic cases vs 78% in converted cases**, with **no significant difference in postoperative complications**; an **open transcortical transventricular approach functioned**

well as the salvage procedure in most cases [YW pp. 1239-1240].

Table 2 · Surgical approaches to a third-ventricular colloid cyst — indication, technical key point and principal risk. Compiled from Youmans & Winn 8e, Ch. 171 pp. 1237-1240; Ch. 170 pp. 1214-1215, 1222-1224, Table 170.3 pp. 1218-1219; Ch. 228 pp. 1734-1735.

Approach	Best indication	Technical key point	Principal risk
Bilateral EVD	Acute decompensation	Both foramina may be blocked	Not definitive; may not restore neurology
VP shunt ± septostomy	Poor surgical candidate; bridge; giant/haemorrhagic cyst	Programmable valve at high pressure or "virtual off"	Cyst progresses; hypothalamic dysfunction; shrinks ventricles for later surgery
Stereotactic aspiration	None (historical)	—	**80% recurrence — abandoned**
Endoscopic transforaminal	Cyst obviously protruding through the foramen; ventriculomegaly; T2-bright fluid contents	Bur hole **4 cm lateral, 4 cm anterior** to the coronal suture; clear the caudate head	Residual capsule, recurrence; forniceal and caudate injury
Endoscopic transseptal	Cyst occluding the foramen; **large cysts**	Bur hole **6 cm lateral, 4 cm anterior** ; cross the septum pellucidum	Same, plus septal vein and deeper trajectory
Interhemispheric transcallosal	Small ventricles; large/adherent cyst; salvage; need for transchoroidal or interforniceal extension	Craniotomy 2/3 anterior-1/3 posterior to the coronal suture; **2-cm callosotomy posterior to the genu**; enter the third ventricle via the **tenia fornicis**	SSS/cortical vein injury and venous infarction; SMA syndrome; abulia; disconnection
Transcortical transventricular	**Dilated ventricles**; endoscopic salvage	1.5-cm corticotomy, **never the dominant superior frontal gyrus**; dynamic retraction only	Seizure (contested), mutism, hemiparesis, memory disturbance, abulia
Port-based MIS (SEP)	Firm, T2-dark, posteriorly pedicled cysts needing bimanual microsurgery	Stereotactic tubular port with mounted endoscope	Limited long-term data
Subfrontal translamina terminalis	Posterior cysts hidden by the third ventricular roof when endoscopy fails	Opens the anterior wall of the third ventricle	Optic apparatus, hypothalamus, pituitary stalk; CSF leak

- **The comparative verdict to quote** — endoscopic and microscopic resection give "**similar rates of shunt dependency, with a trend toward a lower morbidity rate in endoscopic cases**"; a **microscopic transcallosal** approach "may result in **lower neurological complications** than a transcortical endoscopic approach, with similar cyst resection rates"; but "**microsurgical techniques are associated with significantly higher rates of gross total resection and decreased recurrence**" YW p.1735.
- **Complications to enumerate whichever route is chosen** — "**seizures, memory deficits, hemorrhage or hematoma, infarction, meningitis, CSF leak, or motor deficits**" YW p.1240, plus **venous infarction, IVH, hemiparesis, death and aseptic meningitis from spilled cyst contents** YW p.1735. Forniceal damage gives **persistent short-term memory deficit** and ICV/thalamostriate injury may give **thalamic infarction** YW p.1240.

(c) Differential diagnosis of cystic lesions of the ventricles [2]

6. Build the differential by compartment

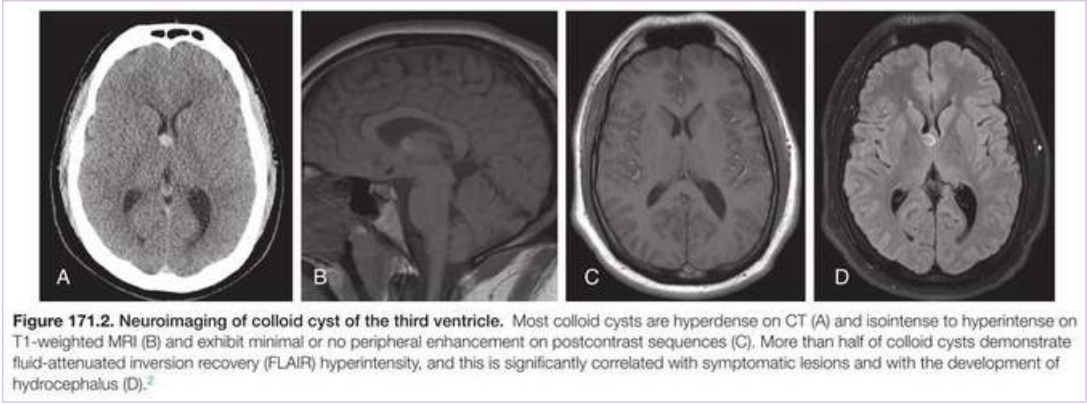


Figure 171.2. Neuroimaging of colloid cyst of the third ventricle. Most colloid cysts are hyperdense on CT (A) and isointense to hyperintense on T1-weighted MRI (B) and exhibit minimal or no peripheral enhancement on postcontrast sequences (C). More than half of colloid cysts demonstrate fluid-attenuated inversion recovery (FLAIR) hyperintensity, and this is significantly correlated with symptomatic lesions and with the development of hydrocephalus (D).[2]

Reproduced from Youmans & Winn 8e, Fig. 171.2, p. 1236 — Label when you reproduce it: (A) CT — hyperdense round mass at the foramen of Monro; (B) T1 — iso- to hyperintense; (C) post-contrast T1 — only minimal/no peripheral rim enhancement; (D) FLAIR — hyperintensity. Use it as the reference imaging signature against which every other intraventricular cyst is compared.

- **Youmans' own list for a cyst at the foramen of Monro** — "**meningioma, glioma (e.g., pilocytic astrocytoma), choroid plexus papilloma, ependymoma/subependymoma, third ventricular craniopharyngioma, blood products around the foramen of Monro, or CSF flow artifact (MRI pseudocyst) caused by turbulent flow near the foramen of Monro**" — plus **cerebral aneurysm**, "suspected when a spheroid lesion extends inferiorly into the third ventricle" YW p.1236.
- **Youmans' classification of ventricular cysts by site** YW p.1204:
  - **Colloid cyst — third ventricle.**
  - **Rathke cyst — suprasellar** (extending into the third ventricle).
  - **Epidermoid cyst — fourth ventricle.**
  - **Dermoid cyst — suprasellar, pineal.**
  - **Choroid plexus cyst — lateral ventricles.**
  - **Arachnoid cyst — lateral ventricles.**
- **Cystic *tumours* that masquerade as cysts — pilocytic astrocytoma** (fourth ventricle, suprasellar; classically a cyst with an avidly enhancing mural nodule) [YW pp. 1204, 1231]; **subependymoma**, whose large examples "may have cystic or calcified components" and which **does not enhance** YW p.1230; **central neurocytoma**, with a **"soap bubble"** appearance from its cystic components and **punctate calcification in over half** YW p.1230; **craniopharyngioma**, with mixed solid/cystic and calcified components extending through the floor of the third ventricle YW p.1853; **ependymoma** , which may contain **cysts, haemorrhage or calcification** YW p.1229; and, in the posterior fossa, **cystic cerebellar astrocytoma**, which may appear as "**a complete cyst that is confused with an arachnoid cyst**" YW p.1820.
- **Non-neoplastic cysts — benign pineal cyst**: overall prevalence **2%**, **higher in females and increasing with age**, up to **2 cm** with a **contrast-enhancing rim representing compressed pineal gland tissue**; "**nearly always asymptomatic and generally do not require treatment unless they cause aqueductal obstruction**", and radiographically they can mimic pilocytic astrocytoma, which is distinguished by its **tendency to progress** YW p.1148.
- **Arachnoid cysts** — "postulated to arise from **splitting of the arachnoid membrane** in early development"; they enlarge by an **osmotic gradient, active secretion by the cyst lining, ectopic choroid-like structures, or CSF movement through a slit-valve communication with the subarachnoid space during venous or arterial pulsation"; with time they "exert mass effect or** obstruct CSF outflow to produce symptomatic hydrocephalus**" [YW p.1735]. Suprasellar arachnoid cysts are a classic cause of** progressively enlarging head from obstructive hydrocephalus in infancy** YW p.1698.
- **Infective cysts — do not forget them in the Indian context** — "Within the CNS, **cysticerci may be located in the brain parenchyma, subarachnoid space, ventricular system, or spinal cord**... **Ventricular cysticerci may be attached to the choroid plexus or may be floating free in the ventricular cavities**" YW p.435.e4. Inflammation around cysticerci produces "**edema, gliosis, thickening of the leptomeninges, entrapment of the cranial nerves, angiitis, hydrocephalus, and ependymitis**", and **calcified cysticerci are dead parasites that should not receive**

cysticidal drugs YW p.435.e4. Neurocysticercosis is explicitly listed among the causes of obstructive hydrocephalus treated by ETV YW p.347.

- **Artefact** — the **"MRI pseudocyst"** produced by **turbulent CSF flow near the foramen of Monro** must be excluded before operating YW p.1236.

Table 3 · Differential diagnosis of a cystic intraventricular lesion — site, imaging discriminator and the one fact that settles it. From Youmans & Winn 8e, Ch. 171 p. 1236; Ch. 170 Table 170.1 p. 1204 and pp. 1229-1232; Ch. 164 p. 1148; Ch. 228 p. 1735; Ch. 240 p. 1820; Ch. 59 p. 435.e4.

Lesion	Usual site	Imaging	Discriminator
Colloid cyst	Third ventricle at the foramen of Monro (>99%)	CT hyperdense; T1 bright in 2/3; T2/FLAIR usually dark; **thin rim enhancement only**; **no diffusion restriction**	Round, fluid-filled, extends from the third ventricle into the foramen; fornices straddle it
Choroid plexus cyst	Lateral ventricles	Small, CSF-like, alongside the glomus	Incidental; no mass effect
Arachnoid cyst	Lateral ventricles, suprasellar, quadrigeminal	**Isointense to CSF on all sequences; no enhancement; no diffusion restriction**	Slit-valve mechanism; may cause obstructive hydrocephalus and macrocephaly in infancy
Epidermoid cyst	Fourth ventricle (~25% of intracranial epidermoids are fourth-ventricular or suprasellar)	Isodense to CSF on CT; isointense on T1 and T2; **does not enhance**	**Restricts diffusion** (arachnoid cyst does not); pearly keratin at surgery; risk of aseptic meningitis
Dermoid cyst	Suprasellar, pineal, midline	**Hypoattenuating on CT from fat**; T1 hyperintense; **fat droplets scattered in the subarachnoid space if ruptured**	Recurrent chemical meningitis; may have a dermal sinus tract
Rathke cleft cyst	Suprasellar, into the third ventricle	Non-enhancing cyst, often with a **T1-bright intracystic nodule**	Intrasellar origin; endocrine and visual presentation
Craniopharyngioma	Suprasellar into the third ventricle	Mixed solid/cystic with **calcification**; nodular and rim enhancement	Calcification plus visual and endocrine failure; bimodal age
Cystic pilocytic astrocytoma	Fourth ventricle, suprasellar, cerebellum	Cyst with **avidly enhancing mural nodule**; may be a pure cyst mimicking an arachnoid cyst	High ADC; thick irregular cyst-wall enhancement means the wall must be resected
Central neurocytoma	Frontal horn, attached to the **septum pellucidum**	**"Soap-bubble"** cystic appearance on T2/FLAIR; **punctate calcification in >50%**; moderate enhancement	Young adult; synaptophysin/NeuN positive
Subependymoma	Fourth (60%) and lateral (30%) ventricles	Hypo/isodense, **non-enhancing** nodule; cysts and calcification in large lesions	WHO I; attached to the ependymal lining; often incidental
Benign pineal cyst	Pineal	Up to 2 cm; **peripheral rim enhancement** (compressed gland)	**2% prevalence, commoner in women, increases with age**; treat only if it obstructs the aqueduct
Neurocysticercosis	Any ventricle; may be **attached to the choroid plexus or free-floating**	Thin-walled cyst ± scolex; ependymitis and hydrocephalus	Endemic exposure; calcified lesions are dead parasites — no cysticidal drugs
CSF flow artefact ("MRI pseudocyst")	Foramen of Monro	Variable, sequence-dependent	Disappears on repeat or alternative sequences

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Histology in one line:** pseudostratified/columnar/cuboidal epithelium with **ciliated columnar cells and goblet cells**, on a capsule of **fibroblasts, collagen and arachnoid cells**, containing gelatinous mucin with CSF, blood products and cholesterol.
- **Origin: ectopic foregut endoderm.** Immunophenotype resembles **Rathke cleft, follicular pituitary and neurenteric cysts**, and shares **few markers with choroid plexus epithelium** — quote that sentence.
- **The cyst is invested by choroid plexus and intimate with, but not adherent to, the fornix** — a small fornix-to-cyst penetrating artery may exist.
- **Roof of the third ventricle = fornix + two layers of tela choroidea + the vessels between them.** The velum interpositum carries the ICVs and medial posterior choroidal arteries.
- **Enter through the tenia fornicis (transchoroidal), not the tenia choroidea (subchoroidal)** — better exposure, fewer veins at risk.
- **Interforniceal raphe: 1-1.5 cm only** before the forniceal commissure is at risk. Described by Busch in 1944 for a giant colloid cyst.
- **Bur holes: transforaminal 4 cm lateral / 4 cm anterior; transseptal 6 cm lateral / 4 cm anterior; large cysts need transseptal.**
- **2-cm callosotomy posterior to the genu** is enough for almost any intraventricular lesion.
- **Never section the fornix at the anterosuperior margin of the foramen of Monro; even unilateral forniceal injury causes anterograde amnesia.**
- **A midline transcallosal trajectory retracts the fornix less than a lateral transcortical one** — that is why the interforniceal technique is not coupled with a transfrontal approach.
- **Aspiration: 80% recurrence, abandoned. Shunt: treats hydrocephalus, not the cyst.**
- **Endoscopy = less morbidity, more residual, more recurrence; microsurgery = higher GTR, less recurrence.** 6/35 endoscopic cases converted for forniceal adhesion; conversion lifted complete capsule removal from 0% to 78%.
- **Cystic ventricular differential by site:** colloid (third ventricle), choroid plexus cyst and arachnoid cyst (lateral), epidermoid (fourth), dermoid (suprasellar/pineal), Rathke (suprasellar), craniopharyngioma, cystic pilocytic astrocytoma, central neurocytoma ("soap bubble"), subependymoma, pineal cyst, neurocysticercosis — and the **MRI pseudocyst** of turbulent flow.
- **DWI separates epidermoid (restricts) from arachnoid cyst (does not)** — the single most useful sequence in this differential.
- **Calcification or avid homogeneous enhancement argues against a colloid cyst** and toward meningioma, ependymoma, craniopharyngioma, CPP or calcified aneurysm.

Pages read for this answer — Youmans & Winn 8e: 347, 435.e4, 1148, 1204, 1205, 1206, 1211, 1214, 1215, 1222, 1224, 1229, 1230, 1231, 1234, 1236, 1237, 1238, 1239, 1240, 1698, 1734, 1735, 1820, 1853

Posterior Third Ventricular / Pineal Region Tumours — 3 questions

Posterior third ventricular tumors:

a) Clinical features. [3]

b) Radiological features. [3]

c) Management. [4]

LONG | DEC 2021 · Paper I · Q9 | 10 marks

Also asked as: Pineal / posterior third ventricular tumours — also asked as OCT 2023 · Paper I · Q5 ("a) Enumerate lesions of pineal region. [3] b) Symptoms and signs of posterior third ventricular lesion. [3] c) Surgical corridors of pineal region tumors. [4]")

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 164 *Pineal Tumors*, §Anatomy, §Pathology, §Clinical Features — Initial Symptoms, §Diagnosis, §Tumor Markers, §Treatment — Management of Hydrocephalus, §Tissue Diagnosis: Biopsy Versus Open Resection, §Surgical Techniques, §Operative Approaches, §Surgical Outcome, §Postoperative Workup, §Outcomes and Follow-up Care Based on Pathology, pp. 1147-1161 (Figs. 164.1, p. 1149; 164.2, p. 1149; 164.3, p. 1150; 164.4, p. 1151; 164.5, p. 1152; 164.11, p. 1160; Tables 164.1, p. 1148; 164.2, p. 1150; 164.3 and 164.4, p. 1152; 164.5, p. 1159). Supplementary: Ch. 170 *Ventricular Tumors*, §Surgical Anatomy — Third Ventricle, §Clinical Presentation, §Infratentorial Supracerebellar Approach, pp. 1204, 1207-1208, 1225 (Fig. 170.7, p. 1208; Table 170.1, p. 1204; Table 170.3, pp. 1218-1219). Ch. 242 *Intracranial Germ Cell Tumors*, §Presentation, §Diagnostic Evaluation, §Surgical Management, pp. 1833-1834 (Fig. 242.1, p. 1833; Box 242.1 and Table 242.1, pp. 1833-1834). Ch. 244 *Pediatric Intraventricular and Periventricular Tumors*, Table 244.1, p. 1849 and §Tumors of the Posterior Third Ventricle, pp. 1853-1854.

1. Anatomy of the posterior third ventricle and pineal region — the framework for everything else

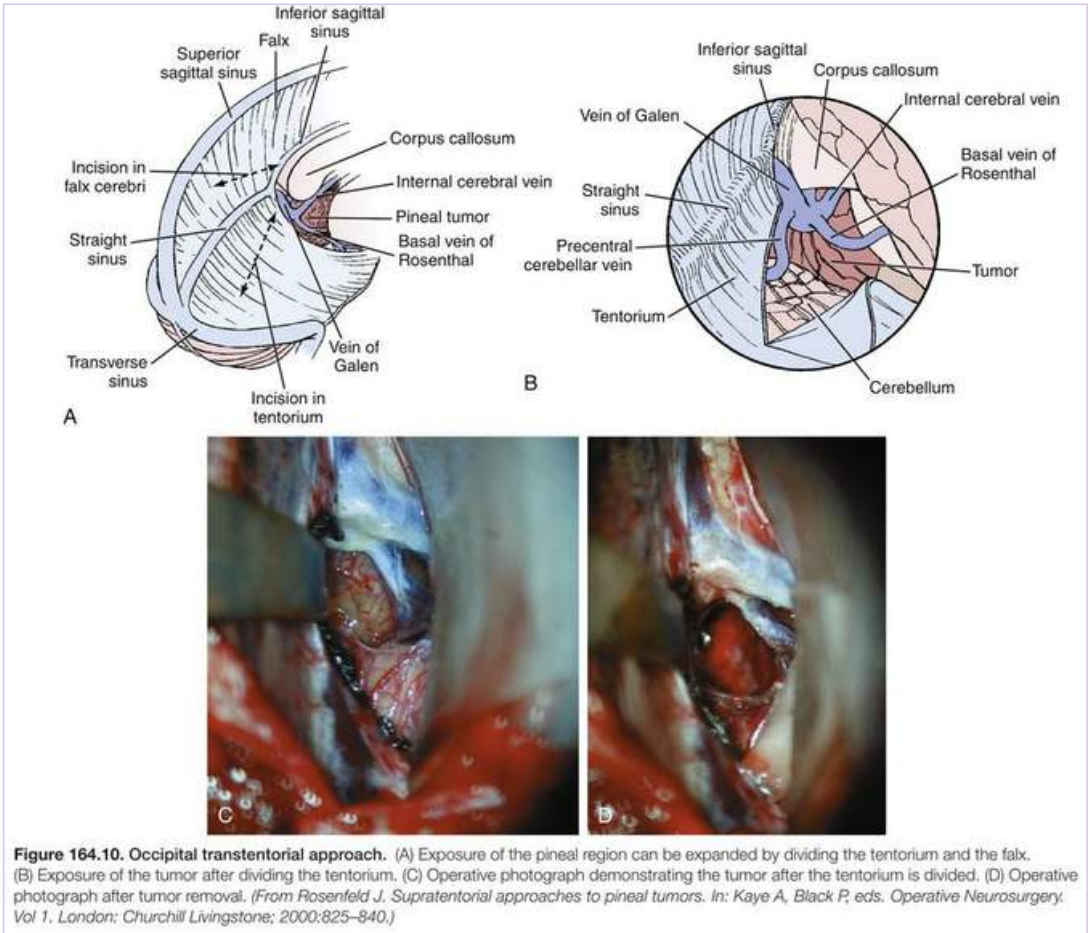


Figure 164.10. Occipital transtentorial approach. (A) Exposure of the pineal region can be expanded by dividing the tentorium and the falx. (B) Exposure of the tumor after dividing the tentorium. (C) Operative photograph demonstrating the tumor after the tentorium is divided. (D) Operative photograph after tumor removal. *(From Rosenfeld J. Supratentorial approaches to pineal tumors. In: Kaye A, Black P, eds. Operative Neurosurgery. Vol 1. London: Churchill Livingstone; 2000:825–840.)*

Reproduced from Youmans & Winn 8e, Fig. 164.1, p. 1149 — Label when you reproduce it: (A) sagittal drawing — internal cerebral vein, velum interpositum, splenium, fornix, inferior sagittal sinus, falx, straight sinus, tentorium, superior vermian vein, vermis, corpora quadrigemina, vein of the cerebellomesencephalic fissure, arachnoid, pineal gland and quadrigeminal cistern; (B) dorsal drawing — habenular commissure, pineal gland, superior and inferior colliculi, pineal vein, internal cerebral veins, medial and lateral posterior choroidal arteries, tela choroidea, fornix, posterior cerebral artery, internal occipital vein, basal vein of Rosenthal and the vein of Galen.

- **The gland** — "The pineal gland is an **encapsulated structure that occupies a deep position near the geometric center of the brain**. The pineal gland is an **extra-axial structure**, a feature that makes pineal lesions amenable to resection because **a natural surgical plane can often be established**" YW p.1147.
- **Immediate relations** — "**the posterior commissure ventrally, the corpus callosum superiorly, and the habenular commissure dorsally**" YW p.1147.
- **Venous relations — the surgical crux** — "**The velum interpositum, which contains the internal cerebral veins and the choroid plexus, is intimate with the dorsal gland. The basal veins of Rosenthal combine with the internal cerebral veins to form the vein of Galen before draining into the straight sinus**" YW p.1147.
- **Arterial supply** — "**from branches of the medial and lateral choroidal arteries through anastomoses to the pericallosal, posterior cerebral, superior cerebellar, and quadrigeminal arteries**" YW p.1148.
- **Growth pattern** — "**Most pineal masses originate infratentorially and expand into the posterior third ventricle.** Further progression can proceed into the **thalamus** or posteriorly over the **dorsal surface of the quadrigeminal plate**. Malignant tumors, particularly of glial origin, can **invade into the midbrain and thalamus**, which ultimately affects tumor resectability" YW p.1148.
- **Boundaries of the posterior third ventricle** — "The posterior border of the third ventricle extends from the **sylvian aqueduct to the suprapineal recess**. Between these structures are the **posterior commissure, pineal body, pineal recess, and the habenular commissure located between the crura of the fornices anterior to the pineal body**" YW p.1208.
- **Roof and velum again** — the roof runs from the **foramen of Monro to the suprapineal recess** and has **four layers from dorsal to ventral: the fornix, the two layers of tela choroidea (with the velum interpositum between them), and the choroid plexus**; the velum contains the **internal cerebral veins, draining posteriorly to the vein of Galen, and the medial posterior choroidal arteries**, which "originate posteriorly and course anteriorly toward the foramen of Monro". The two ICVs "run close to each other **up to the pineal recess, where they deviate from the midline and proceed along the superolateral surface of the pineal body to the deepest point of the splenium** to form the vein of Galen" [YW pp. 1207-1208].

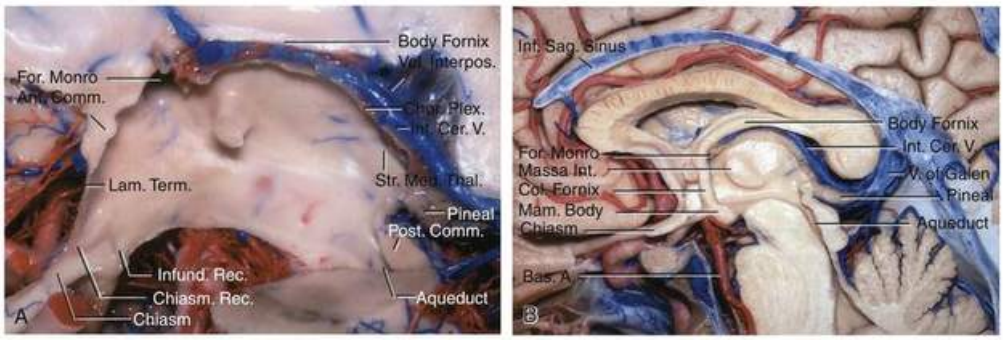


Figure 170.7. Midsagittal views of the third ventricle. (A) Enlarged view to better demonstrate intraventricular contents. (B) Global view to demonstrate the third ventricle's relationship to surrounding structures. (*From Rhoton AL. The lateral and third ventricles. Neurosurgery. 2002;51[4 Suppl]:S207–S271.*)

Reproduced from Youmans & Winn 8e, Fig. 170.7, p. 1208 — Label when you reproduce it: (A) enlarged midsagittal view of the third ventricle — body of fornix, foramen of Monro, anterior commissure, choroid plexus, internal cerebral vein, massa intermedia, lamina terminalis, column of fornix, mammillary body, infundibular recess, chiasmatic recess, chiasm, aqueduct, pineal, posterior commissure; (B) the global midsagittal view adding the inferior sagittal sinus, velum interpositum, vein of Galen, stria medullaris thalami, basilar artery and the relationship of the third ventricle to surrounding structures.

- **Where the tumours of the third ventricle arise** — "Anatomically, tumors affecting the third ventricle originate from any of four primary regions: **(1) suprasellar with expansion into the ventricle** (craniopharyngiomas, pituitary adenomas, meningiomas, optic pathway gliomas), **(2) the ventricular wall** (ependymomas, hypothalamic or thalamic gliomas), **(3) intraventricular structures** (choroid plexus tumours, meningiomas), and **(4) the pineal region** (pineal gland tumours, germ cell tumours, meningiomas, tectal tumours)" YW p.1208.

2. Pathology — the five categories to enumerate

- **Rarity** — pineal tumours are "**only 1.2% of all CNS tumors**", and this, combined with their histological diversity, "has been an obstacle in the study of their biology and outcomes" YW p.1147.
- **Why the histology is so varied** — "The different cell types that make up the pineal gland account for the diverse pathology"; the gland contains **pinealocytes arranged in lobules**, surrounded by **astrocytes and endothelial cells** forming septa, plus **nerve endings from sympathetic innervation**, and along its anterior border **ependymal cells** YW p.1148.
- **Terminology** — "The term **pinealoma** was originally used by Krabbe but is a **misnomer** because it initially pertained to germ cell tumors... it is now **obsolete**. **Pineal region tumor is the preferred general term**" YW p.1148.
- **The five categories, verbatim** — "Pineal tumors have historically been grouped into five main categories: **germ cell tumors, pineal parenchymal cell tumors, glial cell tumors, papillary tumors, and other miscellaneous tumors and cysts**. Within each category, tumors exist along a continuum from benign to malignant, and **mixed tumors of more than one cell type can occur**" YW p.1148.
- **The miscellaneous category** — "**meningioma, hemangioblastoma, choroid plexus papilloma, metastatic tumor, chemodectoma, adenocarcinoma, and lymphoma**", plus vascular lesions: "**cavernous malformations, arteriovenous malformations, and vein of Galen malformations**" YW p.1148.

Table 1 · Lesions of the pineal region and posterior third ventricle, with WHO grade and first-line strategy. Compiled from Youmans & Winn 8e, Ch. 164 pp. 1147-1148, 1159-1160; Ch. 242 Box 242.1, p. 1833; Ch. 170 Table 170.1, p. 1204; Ch. 244 Table 244.1, p. 1849.

Category	Entities	WHO grade	First-line strategy
Germ cell tumours	**Germinoma** (commonest pineal region tumour, adolescent boys/young men)	—	Tissue diagnosis, then radiotherapy ± chemotherapy; long-term control in 90%
	Nongerminomatous: embryonal carcinoma, yolk sac (endodermal sinus) tumour, choriocarcinoma, mature and immature teratoma, mixed germ cell tumour	II or III (Ch. 244)	**Markers positive → treat without biopsy**; chemo-radiotherapy then "second-look surgery"
Pineal parenchymal tumours	**Pineocytoma**	I	Complete resection; GTR gives 100% survival at 40-month median follow-up
	Pineal parenchymal tumour of intermediate differentiation (PPTID)	II or III	Resection ± ventricular radiation; **25% risk of leptomeningeal spread**
	Pineoblastoma	IV	Resection + craniospinal radiation + chemotherapy
Glial tumours	Pilocytic astrocytoma of the pineal gland; tectal glioma; ependymoma; glioblastoma (usually thalamic)	I-IV	GTR where encapsulated; tectal gliomas — ETV then observation
Papillary tumour of the pineal region (PTPR)	Presumed from specialised ependyma of the **subcommissural organ**; first reported 2003, separate entity in the 2007 WHO classification	II or III	Resection; 5-year OS 73% but PFS only 27%
Miscellaneous	Meningioma (often of the velum interpositum), haemangioblastoma, choroid plexus papilloma, metastasis, chemodectoma, adenocarcinoma, lymphoma, epidermoid, dermoid, teratoma	Variable	Resection for benign lesions
Cysts and vascular lesions	**Benign pineal cyst**; cavernous malformation; AVM; **vein of Galen malformation**	—	Pineal cyst: observe unless it obstructs the aqueduct

- **The benign pineal cyst** — "Their overall prevalence of **2%** is **higher in females and increases with age**"; histologically they are "**benign, normal variants of the pineal gland**" consisting of cystic structures surrounded by

normal pineal parenchyma; "They can be up to **2 cm in diameter, with a contrast-enhancing rim representing compressed pineal gland tissue**. They are **nearly always asymptomatic and generally do not require treatment unless they cause aqueductal obstruction**." They may mimic pilocytic astrocytoma, which is distinguished by its **tendency to progress and become symptomatic** YW p.1148.

(a) Clinical features [3]

3. The three mechanisms — state them first, then expand

- **Youmans' framework** — "Pineal region tumors generally become symptomatic via **three potential etiologies**: **(1) increased intracranial pressure from obstructive hydrocephalus, (2) direct brainstem and cerebellar compression, or (3) endocrine dysfunction**" YW p.1148.

3.1 Raised intracranial pressure from obstructive hydrocephalus

- **The commonest symptom** — "The most common initial symptom is **headache**, which is associated with obstructive hydrocephalus secondary to **compression of the aqueduct of Sylvius**" YW p.1148.
- **Progression** — "Further progression of hydrocephalus can lead to **nausea, vomiting, cognitive impairment, papilledema, ataxia, and eventually obtundation**" [YW pp. 1148-1149].
- **Why this region obstructs** — "Tumors in this region are prone to causing obstructive hydrocephalus by **compression of the narrow sylvian aqueduct**" YW p.1204.
- **Pineal apoplexy** — "In rare cases, symptoms can develop **abruptly in association with pineal apoplexy from hemorrhage in a pineal tumor**" YW p.1149.

3.2 Direct midbrain, tectal and cerebellar compression

- **Parinaud syndrome** — "Direct compression of the midbrain, particularly at the level of the **superior colliculus**, can cause disorders of extraocular movement, classically known as **Parinaud syndrome**. This syndrome can consist of **paralysis of upgaze, convergence or retraction nystagmus, and light-near pupillary dissociation**" YW p.1149. Ch. 170 gives the same tetrad as "**up-gaze paralysis, eyelid retraction, convergence-retraction nystagmus, and light-near dissociation**" YW p.1204.
- **Sylvian aqueduct syndrome** — "**paralysis of downgaze or horizontal gaze from further midbrain compression, can be superimposed on Parinaud syndrome**" YW p.1149.
- **Collier sign** — "**Dorsal midbrain compression or infiltration can lead to lid retraction (the Collier sign) or ptosis**" YW p.1149.
- **Fourth nerve** — "Less commonly, **fourth nerve palsies with diplopia and head tilt** may occur" YW p.1149.
- **Cerebellar signs** — "Interference with the cerebellar efferent pathways of the **superior cerebellar peduncles** can cause **ataxia and dysmetria**" YW p.1149.
- **Hearing** — "**Hearing disturbances** have also been reported, likely secondary to **inferior colliculi compression**" YW p.1149.

3.3 Endocrine dysfunction

- **Rarity and mechanism** — "Endocrine dysfunction is **rare**, but it can result from **tumor infiltration into the hypothalamus or secondarily from hydrocephalus**" YW p.1149.
- **Diabetes insipidus** — "Of note, **diabetes insipidus caused by hypothalamic tumor invasion may occur even before such invasion is radiographically apparent**" YW p.1149. In germ cell tumours diabetes insipidus "is almost universally present" with suprasellar lesions, and "**a small percentage of patients who radiologically appear to have purely pineal lesions can also present with diabetes insipidus**, possibly reflecting microscopic tumor spread to the anterior third ventricular floor" YW p.1833.
- **Precocious puberty** — "Although **precocious puberty** has been historically linked to pineal masses, **documented cases are rare**" YW p.1149. Ch. 242 explains the mechanism: it "may be observed in patients with pineal as well as suprasellar lesions, **secondary to secretion of β-human chorionic gonadotropin (β-hCG) by the tumor**" YW p.1833.

3.4 Tempo, and what it tells you

- **NGGCT versus germinoma** — "Given that **NGGCTs tend to be biologically more aggressive** than germinomas, these lesions typically present with a **shorter natural history**. In some patients with germinomas, the symptom duration prior to detection can be **extremely protracted**, with **isolated diabetes insipidus occasionally being present for years** (albeit compensated) prior to diagnosis" YW p.1833.
- **In the infant** — a **bulging anterior fontanelle**, and in some cases a generalised presentation of **failure to thrive and loss of developmental milestones**, such tumours being **extremely large at diagnosis** YW p.1834.
- **Generic intraventricular presentation to fall back on — headache, lethargy, nausea, memory loss, gait disorder, cognitive or mood changes** in adults; in children additionally **delayed milestones or retarded growth**; in infants **increased head circumference, bulging fontanelle, distended scalp veins, failure to thrive**; and "**acute deterioration can occur by means of sudden CSF pathway obstruction or intralesional hemorrhage**" YW p.1203.

(b) Radiological features [3]

4. MRI is the principal test

- **The statement** — "**MRI with gadolinium enhancement is the principal diagnostic test for pineal tumors.** MRI provides information regarding **tumor size, vascularity, homogeneity, anatomic relationships with surrounding structures, and degree of hydrocephalus**. In particular, **venous anatomy can be evaluated, which is helpful in planning surgery**" YW p.1149.
- **The deep venous rule — this is the examinable point** — "**Pineal tumors generally displace the vessels of the deep venous system superiorly along the dorsal periphery of the tumor.** Notable exceptions are **meningiomas arising from the velum interpositum** and **epidermoid or other tumors originating in the corpus callosum. These tumors displace the deep venous system ventrally and inferiorly, thereby providing a diagnostic clue on MRI**" YW p.1149.
- **Why it matters** — "The position of the tumor relative to the deep venous system is important because it may **influence the choice between an infratentorial and a supratentorial approach**. Although the location of the deep venous system may be conspicuous on MRI, **magnetic resonance venography may be desirable** to better delineate it" YW p.1149.

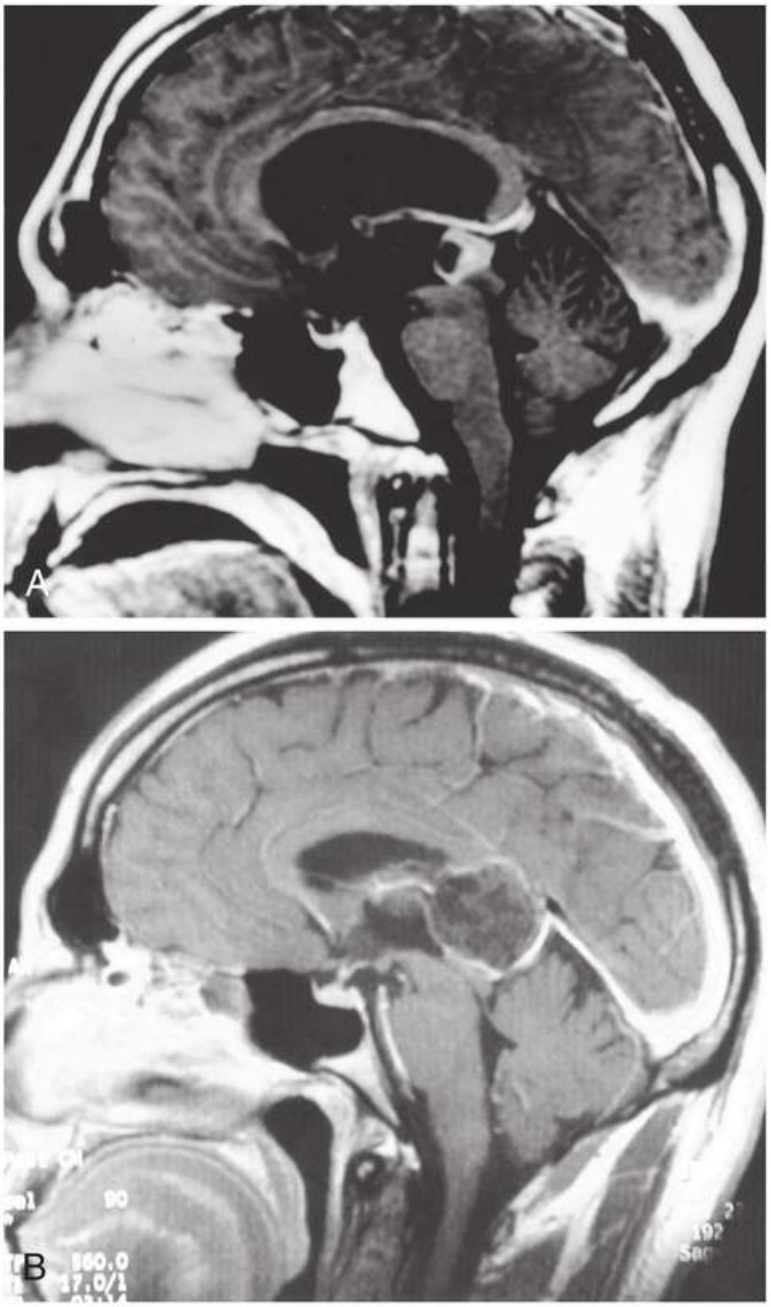


Figure 164.3. MR images showing the variability of the deep venous system in relation to pineal region tumors. (A) The deep venous system is located superior and dorsal to the tumor. This is the most common configuration and is conducive to an supracerebellar infratentorial approach. (B) The deep venous system is located inferior and ventral to this epidermoid tumor and is conducive to a supratentorial approach.

*Reproduced from Youmans & Winn 8e, Fig. 164.3, p. 1150 — Label when you reproduce it: (A) the deep venous system lying **superior and dorsal** to the tumour — the commonest configuration, conducive to a supracerebellar infratentorial approach; (B) the deep venous system lying **inferior and ventral** to this epidermoid tumour, conducive to a supratentorial approach. Mark the internal cerebral veins, vein of Galen and straight sinus on both.*

- **Histology cannot be predicted from imaging** — "Despite advances in high-resolution MRI, **tumor histology cannot be reliably predicted on the basis of imaging features alone**" YW p.1149.
- **The ADC observation, and its limit** — "Some groups have reported **significantly higher ADC signal on MR**

imaging in germinomas compared with pineal cell tumors and even relatively **higher signals in pineoblastomas/PNETs**; however, this sign is **not reliable enough to alter management or avoid surgery**" YW p.1149 .

- **What CT adds** — "CT can complement MRI by providing details of **calcification, blood-brain barrier breakdown, and the degree of vascularity**" YW p.1149.
- **Angiography** — "**Angiography is not necessary unless a vascular anomaly is suspected**" YW p.1149.
- **Heterogeneity on imaging is itself a clue** — mixed germ cell tumours show marked heterogeneity on MRI and on gross pathology, "**such heterogeneity can lead to misdiagnosis if tissue sampling is limited**" YW p.1152.

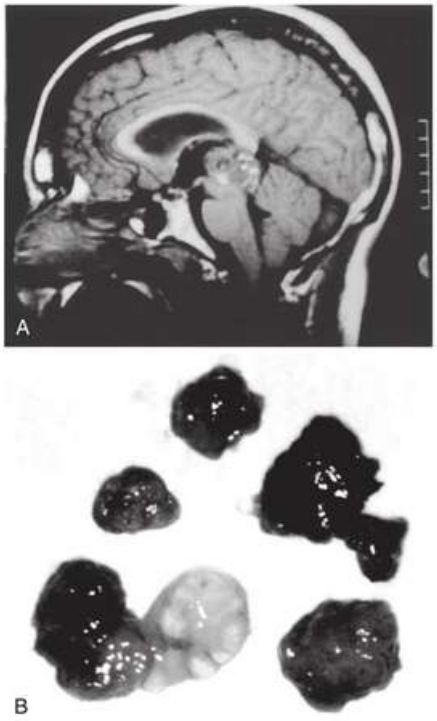


Figure 164.5. Sagittal magnetic resonance image (A) and gross pathology (B) from a patient with a mixed germ cell tumor demonstrating the heterogeneity of the tumor. Such heterogeneity can lead to misdiagnosis if tissue sampling is limited.

TABLE 164.3 Pure versus Mixed Germ Cell Tumors at New York Presbyterian–Columbia University Medical Center (1978–2020)

Tumor Type	Number
PURE GERM CELL TUMORS	
Germinoma	42
Teratoma	9
Epidermoid	4
Immature teratoma	2
Embryonal carcinoma	2
Lipoma	2
Total	**61**
MIXED GERM CELL TUMORS	
Germinoma/teratoma	4
Germinoma/embryonal carcinoma	3
Immature teratoma/germinoma/EST	2
Germinoma/dermoid	1
Germinoma/immature teratoma	1
Choriocarcinoma/teratoma	1
Choriocarcinoma/immature teratoma	1
Embryonal carcinoma/EST	1
EST/embryonal carcinoma/germinoma	1
Germinoma/nongerminomatous malignant germ cell/teratoma	1
EST/nonspecific malignant	1
Nonspecified mixed	2
Total	**21**

EST, Endodermal sinus tumor.

TABLE 164.4 Extent of Resection for 205 Consecutive Pineal Region Surgeries at New York Presbyterian–Columbia University Medical Center (1990–2020)

	Biopsy	Subtotal Resection	Radical Subtotal Resection/ Gross Total Resection
Benign	2	5	79
Malignant	12	29	78
Total	**14 (7%)**	**34 (17%)**	**157 (78%)**

Note: radical subtotal resection = no visible tumor at surgery or on postoperative MRI, but tumor was not well encapsulated.

Reproduced from Youmans & Winn 8e, Fig. 164.5, p. 1152 — Label when you reproduce it: (A) the sagittal MR image of a mixed germ cell tumour and (B) the corresponding gross pathological specimen. Point out the heterogeneous solid and cystic components and state the teaching point: heterogeneity of this degree causes misdiagnosis when sampling is limited, which is the argument for open resection over needle biopsy in germ cell tumours.

4.1 Imaging by histology

- **Germ cell tumours in general** — "GCTs are typically **isointense to gray matter** and often show **avid and/or heterogeneous contrast enhancement**. **Germinomas tend to be symmetrical**, sometimes with spread of the tumor from the pineal to the cerebral hemispheres, and **when in the basal ganglia, they are less likely to enhance**" YW p.1834.
- **Bifocal disease** — "**bifocal lesions involving the pineal and suprasellar regions concomitantly without dissemination are most likely germinomas**" YW p.1834.
- **Choriocarcinoma** — "With significant vascularity, **choriocarcinomas often demonstrate intratumoral hemorrhage on imaging**" YW p.1834.
- **Teratoma** — "can have a **mixture of cystic and solid elements (including fat and bone visible on imaging)**" YW p.1834; Ch. 244 adds **heterogeneous hyperdensity on non-contrast CT representing calcification, fat and soft tissue; T1 hyperintensity from fat; contrast enhancement; diffusion restriction from hypercellularity** YW p.1854.
- **Pineoblastoma** — "**mixed-density appearance on CT with hyperdense solid and calcified portions** and a

heterogeneous appearance on MRI, with heterogeneous contrast enhancement on T1 and **diffusion restriction on DWI**" YW p.1853.

- **Pineocytoma** — "a **noticeably calcified ring on CT** and are **avidly contrast-enhancing on T1**, with **isointensity or hypointensity on non-contrast T1 and hyperintensity on T2**" YW p.1853. Importantly, "**pineoblastomas often appear identical to pineocytomas on MRI**" YW p.1160.
- **Tectal glioma** — "**poorly demarcated and rarely enhance**... usually **hypointense on T1 and hyperintense on T2**. **Enhancing tectal lesions with tumor volume greater than 10 cm³ are usually associated with a worse prognosis**" YW p.1825.
- **The unavoidable caveat** — "most GCTs can **resemble other pineal region and suprasellar tumors radiologically, including pineal parenchymal tumors, gliomas, and metastases**" YW p.1834.

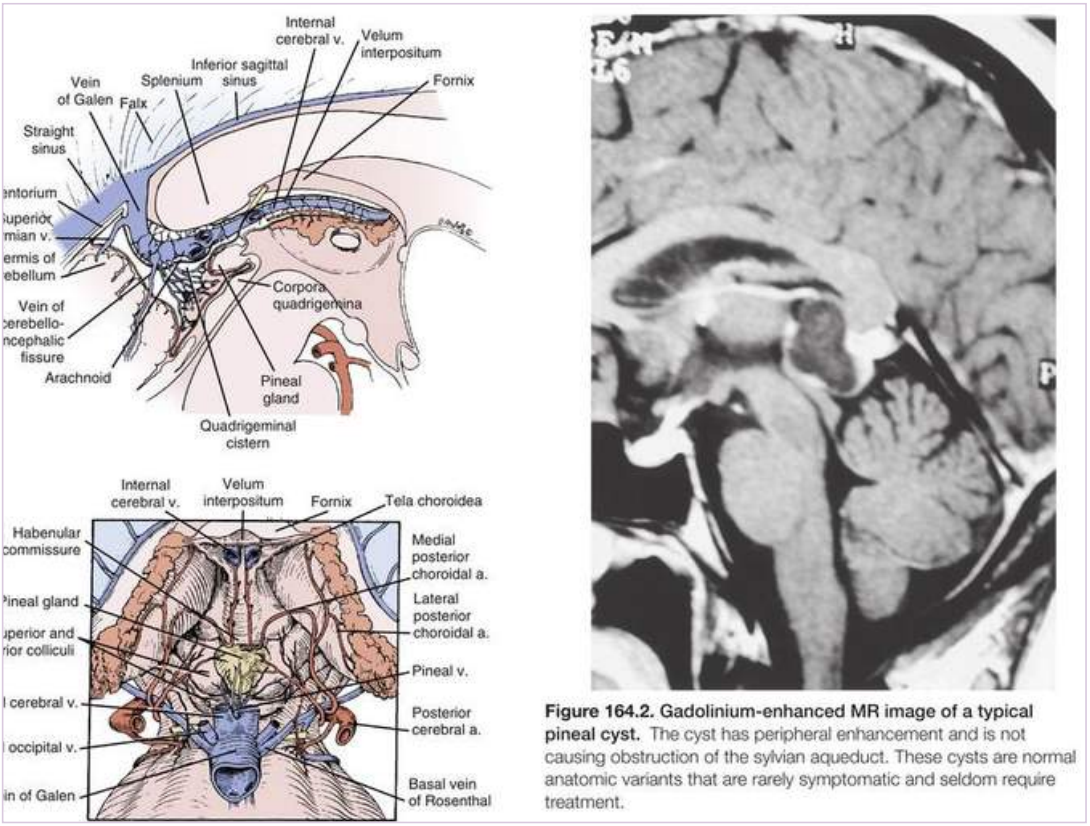


Figure 164.2. Gadolinium-enhanced MR image of a typical pineal cyst. The cyst has peripheral enhancement and is not causing obstruction of the sylvian aqueduct. These cysts are normal anatomic variants that are rarely symptomatic and seldom require treatment.

*Reproduced from Youmans & Winn 8e, Fig. 164.2, p. 1149 — Label when you reproduce it: the gadolinium-enhanced MR image of a typical pineal cyst — point out the **peripheral (rim) enhancement** representing compressed pineal parenchyma, the preserved patency of the sylvian aqueduct and the absence of hydrocephalus. State that these are normal anatomic variants (2% prevalence), rarely symptomatic and seldom needing treatment.*

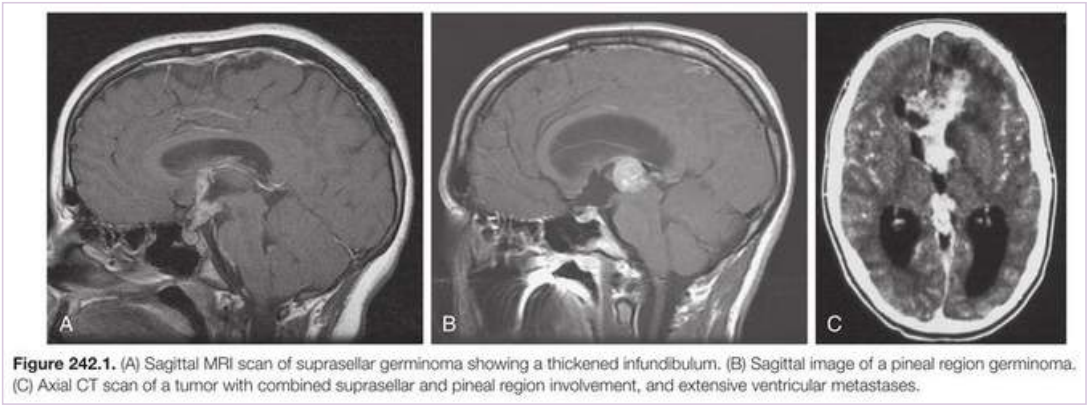


Figure 242.1. (A) Sagittal MRI scan of suprasellar germinoma showing a thickened infundibulum. (B) Sagittal image of a pineal region germinoma. (C) Axial CT scan of a tumor with combined suprasellar and pineal region involvement, and extensive ventricular metastases.

*Reproduced from Youmans & Winn 8e, Fig. 242.1, p. 1833 — Label when you reproduce it: (A) sagittal MRI of a **suprasellar germinoma with a thickened infundibulum**; (B) sagittal image of a **pineal region germinoma**; (C) axial CT of a tumour with **combined suprasellar and pineal involvement and extensive ventricular metastases** — the bifocal pattern that is almost diagnostic of germinoma.*

4.2 Staging imaging

- **Neuraxis imaging** — "Because GCTs can **disseminate within the neuraxis**, **staging by CSF cytology and MRI of the spine is a critical component** of the diagnostic evaluation... **at least 10% of patients have evidence of leptomeningeal or intraventricular tumor spread**" YW p.1834.
- **Who needs spinal MRI** — "**Spinal MRI to look for spinal seeding is required for patients with pineal cell tumors, malignant germ cell tumors, and ependymomas**" YW p.1159.
- **Timing trap** — "MRI of the spine can be **difficult to interpret in the immediate postoperative period** because blood clots or operative debris can **mimic spinal metastasis**. If the images are equivocal, **serial images should be obtained before instituting spinal irradiation**" YW p.1159.
- **Postoperative MRI** — "**Postoperative MRI with gadolinium enhancement should be performed within 72 hours** to determine the extent of resection and guide future management" [YW pp. 1157, 1159].

5. Tumour markers — the investigation that can replace surgery

- **The rule** — "**α-Fetoprotein or β-human chorionic gonadotropin tumor markers should be measured in either serum or CSF in all pineal tumor cases preoperatively. Elevations in these markers are pathognomonic for malignant germ cell elements** and make tissue diagnosis and surgery unnecessary. **Absence of these markers, however, does not rule out such tumors**" YW p.1147.
- **What each marker means** — "**α-Fetoprotein indicates the presence of fetal yolk sac elements**, and levels are **markedly elevated with endodermal sinus tumors**; smaller elevations are seen with some **embryonal cell carcinomas and immature teratomas**. **β-hCG is produced by trophoblastic elements; high levels are found with choriocarcinomas**, whereas low levels can be associated with some, but not all, **embryonal cell carcinomas and germinomas**" YW p.1150.
- **The management consequence** — "Because these markers are reliable indicators of malignant germ cell elements, **their presence makes surgery and biopsy unnecessary, and such patients should be managed with radiotherapy and chemotherapy**" YW p.1150.
- **The two traps** — "**although the presence of germ cell markers indicates a malignant germ cell tumor, absence of these markers does not rule out malignant germinoma or embryonal cell carcinoma**"; and "**if α-fetoprotein is elevated in the presence of a germinoma, it is likely that an embryonal cell carcinoma or endodermal sinus tumor is present as part of a mixed tumor**" YW p.1150.
- **Quantitative thresholds** — "**Expression of high levels of β-hCG (>50-100 IU/L) in the CSF or serum, or AFP >5-10 ng/mL or above institutional norms, is diagnostic of an NGGCT, and histologic confirmation is not required.** Whereas **AFP is never elevated in pure germinoma**, low-level expression of β-hCG (50-100 IU) is often observed in **germinomas with syncytiotrophoblastic cells**" YW p.1834. **CSF levels are considered more sensitive**

and therefore more reliable than serum YW p.1834.

- **Markers that are not useful in serum/CSF** — "**lactate dehydrogenase isoenzymes and placental alkaline phosphatase**... have **diagnostic value when used for the immunohistochemical analysis of histologic specimens but are not useful as serum or CSF markers**"; the same applies to **melatonin and S-antigen** for pineal parenchymal tumours YW p.1150.
- **Follow-up use** — "these tumor markers are also useful for **monitoring response to adjuvant therapy or as an early sign of recurrence**" YW p.1150.

Table 2 · Biologic markers in germ cell tumours — reproduced in full from Youmans & Winn 8e, Table 164.2, p. 1150, with the thresholds from Ch. 242, p. 1834.

Tumour	-human chorionic gonadotropin	-Fetoprotein
Benign germ cell	–	–
Immature teratoma	–	+/–
Germinoma	–	–
Germinoma with syncytiotrophoblastic cells	+	–
Embryonal cell carcinoma	+/–	–
Choriocarcinoma	++	–
Endodermal sinus tumour	–	++
Diagnostic threshold for NGGCT	**β-hCG >50-100 IU/L**	**AFP >5-10 ng/mL**

(c) Management [4]

6. Step 1 — manage the hydrocephalus

- **Why first** — "Because many patients initially present with obstructive hydrocephalus, **initial CSF diversion may be necessary**, providing not only symptomatic benefit but also **an opportunity for CSF tumor marker sampling**" YW p.1150.
- **The options, matched to urgency** YW p.1150:
  - **Life-threatening obstruction → bedside external ventricular drain.**
  - **Less emergent but significantly symptomatic → stereotactic-guided endoscopic third ventriculostomy**, "to allow **gradual reduction of intracranial pressure** and resolution of symptoms before tumor resection. **This method is preferable to ventriculoperitoneal shunting because it eliminates potential complications such as infection, overshunting, subdural hematoma, and peritoneal seeding of malignant cells.** Endoscopic third ventriculostomy **may also facilitate endoscopically assisted biopsy** of the pineal mass."
  - **Mildly symptomatic with anticipated gross total resection → temporary ventricular drain placed at the time of resection**, later removed or converted to a shunt.
  - **Mild asymptomatic hydrocephalus** — "frequently **resolves following resection** of a pineal mass, as the third ventricle is communicated with the quadrigeminal cistern during the surgery, or compression of the third ventricle outflow and aqueduct is relieved with tumor resection, **obviating the need for CSF diversion**."
- **Ch. 242 on the same decision** — historically VP shunt was used, but "given that shunting may place the patient at risk for **myriad shunt-related complications, including metastases**, this approach has become **less common as a primary management strategy**"; **ETV has emerged as the more popular alternative** because it "allows biopsy in many cases, permits CSF sampling for markers and cytology, and achieves internal CSF diversion". ETV "is **not applicable for patients with significant tumor involvement of the third ventricular floor**, a situation that applies in most suprasellar GCTs, and in such cases, **shunt insertion remains a valuable option**" YW p.1834.

7. Step 2 — get a tissue diagnosis (unless markers have already given it)

- **The principle** — "Given the **diverse pathology** that can occur in the pineal region, **a histologic diagnosis is necessary to guide management decisions**... **CSF cytology and radiographic examination** provide insight but "are **not sufficiently sensitive to supplant a tissue diagnosis**. **CSF cytology occasionally reveals malignant cells but is rarely diagnostic**" YW p.1151.
- **The only exception** — "the only time that a tissue diagnosis is precluded is **when malignant germ cell markers are present**. In this case, **chemotherapy and radiotherapy should be pursued straightaway**" YW p.1151.
- **Open resection — the case for it** YW p.1151:
  - "**the ability to obtain larger amounts of tissue and more extensive tissue sampling**. This is particularly important for pineal region lesions in general and **germ cell tumors in particular because heterogeneity and mixed cell populations are common**."
  - **Sampling error**: "several studies have suggested **sampling errors of roughly 18% to 21%** when comparing initial pathology on stereotactic biopsy and final pathology on open resection."
  - **For one-third of benign tumours, resection is complete and curative**, "thus making open surgery the procedure of choice."
  - Aggressive debulking "can **reduce mass effect on critical structures; relieve obstructive hydrocephalus, obviating the need for permanent CSF diversion; and reduce the risk for postoperative hemorrhage into an incompletely resected tumor bed**."
  - The price: "**higher short-term surgical morbidity than stereotactic needle biopsies**, although this may be balanced by the **long-term advantage of tumor control**."
- **Stereotactic biopsy — the case for and against** [YW pp. 1151-1152]:
  - **For**: "relative **ease of performance and reduced complications** when compared with an open procedure"; a retrospective multicentre study of **370 patients reported a mortality rate of 1.3%**.
  - **Against**: "**the pineal region is one of the most hazardous locations to safely perform stereotactic biopsy** given surrounding structures, and **extreme care must be taken in target and trajectory planning**". Haemorrhage arises from **highly vascular tumours, damage to the deep venous system, and bleeding into the ventricle, where tissue turgor is insufficient to tamponade minor bleeding**. There is also a report of **metastatic seeding along the biopsy tract after biopsy of a pineoblastoma**.
  - **Technique**: the commonest trajectory is a **precoronal entry with an anterolaterosuperior approach** that "avoids the interior surface of the lateral ventricle and comes **inferior and lateral to the internal cerebral veins**"; the alternative is a **posterolaterosuperior approach near the parieto-occipital junction** for tumours extending laterally or superiorly. Take **multiple cores**, prefer a **side-cutting cannula over cup forceps**, irrigate continuously for up to **15 minutes** if bleeding, and obtain an **immediate postoperative CT** if bleeding is suspected YW p.1152.
- **Endoscopic biopsy** — flexible endoscopes allow **third ventriculostomy and biopsy through the same bur hole**; but "the biopsy of the tumor is taken along its **ventricular surface, where there is no tissue turgor to tamponade bleeding**", and in a series of **293 patients (33% pineal), moderate to severe bleeding occurred in 19%, including one death from uncontrollable bleeding**; simultaneous biopsy and ventriculostomy can be difficult because **separate trajectories are required** [YW pp. 1151-1152].
- **When biopsy is the better choice** — "biopsy may be most appropriate in patients with **known primary systemic tumors, multiple lesions, or medical conditions that make open resection dangerous**"; **radiographic evidence of brainstem invasion** may also favour biopsy, "**However, imaging is often misleading, and tumors that appear to be infiltrative may actually have a discernable and dissectable capsule amenable to resection**" YW p.1151.

8. Step 3 — choose the corridor

- **The two families** — "Several variations on approaches to the pineal region exist, but essentially they are categorized as **supratentorial or infratentorial**" YW p.1152. The named approaches are the **supracerebellar infratentorial (SCIT),**

CHAPTER 11

Cerebrovascular II: AVM, Fistulae, Stroke & Venous Disease

18
QUESTIONS SOLVED

Arteriovenous Malformation (cerebral & spinal) — 5 questions

Spinal AVM:
a) Classification.
b) Clinical presentations.
c) Angiographic finding.

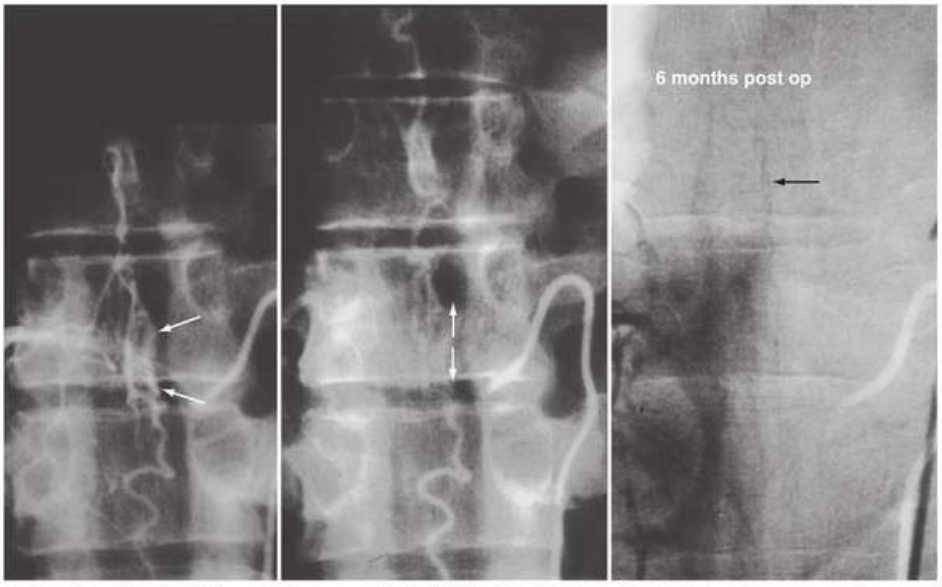
LONG | JUN 2020 · Paper II · Q4 | 10 marks

Also asked as: Arteriovenous Malformation (cerebral & spinal) — also asked as DEC 2020 · Paper II · Q10 ("Spinal AV fistula's: Classification and management")

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 462 *Classification of Spinal Arteriovenous Lesions* (Mooney, Kim, Spetzler), §Introduction, §Historical Classification Systems and §Spetzler Classification System, pp. 3779-3783 (Fig. 462.1 algorithm, p. 3780; **Table 462.1 — Comparison of Spetzler Classification with Previous Nomenclature**, p. 3780; Figs. 462.2-462.7, pp. 3781-3783). Ch. 464 *Microsurgical Treatment of Spinal Vascular Malformations* (Oldfield et al.), §Anatomy, §Classification, §Etiology, Pathophysiology, Clinical Presentation and Natural History, §Diagnostic Imaging, §Selective Spinal Arteriography and §Microsurgical Management, pp. 3797-3818 (Figs. 464.1-464.28; **Box 464.1 — Classification of Spinal Vascular Abnormalities Based on Distinct Biologic Features**, p. 3805; **Table 464.1**, p. 3806; **Tables 464.2 and 464.3**, pp. 3806-3807; **Table 464.4**, p. 3811). Supplementary: Ch. 463 *Endovascular Treatment of Spinal Vascular Malformations*, pp. 3788-3794 (Fig. 463.4, p. 3792).

1. Fix the vocabulary before you write a word

- **Two families only — fistula or malformation.** Youmans is explicit: "like vascular lesions affecting other tissues, spinal vascular malformations are divided into two groups: **AVFs and AVMs**. AVFs are further segregated into **extradural, dural, and intradural** lesions" YW p.3800. Everything else in the literature is a re-labelling of these two families.
- **The single discriminating question on angiography** — *is there an arteriovenous nidus?* The Spetzler algorithm (Fig. 462.1) begins with exactly that question: **no nidus → AVF; nidus → AVM** YW p.3780.
- **AVF** = a direct artery-to-vein shunt with **no intervening capillary bed and no nidus**. The microangiographic proof is definitive: microarteriography of a "type I" lesion shows a dural artery splitting into loops that coalesce and join a medullary vein, with **"the absence of any true glomus of capillaries, a finding indicating that these lesions are arteriovenous fistulas, not arteriovenous malformations"** YW p.3797.
- **AVM** = a true nidus of abnormal vessels, intramedullary (glomus) or extending beyond the cord (juvenile/metameric) [YW pp. 3799, 3802].
- **Why the shift from numbers to descriptors** — Spetzler's group argue that "rather than using the terms type I to type IV, nomenclature is based on the anatomic descriptors **intradural versus extradural, intramedullary versus extramedullary, and ventral versus dorsal**", because "most modern classification schemes for diseases are based on knowledge of the biology of the disorders, rather than simply the anatomy of the lesion" [YW pp. 3780, 3800].



. Posterolateral perimedullary arteriovenous fistula (AVF). *Left,* Selective spinal arteriography demonstrating that the nidus of this pial AVF is supplied by the descending limb of a posterior spinal artery, that there is more than one arteriovenous shunt, and that the us shunting occurs at a moderate pace. The site of the nidus *(arrows)* is identified just proximal to the site of initial venous dilation from which the venous flow diverges rostrally and caudally *(middle, arrows). Right,* The feeding vessel *(arrow)* has returned to a more nonths after surgical excision and the absence of filling of the AVF.

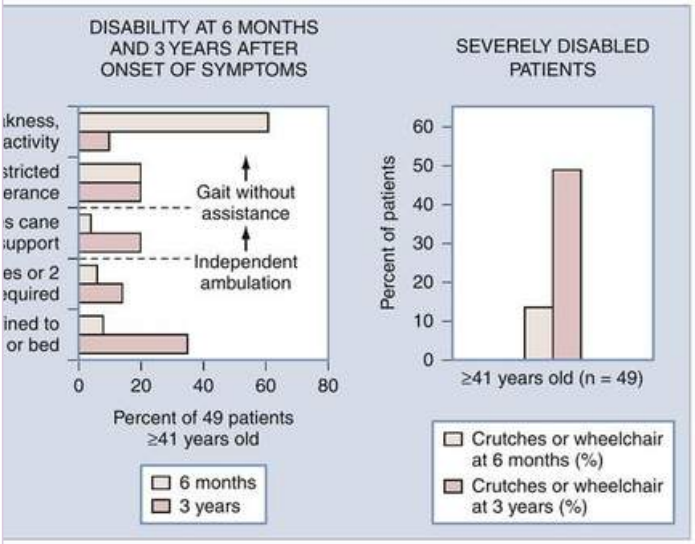


Figure 464.13. Degree of functional disability at 6 months and 3 years after the onset of symptoms in 49 patients 41 years of age or older reported by Aminoff and Logue.[42] Almost all patients had spinal dural arteriovenous fistulas. Note that the greatest change in function between 6 months and 3 years was in patients with minimal neurological deficit who progressed to severe functional disability. By 3 years, one-half of the patients were confined to a wheelchair or had to use crutches to ambulate. *(From Oldfield E. Spinal vascular malformations. In: Swash M, ed. Outcomes in Neurological and Neurosurgical Disorders. Cambridge, UK: Cambridge University Press; 1998.)*

*Reproduced from Youmans & Winn 8e, Fig. 464.1, p. 3797 — Label when you reproduce it: the spinal ramus of the intercostal artery entering the intervertebral foramen and dividing into (1) the **radicular arteries** to the anterior and posterior nerve roots, (2) the **dural artery** to the spinal dura and nerve root sleeve, and (3) at some levels the **medullary artery**, which pierces the dura next to the root ganglion, ascends and joins the anterior or a posterior spinal artery. On the venous side label the **radial veins** draining the cord to the **coronal venous plexus** in the pia, the **sulcal veins**, and the **medullary veins** that pierce the dura beside the roots to reach the extradural veins. This one diagram explains every lesion in the classification: a dural artery-to-medullary vein shunt is a dural AVF, a shunt on a spinal artery is intradural, and a shunt outside the dura is extradural.*

2. Normal spinal vascular anatomy — the substrate every classification is built on

2.1 Arterial

- **Anterior spinal artery** — formed by two small branches from the medial aspect of the vertebral arteries uniting in the midline at the **cervicomedullary junction**; it descends the whole cord in the **anterior median fissure** YW p.3797.
- **Sulcal arteries** arise from the anterior spinal artery **at a 90-degree angle** and perfuse **the anterior two-thirds of the cord — anterior horns, corticospinal tracts and spinothalamic tracts** YW p.3797.

- **Posterior spinal arteries** (paired) arise from the vertebral artery or PICA and supply **the posterior one-third**, i.e. **the entirety of the posterior columns and a portion of the corticospinal tracts**; inferiorly the paired posterior spinal arteries and the anterior spinal artery **anastomose at the conus** YW p.3798.
- **Medullary arteries** — paired at every segment in the first 6 fetal months; most regress by the third trimester, leaving only **6 to 10 medullary arteries in the adult**. Cervical medullary arteries arise from the vertebral arteries and the thyrocervical trunk YW p.3798.
- **Artery of Adamkiewicz (arteria radicularis magna)** — the largest medullary artery, supplying the middle/lower thoracic and lumbar cord; **most commonly from the left between T8 and L2**, but it may arise **anywhere between T3 and L4** and may come from the right YW p.3798.
- **Watershed** — "the spinal 'watershed' zone lies in the region of **T2-T4**, between the well-collateralized cervical region and the uppermost region supplied by the artery of Adamkiewicz. **Profound hypotension may lead to ischemia and infarction in this region**" YW p.3798.
- **Filum terminale** — a single **artery of the filum terminale** arises from the termination of the anterior spinal artery; the **vein of the filum**, continuous with the anterior spinal vein, runs on its ventral aspect and traverses the dura to the epidural sacral plexus, **allowing potential bidirectional flow** — which is why filum fistulas transmit venous hypertension cranially [YW pp. 3798-3799].

2.2 Venous — and the valve that makes the disease possible

- Three plexuses: **intramedullary veins** (sulcal veins in the anterior median fissure draining grey matter; radial veins traversing anterolateral and dorsal cord), all draining to the **coronal venous plexus** — an intradural extramedullary plexus on the pial surface; and **medullary veins**, inconsistent and sporadic, which cross the subarachnoid space and drain the coronal plexus into the **epidural venous plexus**, piercing the dura adjacent to the dural penetration of the nerve roots [YW pp. 3798-3799].
- **The key valve** — "at the point of dural penetration, **valves prevent venous reflux from the epidural venous plexus into the valveless intrathecal venous system**" YW p.3799. Extradural AVFs cause myelopathy only when that valve is **incompetent** YW p.3800.
- **The pathophysiological consequence** — arterialised flow in the coronal venous plexus "transmits high pressure to the **valveless radial and sulcal veins** within the substance of the cord, leading to **venous congestion, venous hypertension, diminished arterial perfusion, ischemia, and myelopathy**" YW p.3799.

(a) Classification of spinal arteriovenous lesions [5]

3. The historical systems — know them, because the examiner will use the old numbers

- **Gaupp 1888** gave the first autopsy description of a spinal AVM; **Krause 1911** performed the first surgical ligation of a spinal AVF YW p.3779.
- **Wyburn-Mason 1943** — 110 patients; two types: **angioma racemosum venosum** (a mass of turgid pial veins, usually posterior and below the mid-thoracic cord) and **angioma racemosum arteriovenosum** (a fistulous capillary bed, commonly at the cervical or lumbar enlargement). Today these are the **intradural dorsal AVF** and the **intramedullary AVM** respectively YW p.3779.
- **Di Chiro and colleagues, 1960s** — three types: **type I "single coiled vessel"** (thought commonest), **type II "glomus"** (clear nidus), **type III "juvenile"** (extensive, encompassing an entire somite). All three were originally believed to be true AVMs with a nidus in the pia YW p.3779.
- **Aminoff & Logue and Kendall & Logue (1977)** showed the type I "single coiled vessel" was in fact **an AVF located along the dural sheath of a nerve root**, and advocated **simple excision of the fistula** rather than removing a large section of the coiled vessel — the single most important conceptual correction in the field YW p.3779.
- **Djindjian 1977 and Heros** added **type IV = perimedullary fistula**, ventral, fed by the anterior spinal artery [YW pp. 3779, 3797].

- **Borden et al.** — a three-point anatomic classification using the term *dural arteriovenous fistulous malformation* YW p.3779.
- **Niimi and Berenstein** — spinal vascular lesions (dural and extradural fistulas) versus spinal cord vascular lesions (AVMs, AVFs, metameric forms) YW p.3779.
- **Bao and Ling** — intramedullary AVMs, intradural AVFs, dural AVFs, paravertebral AVMs, **Cobb syndrome** YW p.3779.
- **Rosenblum et al.** — 81 patients, two major types by location of the nidus: **intradural versus dural**; intramedullary lesions further subclassified as **glomus (compact)** and **juvenile (diffuse)** YW p.3779.

Table 1 · Comparison of the Spetzler classification of spinal arteriovenous lesions with previous nomenclature — reproduced in full from Youmans & Winn 8e, Table 462.1, p. 3780. Column headings are the Spetzler categories. N/A = not applicable.

Reference(s)	Intradural Dorsal (AVF)	Intradural Ventral (AVF)	Extradural (AVF)	Intramedullary (AVM)	Extradural-Intradural (AVM)	Conus Medullaris (AVM)
Wyburn-Mason	Angioma racemosum venosum	N/A	N/A	Angioma racemosum arteriovenosum	N/A	N/A
Rosenblum et al.	Dural AVF	Intradural AVF	N/A	Intradural AVM (glomus and juvenile)	N/A	N/A
Di Chiro; Di Chiro et al.; Djindjian et al.; Heros et al.	Type I	Type IV (perimedullary fistula)	N/A	Type II (glomus)	Type III (juvenile)	N/A
Borden et al.	Type III	N/A	Type I	N/A	Type II	N/A
Niimi and Berenstein	Spinal dural fistula	Spinal dural fistula	Spinal extradural AVF	Isolated spinal cord AVM	Multiple spinal cord AVMs	N/A
Bao and Ling	Dural AVF	Intradural AVF	N/A	Intramedullary AVM (glomus and juvenile)	N/A	N/A

4. The Spetzler six-type (anatomic) classification — the one to write first

"The classification scheme is broken into **six types** of lesions: (1) **extradural AVFs**, (2) **intradural dorsal AVFs**, (3) **intradural ventral AVFs**, (4) **extradural-intradural AVMs**, (5) **intramedullary AVMs**, and (6) **conus medullaris AVMs**" YW p.3780.

4.1 Extradural AVF

- **Anatomy** — "an anomalous connection between the **epidural segment of a radicular artery before it enters the dural sleeve** of a nerve root and the **epidural venous plexus**" YW p.3780.
- **Mechanism** — with an extensive epidural venous network, "this type of fistula can result in **marked venous engorgement and compression on the thecal sac and adjacent nerve roots**"; a **vascular steal phenomenon** may also shunt blood away from the cord and contribute to myelopathy [YW pp. 3780-3781]. Youmans (Ch. 464) adds that venous drainage reaches the intrathecal system **through an incompetent valve in the spinal dura**, so that "at arteriography, the intrathecal portion of the venous drainage of these lesions has an appearance and pathophysiology **identical to those produced by spinal dural AVFs**" YW p.3800.
- **Treatment** — "endovascular embolization can be **curative**, with surgical resection reserved for a persistent fistula or neural compression requiring an open approach" YW p.3781.

4.2 Intradural dorsal AVF — the commonest lesion of all

- **Anatomy** — "the **most common spinal vascular malformation** and correspond to the **type I** spinal fistulas in the classical nomenclature… a direct connection between a **radicular artery** and a **medullary or radicular vein within**

the dural sleeve of the associated nerve root" YW p.3781. Ch. 464 words the same lesion as a **dural artery** (a branch of the spinal arterial ramus arising within the intervertebral foramen) forming a fistulous connection **within the dura** with a medullary vein at the point of dural penetration, "usually at the site of dural penetration of a spinal nerve root" YW p.3799.

- **Mechanism** — medullary veins anastomose with the dorsal venous plexuses, so these fistulas show **long, tortuous early-draining veins through the coronal venous plexus**; venous hypertension and engorgement create local mass effect and **venous congestion causes myelopathy** YW p.3781.
- **Surgery** — a **unilateral hemilaminotomy at the target level** can be enough; identify the arterialised vein under the microscope, trace it to its connection at the dural root sleeve, and **bipolar coagulate and sharply section the vein at the dural sleeve**; ICG or intraoperative angiography confirms obliteration YW p.3781.

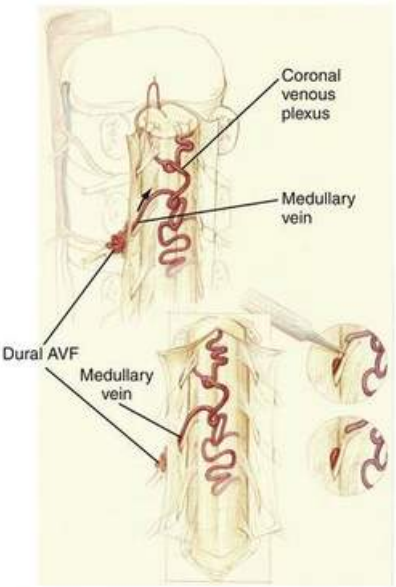


Figure 464.3. Vascular anatomy of a dural arteriovenous fistula *(AVF).* Dural AVFs are supplied by a dural artery and drained by a medullary vein, which carries the arterialized blood retrograde to the normal direction of venous drainage to the coronal venous plexus, which becomes elongated, tortuous, and dilated by the reception of arterial blood. Because of the valveless nature of the intradural venous system, the increased venous pressure within the coronal venous plexus is transmitted to the spinal cord and causes venous congestion and myelopathy. Almost all dural AVFs can be permanently obliterated by identifying the site of intradural penetration of the arterialized vein draining the dural AVF (almost always next to the dural penetration of the nerve root), coagulating a segment of it with bipolar forceps, and sharply dividing it. *(Drawing by Howard Bartner, National Institutes of Health; from Oldfield EH, Doppman JL. Spinal arteriovenous malformations. Clin Neurosurg. 1988;34:161–183.)*

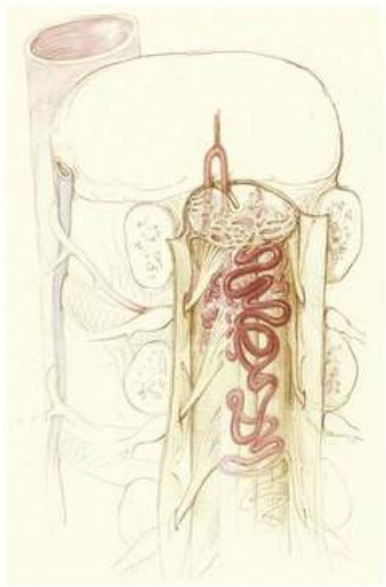


Figure 464.4. Vascular anatomy of the juvenile type of intramedullary arteriovenous malformation (AVM). Juvenile-type intramedullary AVMs are fed by enlarged medullary arteries through dilated anterior and posterior spinal arteries. The nidus of the AVM is often extensive, filling the spinal canal, and commonly contains neural tissue within the interstices of the vessels of the AVM. *(Drawing by Howard Bartner, National Institutes of Health; from Oldfield EH, Doppman JL. Spinal arteriovenous malformations. Clin Neurosurg. 1988;34:161–183.)*

The artery of Adamkiewicz, or the arteria radicularis magna is the largest medullary artery and supplies the middle and lowe thoracic and lumbar segments. It most commonly arises fron the left side between T8 and L2, but it may originate anywher between T3 and L4 and may originate from the right.[18] Th

*Reproduced from Youmans & Winn 8e, Fig. 464.3, p. 3798 — Label when you reproduce it: the **dural AVF** embedded in the dural nerve-root sleeve, the feeding **dural artery**, the **medullary vein** carrying arterialised blood *retrograde* to the normal direction of venous drainage, and the **coronal venous plexus** rendered elongated, tortuous and dilated. Write beside the drawing the two sentences that earn the marks: the intradural venous system is **valveless**, so coronal plexus pressure is transmitted to the cord, causing venous congestion and myelopathy; and almost all dural AVFs are cured by coagulating and sharply dividing the arterialised vein at its point of intradural penetration, almost always next to the dural penetration of the nerve root.*

4.3 Intradural ventral AVF (perimedullary / pial; old type IV)

- **Anatomy** — located **in the subarachnoid space**, an abnormal communication between the **anterior spinal circulation** and the venous drainage of the cord; previously classified as **type IV** AVFs YW p.3781. Ch. 464 defines the pial type as "an arteriovenous shunt **in the pia** that is a direct communication between an intradural spinal artery and the coronal venous plexus", distinguished from glomus AVMs by **lack of an intramedullary component and lack of intervening small branches between arteries and veins**, and frequently associated with a **venous varix** at the fistulous point YW p.3800.
- **The angiographic rule for the ward round** — "on standard anteroposterior spine angiograms, intradural ventral AVFs may be differentiated from intradural dorsal AVFs by a **midline fistulous pouch versus a lateral fistulous pouch**" YW

p.3781.

- **Anson and Spetzler subtypes** YW p.3781:
  - **Type A** — small, simple fistula with **a single feeding artery from the anterior spinal artery**.
  - **Type B** — larger fistula with a **primary anterior-spinal feeder plus small feeders from adjacent arteries**.
  - **Type C** — **giant fistula with multiple arterial pedicles and immensely engorged venous outflow channels**.
- **Merland's parallel subtypes** (Ch. 464) [YW pp. 3803, 3816]:
  - **Type I** — slow flow, relatively mild venous hypertension; usually **conus or filum terminale**; a **single fistulous connection between the terminal portion of a long thin anterior spinal artery and the coronal venous plexus**; minimal venous dilation and tortuosity.
  - **Type II** — posterolateral or anterolateral to the cord; **one or two main dilated feeders** from the anterior or posterior spinal arteries with **multiple discrete shunts** into a dilated tortuous venous system; relatively higher flow.
  - **Type III** — **the most common pial fistula**; high flow, **multiple extremely dilated feeders converging into a single shunt draining into a giant venous ectasia**.
- **Treatment logic** — microsurgery is preferred over embolization "to avoid the risk of embolization through the anterior spinal artery", although embolization may be useful or necessary in **giant type C** lesions; the surgical approach must **maximise exposure of the anterior spinal artery** and success "hinges on the surgeon's ability to identify and preserve the normal branches of the anterior spinal artery" YW p.3781. Type I lesions are "**nearly uniformly treated with microsurgical obliteration** because embolization of the single long anterior spinal artery feeding pedicle… is unsafe"; **embolization alone of type II fistulas is generally not curative** because of the multiple isolated shunts; type III can be treated with **coils, microsurgery or both** YW p.3816.

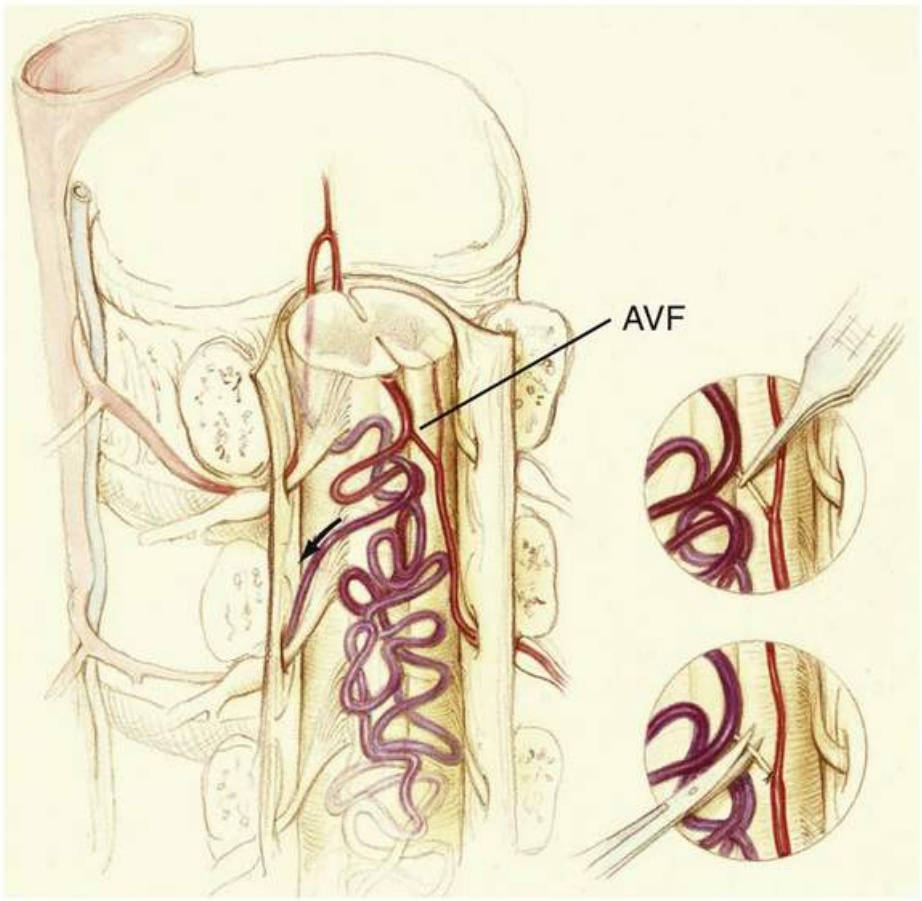


Figure 464.6. Vascular anatomy of a perimedullary (pial) arteriovenous fistula *(AVF).* Medullary arteries provide the arterial supply, in this instance via a posterior spinal artery. Most intradural AVFs occur in the lower thoracic or lumbar area and are supplied by the anterior spinal artery. Large perimedullary AVFs often have associated venous varices at the junction of the arterial and venous elements in which the portion of the vein just distal to the arteriovenous shunt is dilated. Many of these lesions are not as simple as the one illustrated here. They can have more than one simple fistula in the same region of the pia, and at surgery, the tortuosity and dilation of the venous drainage often obscure the site of the AVF beneath a nest of blood vessels. *(Drawing by Howard Bartner, National Institutes of Health; from Oldfield EH, Doppman JL. Spinal arteriovenous malformations. Clin Neurosurg. 1988;34:161–183.)*

*Reproduced from Youmans & Winn 8e, Fig. 464.6, p. 3799 — Label when you reproduce it: the **perimedullary (pial) AVF** — the medullary artery (here a posterior spinal artery) feeding a direct shunt on the pial surface, and the **venous varix** at the arterio-venous junction, i.e. the dilated portion of the vein just distal to the shunt. Note in your label the two traps the caption warns about: most intradural AVFs are in the **lower thoracic or lumbar** region and are supplied by the **anterior spinal artery**, and at surgery "the tortuosity and dilation of the venous drainage often obscure the site of the AVF beneath a nest of blood vessels."*

4.4 Extradural-intradural AVM (juvenile, type III, metameric, Cobb)

- "Extensive and can encompass an **entire somite** of the spine and involve **bone, muscle, skin, and nerve tissue**. Hence they reside in the extradural and intradural space and even **extend beyond the spine**" YW p.3782.

- "These AVMs correspond to **juvenile type III lesions** in the classical nomenclature and are also called **metameric AVMs**. When these lesions are so extensive as to encompass an entire somite, they are referred to as **Cobb syndrome**" YW p.3782.
- **Angioarchitecture** — fed by **multiple enlarged medullary arteries**, filling a large nidus with intramedullary and intradural-extramedullary components; "the nidus **contains neural tissue within its interstices**"; **high-flow, high-pressure**, and "may be associated with **intranidal aneurysms and aneurysms of the feeding artery**" YW p.3799.
- **Treatment goals are usually palliative** — "removal of mass effect and palliation of symptoms of vascular steal and venous hypertension are often the primary treatment goals"; individually tailored approaches involving open vascular, endovascular and additional surgical disciplines YW p.3782.

4.5 Intramedullary AVM (glomus, type II)

- "True AVMs of the spinal cord parenchyma that are **similar to cerebral AVMs**… the feeding arteries are from either the **posterior or anterior spinal artery** with an **intervening nidus**, and their drainage is through the **coronal venous plexus**" YW p.3782.
- **Compact or diffuse**; symptoms arise from **acute hemorrhage or steal** from the cord parenchyma YW p.3782. The compact nidus is **intramedullary, usually in the anterior half of the cord, confined to a short segment**, with **one or two feeding vessels** from the anterior or posterior spinal arteries YW p.3799.
- **Surgery is primary**, with embolization as **adjunct or salvage**; resection must adhere "tightly to the coils of the AVM or the pial resection technique to avoid overresection of adjacent functional spinal cord tissue"; ICG angiography delineates the anatomy and confirms obliteration YW p.3782.

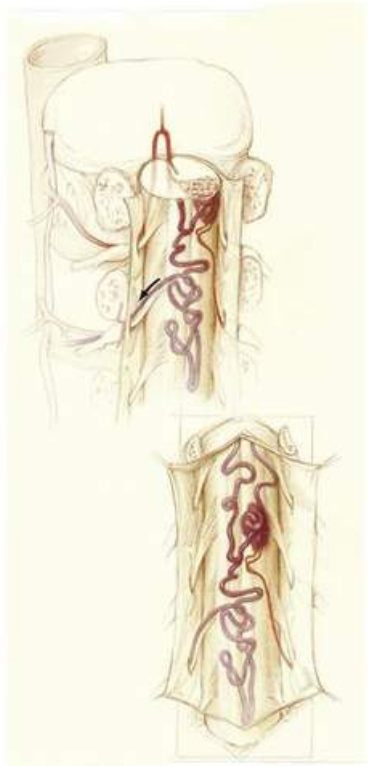


Figure 464.5. Vascular anatomy of the glomus type of intramedullary arteriovenous malformation (AVM). The nidus of glomus-type intramedullary AVMs is a tightly packed mass of blood vessels confined to a short segment of the spinal cord. These AVMs, commonly found in the anterior half of the spinal cord, are usually supplied by the anterior spinal artery. *(Drawing by Howard Bartner, National Institutes of Health; from Oldfield EH, Doppman JL. Spinal arteriovenous malformations. Clin Neurosurg. 1988;34:161–183.)*

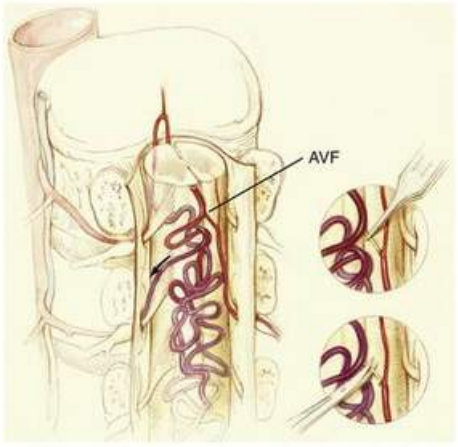


Figure 464.6. Vascular anatomy of a perimedullary (pial) arteriovenous fistula *(AVF)*. Medullary arteries provide the arterial supply, in this instance via a posterior spinal artery. Most intradural AVFs occur in the lower thoracic or lumbar area and are supplied by the anterior spinal artery. Large perimedullary AVFs often have associated venous varices at the junction of the arterial and venous elements in which the portion of the vein just distal to the arteriovenous shunt is dilated. Many of these lesions are not as simple as the one illustrated here. They can have more than one simple fistula in the same region of the pia, and at surgery, the tortuosity and dilation of the venous drainage often obscure the site of the AVF beneath a nest of blood vessels. *(Drawing by Howard Bartner, National Institutes of Health; from Oldfield EH, Doppman JL. Spinal arteriovenous malformations. Clin Neurosurg. 1988;34:161–183.)*

a spinal nerve root (Fig. 464.9).[20] Examination of specimens with microarteriography shows a small number of arterial branches within the dura converging into a medullary vein just beneath the inner layer of the dura (see Fig. 464.2).[21] The medullary vein, which in most cases represents the only outflow for the AVF, carries arterialized blood flow retrograde into the coronal venous plexus. Under normal circumstances, the venous blood flow in the coronal venous plexus is diverted through the dura and into the extradural venous system. With spinal dural AVFs, the arteri-

*Reproduced from Youmans & Winn 8e, Fig. 464.5, p. 3799 — Label when you reproduce it: the **glomus-type intramedullary AVM** — a tightly packed nidus of vessels confined to a short segment of cord, sited in the anterior half, supplied by the anterior spinal artery. Contrast it in your caption with Fig. 464.4 (juvenile type), in which enlarged medullary arteries feed dilated anterior and posterior spinal arteries and an extensive nidus fills the spinal canal and contains neural tissue in its interstices.*

4.6 Conus medullaris AVM — the type Spetzler added

- "Lesions **centered in the conus medullaris and upper cauda equina**… tend to be **diffuse** and classically have **multiple feeding vessels from both the posterior and the anterior spinal arteries**" YW p.3783.
- "Because of the **increased cerebrospinal fluid space** in the area of the conus, **large dilated venous ectasia can occur** ", producing mass effect, myelopathy, venous compression, venous congestion and arterial steal from the conus YW p.3783.
- **The examination point** — "a **cauda equina-type syndrome** can result owing to compression on nerve roots as they exit the conus. Therefore these lesions can manifest with **both upper and lower motor neuron signs**, which is unique compared with other arteriovenous lesions" YW p.3783.
- **Management** — "a **combined endovascular and microsurgical** therapeutic approach is recommended… early identification and preservation of the **anterior spinal artery** is crucial" YW p.3783.

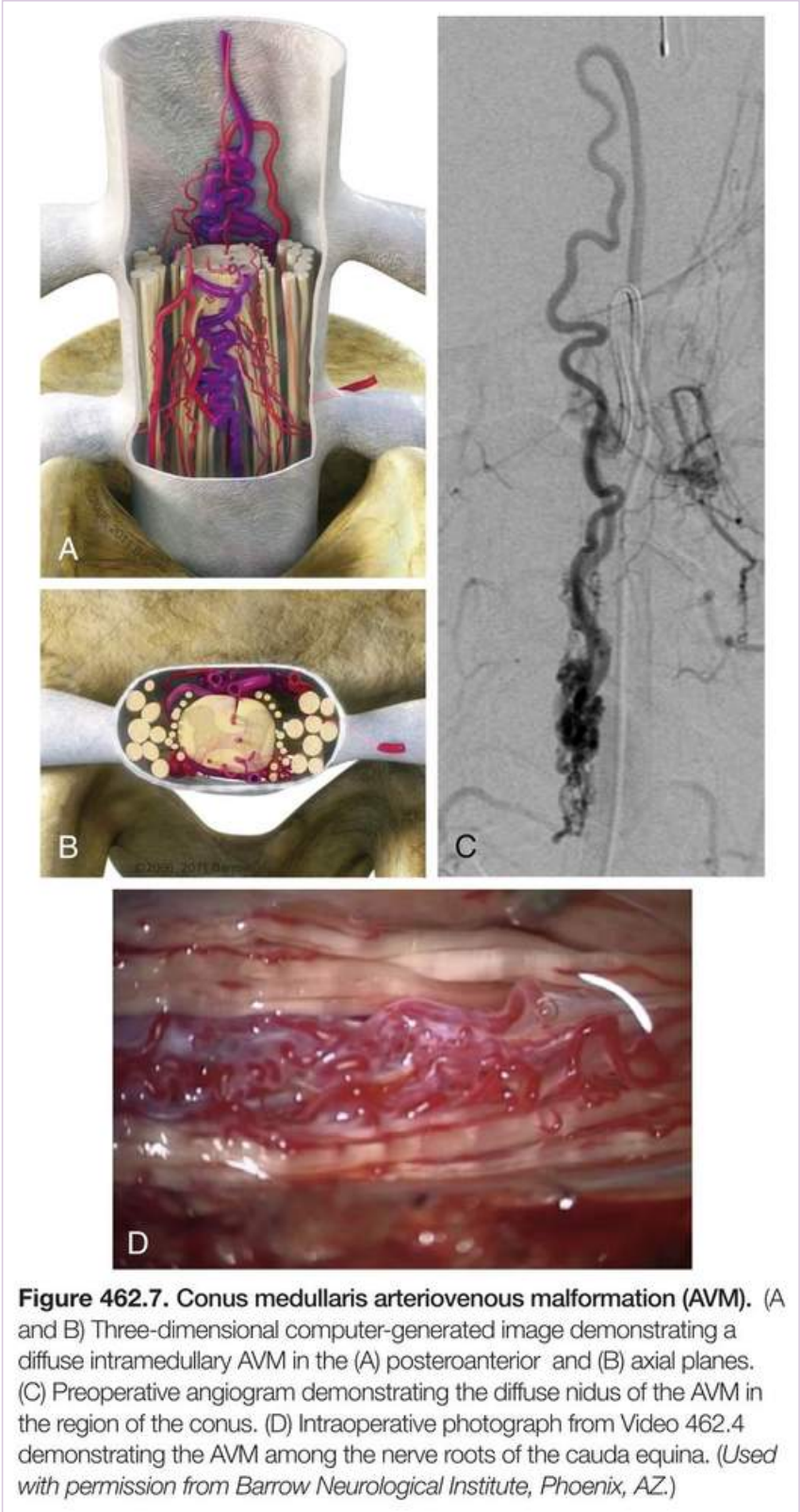


Figure 462.7. Conus medullaris arteriovenous malformation (AVM). (A and B) Three-dimensional computer-generated image demonstrating a diffuse intramedullary AVM in the (A) posteroanterior and (B) axial planes. (C) Preoperative angiogram demonstrating the diffuse nidus of the AVM in the region of the conus. (D) Intraoperative photograph from Video 462.4 demonstrating the AVM among the nerve roots of the cauda equina. (*Used with permission from Barrow Neurological Institute, Phoenix, AZ.*)

*Reproduced from Youmans & Winn 8e, Fig. 462.7, p. 3783 — Label when you reproduce it: the **conus medullaris AVM** in (A) posteroanterior and (B) axial three-dimensional reconstructions, (C) the preoperative angiogram showing the diffuse nidus in the region of the conus, and (D) the intraoperative photograph of the malformation lying among the nerve roots of the cauda equina. Mark the feeders arising from both anterior and posterior spinal arteries and the dilated venous ectasia — the anatomical reason this is the one spinal AVM that gives both upper and lower motor neuron signs.*

5. The parallel biological classification — Oldfield's Box 464.1

Youmans' other authorship prefers a classification "based on **distinct biologic features**" rather than pure anatomy YW p.3805:

Table 2 · Classification of spinal vascular abnormalities based on distinct biologic features — reproduced from Youmans & Winn 8e, Box 464.1, p. 3805, with the Spetzler equivalents added from Ch. 462, pp. 3780-3783 for cross-referencing.

Oldfield biological category	Spetzler anatomic equivalent	Classical Di Chiro number	Core biology
Dural AVFs	Intradural dorsal AVF	Type I	**Acquired**; dural artery to medullary vein in the root sleeve; venous congestive myelopathy
Intradural AVMs — spinal cord AVMs — juvenile AVMs	Extradural-intradural AVM	Type III (juvenile/metameric)	Congenital; multiple feeders, huge nidus containing neural tissue, high flow, somite distribution (Cobb)
Intradural AVMs — spinal cord AVMs — glomus AVMs	Intramedullary AVM	Type II (glomus)	Congenital; compact intramedullary nidus, short cord segment, high flow, nidal/feeder aneurysms
Intradural AVMs — perimedullary AVFs	Intradural ventral AVF (and conus AVM)	Type IV	Direct pial shunt, no nidus, venous varix; Merland I-III / Anson-Spetzler A-C
Cavernous angiomas	(not in the Spetzler AV scheme — angiographically occult)	—	**5% to 12%** of all spinal vascular abnormalities; dilated venous channels without intervening neural tissue; sporadic 80%, familial 20%; CCM1 (7q21.2), CCM2 (7p15-p13), CCM3 (3q25.2-q27)
Extradural AVFs (added, Ch. 462)	Extradural AVF	(not classified)	Radicular artery to epidural plexus through an incompetent dural valve

- **Cavernous angioma detail worth quoting** — "cavernous angiomas, which account for **5% to 12%** of all spinal vascular abnormalities… are most commonly **intramedullary**, and are rarely found to be epidural lesions… composed of **dilated venous channels without intervening normal nervous tissue**." They occur **sporadically (80%) or in a familial form (20%)**; within the Hispanic-American community the familial proportion may be **as high as 50%**; in 80% of cases familial disease is caused by a heterozygous germline mutation at **CCM1 (7q21.2), CCM2 (7p15-p13) or CCM3 (3q25.2-q27)**; the condition may also follow **brain and spinal irradiation** YW p.3806.
- **A modern addition to know** — Hiramatsu's **five-tier classification of craniocervical junction AVFs (2018)**, based on feeding vessel, shunt point and draining vessel: **type I dural AVF (37%)**, **type II radicular AVF (29%)**, **type III epidural AVF with pial feeders (14%)**, **type IV epidural AVF (10%)**, **type V perimedullary AVF (10%)**. Because **98%** were fed from branches of the radiculomeningeal artery the authors proposed the collective term **radiculomedullary AVF**. All types were prone to **rupture with subarachnoid haemorrhage (63% overall)**, with a predilection for **type II (94%)** and **type III (62%)** YW p.3800.

(b) Clinical presentations [2]

6. Two utterly different clinical pictures — dural AVF versus intradural AVM

6.1 Spinal dural AVF — the "old man with a progressive myelopathy"

- **Acquired, not congenital** — "these lesions are generally believed to be **acquired**. Factors supporting this include **onset of symptoms later in life** and **dural AVF formation following trauma or spinal surgery**" YW p.3804.
- **Demographics** — "most patients (**80%**) are **men** who develop symptoms **beyond 40 years of age**" YW p.3804; the mean age at diagnosis is **46 years** versus 24 for intradural AVMs YW p.3806.
- **Level** — "patients **rarely present with upper extremity involvement** because of the strong predilection for dural AVFs to occur in the **lower thoracic and lumbar** regions" YW p.3804.

- **Tempo** — "**low back or radicular pain followed by gradual but progressive onset of myelopathic symptoms (85% to 95%)**", with increasing weakness, sensory disturbance and **bowel and bladder dysfunction** YW p.3804. Onset is gradual in **85%** of dural AVFs versus acute in **37%** of intradural AVMs YW p.3806.
- **Neurogenic claudication — the classic trap** — "worsening symptoms with walking or when in certain positions… **similar to the neurogenic claudication occasionally associated with lumbar stenosis**". Symptoms are exacerbated by activity in **70%** of dural AVFs versus 15% of intradural AVMs [YW pp. 3804, 3806].
- **The misdiagnosis that harms patients** — intradural AVFs of the filum terminale "often occur concurrently with lumbosacral degenerative disease, occasionally resulting in **delayed or missed diagnosis and potentially unnecessary spinal surgeries** solely addressing the degenerative disease"; initial surgery has been reported for presumed **lumbar disc herniation, tethered cord syndrome and severe lumbar stenosis**, and "**misdiagnosis and laminectomy for presumed symptomatic lumbar stenosis… can result in acute neurological deterioration**" [YW pp. 3804-3805].
- **No spinal bruit and no SAH** — spinal bruit occurs in **0%** of dural AVFs (6% of intradural AVMs) and SAH in **0%** (50% of intradural AVMs) YW p.3806.
- **Foix-Alajouanine syndrome** — described in 1926 in two young men with a severe rapidly progressive myelopathy that proved fatal; autopsy showed **extensive necrosis and hypertrophy of the pial and intramedullary veins**. "A small subset of type I dural AVF patients develop Foix-Alajouanine syndrome, an **acute neurological deterioration from extreme venous hypertension and possibly subsequent venous thrombosis**. Therefore this presentation is a **true emergency** because relief of the venous hypertension before it progresses to thrombosis **can reverse neurological deficits**, whereas failure to do so leads to **irreversible spinal cord injury**" YW p.3805.

6.2 Intradural AVM — the "young patient who bleeds"

- **Congenital, sex-neutral, evenly distributed** — "in contrast with dural AVFs, spinal AVMs appear to be **congenital lesions** resulting from aberrant vascular embryogenesis… occur with a **nearly identical incidence in males and females**. Symptom onset is usually **early in life**… distributed **more evenly throughout the long axis of the spine**" YW p.3805.
- **Haemorrhage** — "the high-flow and high-pressure characteristics of spinal AVMs can result in **venous hypertension and hemorrhage**. Symptom onset is often **subacute or acute**… patients with hemorrhage complain of an acute onset of **back or suboccipital pain, meningismus, or a loss of consciousness**. Sudden deterioration in motor function is also common. **Subarachnoid or intramedullary hemorrhage is the initial finding on diagnostic imaging in approximately 35% of patients**" YW p.3805.
- **Children bleed more** — "Riché and colleagues reported an **acute onset of initial symptoms in 84% of children** with spinal AVMs" YW p.3805.
- **Triggers** — recurrence and deterioration are associated with **"violent physical effort", pregnancy, minor trauma, exertion, posture (17%), activity (15%), pregnancy (6%), Valsalva manoeuvre (13%) and injury (13%)** YW p.3807.
- **Disability at presentation** — in Rosenblum's 54 patients: **paresis 93%, sensory loss 74%, bladder dysfunction 74%, haemorrhage 52%**; at treatment **74% were moderately or severely disabled** (cane, crutches or wheelchair) and only 26% had unaided ambulation YW p.3807.

6.3 Conus AVM and cavernous angioma

- **Conus medullaris AVM** — the only spinal AV lesion producing **both upper and lower motor neuron signs**, through myelopathy plus a cauda equina syndrome from root compression YW p.3783.
- **Spinal cavernous angioma — four clinical patterns** YW p.3806:
  - **Discrete acute episodic progression over months to years.**
  - **Slowly progressive decline in function over months to years.**
  - **Acute onset and rapid progression.**
  - **Slowly progressive loss of function after acute onset of mild neurological symptoms.**

Table 3 · Comparison of clinical syndromes of dural AVFs and intradural AVMs — reproduced in full from Youmans & Winn 8e, Table 464.1, p. 3806 (Rosenblum et al., 81 patients). The intradural AVM column includes perimedullary AVFs.

Feature	Dural AVF (n = 27)	Intradural AVM (n = 54)
Gender	Predominantly male	Male or female
Mean age at diagnosis (years)	**46**	**24**
Onset of symptoms	**Gradual (85%)**	**Acute (37%)**
SAH	**0**	**50%**
First symptom	**Paresis (44%)**	**SAH (32%)**
Spinal bruit	0	6%
Exacerbation of symptoms by activity	**70%**	15%
Arms affected	0	11%

- **The natural-history counterpart (Table 464.2)** — acquired dural AVF: male predominance, onset in the **later half of adulthood**, **never** associated with congenital malformation, **lower half** of the spine, **normal spinal venous pathways absent**. Congenital cord AVM: either sex, **child or young adult**, **occasionally** associated with congenital malformation, **diffuse** distribution, **normal venous pathways present** YW p.3806.
- **Untreated course of a dural AVF** — Aminoff and Logue's patients showed "**20% requiring crutches for ambulation or being nonambulatory within 6 months** of onset of symptoms other than pain. Within 3 years, a large percentage were severely disabled… untreated dural AVFs result in a **gradual progressive decline in motor and sensory function over a period of 2 to 3 years**" YW p.3805. By 3 years **one-half of the patients were confined to a wheelchair or had to use crutches** YW p.3804.

(c) Angiographic findings [3]

7. Selective spinal arteriography — the gold standard and what it must answer

- **Status** — "arteriography remains the **gold standard** for imaging of spinal vascular malformations and defines the **four components of the angioarchitecture** that are critical to selection of treatment" YW p.3810:
  1. **The type of vascular malformation.**
  2. **The spinal level and anatomic configuration of the fistula or nidus.**
  3. **Identification of feeding vessels.**
  4. **Delineation of the (normal) spinal cord vasculature.**

7.1 Dural AVF on angiography

- "Selective injection of the feeding artery results in **intradural drainage of the fistula through an arterialized medullary vein that communicates with a dilated coronal venous plexus**" YW p.3810.
- "The dilated coronal venous plexus most commonly occurs **along the posterior surface** of the cord; however, spinal dural AVFs can occur **anterior** to the cord, particularly in the **lumbar** region" YW p.3810.
- "Arteriography identifies the **nidus of the fistula in the intervertebral foramen and the lateral aspect of the spinal canal**" YW p.3810 — compare with Ch. 462's teaching that intradural **ventral** fistulas show a **midline** pouch and intradural **dorsal** fistulas a **lateral** pouch on AP views YW p.3781.
- **A technical point that wins marks** — "**prolonged views of the venous phase (approximately 15 seconds) are often necessary** to completely define the venous drainage patterns in these **low-flow** lesions" YW p.3810.
- **Slow flow and long tortuous veins** — the hallmark is **long, tortuous, early-draining veins through the coronal venous plexus** YW p.3781, with **slow arteriovenous transit** compared with an AVM.

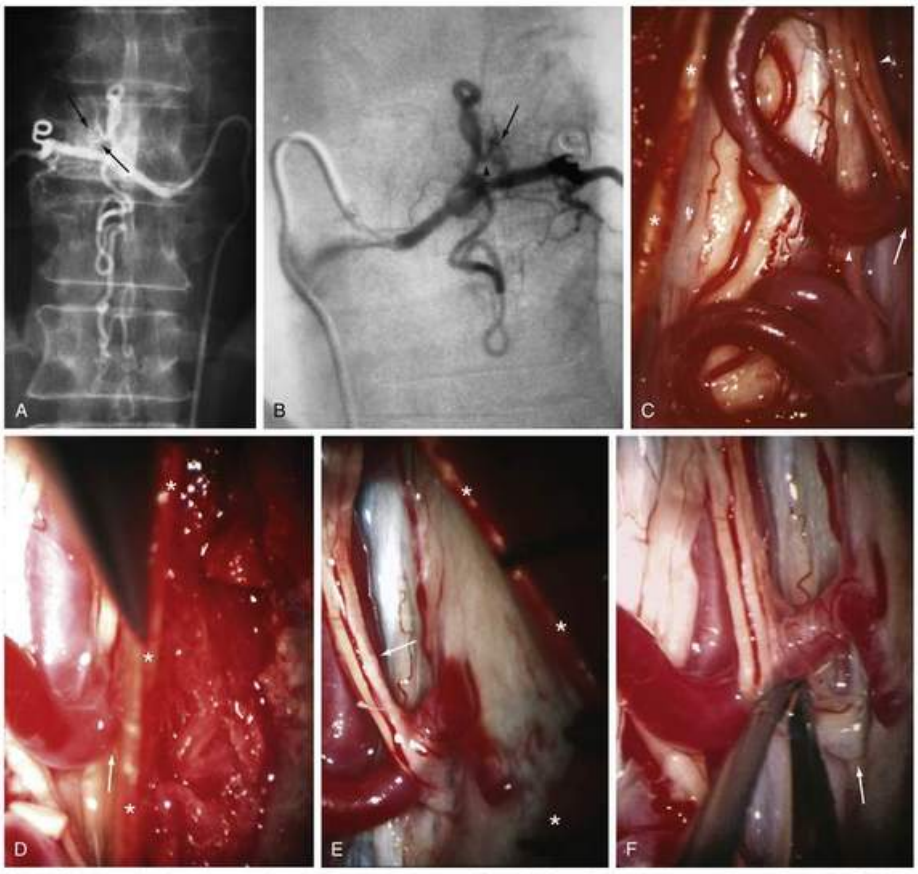


Figure 464.9. (A) Selective spinal arteriogram of a spinal dural arteriovenous fistula (AVF) embedded in the root sleeve of the ninth right thoracic nerve root and the adjacent spinal dura. The nidus of a spinal dural AVF *(arrows)* is typically in the intervertebral foramen and the lateral aspect of the spinal canal and drains into dilated, tortuous intradural veins on the cord surface. (B) Subtraction arteriogram in which the image has been reversed so that the vascular pattern corresponds to the view at surgery (C–F) with the patient in the prone position. The *upward-pointing arrowheads* in B and C indicate the caudal loop of the medullary vein draining the dural AVF. Correspondence of the shape of the veins, as seen on the arteriogram (B) and at surgery (C), provides a road map to the site of the dural AVF. The *left-pointing arrowheads* in C indicates the right T9 sensory root, and the *arrow* points to the site of dural penetration of the vein draining the AVF and the sensory root. (D) The forceps grasp the dura *(asterisks)*. This intradural and extradural view shows the AVF embedded in the dura *(to the right of the dura in the image)* and the site of intradural penetration of the medullary vein draining the AVF intradurally *(arrow)*. (E–F) The dura *(asterisks in E)* is retracted laterally to reveal the relationship of the nerve root and the dural penetration of the arterialized medullary vein that drains the blood from the fistula intradurally to the spinal venous system. This vein typically can be identified as it penetrates the inner surface of the dura next to (E) or slightly separate from (F) the dural penetration of the sensory root *(arrow in F)*. In E and F, note the convergence of the individual vessels of the AVF just beneath the thin inner layer of the dura into a single draining vessel and the normal radicular vein on the nerve root. *(A, D, and E from Oldfield E, Di Chiro G, Quindlen E, et al. Successful treatment of a group of spinal cord arteriovenous malformations by interruption of dural fistula. J Neurosurg. 1983;59(6):1019–1030; B, C, and F from Oldfield EH. Spinal vascular malformations. In: Macdonald RL, ed. Neurosurgical Operative Atlas: Vascular Neurosurgery. 2nd ed. New York: Thieme; 2008:190–199. Reprinted with permission.)*

*Reproduced from Youmans & Winn 8e, Fig. 464.9, p. 3802 — Label when you reproduce it: (A) the selective spinal arteriogram of a dural AVF embedded in the **root sleeve of the right T9 nerve root** — arrows on the nidus lying in the **intervertebral foramen and lateral spinal canal**, draining into dilated tortuous intradural veins on the cord surface. (B) The subtraction arteriogram **reversed** so the vascular pattern matches the surgeon's view with the patient prone — this "road map" trick is the single most useful intraoperative aid. (C-F) The corresponding operative photographs: the caudal loop of the draining medullary vein, the T9 sensory root, the site of dural penetration of the draining vein next to the root, and the convergence of the individual vessels of the AVF beneath the thin inner dural layer into a single draining vessel.*

7.2 Intradural AVM on angiography

- **Glomus type** — "defined by a **compact nidus of tangled vessels confined to a short segment** of the spinal cord. Feeding vessels arise from the **anterior spinal artery or a combination of the anterior and posterior spinal arteries** " YW p.3811; the classical image is a glomus nidus **supplied by the anterior spinal artery via the artery of Adamkiewicz** YW p.3803.
- **Juvenile type** — "**larger, fed by a larger number of feeding vessels, and may extend into the vertebral column and surrounding soft tissues (metameric form). Intranidal and feeding artery aneurysms may also be observed**" YW p.3811. The nidus of a juvenile AVM may fill the spinal canal **from front to back and from side to side** YW p.3803 .
- **Perimedullary fistula** — "fed by the anterior or posterior spinal arteries and located on the **pial surface of the cord or**

on the filum terminale. **Type III AVFs often demonstrate significant venous enlargement and varices.** In the rarer type I fistulas, the **fistulous point can be identified where the feeding artery dilates at the site of its abnormal connection** with its venous drainage" YW p.3811.

- **Flow rate is the discriminator** — rapid flow is present in **80%** of intradural AVMs and **0%** of dural AVFs; **associated spinal aneurysm in 44%** versus 0%; **common supply of the malformation and a medullary artery in 100%** versus 15% YW p.3811.
- **Speed can defeat the camera** — in one intradural AVF "flow through the lesion was so fast that it could be clearly demonstrated only… by using **rapid-sequence (10 frames/sec) imaging**", which then showed the fistula, a small aneurysm just proximal to it and the large varix distal to it YW p.3818.

Table 4 · Radiographic features distinguishing dural from intradural malformations — reproduced in full from Youmans & Winn 8e, Table 464.4, p. 3811 (Rosenblum et al.). The intradural column includes perimedullary AVFs.

Feature	Dural AVF (n = 27)	Intradural AVM (n = 54)
Site of nidus	**100% in the lateral canal**	**80% within the cord**; 11% on the ventral cord surface; 9% on the dorsal cord surface
Level of spine	**Lower half**	**Diffuse**
Rapid flow	**0**	**80%**
Associated spinal aneurysm	**0**	**44%**
Common supply of the malformation and a medullary artery	15%	**100%**
Route of venous drainage	**100% rostral**; 4% caudal	81% rostral; 72% caudal

7.3 When the angiogram is negative — the three rules

- **Rule 1 — inject the head.** "When spinal arteriography is negative, yet MRI, CTA, or myelography demonstrates a dilated and tortuous coronal venous plexus, **selective injections of the major cranial vessels should be performed**. Patients with dural AVFs in the uppermost portions of the cervical spine and **intracranial dural AVFs of the posterior fossa or tentorium** fed by branches of the internal or external carotids, vertebral arteries, or basilar artery **can present with myelopathy and mimic spinal dural AVFs**" [YW pp. 3810-3811]. The mechanism is that arterialised veins of the intracranial circulation drain into the **valveless veins of the spinal cord** YW p.3811.
- **Rule 2 — inject both vertebral arteries.** "A **unilateral injection with retrograde flow down the contralateral vertebral artery may not identify all fistulas**" YW p.3811.
- **Rule 3 — go down to the pelvis.** "In the lumbosacral region, **selective injections of the iliac arteries and their branches may be necessary** to identify dural AVFs not initially seen on standard spinal arteriography." Rarely **atherosclerosis at the origin of the feeding vessel** precludes identification, and open surgical exploration must proceed on CTA or MRA findings YW p.3811.

8. Cross-sectional imaging — what the MRI shows before you go to the catheter lab

- **MRI is the screening modality of choice** for myelopathy; a **minimum 1.5-T machine with a spinal coil** should be used when a spinal vascular malformation is suspected YW p.3806.
- **The presence of a malformation** is identified by **dilated serpiginous vascular flow voids** — signal dropout on T1 and T2; axial and sagittal T2 shows **cord edema, myelomalacia, infarction and hemorrhage**; hemosiderin from remote haemorrhage is low signal on both sequences; **recent haemorrhage (3 days to 3 months) is hyperintense on T1** YW p.3806.
- **Dural AVF specifics** — focal cord expansion on T1 and T2; **T2 hyperintensity within the cord, consistent among symptom-producing lesions**, "usually based in the **posterior** aspect of the spinal cord and extends forward, reflecting

greater involvement of the posterior veins." **Gilbertson and colleagues found increased T2 signal in 100% of 66 patients with spinal dural AVFs**, extending over an average of **seven levels** and involving the **tip of the conus in 87%** YW p.3807.

- **Gadolinium** — immediate post-contrast T1 enhances the dilated coronal venous plexus and congested cord segments; **delaying imaging after gadolinium leads to more profound cord enhancement**; the mechanism may be edema, venous congestion or breakdown of the blood-cord barrier YW p.3807.
- **The trap** — "MRI findings may be **normal or only nonspecifically abnormal** in patients with spinal dural AVFs" YW p.3809, and "it is possible for intramedullary AVMs to remain **radiographically silent on noncontrasted MRI**. As a result, in patients with unexplained progressive myelopathy, **postcontrast T1 images are recommended**" YW p.3809.
- **Post-treatment MRI** — obliteration produces **reduced T2 hyperintensity and a reduction in the diameter of the swollen cord**, with dilated vessels no longer evident in many patients YW p.3807.
- **Cavernous angioma** — MRI is definitive because these lesions are **angiographically occult**; a well-defined nodular lesion of **heterogeneous intensity**, low signal from hemosiderin within and around the lesion, perilesional edema on T2, and the classical **"target" appearance** YW p.3809.
- **CTA and myelography** — CTA evaluates the cord parenchyma poorly but identifies fistula, feeders and draining veins accurately; some reports suggest **3-T dynamic contrast-enhanced MRA localises the level of a spinal dural AVF more reliably than 64-row multidetector CTA** YW p.3810. Myelography shows **dilated serpentine filling defects**; a lack of such vessels greatly reduces the likelihood of a malformation, and positive studies still require arteriography to establish type and level YW p.3810.



Figure 464.19. Sagittal spinal magnetic resonance imaging (MRI) scan of a 66-year-old male patient with a spinal dural arteriovenous fistula (AVF) at T9–T10. Before injection of contrast material, T1-weighted (TE 400, TR 16) images reveal an area of focal cord expansion affecting the conus (A) and increased signal intensity on T2-weighted (TR 2000, TE 20) proton-density imaging (B) in the thoracolumbar segments of a cord swollen from venous congestion. Immediately after the injection of gadolinium–diethylenetriaminepentaacetic acid (DTPA) (C), T1-weighted (TR 400, TE 16) images reveal enhancement of the vessels of the coronal venous plexus (compare the same MRI technique without enhancement in A). T2-weighted imaging techniques that show cerebrospinal fluid brightly often prominently depict the abnormal vessels on the surface of the cord (D) and in the cerebrospinal fluid. As seen on T1-weighted (TR 417, TE 16) images performed after injection of gadolinium-DTPA 8 months after excision of the spinal dural AVF (E), elimination of the fistula resulted in resolution of the swollen appearance of the spinal cord and disappearance of the abnormal enhancing vessels on the cord surface. *(From Thompson B, Oldfield E. Spinal vascular malformations. In: Carter LP, Spetzler RF, Hamilton MG, eds. Neurovascular Surgery. New York: McGraw-Hill; 1994:1167–1195.)*

*Reproduced from Youmans & Winn 8e, Fig. 464.19, p. 3810 — Label when you look at it: the sagittal MRI sequence of a 66-year-old man with a spinal dural AVF at T9-T10. (A) Pre-contrast T1 — **focal cord expansion affecting the conus**. (B) T2/proton density — **increased signal intensity in the thoracolumbar cord swollen from venous congestion**. (C) Immediately after gadolinium-DTPA — **enhancement of the vessels of the coronal venous plexus**. (D) T2 with bright CSF — **the abnormal serpiginous vessels on the surface of the cord**. (E) Eight months after excision of the fistula — **resolution of the cord swelling and disappearance of the abnormal enhancing vessels**. This single figure carries the entire radiological answer for a dural AVF.*

9. Treatment in one page (for the DEC 2020 variant of this question)

- **Dural AVF** — "open surgical treatment of these lesions has repeatedly proven to be **safe, effective, and durable**"; certain fistulas are **not candidates for embolization** (arterial feeder arising from the same vessel as a medullary artery; inability to penetrate to the venous side with glue), and follow-up has shown **recanalisation in many patients whose embolization originally appeared successful** YW p.3811.
- **Technique** — prone on a Jackson table with the abdomen hanging free; level localised by C-arm, ideally with **a coil placed in the feeding artery at the diagnostic angiogram** so the level can be found on fluoroscopy; laminectomy one

level above and below; dura opened linearly with arachnoid intact, then arachnoid opened and clipped laterally; the dilated tortuous medullary vein traced from the coronal plexus to its point of dural penetration **almost always next to the dural penetration of the nerve root**; the pattern is compared with the flipped preoperative arteriogram to **avoid mistaking a medullary artery for the vein**; the arterialised vein is **cauterised over a 4- to 6-mm segment and sectioned at its point of dural penetration**; the coronal plexus slackens and may turn from red to blue; **ICG videoangiography** confirms obliteration and **formal arteriography is performed in the immediate postoperative period** [YW pp. 3811-3812].

- **Results** — Steinmetz's meta-analysis: **microsurgery obliterated the fistula in 98% after the initial treatment compared with only 46% after embolization**; Saladino's 154-patient series achieved **complete obliteration in 95%** with **no major neurological complications**, and at follow-up **82.2% improved and 14.4% were stable** in motor function, **numbness improved in 51.5%** and **sphincter dysfunction in 45%** [YW pp. 3812-3813].
- **The governing principle for every subtype** — "the clinical outcome **correlates directly with the patient's preoperative functional status**, hence the importance of diagnosis and treatment before symptom progression to a severe stage. The progressive symptoms and occasional rapid deterioration **argue against conservative management in all scenarios**" YW p.3812. Of patients presenting with Aminoff-Logue grade 3 to 5, **37 of 49 (76%) improved their gait postoperatively**, and **96% of those with minor disability but unaided locomotion retained independent ambulation** YW p.3812.
- **Glomus AVM** — posterior approach, laminectomy one level above and below, bone removal to the ipsilateral pedicle if lateral extension, **costotransversectomy** for anterolateral exposure, **section of the dentate ligaments** to roll the cord; myelotomy tailored to the most superficial location (**midline dorsal, dorsal root entry zone, lateral or anterior midline**); mobilise within the **gliotic plane**, preserving major draining veins until the end; **the resection plane must not stray into normal cord** YW p.3814.
- **Cavernous angioma** — posterior approach; lateral lesions via costotransversectomy, dentate section and rolling the cord; **cavernomas of the posterior half of the cord have a lower incidence of iatrogenic injury and a more favourable prognosis than ventral lesions**; identify by **hemosiderin staining and blue pial discoloration**; open the pia where the mass presents, dissect in the gliotic plane, coagulate and collapse; **complete resection is necessary because residual pieces often cause symptomatic rehemorrhage** [YW pp. 3816-3817].

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **First line of your answer: "spinal arteriovenous lesions are divided by the presence or absence of an angiographic nidus into AVFs and AVMs."** Then give the Spetzler six types.
- **Spetzler six types: extradural AVF, intradural dorsal AVF, intradural ventral AVF, extradural-intradural AVM, intramedullary AVM, conus medullaris AVM.**
- **Translation table: dorsal = Di Chiro I; intramedullary glomus = II; extradural-intradural juvenile/metameric = III; ventral perimedullary = IV.**
- **The intradural dorsal (dural) AVF is the commonest spinal vascular malformation** — and its shunt is **in the dural root sleeve**, not in the cord.
- **Male, over 40, lower thoracolumbar, gradually progressive myelopathy with neurogenic claudication = dural AVF until proven otherwise** (80% men, 85-95% gradual, 70% activity-exacerbated, 0% SAH).
- **Young patient, either sex, sudden back pain with meningismus, SAH in 50% = intradural AVM.** Mean age 24 versus 46.
- **Foix-Alajouanine syndrome is a surgical emergency** — venous hypertension progressing to venous thrombosis; relieve it before thrombosis and deficits can reverse.
- **Conus AVM is the only one that gives both upper and lower motor neuron signs.**
- **Anson-Spetzler A/B/C and Merland I/II/III subdivide the ventral perimedullary fistula** — A/I single ASA feeder, B/II multiple feeders, C/III giant with venous ectasia.
- **Angiography: dural AVF nidus lies in the intervertebral foramen and lateral canal; ventral AVF has a midline pouch, dorsal AVF a lateral pouch.**
- **Hold the venous phase for about 15 seconds** in a suspected dural AVF — the lesion is low flow and the drainage will be missed otherwise.
- **Rapid flow 80%, spinal aneurysm 44%, nidus within the cord 80% — all point to an intradural AVM, never**

to a dural AVF.

- **A negative spinal angiogram is not the end: inject both vertebral arteries and the cranial vessels** (posterior fossa/tentorial DAVFs cause myelopathy through spinal medullary drainage), then the iliacs.
- **Gilbertson: T2 cord hyperintensity in 100% of dural AVFs, averaging seven levels and reaching the conus tip in 87%** — but MRI can still be normal, so use post-gadolinium T1.
- **Artery of Adamkiewicz: left, T8-L2 commonest, range T3-L4; watershed T2-T4.** Never sacrifice it at the root sleeve — identify it by its **straight rostral course** after dural penetration.
- **Microsurgery obliterates a dural AVF in 95-98% versus 46% for embolization**, and outcome depends on preoperative functional grade — so operate early.

Pages read for this answer — Youmans & Winn 8e: 3779, 3780, 3781, 3782, 3783, 3797, 3798, 3799, 3800, 3802, 3803, 3804, 3805, 3806, 3807, 3809, 3810, 3811, 3812, 3813, 3814, 3816, 3817, 3818

a) Clinical presentations of cerebral AVMs. [4]
b) Molecular biology and genetics of AVMs. [2]
c) Classification of AVM. [4]

LONG | APR 2023 · Paper II · Q6 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 450 *Pathobiology of True Arteriovenous Malformations* (Gavin and Kitchen), §Arteriovenous Malformations — Pathology, Pathogenesis and Pathophysiology, §Staging, Grading or Classification Criteria, §Genetics of Arteriovenous Malformations, §Biology of Vasculogenesis and Angiogenesis and §Recent Developments, pp. 3659-3669 (Figs. 450.1-450.7, pp. 3660-3667). Ch. 455 *Microsurgery of Arteriovenous Malformations*, §Clinical Presentation and Pathophysiology, §Natural History, §Imaging and §Grading of Arteriovenous Malformations, pp. 3695-3699 (Figs. 455.1-455.2, p. 3698; **Table 455.1 — Natural History Studies of Arteriovenous Malformations**, p. 3696). Ch. 452 *Therapeutic Decision Making in the Management of Arteriovenous Malformations of the Brain*, §Key Concepts and §Surgery, pp. 3677, 3677.e2, 3677.e8 (**Table 452.1 — Grading System of Spetzler and Martin**, p. 3677.e2). Ch. 451 *Epidemiology and Natural History of Cerebral Vascular Malformations*, pp. 3673-3675. Supplementary: Ch. 300, §Radiosurgery-Based AVM Grading Scales, p. 2353 (**Table 300.1**).

1. Definitions first — what a true AVM is, and what it is not

- **The three morphological components** — "three morphologic features are typical of these lesions: **feeding arteries, draining veins, and a dysplastic vascular nidus** composed of a tangle of abnormal vessels that acts as a **shunt from the arterial to venous system**" YW p.3659.
- **The defining absence** — "gross pathologic features include the **absence of a capillary bed** and the presence of small feeding arteries composed of variable amounts of smooth muscle and elastic laminae, with single or multiple direct arteriovenous connections. **The lack of a capillary bed results in low resistance and, with the AV connections, permits high-flow AV shunting**" YW p.3659.
- **The nidus** — Latin for "nest", described by Cushing and Bailey as a **"snarl"**; it is "a conglomeration of numerous AV shunts **without interposed brain tissue and no capillary bed**"; microscopically it shows **thin collagenous walls in the venous elements with muscular elastic walls in the feeding arteries** YW p.3659.
- **What the shunt does to its own vessels** — "this chronic high-flow shunt produces **secondary structural changes in the feeding and draining vessels, dilation of the feeding arteries, and dilation and thickening of the draining veins** . The feeding arteries develop **smooth muscle hyperplasia associated with fibroblasts and connective tissue elements known as fibromuscular cushions**" YW p.3659.
- **Where AVMs differ from cavernomas histologically** — "in contrast to CMs, **intervening neural parenchyma may be present** within the compact network of dysplastic vascular channels that forms the nidus. Parenchymal elements tend to be **gliotic, hemosiderin stained, and nonfunctional**. Vascular or interstitial **calcification** is often a feature" YW p.3659.
- **The perinidal capillary network** — "dilated capillaries (**10-25 times larger than normal capillaries**) form a **ring (1-7 mm) around the nidus**", connected to the nidus, the feeders, the draining veins and to surrounding normal brain vessels; this "may be a cause of **recurrence of surgically resected AVMs**" YW p.3659.

- **AVMs are dynamic, not static** — "AVMs are increasingly recognized as **dynamic lesions that may enlarge, regress, obliterate, and recur**. Spontaneous obliteration does occur, but recurrence following confirmed obliteration is rare"; a case of haemorrhage from a recurrent cerebellar AVM **15 years after angiographically confirmed spontaneous obliteration** is on record YW p.3659. Review of interval angiograms in 106 patients (mean follow-up 8.4 years) showed **more than half enlarged and about one-fifth decreased in size or vanished** YW p.3666.
- **The one variant to name** — "there is a type of **proliferative or diffuse AVM without a focal nidus** often seen in pediatric patients. Lasjaunias referred to this as **cerebral proliferative angiopathy**" YW p.3659.

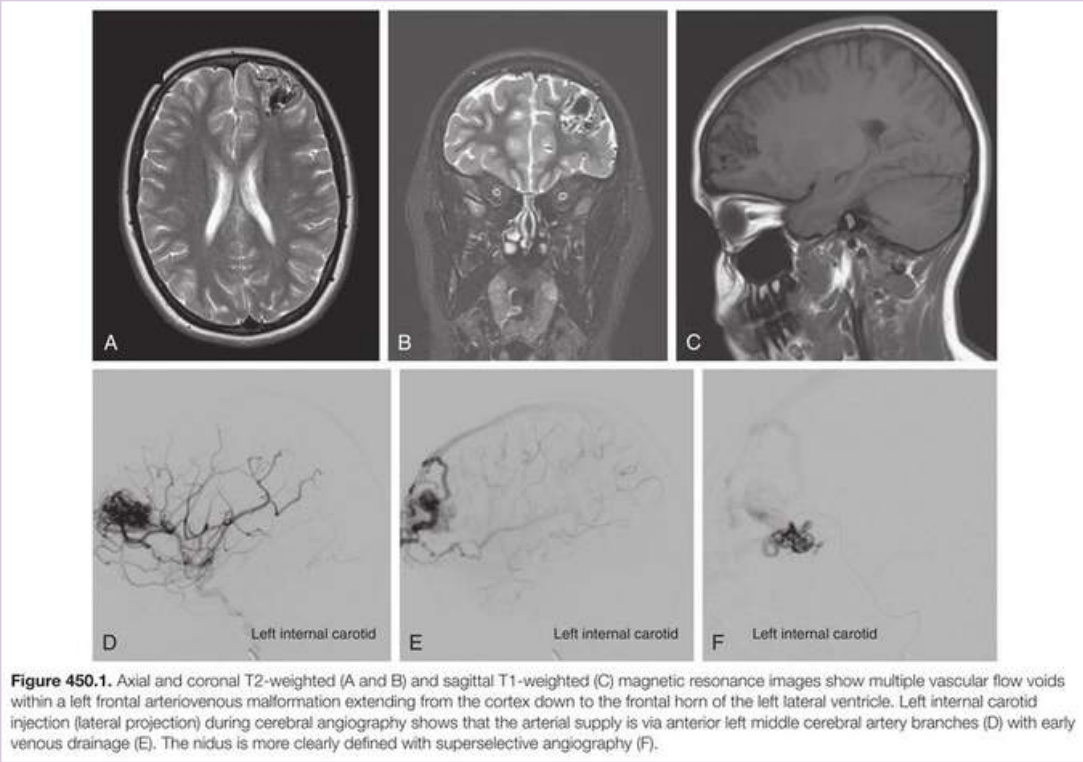


Figure 450.1. Axial and coronal T2-weighted (A and B) and sagittal T1-weighted (C) magnetic resonance images show multiple vascular flow voids within a left frontal arteriovenous malformation extending from the cortex down to the frontal horn of the left lateral ventricle. Left internal carotid injection (lateral projection) during cerebral angiography shows that the arterial supply is via anterior left middle cerebral artery branches (D) with early venous drainage (E). The nidus is more clearly defined with superselective angiography (F).

*Reproduced from Youmans & Winn 8e, Fig. 450.1, p. 3660 — Label when you reproduce it: (A-C) axial and coronal T2 and sagittal T1 MRI of a left frontal AVM — mark the **multiple vascular flow voids** and the extension of the nidus **from the cortex down to the frontal horn of the left lateral ventricle** (i.e. deep venous drainage and ependymal involvement). (D) Left internal carotid lateral injection, arterial phase — **arterial supply from anterior middle cerebral artery branches**. (E) The same injection showing **early venous drainage**, the angiographic signature of arteriovenous shunting. (F) Superselective angiography **defining the nidus more clearly**. Use this figure to state the three components — feeders, nidus, draining veins — and the two diagnostic angiographic findings: a tangle of vessels and early venous filling.*

(a) Clinical presentations of cerebral AVMs [4]

2. The five categories — memorise the list, then the numbers

"The clinical presentation or discovery of AVMs can be classified into the following **five basic categories: intracerebral hemorrhage, seizures, progressive neurological deficit, headaches, and incidental or asymptomatic lesions**" YW p.3695.

2.1 Intracerebral haemorrhage — the commonest and most dangerous

- **Frequency** — "intracerebral hemorrhage remains the **most common and most dangerous presentation**. Historically, AVM rupture was responsible for **greater than 70%** of initial diagnoses. A more recent review of large modern series revealed that **45% to 72%** of patients present with hemorrhage" YW p.3695. Ch. 450 puts it at approximately **65% of symptomatic lesions** YW p.3662.
- **Epidemiological weight** — "AVMs are responsible for **one-third of hemorrhagic strokes in young adults**, second only to rupture of an arterial aneurysm" YW p.3695; they "account for **2% of all strokes and 38% of intracerebral**

hemorrhages in patients between 15 and 45 years of age" YW p.3695.

- **Type of bleed** — "**intraparenchymal hemorrhage is the most common type of bleeding episode, followed by intraventricular and subarachnoid hemorrhages**" YW p.3695.
- **Age** — "most patients experience their **first hemorrhage when they are 20 to 40 years of age**" YW p.3695; most AVMs become symptomatic between the ages of **20 and 50** YW p.3662.
- **Consequences** — "estimated mortality and permanent morbidity with each hemorrhage are **10% to 30% and 20% to 30%**, respectively" YW p.3695. Ch. 450 quotes mortality from AVM haemorrhage as **6% to 29%** YW p.3662. Ch. 452 reports the risk of death from the **first** haemorrhage as ranging from **3% to 58%** and combined morbidity and mortality from **35% to 89%**, with the pooled figures being **mortality 25% and combined morbidity/mortality about 55%**, and the boundaries within which most studies' 95% confidence intervals fall being **mortality 17%-19% and combined morbidity/mortality 34%-54%**; for decision-making the author uses **40%** as the combined morbidity and mortality of a future haemorrhage [YW pp. 3677.e4, 3677.e5].
- **Source of bleeding** — "bleeding is typically from **rupture of a draining vein**, associated with dilation, kinking, and thrombosis, or from **rupture of flow-related aneurysms**" YW p.3661; in children flow-related aneurysms are **more prevalent than in adults** YW p.3661.

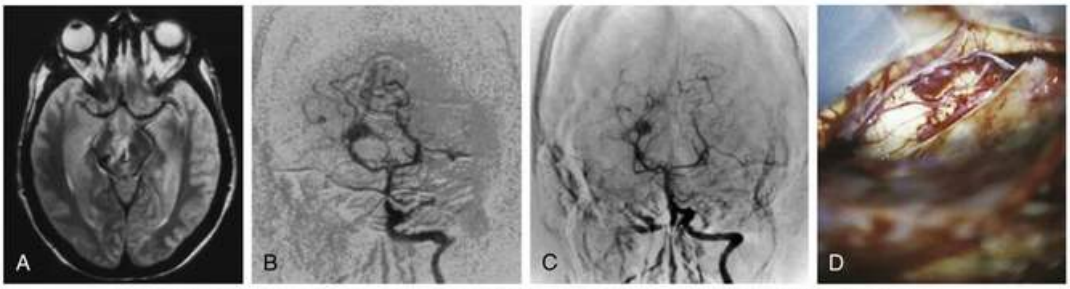


Figure 455.13. (A) Magnetic resonance imaging of thalamic arteriovenous malformation (AVM). (B–C) AVM of the thalamus fed by a deep thalamic perforator that received embolization before surgery. (D) Intraoperative photograph of the subtemporal approach to the AVM.

*Reproduced from Youmans & Winn 8e, Fig. 455.1, p. 3698 — Label when you reproduce it: (A) non-contrast CT of an **unruptured** AVM — point to the **calcification**, one of the three things a plain CT can show (acute blood, hydrocephalus, calcification or encephalomalacia from previous rupture). (B) contrast CT of a **ruptured** AVM with a **large intracerebral haematoma** — the study Youmans calls "particularly valuable as a quick study in the setting of a life-threatening hemorrhage before surgical evacuation" because it also gives the AVM location, nidus, feeders and draining veins.*

2.2 Seizures

- **Frequency** — "seizures represent the **second most common type of presentation** in patients with supratentorial AVMs, occurring in **almost 70%** of patients. **Seizures without obvious hemorrhage are seen in 25% to 50% of cases.** In approximately **18% to 35%** of patients an AVM is diagnosed during evaluation for a seizure" YW p.3695. Ch. 450 gives **15% to 35%** as the proportion manifesting with seizures YW p.3662; Ch. 452 notes seizure presentation accounts for **about 25%** of detected cases YW p.3677.e9.
- **Age and type** — "the average age of onset is **25 years**. **Simple and complex partial seizures** are the most common type recognized" YW p.3695.
- **Mechanism** — "mass effect and cortical irritation, hemodynamic alterations leading to ischemia, or **gliosis**" YW p.3695.
- **Which AVMs fit** — "seizures have been found to occur more frequently with AVMs having one or more of the following features: **large size, middle cerebral artery distribution, cortical location of the nidus or arterial feeders, and presence of venous varices**" YW p.3695.
- **Risk of postoperative seizures** — for supratentorial AVMs both **size >4 cm** and **more than two preoperative seizures** are risk factors for at least one postoperative seizure; even in the most favourable circumstance (fewer than three preoperative seizures, AVM <4 cm), **more than 10% of patients will have at least one postoperative seizure within 5 years** YW p.3677.e9.

2.3 Progressive neurological deficit

- **Frequency** — "approximately **3% to 10%** of patients harboring a cerebral AVM present with a **progressive neurological deficit in the absence of hemorrhage**" YW p.3695.
- **Two mechanisms** YW p.3695:
  - **Mass effect** — "direct pressure by the AVM or cerebral edema in the surrounding parenchyma".
  - **Ischaemic steal** — "the high-flow, low-resistance pathway created by the AVM. Cerebral blood flow from the adjacent tissue is thought to be **'stolen'** by the pathologic malformation." Larger AVMs and certain shunt characteristics are more likely to cause symptomatic steal; **transcranial Doppler shows higher velocities and greater flow volumes** in this group.
- **The physiology behind the steal** — "patients with AVMs have a **progressive decrease in arterial pressure, which proceeds from the circle of Willis to the AVM nidus**. In patients with large, high-flow AV shunts, there may be normal brain regions in which **cerebral arterial hypotension is below the range of normal autoregulation**. Despite significant cerebral arterial hypotension, the **majority of patients do not experience ischemic symptoms**", because hypotensive regions maintain relatively normal tissue perfusion by adaptive reduction in total cerebrovascular resistance YW p.3666.

2.4 Headache

- **Frequency** — "approximately **6% to 14%** of patients with cerebral AVMs present with **chronic headaches without hemorrhage**" YW p.3695.
- **Character** — "typically **hemicranial (ipsilateral or contralateral to the malformation) and similar to migraines**; however, **the incidence of migraine headaches in patients with AVMs does not exceed that of the general population**" YW p.3695.
- **The occipital AVM rule — a favourite viva point** — "**occipital AVMs may be more prone to headache presentation.** When the headaches are migrainous in character in patients with occipital AVMs, they usually occur **on the side of the AVM**, and the visual phenomena, when they occur, are **always on the contralateral visual field**. This consistency in the lateralization of the migraine differentiates these patients from patients with classical migraine, in which the headaches typically change sides. Therefore when a patient with migraines **consistently reports that the headache and visual phenomena occur always on the same side, an imaging study is indicated**" [YW pp. 3695-3696].
- **Mechanism** — "recruitment of **meningeal arteries** and increased blood flow" YW p.3696.

2.5 Asymptomatic / incidental

- "With the increased use of noninvasive imaging, incidental discovery is not uncommon. **This proportion has increased to 10% in modern series compared with a historical rate of less than 2%.**" In one population-based study of intracerebral vascular malformations, **40% were asymptomatic** YW p.3696.

2.6 Special presentations to add for extra marks

- **Neonates and infants** — "if there is sufficient AV shunting, **neonates and infants may present with congestive cardiac failure**" YW p.3661.
- **Older children** — "large AVMs generate an **arterial steal phenomenon**, and older children may present with **progressive neurological deterioration and chronic epilepsy**" YW p.3661.
- **Paediatric weight of disease** — "**AVMs are the most common cause of spontaneous brain hemorrhage in children** (excluding the neonatal period)"; **3% to 20% of sporadic AVMs are diagnosed in children** YW p.3661.
- **Multiplicity** — usually solitary, but **multiple lesions in 1% to 9%** of patients YW p.3695; multiple brain AVMs are typically part of **HHT** or a **metameric syndrome** YW p.3661.
- **Location** — most are **supratentorial**; "the **cerebellum is the most common location in the posterior fossa**, whereas **brainstem and ventricular locations are less common**" YW p.3695.
- **No consistent sex predominance** YW p.3695.

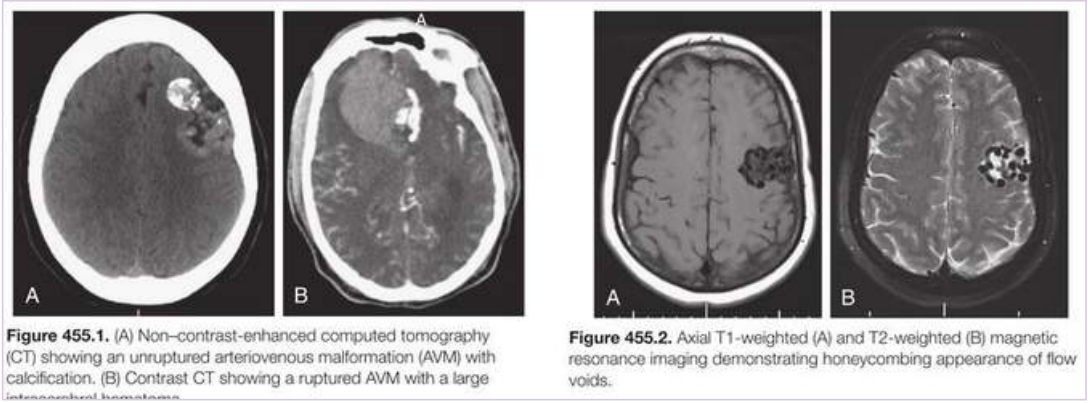


Figure 455.1. (A) Non–contrast-enhanced computed tomography (CT) showing an unruptured arteriovenous malformation (AVM) with calcification. (B) Contrast CT showing a ruptured AVM with a large

Figure 455.2. Axial T1-weighted (A) and T2-weighted (B) magnetic resonance imaging demonstrating honeycombing appearance of flow voids.

*Reproduced from Youmans & Winn 8e, Fig. 455.2, p. 3698 — Label when you reproduce it: axial T1 (A) and T2 (B) MRI showing the **"honeycomb" appearance of flow voids** that is the MRI signature of an AVM. In your label state why MRI matters: it is superior to CT in delineating the macroarchitecture of the AVM and defining its exact relationship to the surrounding brain, and shows secondary changes — mass effect, oedema and ischaemic change — but **in acute haemorrhage it is not useful because the haematoma obscures all detail**, so a formal angiogram must be obtained.*

3. Natural history — the numbers that justify everything you do next

Table 1 · Natural history studies of cerebral arteriovenous malformations — reproduced in full from Youmans & Winn 8e, Table 455.1, p. 3696.

Study	Type of study	No. patients	Average follow-up	Annual haemorrhage rate
Graf et al., 1983	Retrospective	191	4.8 years	**2%-3% without prior hemorrhage; 6% in the first year after hemorrhage, then 2%**
Crawford et al., 1986	Retrospective	217	10.4 years	**2%; 36% cumulative risk at 10 years with prior hemorrhage; 17% without**
Brown et al., 1988	Retrospective	168 (all unruptured)	8.2 years	**2.2%**
Ondra et al., 1990	Retrospective	160	23.7 years	**4% overall; 3.9% with hemorrhage; 4.3% with seizure; 3.9% with other symptoms**
Mast et al., 1997	Prospective	281	1 year	**2.2% without hemorrhage; 17.8% with hemorrhage**
Halim et al., 2004	Retrospective	790	4 years	**7% for the first year, then 3%**
Stapf et al., 2006	Prospective database	622	102 days	**1.3% for unruptured; 5.9% for AVMs presenting with hemorrhage**
Hernesniemi, 2008	Retrospective	238	13.5 years	**2.4% overall; 3 times higher in the first 5 years (4.6%) than subsequently (1.6%)**
Al-Shahi et al., 2014	Prospective cohort	204	6.9 years	50% received intervention; in the first 4 years death and morbidity were **lower with observation**; after 4 years rates were similar; **risk of haemorrhage lower with observation (14 vs. 38 events)**

- **The pooled modern estimate** — Gross and Du's meta-analysis: **2.2% per year (95% CI 1.7%-2.7%) for unruptured** and **4.5% per year (95% CI 3.7%-5.5%) for ruptured** bAVM. Kim's series of more than 2500 untreated AVMs gave **1.3% (95% CI 1.0%-1.7%)** for unruptured and **4.8% (95% CI 3.9%-5.9%)** for ruptured [YW pp. 3677.e2, 3677.e3].
- **Risk factors for future haemorrhage** — "previous hemorrhage, deep location, exclusively deep venous drainage, and associated aneurysm"; the summary sentence to quote is: "factors that increase the likelihood of rupture of unruptured

bAVMs include the presence of **aneurysms**, **deep location (or exclusively deep venous drainage)**, and **age (possibly)**. **Size should not be considered a risk factor**" [YW pp. 3677.e2, 3677.e3].

- **Stapf's stratified risk — the single most useful table in the viva** YW p.3697:
  - Superficial location, no deep venous drainage: **0.9%/yr unruptured; 4.5%/yr ruptured.**
  - Superficial location with deep venous drainage: **2.4%/yr unruptured; 11.4%/yr ruptured.**
  - Deep location, no deep venous drainage: **3.1%/yr unruptured; 14.8%/yr ruptured.**
  - Deep location with deep venous drainage: **8%/yr unruptured; 34.3%/yr ruptured.**
  - "This reveals a risk ranging from **0.9% to 34.3%** based on previously defined risk factors."
- **Ten-year framing for consent** — "a **10-year risk for first hemorrhage of more than 15% and less than 25%**; for ruptured bAVM, a **10-year risk of more than 20% and less than 35%**. The consequence of each future hemorrhage includes a **40% risk of a permanent neurological deficit or death**" YW p.3677.
- **Lifetime risk shortcut** — "assuming an annual hemorrhage rate of 2% to 4% and an average life expectancy of 70 years, the cumulative risk (in percentage) of AVM rupture may be estimated by the formula: **105 minus the patient's age in years**" YW p.3701.
- **Why small AVMs seem to bleed more** — "**small AVMs are more likely to manifest with hemorrhage because they do not manifest with symptoms secondary to mass effect or seizures**; however, once these AVMs occur, they are **less likely to rebleed than large AVMs**" YW p.3697. Spetzler reported hemorrhagic presentation in **82% of small (<3 cm) versus 21% of large (>6 cm)** AVMs, and found **significantly higher feeding artery pressures in small AVMs** YW p.3699.

(b) Molecular biology and genetics of AVMs [2]

4. The genetic architecture

4.1 The three genetic categories

"Three general categories of cerebral AVMs are recognized: **AVMs as part of an inherited disease in which a genetic factor has been clearly identified (e.g., HHT)**, **familial cases of AVMs without a known genetic cause**, and **AVMs as part of a developmental neurocutaneous disorder (e.g., Wyburn-Mason syndrome)**" YW p.3664.

4.2 Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu) — the model disease

- **Definition** — "a rare **autosomal dominant** vascular dysplasia characterized by vascular malformations in multiple organ systems. **Nasal, mucocutaneous, pulmonary, cerebral, gastrointestinal, and hepatic** vascular beds are most commonly affected" YW p.3664.
- **Curaçao criteria — three of four** YW p.3664:
  1. **Recurrent spontaneous epistaxis.**
  2. **Mucocutaneous telangiectasia.**
  3. **Visceral involvement** — pulmonary and cerebral or spinal AVMs, gastrointestinal bleeding, or intrahepatic shunting.
  4. **Family history of HHT.**
- **Burden of cerebral disease** — "symptomatic cerebral AVMs are present in up to **5%** of patients with HHT. Screening for asymptomatic lesions reveals a higher incidence of nearly **13%**." Up to **one-third of HHT patients harbouring AVMs have multiple lesions**, which "tend to be **small and cortical** in location". HHT has **age-dependent penetrance, almost complete by age 40** YW p.3664.
- **The loci** [YW pp. 3664-3665]:
  - **HHT1 (OMIM 187300)** — *ENG* (**endoglin**) at **9q33-q34.1**; associated with a **higher prevalence of pulmonary and cerebral AVMs**.
  - **HHT2 (OMIM 600376)** — *ACVRL1* (**ALK-1**) at **12q11-q14**; **milder disease expression and later age of onset**.

  - **HHT3** — **5q31.3-32**, causative gene unidentified.
  - **HHT4** — **7q14**, causative gene unidentified.
  - **HHT5** — *BMP9* / *GDF2*, a ligand for the ACVRL1 gene product ALK1.
  - **Juvenile polyposis + HHT (OMIM 175050)** — *MADH4*.
  - **RASA1** — an HHT-like syndrome; also implicated in **vein of Galen malformation, Parkes Weber syndrome and capillary malformation-AVM syndrome**; encodes **p120-RasGAP**.
  - **About 20% of HHT families remain unsolved** after *ENG* and *ACVRL1* analysis.
- **The pathway** — both proteins act in **TGF-β signalling**. "Binding of TGF-β to type II TGF-β receptors, which is **accelerated in the presence of endoglin**, results in phosphorylation of the type I TGF-β receptors **ALK1 and ALK5**. Phosphorylated ALK1 and ALK5 activate downstream **Smad proteins** that enter the nucleus and regulate gene transcription involved in angiogenesis" YW p.3665.
- **The mechanism is haploinsufficiency, not dominant negative** — in HHT1, normal endoglin dimers are still expressed at the cell surface but are **reduced by 50%**; mutant endoglin is found only as an **intracellular homodimer** and is not secreted, so it cannot act as a dominant negative. "This supports a model of **haploinsufficiency** — namely that **reduced levels of functional endoglin** are the mechanism by which vascular abnormalities occur in HHT1"; ALK1 levels are likewise reduced in HHT2 endothelial cells, and "most mutations of *ENG* and *ACVRL1* identified to date create **null alleles** that lead to reduced mRNA or protein levels" YW p.3665.
- **Modifier genes** — **PTPN14** variants influence clinical severity and associate with pulmonary AVMs; **ADAM17** variants associate with pulmonary AVMs in HHT1 but not HHT2, acting through effects on circulating endothelial progenitor cells and TGF-β activity YW p.3665.
- **Sporadic AVMs are not simply endoglin deficient** — "analysis of endoglin expression in sporadic AVMs has revealed **no reduction or mutant forms**", though the **ACVRL1 polymorphism IVS3-35A>G** was significantly associated with sporadic bAVM in one 2005 study (not replicated in a Dutch cohort) YW p.3665.

4.3 Familial and congenital syndromic AVMs

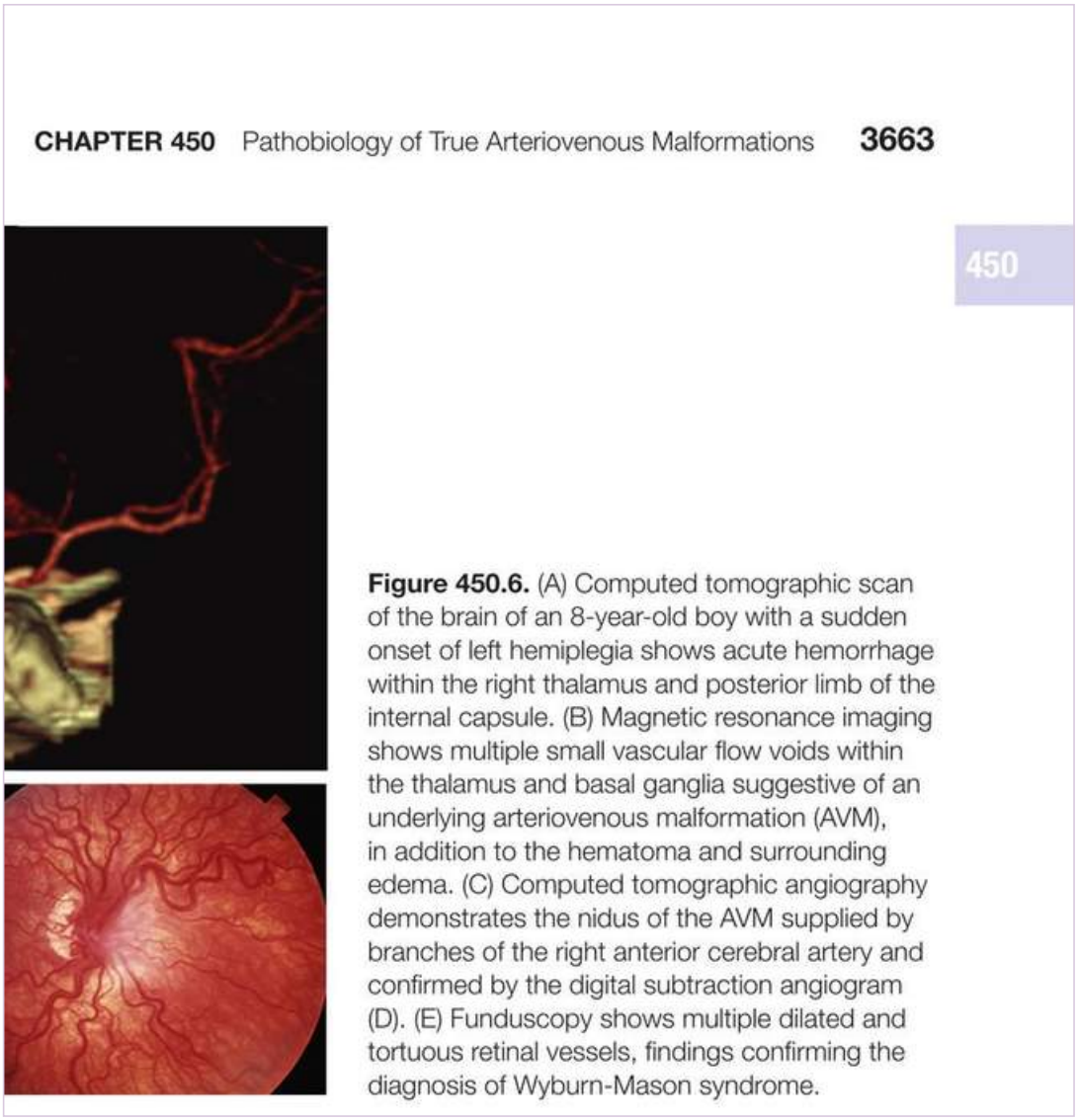
- **Familial non-syndromic AVM is very rare** — "**only about 20 cases of familial AVMs have been documented**"; **autosomal dominant with variable penetrance** and an **X-linked recessive** pattern have both been proposed. Clinical manifestations and location do not differ from sporadic lesions, but "**the age of diagnosis tends to be younger, and a higher proportion of such patients appear to have multiple AVMs**". Prevalence among first-degree relatives of Dutch AVM patients was **slightly but not significantly increased — not enough to justify screening** YW p.3665.
- **Cerebrofacial arteriovenous metameric syndromes (CAMS)** [YW pp. 3661-3662]:
  - **CAMS-1** — **prosencephalic** AVMs affecting the **hypothalamus or hypophysis** with facial AVMs of the **nose**.
  - **CAMS-2** — **lateral prosencephalon** (occipital lobe, thalamus) with facial AVMs of the **maxilla**.
  - **CAMS-3** — **rhombencephalon** (cerebellum, pons) with facial AVMs of the **mandible**.
- **Wyburn-Mason syndrome** — "**unilateral retinocephalic vascular malformation**, consists of **cutaneous vascular nevi, retinal and optic nerve vascular malformations and ipsilateral or bilateral mesencephalic cerebral AVMs**"; the AVM is "usually of the **diencephalon-optic pathway or midbrain-thalamus**, occurring in conjunction with **retinal vascular malformations seen at funduscopy**"; the genetic defect is unknown but an association with the HHT genes has been postulated [YW pp. 3661, 3666].
- **Sturge-Weber** and **Osler-Weber-Rendu** are the other named genetic disorders listed in Ch. 455 as associated with cerebral vascular malformations; Sturge-Weber (encephalotrigeminal angiomatosis) has **no obvious mode of genetic transmission** and is characterised by a facial **port-wine stain** in the trigeminal distribution with an **ipsilateral leptomeningeal vascular malformation**, an atrophic parieto-occipital lobe, dystrophic calcification producing **"tram-track" double parallel lines** on plain films or CT, **severe intractable early epilepsy** and possible intellectual disability YW p.3695.

4.4 The molecular biology of the nidus — angiogenic drivers

- **Active angiogenesis is proven, not inferred** — endothelial cell proliferation measured by **Ki-67** was **2.5% in AVMs versus 0.5% in control cortex**; a larger study of 37 AVM and 5 control specimens found "an approximate **sevenfold**

increase in nonresting endothelial cells in AVMs". "The EC turnover rate in AVMs appears to be **somewhere between that of normal quiescent ECs and ECs in progressing tumors**" YW p.3666.

- **VEGF** — "**VEGF type A is a potent EC mitogen and morphogen**", with five isoforms and two vascular receptors, **VEGF-R1 (flt-1)** and **VEGF-R2 (flk-1/KDR)**. Increased VEGF expression in AVM vessel walls has been shown at **both protein and mRNA level**; children with **recurrent** AVMs had a high degree of **astrocytic VEGF expression** in the original operative specimen compared with non-recurrent AVMs [YW pp. 3666-3667].
- **HIF-1α** — "a **major upstream activator of VEGF**", regulated by destruction of the α subunit; expressed in a majority of both embolized and non-embolized AVM samples. The paradox to quote: "AVM blood vessels are generally exposed to **abnormally high blood flow**… **mechanical stress** on cells inside vascular walls induced by abnormally high blood flow may be triggering HIF-1α expression" rather than hypoxia [YW pp. 3667-3668].
- **Angiopoietin / Tie-2** — **Ang-1 is the agonist** of Tie-2 and stabilises vessels by promoting endothelial-to-pericyte interaction; **Ang-2 is the antagonist** and destabilises those attachments. "In AVM tissues, **Ang-2 (antagonist) is markedly increased and Ang-1 (agonist) is decreased** compared with control brain tissues", with **decreased Tie-2** at mRNA and protein level. "The abnormal balance in angiopoietins in AVMs… would be expected to result in an **overall decrease in Tie-2 signaling, leading to vascular instability**… This may explain in part the aberrant vascular phenotype in AVMs (i.e. **dilated vessels with a relative lack of mature peri-endothelial support**)" YW p.3668. **Tie-2 is mutated in a familial venous malformation syndrome** YW p.3668.
- **Matrix metalloproteinases** — "there is **markedly increased MMP-9 activity** in AVM samples compared with control brain samples. MMP-9 is expressed in the **EC and peri-EC layer**… the increased activity can be expected to cause **degradation of the vascular matrix, thereby impairing the structural stability of AVM vessels**." High MMP-9 is also found in **cerebral aneurysms, abdominal aortic aneurysms and atherosclerotic carotid arteries**; **doxycycline at subantimicrobial doses inhibits MMPs**, and "clinical trials are currently under way to assess the feasibility of **tetracycline as potential vasculostatic therapy for AVMs**" [YW pp. 3668-3669].
- **The synthesis (Hashimoto and Young)** — an unknown inciting event (e.g. **localised microvascular thrombosis** from prenatal/postnatal minor cranial trauma or relative thrombophilia) creates **venous hypertension → HIF-1 → VEGF → focal angiogenesis → interleukin-6 and leukocyte/macrophage recruitment → further MMP expression → endothelial proliferation, migration and microvessel sprouting**. "Development of a vascular malformation might become **self-sustaining through the opening of AV shunts and increased flow. High flow increases endothelial shear and activates nitric oxide synthase and nitric oxide production, thus further driving VEGF stimulation. Downstream activation of MMPs ultimately destabilizes the vascular walls and sets the stage for rupture**" YW p.3669.
- **The headline of the last decade — KRAS** — "perhaps the most exciting recent development… is the discovery that **somatic activating mutations in the KRAS gene (OMIM 190070) have been identified as a cause of AVM**." Studies identified **somatic KRAS mutations (p.Gly12Val/Asp)** in AVMs, "which **activate the MAPK-ERK signaling pathway in brain endothelial cells** and were found to be **inhibited in vitro using a MEK inhibitor**." More recently a **high prevalence of KRAS/BRAF mutations (87.1%)** has been reported in AVMs by next-generation sequencing; "given the high prevalence… **novel agents that specifically inhibit the Ras/Raf pathway could be developed to treat or modify the clinical course of AVMs**" [YW pp. 3659, 3669].
- **Whole-exome evidence** — whole-exon sequencing of **100 Chinese patients with sporadic AVMs and their normal parents** "confirmed the significant role of **BMP/TGF-β and VEGF/VEGF receptor signaling** in the pathogenesis of AVMs"; **microRNA-18a** normalises dysfunctional endothelial cells from cerebral AVMs by **decreasing VEGF secretion and increasing thrombospondin-1**, a physiologic VEGF antagonist [YW pp. 3659, 3669].
- **Embryology** — AVMs "result from a **persistent direct connection between the arterial and venous portions of the primitive vascular plexus in the embryo before the fourth week of gestation**", with "**failure of development of an interposed capillary network**" [YW pp. 3664, 3666]. The counter-argument that AVMs are acquired is explicitly acknowledged: "bAVMs may **develop after birth** (not discounting a congenital development for an unknown proportion)" YW p.3677.e11.



*Reproduced from Youmans & Winn 8e, Fig. 450.6, p. 3663 — Look at the two panels that reproduce: the **three-dimensional CT angiogram** demonstrating the nidus of a thalamic/basal ganglia AVM supplied by branches of the right anterior cerebral artery, and the **funduscopic photograph** showing **multiple dilated and tortuous retinal vessels — the retinal vascular malformation that confirms Wyburn-Mason syndrome** in this 8-year-old boy who presented with sudden left hemiplegia from a right thalamic and internal capsular haemorrhage. Use it to make the point that a cerebral AVM in a child mandates funduscopy and a search for a metameric (CAMS) or HHT phenotype.*

(c) Classification of AVM [4]

5. Classification 1 — histopathological (McCormick; Russell and Rubenstein)

- "Cerebrovascular malformations are classified **based on their histopathologic features: AVM, venous angioma, cavernous malformation (CM), and capillary telangiectasia**" — the four types described by **McCormick in 1966** and **Russell and Rubenstein in 1971**, "now accepted as the current nomenclature" YW p.3659.
- "A possible **fifth category** of cerebrovascular malformations includes **direct fistulas, or arteriovenous fistulas (AVFs)**. These are regarded as **acquired** lesions that involve single or multiple dilated arterioles that connect directly to a vein **without a nidus**. Examples are **vein of Galen aneurysmal malformations, dural AVFs, and carotid cavernous fistulas**" YW p.3659.

Table 2 · The four (five) histopathological categories of cerebrovascular malformation, with the defining features and the numbers Youmans supplies — assembled from Ch. 450, pp. 3659-3663 and Ch. 451, pp. 3673-3675.

Lesion	Defining histology	Key epidemiological/clinical numbers
True AVM	Feeding arteries + dysplastic nidus of AV shunts with **no capillary bed**; intervening gliotic, haemosiderin-stained, non-functional neural parenchyma may be present; calcification common	Haemorrhage in ~65% of symptomatic lesions; seizures 15%-35%; mortality of haemorrhage 6%-29%; annual detection ≤1.5 per 100,000
Venous angioma / developmental venous anomaly (DVA)	Anomalous veins **separated by normal brain tissue**; walls thickened and hyalinised, lacking elastic tissue and smooth muscle; drains **normal** cerebral tissue	**The most common intracranial vascular malformation — up to 65% of all cerebral vascular malformations**; prevalence 2.6% at autopsy, 0.5%-11.6% on clinical imaging; prospective bleeding risk **0.15%-0.34% per year**
Cavernous malformation	**Sinusoidal caverns lined by a single endothelial layer**, separated by collagenous stroma devoid of elastin and smooth muscle; **lack of intervening brain parenchyma is the pathologic hallmark**; "mulberry" appearance	Prevalence 0.2%-0.7%; 80%-85% sporadic, 15%-20% familial (**KRIT1/CCM1, malcavernin/CCM2, PDCD10/CCM3**); presentation: bleeding 20%-30%, seizure without haemorrhage 30%-40%, focal deficit without haemorrhage 10%, incidental 10%-40%
Capillary telangiectasia	**Dilated capillaries with normal intervening neural tissue**; no smooth muscle, no elastic fibres, no feeding or draining vessels; usually <2 cm, solitary in 78%	Second most common vascular malformation of the brain; autopsy prevalence 0.06%-0.4% (Ch. 450 gives 0.3%); **78% are in the pons**; 12.4% of angiographically occult malformations but only 2.6% of symptomatic ones
(Fifth) Direct arteriovenous fistula	Single or multiple dilated arterioles connecting directly to a vein, **no nidus**; acquired	Vein of Galen aneurysmal malformation, dural AVF, carotid-cavernous fistula. DAVFs = ~10% of intracranial vascular malformations, present age 50-70, overall unruptured haemorrhage risk **1.5%-2% per year**

6. Classification 2 — Spetzler-Martin, the grading scale the examiner wants

- **What it is for** — "the Spetzler-Martin grading system has become one of the most useful and widely accepted classification systems for both **communication of information** regarding cerebral AVMs and **prediction of the technical difficulty and risks associated with surgical resection**" YW p.3698.
- **The critical caveat** — "this grading scale… attempts to predict **risk for surgical resection, not hemorrhagic risk** of the AVM if not treated. This is an important distinction because **high-grade AVMs simply equate higher risk for neurological deficit if resected and may not necessarily correspond to a higher risk for bleeding**" YW p.3698.

Table 3 · Grading system of Spetzler and Martin for arteriovenous malformations — reproduced in full from Youmans & Winn 8e, Table 452.1, p. 3677.e2 (also Table 7.7, p. 120). Grade = Size + Eloquence + Venous drainage; the total allocates AVMs to grades I-V.

Graded feature		Points assigned
AVM size (diameter)	Small (<3 cm)	**1**
	Medium (3-6 cm)	**2**
	Large (>6 cm)	**3**
Eloquence of adjacent brain	Noneloquent	**0**
	Eloquent	**1**
Pattern of venous drainage	Superficial only	**0**

	Deep	1

- **Size** — "scored by measuring the **greatest diameter of the AVM nidus** on DSA, CT, or MRI"; size "serves as a **surrogate for the number of feeding arteries, the amount of flow through the AVM, and the degree of hemodynamic effect** on the adjacent brain" YW p.3699.
- **Eloquence — learn the list verbatim** — "**sensory, motor, language, and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncles; and deep cerebellar nuclei**". Non-eloquent regions include the **frontopolar and cerebellar cortex** YW p.3699. Ch. 452 words it identically: "sensorimotor, language, and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncle; deep cerebellar nuclei" YW p.3677.e2.
- **Venous drainage** — "scored as **superficial if all** the draining veins are components of the cortical venous system and as **deep if any or all** of the drainage is through the **internal cerebral veins or galenic system**"; Ch. 452 adds **the basal vein and precentral cerebellar veins** [YW pp. 3699, 3677.e2]. "In the posterior fossa, **only the cerebellar cortical veins that drain directly into the dural sinuses are considered superficial**" YW p.3699.
- **What deep drainage really means** — "the presence of deep venous drainage is simply a **surrogate for deeper location**… it indicates that the AVM involves the **ventricular wall** or extends to the deeper regions of the brain, which are difficult to access and are **invariably supplied by deep penetrating arteries even if not visualized angiographically**. Furthermore, involvement of the ventricular wall is associated with **arterialized subependymal veins, which are fragile, resist coagulation, and tend to retract into the ventricles**." Paradoxically, "deep venous drainage may actually be an **advantage intraoperatively** because the draining veins are hidden away from the surgeon until the last moments of the resection" YW p.3699.
- **Grade-related morbidity** — "low-grade AVMs (**grades I and II**) have low morbidity rates (**0%-5%**)… whereas high-grade AVMs (**grades IV and V**) have high morbidity rates (**12%-38%**)" YW p.3699.

7. Classification 3 — the derivatives of Spetzler-Martin

7.1 Spetzler-Ponce three-tier classification (SPC)

- "**SPC class A is Spetzler-Martin grades I and II**, **SPC class B is Spetzler-Martin grade III**, and **SPC class C is Spetzler-Martin grades IV and V**" YW p.3677.e2.
- "There is significant separation of SPC class by adverse outcomes from surgery, with **10% for SPC class A, 18% for SPC class B, and more than 30% for SPC class C**. In a number of series, the long-term adverse outcome risk for **SPC class A is no greater than 4%**" YW p.3677.e7.

7.2 Subdivision of the heterogeneous grade III

- **Lawton / UCSF (74 patients)** — surgical risk (new deficit or death) was **2.9% for S1V1E1** (small AVMs), **7.1% for S2V1E0** (medium/deep) and **14.8% for S2V0E1** (medium/eloquent). Accordingly: **grade III− (S1V1E1)** behaves like a low-grade AVM and can be safely resected; **grade III+ (S2V0E1)** behaves like a high-grade AVM and is best managed conservatively; **grade III (S2V1E0)** has intermediate risk and requires judicious selection. Interestingly " **there were no large grade III AVMs (S3V0E0) in this series**" YW p.3699.
- **de Oliveira** — grade **IIIA** if large; grade **IIIB** if small but with deep venous drainage or eloquent location; generally **embolization then surgery for IIIA, radiosurgery for IIIB** YW p.3699.

7.3 Lawton-Young supplementary grading system

- "A further characteristic identified as a risk factor for new postoperative deficits is **diffuse nidus**. This has led to the development and validation of a new grading system, the **Lawton-Young grading system**, adding to the Spetzler-Martin grade **1 point for age younger than 20 years, 2 points for age 20-40 years, and 3 points for age older than 40 years**. In addition, **1 point is added for diffuse bAVM** and **1 point for bAVMs that are unruptured**. This results in a range of **Lawton-Young grades of 2-10**" YW p.3677.e8.
- **Predicted adverse outcome by Lawton-Young grade in SPC class B** — approximately **10%, 20%, 25%, 40% and 65% for grades 4, 5, 6, 7 and 8** respectively YW p.3677.e8.

- **Two worked examples to quote** YW p.3677.e8:
  - **Unruptured Spetzler-Martin grade II, diffuse, patient over 40 (Lawton-Young 7)** — adverse outcome risk about **40%**, so despite being SPC class A "**such cases may best be managed by an alternate pathway**".
  - **Ruptured Spetzler-Martin grade IV, compact, patient under 20 (Lawton-Young 4)** — adverse outcome risk **10%**, so despite being SPC class C "**these patients may be managed by surgery**".
- The summary rule: "a **Lawton-Young grade of 7 or greater** is more likely to lead to a permanent deficit or death from surgery in comparison to conservative treatment **for at least the first 40 years after diagnosis**" YW p.3677.

7.4 Radiosurgical grading systems

- **Pollock-Flickinger score** = **0.1 × volume (mL) + 0.02 × age (years) + 0.5 (if bAVM is located in basal ganglia, thalamus or brainstem)**. Obliteration without deficit at a mean follow-up of 70 months is approximately **90% for scores ≤1, 70% for >1 and ≤1.5, 60% for >1.5 and ≤2, and less than 50% for >2**; modified Rankin decline in the 95% CI range **0%-10%, 10%-20%, 15%-30% and 25%-50%** respectively. Volume is estimated as **(x × y × z)/2** in cm YW p.3677.e4. The Mayo/Pittsburgh **radiosurgery-based AVM scale (RBAS)** built on the same score gives excellent outcomes in **89%, 70%, 64% and 46%** and mRS decline in **0%, 13%, 20% and 36%** for scores ≤1.00, 1.01-1.50, 1.51-2.00 and >2.00; it has been called "**the radiosurgical equivalent of the Spetzler-Martin grading system**" YW p.2353.
- **Virginia Radiosurgery AVM Scale (VRAS)** — sum of points for **volume (2-4 cm³ = 1 point; smaller = 0; larger = 2)** plus **1 point each for a history of haemorrhage and for eloquent location** (eloquence as defined by Spetzler-Martin). Over a mean of 7 years there was a **favourable outcome in 81%, 75%, 66%, 47% and 41% for VRAS scores 1 through 5**; favourable outcome is defined as **freedom from residual bAVM, from radiosurgical permanent disabling deficit and from post-treatment haemorrhage**. By Spetzler-Martin grade, favourable outcome after radiosurgery was **75%, 69%, 61% and 37% for grades I through IV** [YW pp. 3677, 3677.e5, 3677.e6].
- Also named in the book: the **Heidelberg Score (HS)** and the **Proton Radiosurgery AVM Scale (PRAS)**. "Each grading scale has some measure of **size or volume**, three include **location** (RBAS, VRAS, PRAS), two include **patient age** (RBAS, HS), and one includes **presentation** (VRAS)" YW p.2353.

7.5 What Spetzler-Martin omits — the extra marks

"The classification **fails to directly address** several important factors such as the **pattern of arterial supply (superficial versus deep perforating)**, **configuration of the nidus (compact versus diffuse)**, and **presence of feeding artery aneurysms**. Furthermore… the grading system **does not take into consideration the surgeon's personal experience**. The surgical risks quoted in the grading series are from **experienced AVM surgeons**" YW p.3699. Other modifiers named in the book are **lenticulostriate supply** (identified as a risk factor, then not confirmed) and **interobserver reliability of assigning the points, which is far from perfect** [YW pp. 3677.e7, 3677.e8].

8. Classification 4 — associated aneurysms, a classification in its own right

- **Frequency** — AVM-associated aneurysms are found in **2.3% to 16.7%** of AVMs (Ch. 450) or **2.7% to 58%** across series with an overall average of about **10%** (Ch. 455) [YW pp. 3660, 3700].
- **The practical three-way classification** — "**intranidal aneurysms (which can be arterial or venous), flow-related aneurysms (in the arterial pedicles feeding the AVM), and unrelated aneurysms (on arteries not directly feeding the AVM)**" YW p.3700.
- **The formal classification** — "AVM-associated aneurysms are classified by location as either **flow related (85%)** or **unrelated (15%)**. Flow-related aneurysms are classified as being either **proximal** (from arteries on the circle of Willis or the proximal feeding vessels up to a primary bifurcation) or **distal** (from the feeding vessel distal to its origin from the parent artery at its primary bifurcation). **Intranidal aneurysms** occur within the nidus and show **early filling during angiography**; they account for **5.5% of flow-related aneurysms**" YW p.3660.
- **Risk** — coexisting unruptured AVM and unruptured aneurysm carried a haemorrhage risk of **7% at 1 year and still 7% per year at 5 years, versus 3% and 1.7% per year for AVM alone**; in the Toronto series the annual bleeding rate with untreated **intranidal aneurysms was 9.8%**, and with untreated flow-related aneurysms and no AVM treatment

5.3% per year, giving a **combined rate of about 7%** YW p.3700.

- **Varix** — "varix formation may be associated with AVMs, especially those with a **paucity of venous drainage**… Valavanis and Yasargil associated this with an **increased risk of hemorrhage**" YW p.3660.
- **Draining vein stenosis** — "AVM draining vein stenosis most commonly occurs at or near the **venous-dural sinus junction**, and this stenosis is **progressive with age** and other vascular risk factors" [YW pp. 3660-3661]. Ch. 452 notes venous outflow stenosis "has an intellectually attractive basis as a risk factor" — raising intranidal pressure and reducing laminar wall shear stress — "however, venous outflow stenosis has **yet to be confirmed as a risk factor with prospective data**" YW p.3677.e3.

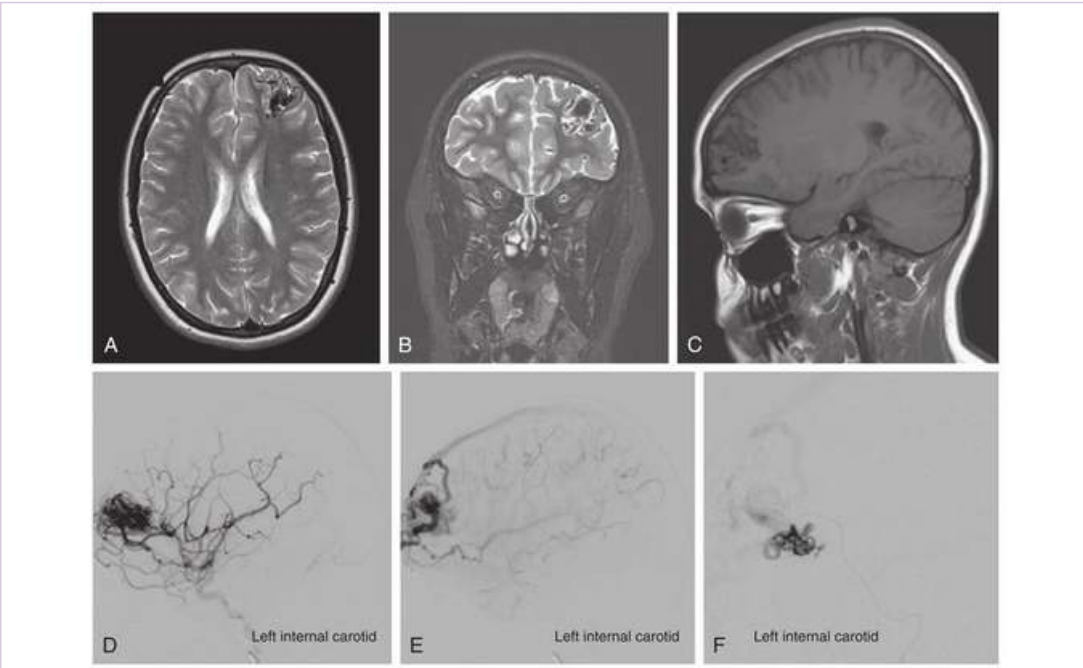


Figure 450.1. Axial and coronal T2-weighted (A and B) and sagittal T1-weighted (C) magnetic resonance images show multiple vascular flow voids within a left frontal arteriovenous malformation extending from the cortex down to the frontal horn of the left lateral ventricle. Left internal carotid injection (lateral projection) during cerebral angiography shows that the arterial supply is via anterior left middle cerebral artery branches (D) with early venous drainage (E). The nidus is more clearly defined with superselective angiography (F).

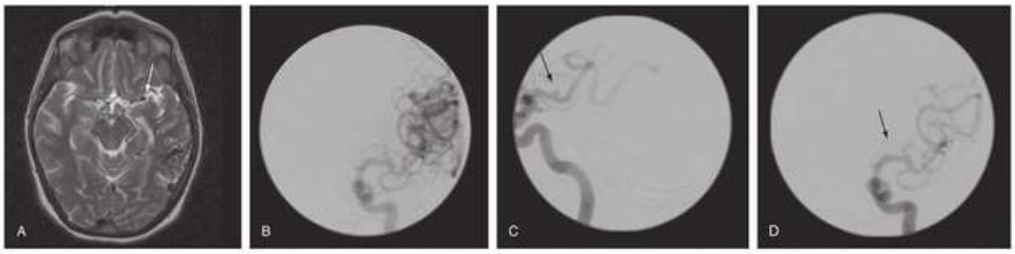


Figure 450.2. (A) Axial T2-weighted magnetic resonance image shows a left temporoparietal pial arteriovenous malformation (AVM) with a left middle cerebral artery (MCA) flow aneurysm *(arrow)*. (B) Left internal carotid injection (anteroposterior projection) of the cerebral digital subtraction angiogram shows the nidus of the AVM supplied by left MCA branches. (C and D) The left MCA bifurcation aneurysm is seen less clearly than on the earlier runs *(arrow)*.

*Reproduced from Youmans & Winn 8e, Fig. 450.2, p. 3660 — Label when you reproduce it: (A) axial T2 MRI of a left temporoparietal pial AVM with an **arrowed left MCA flow aneurysm**; (B) left internal carotid AP DSA showing the **nidus supplied by left MCA branches**; (C-D) the **MCA bifurcation aneurysm seen less clearly than on the earlier runs**. This is the figure to use when asked about AVM-associated aneurysms: mark the aneurysm as **flow-related, proximal type** and say that its presence increases the annual rupture risk to about 7%.*

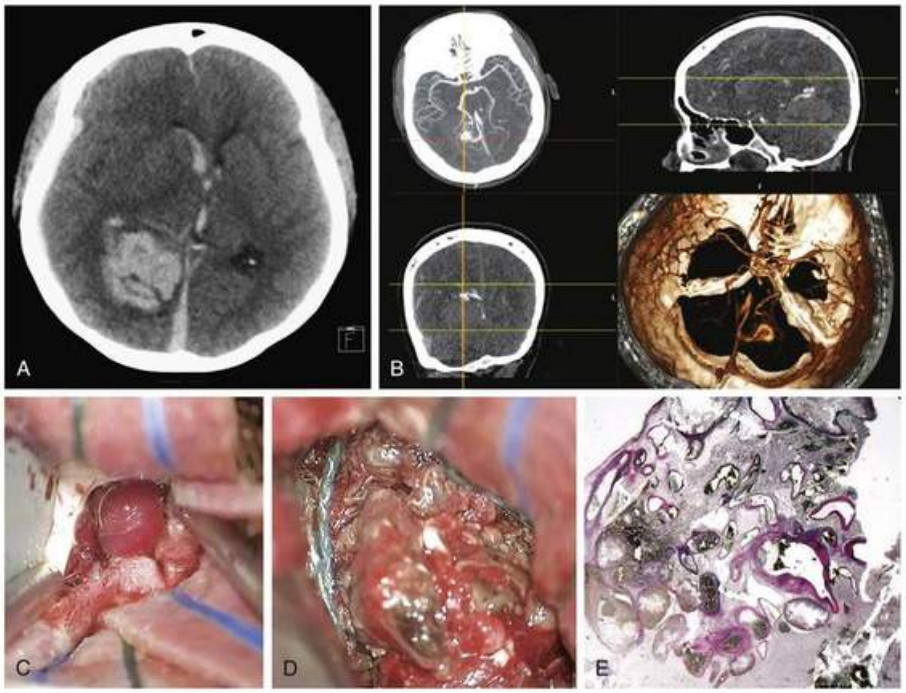


Figure 450.3. (A) Computed tomographic scan of the brain of a 26-year-old woman who presented in a coma with acute right occipital intracerebral hemorrhage with intraventricular and subdural extension. (B) Computed tomographic angiography demonstrates the nidus of the arteriovenous malformation (AVM) supplied by branches of the right posterior cerebral artery and draining via a varix into the straight sinus. (C) Intraoperative photograph demonstrating the AVM and varix. (D) Intraoperative photograph of the AVM nidus. (E) Histologic section of the AVM.

*Reproduced from Youmans & Winn 8e, Fig. 450.3, p. 3661 — Label when you reproduce it: (A) CT of a 26-year-old woman in coma with an **acute right occipital intracerebral haemorrhage with intraventricular and subdural extension**; (B) CT angiography showing the **nidus supplied by branches of the right posterior cerebral artery and draining via a varix into the straight sinus**; (C) the intraoperative photograph of the **AVM and its varix**; (D) the intraoperative photograph of the **nidus**; (E) the **histologic section** of the AVM. This one figure carries presentation, imaging, operative appearance and pathology — use it for any "clinical presentation of AVM" question.*

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Five presentations: haemorrhage, seizure, progressive deficit, headache, incidental.** Give the percentages — haemorrhage 45%-72% (historically >70%), seizure ~70% of supratentorial AVMs (25%-50% without haemorrhage), progressive deficit 3%-10%, headache 6%-14%, incidental 10% in modern series.
- **AVMs cause 2% of all strokes but 38% of intracerebral haemorrhages in patients aged 15-45**, and are the commonest cause of spontaneous brain haemorrhage in children.
- **Each haemorrhage carries 10%-30% mortality and 20%-30% permanent morbidity** — use **40% combined morbidity/mortality** when counselling, as Ch. 452 does.
- **Occipital AVM headache is migrainous, always on the same side, with contralateral visual phenomena** — classical migraine changes sides.
- **Bleeding comes from the draining vein (dilated, kinked, thrombosed) or a flow-related aneurysm**, not usually from the feeders.
- **Cumulative lifetime rupture risk ≈ 105 minus the patient's age in years.**
- **Small AVMs present with haemorrhage more often (82% vs 21%) because they have no other way of declaring themselves** — and they have higher feeding-artery pressures.
- **Spetzler-Martin = size (1/2/3) + eloquence (0/1) + deep venous drainage (0/1).** It predicts *surgical* risk, not rupture risk.
- **Eloquence list, verbatim: sensorimotor, language and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncles; deep cerebellar nuclei.**
- **Spetzler-Ponce: A = I+II (adverse outcome ~10%, often <4%), B = III (18%), C = IV+V (>30%).**
- **Lawton-Young adds age (<20 = 1, 20-40 = 2, >40 = 3), diffuse nidus (+1) and unruptured (+1); range 2-10.** Grade ≥7 favours conservative management.
- **Pollock-Flickinger = 0.1 × volume + 0.02 × age + 0.5 (BG/thalamus/brainstem).** VRAS = volume + haemorrhage

+ eloquence, 1-5.

- **Four histological types (McCormick; Russell & Rubenstein): AVM, venous angioma/DVA, cavernous malformation, capillary telangiectasia — plus direct AVFs as a fifth, acquired category.**
- **HHT: autosomal dominant, Curaçao criteria (epistaxis, telangiectasia, visceral involvement, family history — three of four). ENG/endoglin = HHT1 (9q34), ACVRL1/ALK1 = HHT2 (12q). Mechanism is haploinsufficiency of TGF-β signalling.** Cerebral AVMs symptomatic in 5%, on screening 13%.
- **KRAS somatic activating mutations (p.Gly12Val/Asp) cause sporadic brain AVMs via MAPK-ERK, with KRAS/BRAF mutations in 87.1% of AVMs — and MEK inhibition reverses the phenotype in vitro.** This is the newest fact in the chapter and the one that impresses.
- **Ang-2 up, Ang-1 down, Tie-2 down, VEGF up, HIF-1α up, MMP-9 up** — one line, and you have the molecular biology of the nidus.

Pages read for this answer — Youmans & Winn 8e: 2353, 3659, 3660, 3661, 3662, 3664, 3665, 3666, 3667, 3668, 3669, 3677, 3677.e2, 3677.e3, 3677.e4, 3677.e5, 3677.e6, 3677.e7, 3677.e8, 3677.e9, 3677.e11, 3695, 3696, 3697, 3698, 3699, 3700, 3701

a) Clinical manifestations of spinal AVMs. [4]
b) Spinal AVMs classification. [3]
c) Spinal arachnoiditis - radiology and treatment. [3]

LONG | OCT 2023 · Paper II · Q9 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 464 *Microsurgical Treatment of Spinal Vascular Malformations* (Oldfield et al.), §Etiology, Pathophysiology, Clinical Presentation and Natural History, §Foix-Alajouanine Syndrome, §Cavernous Angiomas and §Diagnostic Imaging, pp. 3797-3818 (Figs. 464.3-464.7, pp. 3798-3800; Figs. 464.13-464.20, pp. 3804-3810; **Table 464.1**, p. 3806; **Table 464.2**, p. 3806; **Table 464.3 — Clinical Findings and Natural History of Intradural Arteriovenous Malformations**, p. 3807; **Box 464.1**, p. 3805). Ch. 462 *Classification of Spinal Arteriovenous Lesions*, §Spetzler Classification System, pp. 3779-3783 (**Table 462.1**, p. 3780; Figs. 462.2-462.7). Ch. 334 *Adult Syringomyelia*, §Arachnoiditis and §Treatment, pp. 2602-2606 (**Table 334.1 — Classification of Syringomyelia**, p. 2602; **Table 334.2 — MRI Findings Associated With Lumbar Arachnoiditis**, p. 2605; Figs. 334.3-334.4, pp. 2605-2606). Supplementary: Ch. 463 *Endovascular Treatment of Spinal Vascular Malformations*, pp. 3788-3794.

(a) Clinical manifestations of spinal AVMs [4]

1. Open by separating the two biological diseases

- Youmans' central teaching is that spinal arteriovenous lesions are **two biologically distinct diseases that happen to share a segment of anatomy**: an **acquired dural arteriovenous fistula** of late adult life that produces a **venous congestive myelopathy**, and a **congenital intradural arteriovenous malformation** of childhood and young adult life that produces **haemorrhage** [YW pp. 3804-3806].
- "**Dural AVFs are distinguished from spinal AVMs by multiple factors, including their demographics, pathophysiology, and clinical presentation**" [YW pp. 3803-3804].
- The distributions of the three lesion groups by gender, age at diagnosis and spinal level are so different that "**the distinct differences… indicate that they are biologically discrete disorders**" YW p.3801.

Table 1 · Acquired versus congenital spinal vascular malformation — reproduced in full from Youmans & Winn 8e, Table 464.2, p. 3806 (Oldfield and Doppman).

Feature	Acquired dural AVF	Congenital AVM of the spinal cord
Gender	Predominantly male	Male or female
Onset of symptoms	**Later half of adulthood**	**Child or young adult**
Associated congenital malformation	**Never**	**Occasionally**
Distribution along the spine	**Lower half**	**Diffuse**

Normal spinal venous pathways	**Absent**	**Present**

2. Spinal dural AVF (intradural dorsal AVF, type I) — the venous congestive myelopathy

2.1 The mechanism that produces every symptom

- The shunt is between a **dural artery** and a **medullary vein** in the dural nerve root sleeve; the medullary vein, "which in most cases represents the **only outflow** for the AVF, carries arterialized blood flow **retrograde** into the coronal venous plexus" YW p.3799.
- "**Under normal circumstances, the venous blood flow in the coronal venous plexus is diverted through the dura and into the extradural venous system**", and valves at the dural penetration prevent reflux. With the fistula, arterialised flow produces the dilated serpiginous surface veins and "**transmits high pressure to the valveless radial and sulcal veins within the substance of the cord, leading to venous congestion, venous hypertension, diminished arterial perfusion, ischemia, and myelopathy**" YW p.3799.
- There is therefore **no steal, no mass lesion and no nidus** — the myelopathy is entirely a venous hypertensive phenomenon, and it is **potentially reversible if treated before infarction**.

2.2 The clinical picture — nine features to write down

- **Acquired, not congenital** — "these lesions are generally believed to be **acquired**. Factors supporting this include **onset of symptoms later in life** and **dural AVF formation following trauma or spinal surgery**" YW p.3804.
- **Sex and age** — "**most patients (80%) are men who develop symptoms beyond 40 years of age**"; mean age at diagnosis **46 years** [YW pp. 3804, 3806].
- **Level** — "patients **rarely present with upper extremity involvement** because of the **strong predilection for dural AVFs to occur in the lower thoracic and lumbar regions**" YW p.3804; arms are affected in **0%** of dural AVFs versus 11% of intradural AVMs YW p.3806.
- **The prodrome** — "the history is often significant for **low back or radicular pain**" YW p.3804.
- **The syndrome** — "**gradual but progressive onset of myelopathic symptoms (85% to 95%)**. Patients complain of **increasing weakness and sensory disturbance and bowel and bladder dysfunction**" YW p.3804; the **first symptom is paresis in 44%** YW p.3806.
- **Neurogenic claudication — the single most quoted feature** — "**importantly, neurogenic claudication (worsening symptoms with walking or when in certain positions) is similar to the neurogenic claudication occasionally associated with lumbar stenosis**" YW p.3804. Symptoms are **exacerbated by activity in 70%** of dural AVFs versus 15% of intradural AVMs YW p.3806.
- **No SAH, no bruit** — SAH occurs in **0%** and a spinal bruit in **0%** of dural AVFs YW p.3806.
- **The diagnostic trap that causes iatrogenic harm** — "intradural AVFs of the **filum terminale often occur concurrently with lumbosacral degenerative disease**, occasionally resulting in **delayed or missed diagnosis and potentially unnecessary spinal surgeries** solely addressing the degenerative disease. Multiple reports have identified initial surgical intervention for diagnoses such as **lumbar nucleus pulposus herniation, tethered cord syndrome, and severe lumbar stenosis**"; "**misdiagnosis and laminectomy for presumed symptomatic lumbar stenosis have been reported in patients with spinal dural AVFs and can result in acute neurological deterioration**" [YW pp. 3804-3805].
- **Acute deterioration does occur** — "acute deterioration occurs from **rupture of the fistula**, which, in the rare instances in which it occurs, is **more likely with dural AVFs in the cervical region**" YW p.3805.

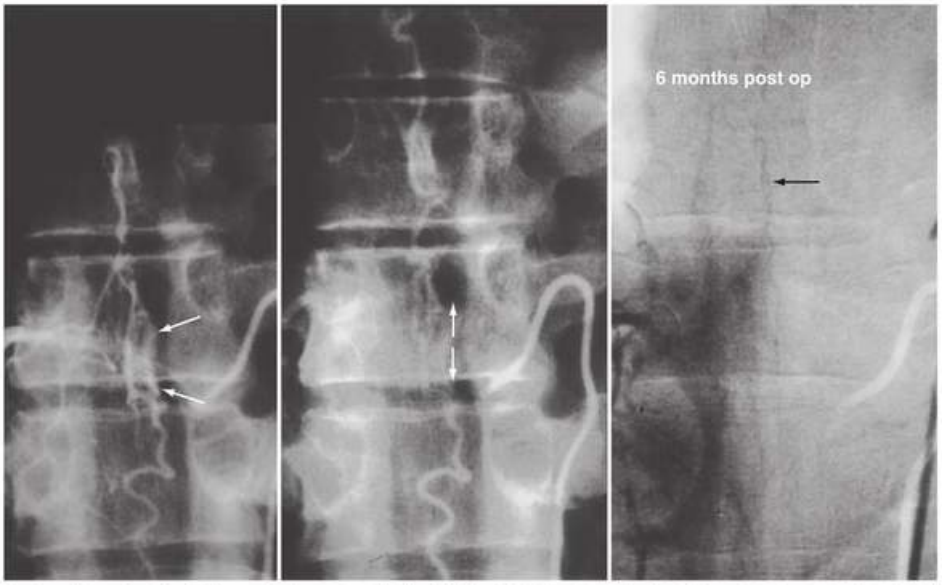
2.3 Foix-Alajouanine syndrome — the emergency

- **History** — "in 1926, Foix and Alajouanine published their findings in the cases of **two young men** who suffered from a **severe and rapidly progressive myelopathy that ultimately culminated in their deaths**. Pathologic examination of the spinal cords revealed **extensive necrosis and hypertrophy of the pial and intramedullary veins**" YW p.3805.

- **Modern interpretation** — "looking back, it appears as though these patients suffered from **untreated type I dural AVFs** that led to extreme venous hypertension. In the decades since, **venous thrombosis secondary to prolonged venous hypertension** has been included in the description of the syndrome" YW p.3805.
- **The clinical rule** — "a small subset of type I dural AVF patients develop Foix-Alajouanine syndrome, an **acute neurological deterioration from extreme venous hypertension and possibly subsequent venous thrombosis**. Therefore **this presentation is a true emergency** because **relief of the venous hypertension before it progresses to thrombosis can reverse neurological deficits**, whereas **failure to do so leads to irreversible spinal cord injury**" YW p.3805.

2.4 Natural history of the untreated dural AVF

- **Aminoff and Logue's cohort** — predominantly adult men with thoracolumbar malformations that had **never haemorrhaged**: "the clinical course consisted of **progressive neurological decline resulting in 20% requiring crutches for ambulation or being nonambulatory within 6 months** of onset of symptoms other than pain. **Within 3 years, a large percentage were severely disabled** or had activity restrictions. In general, untreated dural AVFs result in a **gradual progressive decline in motor and sensory function over a period of 2 to 3 years**" YW p.3805.
- **The figure to quote** — "by 3 years, **one-half of the patients were confined to a wheelchair or had to use crutches to ambulate**", and "the **greatest change in function between 6 months and 3 years was in patients with minimal neurological deficit who progressed to severe functional disability**" YW p.3804.
- **Why there is no prospective natural history study** — "the 1977 report first describing dural AVFs also established microsurgical treatment as **simple, safe, and effective**. As a result, **no prospective study of the natural history of these lesions has been performed or likely will be**" YW p.3805.



. Posterolateral perimedullary arteriovenous fistula (AVF). *Left,* Selective spinal arteriography demonstrating that the nidus of this pial AVF is supplied by the descending limb of a posterior spinal artery, that there is more than one arteriovenous shunt, and that the us shunting occurs at a moderate pace. The site of the nidus *(arrows)* is identified just proximal to the site of initial venous dilation from which the venous flow diverges rostrally and caudally *(middle, arrows). Right,* The feeding vessel *(arrow)* has returned to a more nonths after surgical excision and the absence of filling of the AVF.

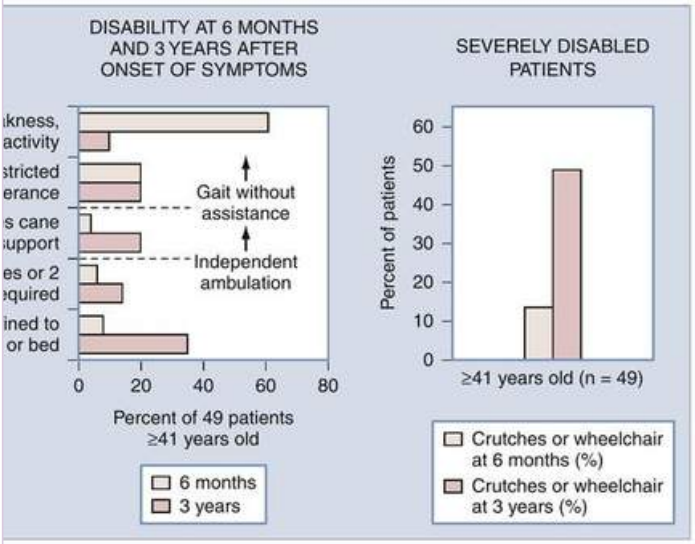


Figure 464.13. Degree of functional disability at 6 months and 3 years after the onset of symptoms in 49 patients 41 years of age or older reported by Aminoff and Logue.[42] Almost all patients had spinal dural arteriovenous fistulas. Note that the greatest change in function between 6 months and 3 years was in patients with minimal neurological deficit who progressed to severe functional disability. By 3 years, one-half of the patients were confined to a wheelchair or had to use crutches to ambulate. *(From Oldfield E. Spinal vascular malformations. In: Swash M, ed. Outcomes in Neurological and Neurosurgical Disorders. Cambridge, UK: Cambridge University Press; 1998.)*

*Reproduced from Youmans & Winn 8e, Fig. 464.13, p. 3804 — Label when you reproduce it: the Aminoff-Logue disability scale down the left side — **1 leg weakness with unrestricted activity, 2 restricted exercise tolerance, 3 requires a cane or support, 4 crutches or 2 canes required, 5 confined to wheelchair or bed** — and the bar chart at 6 months versus 3 years in the 49 patients aged 41 or over. The teaching point to write beneath it: the greatest deterioration occurred in patients who began with minimal deficit, and **by 3 years half the patients needed crutches or a wheelchair**. This is the figure that justifies operating early.*

3. Intradural AVM (glomus and juvenile) and perimedullary AVF — the haemorrhagic disease

- **Congenital** — "in contrast with dural AVFs, spinal AVMs appear to be **congenital lesions resulting from aberrant vascular embryogenesis**. These lesions occur with a **nearly identical incidence in males and females**. Symptom onset is usually **early in life**, and lesions are **occasionally associated with additional vascular abnormalities**" YW p.3805. Mean age at diagnosis is **24 years** YW p.3806.
- **Distribution** — "intradural spinal AVMs are distributed **more evenly throughout the long axis of the spine** compared with spinal dural AVFs" YW p.3805.
- **Haemorrhage is the mode of presentation** — "the **high-flow and high-pressure** characteristics of spinal AVMs can

result in **venous hypertension and hemorrhage**. Symptom onset is often **subacute or acute**, with the most dramatic presentations caused by hemorrhage. Patients with hemorrhage complain of an **acute onset of back or suboccipital pain, meningismus, or a loss of consciousness**. **Sudden deterioration in motor function is also common.** Subarachnoid or intramedullary hemorrhage is the initial finding on diagnostic imaging in **approximately 35% of patients**" YW p.3805.

- **In the comparative series, SAH occurred in 50% of intradural AVMs and was the first symptom in 32%; a spinal bruit was audible in 6%** YW p.3806.
- **Children bleed far more** — "**children appear to be more prone to hemorrhage**; Riché and colleagues reported an **acute onset of initial symptoms in 84% of children** with spinal AVMs" YW p.3805.
- **Triggers of deterioration** — recurrent haemorrhage has been associated with **"violent physical effort", pregnancy and minor trauma**; Rosenblum's series lists **posture 17%, activity 15%, pregnancy 6%, Valsalva manoeuvre 13% and injury 13%** YW p.3807.
- **Disability at diagnosis** — Rosenblum's 54 patients: **paresis 93%, sensory loss 74%, bladder dysfunction 74%, haemorrhage 52%**; at treatment **74% were moderately or severely disabled (cane, crutches or wheelchair)** and only **26% had unaided ambulation** YW p.3807.
- **Stepwise course** — Hurth's 90 patients showed **recurrent SAH in 39% of those who had bled (one fatal) and stepwise progression in 69%**; Riché's paediatric series showed **71% with successive acute attacks and 17% with gradually progressive evolution**; Yasargil's intramedullary series showed **stepwise progression in 40%** YW p.3807.

Table 2 · Clinical findings and natural history of intradural arteriovenous malformations — reproduced in full from Youmans & Winn 8e, Table 464.3, p. 3807. All series include perimedullary AVFs except Yasargil (intramedullary AVMs only) and Biondi (thoracic intramedullary AVMs only).

Study	No. of patients	Age at onset	Initial symptoms	At diagnosis or treatment	Progressive evolution	Associated with deterioration
Hurth et al., 1978	90	**86% <40 yr**	**SAH in 36%**	SAH in 39%; SAH in **55% of patients <15 yr**	**Recurrent SAH (1 fatal) in 39%** of patients with SAH; **stepwise progression in 69%**	SAH with **"violent physical effort", pregnancy, minor trauma**
Riché et al., 1982 (all <15 yr)	38	**All <15 yr**	**Acute onset in 84%**, with sudden motor impairment in 19 of 32 (59%)	**SAH in 55%**	**71% with successive acute attacks; 17% gradually progressing**	**Exertion**
Rosenblum et al., 1987	54	**Mean 27 yr**	**Acute onset in 50%**; SAH in 10 of 14 (71%) with glomus AVMs	**Paresis 93%, sensory loss 74%, bladder dysfunction 74%, hemorrhage 52%**; at treatment **74% moderately or severely disabled**, only **26% unaided ambulation**	—	**Posture 17%, activity 15%, pregnancy 6%, Valsalva 13%, injury 13%**
Biondi et al., 1990	40	**Mean 20 yr**	**SAH in 58%**	**SAH in 68%; 75% moderately or severely disabled**	**31% relapsed with worsening between treatments** over 6-yr mean follow-up	—

Yasargil et al., 1984	41	**76% <41 yr**	**SAH in 59%**	**SAH in 76%; 63% moderately or severely disabled**	**Stepwise progression in 40%**	—

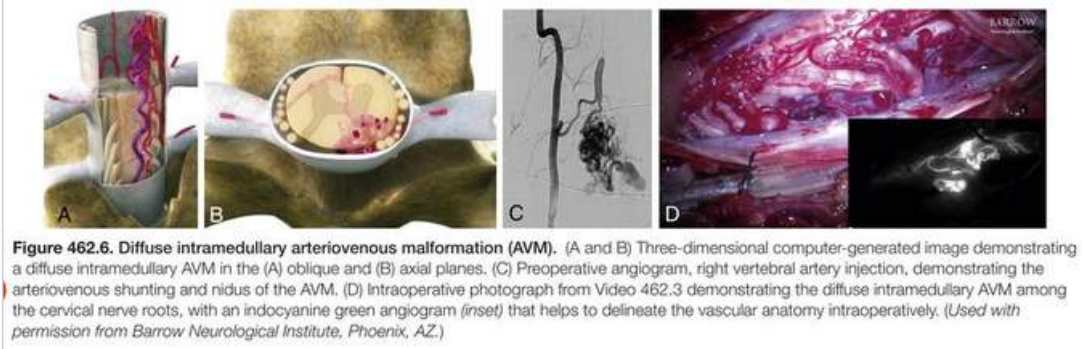


Figure 462.6. Diffuse intramedullary arteriovenous malformation (AVM). (A and B) Three-dimensional computer-generated image demonstrating a diffuse intramedullary AVM in the (A) oblique and (B) axial planes. (C) Preoperative angiogram, right vertebral artery injection, demonstrating the arteriovenous shunting and nidus of the AVM. (D) Intraoperative photograph from Video 462.3 demonstrating the diffuse intramedullary AVM among the cervical nerve roots, with an indocyanine green angiogram *(inset)* that helps to delineate the vascular anatomy intraoperatively. *(Used with permission from Barrow Neurological Institute, Phoenix, AZ.)*

*Reproduced from Youmans & Winn 8e, Fig. 462.6, p. 3783 — Label when you reproduce it: the **diffuse intramedullary AVM** in (A) oblique and (B) axial three-dimensional reconstruction, (C) the preoperative right vertebral artery injection showing **arteriovenous shunting and the nidus**, and (D) the intraoperative photograph of the diffuse malformation **among the cervical nerve roots**, with the inset **indocyanine green angiogram** delineating the vascular anatomy. Mark the feeders from the anterior and posterior spinal arteries, the nidus within the cord parenchyma and the coronal venous plexus drainage — and note in your label that ICG is used both to define the anatomy and to confirm obliteration.*

4. The other two intradural presentations

4.1 Conus medullaris AVM — the only lesion with both UMN and LMN signs

- "Because of the **increased cerebrospinal fluid space** in the area of the conus medullaris, **large dilated venous ectasia can occur**. Dilated venous structures in turn exhibit **mass effect** on the region and result in **myelopathy, venous compression, venous congestion, and arterial steal from the conus**" YW p.3783.
- "A **cauda equina-type syndrome** can result owing to compression on nerve roots as they exit the conus. Therefore these lesions can manifest with **both upper and lower motor neuron signs, which is unique** compared with other arteriovenous lesions" YW p.3783.

4.2 Perimedullary (pial) AVF of the filum terminale

- "Fistulas of the filum terminale most often present as **type I low-flow lesions, accounting for one-fourth of AVFs found below the level of the conus medullaris**… Symptom onset tends to be **insidious and in the form of progressive myelopathy secondary to venous congestion** of the spinal cord" YW p.3803.
- The proposed mechanism is instructive: chronic severe lumbar stenosis causes **inflammation of the arachnoid of the lumbar cistern**; "prolonged inflammation and the development of **adhesions**, in turn, may result in **hyalinization and fibrosis, limited physiologic motion, and increased tension within the filum**. Repetitive microtrauma and sustained inflammation within the filum may result in a **positive feedback loop and eventual fistula formation**" YW p.3804. This is the conceptual bridge to part (c).

4.3 Spinal cavernous angioma — four clinical patterns

- "Symptomatic cavernous angiomas commonly manifest in one of **four** ways: **discrete acute episodic progression over months to years; slowly progressive decline in function over months to years; acute onset and rapid progression; or slowly progressive loss of function after acute onset of mild neurological symptoms**" YW p.3806.
- "Cavernous angiomas of the spinal cord **seem to be more commonly symptomatic than those located in the cerebral hemispheres**, although this may simply reflect the greater incidence of brain imaging and detection of asymptomatic lesions" YW p.3806.
- Frequency: **5% to 12% of all spinal vascular abnormalities**; **80% sporadic, 20% familial** (up to **50% familial in the Hispanic-American community**); **CCM1 7q21.2, CCM2 7p15-p13, CCM3 3q25.2-q27**; may follow **brain and**

spinal irradiation YW p.3806.

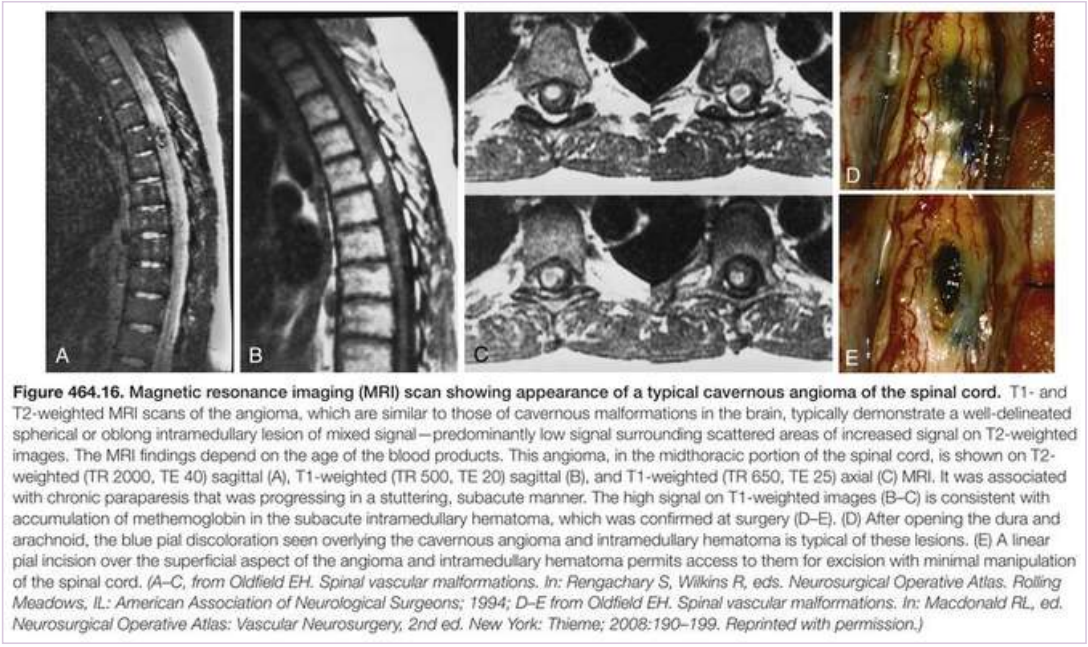


Figure 464.16. Magnetic resonance imaging (MRI) scan showing appearance of a typical cavernous angioma of the spinal cord. T1- and T2-weighted MRI scans of the angioma, which are similar to those of cavernous malformations in the brain, typically demonstrate a well-delineated spherical or oblong intramedullary lesion of mixed signal—predominantly low signal surrounding scattered areas of increased signal on T2-weighted images. The MRI findings depend on the age of the blood products. This angioma, in the midthoracic portion of the spinal cord, is shown on T2-weighted (TR 2000, TE 40) sagittal (A), T1-weighted (TR 500, TE 20) sagittal (B), and T1-weighted (TR 650, TE 25) axial (C) MRI. It was associated with chronic paraparesis that was progressing in a stuttering, subacute manner. The high signal on T1-weighted images (B–C) is consistent with accumulation of methemoglobin in the subacute intramedullary hematoma, which was confirmed at surgery (D–E). (D) After opening the dura and arachnoid, the blue pial discoloration seen overlying the cavernous angioma and intramedullary hematoma is typical of these lesions. (E) A linear pial incision over the superficial aspect of the angioma and intramedullary hematoma permits access to them for excision with minimal manipulation of the spinal cord. *(A–C, from Oldfield EH. Spinal vascular malformations. In: Rengachary S, Wilkins R, eds. Neurosurgical Operative Atlas. Rolling Meadows, IL: American Association of Neurological Surgeons; 1994; D–E from Oldfield EH. Spinal vascular malformations. In: Macdonald RL, ed. Neurosurgical Operative Atlas: Vascular Neurosurgery, 2nd ed. New York: Thieme; 2008:190–199. Reprinted with permission.)*

*Reproduced from Youmans & Winn 8e, Fig. 464.16, p. 3808 — Label when you look at it: the typical MRI of a **spinal cord cavernous angioma** — a well-delineated spherical or oblong intramedullary lesion of **mixed signal, predominantly low signal surrounding scattered areas of increased signal on T2**, in (A) sagittal T2, (B) sagittal T1 and (C) axial T1. The **high signal on T1** indicates **methaemoglobin in a subacute intramedullary haematoma**. (D) After opening dura and arachnoid, the **blue pial discoloration** overlying the lesion; (E) the **linear pial incision** over the most superficial aspect of the angioma permitting excision with minimal cord manipulation. Note in your label that appearance depends on the age of the blood products, and that complete excision is mandatory because residual cavernoma rehaemorrhages.*

(b) Spinal AVM classification [3]

5. Give the modern scheme first, then translate the old numbers

- **The first question is binary** — Spetzler's algorithm starts with "**arteriovenous nidus on angiography?**": **no → AVF; yes → AVM** YW p.3780.
- **The six anatomic types** — "(1) **extradural AVFs**, (2) **intradural dorsal AVFs**, (3) **intradural ventral AVFs**, (4) **extradural-intradural AVMs**, (5) **intramedullary AVMs**, and (6) **conus medullaris AVMs**" YW p.3780.
- **Why descriptors replaced numbers** — nomenclature is now based on "the anatomic descriptors **intradural versus extradural, intramedullary versus extramedullary, and ventral versus dorsal**", because "most modern classification schemes for diseases are based on knowledge of the **biology** of the disorders, rather than simply the anatomy of the lesion" [YW pp. 3780, 3800].

*Table 3 · The Spetzler six-type classification of spinal arteriovenous lesions, with the classical Di Chiro number, the shunt anatomy and the treatment implication — assembled from Youmans & Winn 8e, Ch. 462, pp. 3780-3783, **Table 462.1**, p. 3780, and Ch. 464, pp. 3799-3803.*

Spetzler type	Classical name/number	Shunt anatomy	Haemodynamic consequence	Treatment implication
1. Extradural AVF	Borden type I spinal extradural AVF (not in Di Chiro)	Epidural segment of a **radicular artery** to the **epidural venous plexus**, outside the dura	Epidural venous engorgement with **compression of the thecal sac and roots**; myelopathy via an **incompetent dural valve** plus **steal**	**Embolization can be curative**; surgery for persistent fistula or neural compression

2. Intradural dorsal AVF	**Di Chiro type I**; "single coiled vessel"; dural AVF	**Radicular/dural artery to a medullary or radicular vein within the dural root sleeve**	Retrograde arterialisation of the coronal venous plexus → **venous congestive myelopathy**	**Hemilaminotomy, coagulate and sharply divide the arterialised vein at the dural sleeve**; ICG confirmation
3. Intradural ventral AVF	**Di Chiro type IV**; perimedullary/pial AVF	**Anterior spinal artery to the coronal venous plexus** in the subarachnoid space; **midline** pouch on AP views	Venous hypertension ± **venous varix**; giant lesions cause cord compression	**Anson-Spetzler A/B/C** (single ASA feeder / multiple feeders / giant with multiple pedicles); **microsurgery preferred** to avoid ASA embolization; embolization for giant type C
4. Extradural-intradural AVM	**Di Chiro type III**; juvenile; metameric; **Cobb syndrome**	Multiple enlarged medullary arteries, **huge nidus containing neural tissue in its interstices**, involving bone, muscle, skin, dura	**High flow, high pressure**; intranidal and feeder aneurysms; mass effect + venous congestion + steal	Usually **palliative** — relief of mass effect and of steal/venous hypertension; multidisciplinary, staged
5. Intramedullary AVM	**Di Chiro type II**; glomus	**Compact intramedullary nidus** confined to a short cord segment, usually in the anterior half, fed by 1-2 branches of the anterior ± posterior spinal arteries	Haemorrhage or **steal** from cord parenchyma	**Microsurgical resection primary**; embolization as adjunct/salvage; pial resection technique; ICG
6. Conus medullaris AVM	(added by Spetzler; not in Di Chiro)	**Diffuse**, multiple feeders from **both anterior and posterior spinal arteries**, large venous ectasia in the roomy conus cistern	Myelopathy **plus cauda equina compression — UMN and LMN signs together**	**Combined endovascular and microsurgical**; **identify and preserve the anterior spinal artery**

- **The biological alternative (Oldfield, Box 464.1) — dural AVFs; intradural AVMs (spinal cord AVMs — juvenile and glomus; perimedullary AVFs); cavernous angiomas** YW p.3805. Its advantage is that it **includes the angiographically occult cavernoma**, which the angiographic schemes cannot.
- **Sub-classifications to name** [YW pp. 3781, 3803]:
  - **Anson and Spetzler A/B/C** for intradural ventral AVFs — **A** small simple single ASA feeder; **B** larger with a primary ASA feeder plus small adjacent feeders; **C** giant with multiple pedicles and engorged venous outflow.
  - **Merland I/II/III** for perimedullary AVFs — **I** slow flow, single shunt, conus/filum, minimal venous dilation; **II** posterolateral/anterolateral, one or two dilated feeders with multiple discrete shunts, higher flow; **III** the commonest, high flow, multiple extremely dilated feeders converging on a single shunt into a **giant venous ectasia**.
  - **Hiramatsu five-tier craniocervical junction AVF classification (2018) — I dural (37%), II radicular (29%), III epidural with pial feeders (14%), IV epidural (10%), V perimedullary (10%)**; **98% fed by radiculomeningeal branches**, so the authors proposed the collective term **radiculomedullary AVF**; **63% presented with rupture and SAH**, highest in **type II (94%)** and **type III (62%)**.
- **The historical systems to acknowledge** — **Wyburn-Mason** (angioma racemosum venosum/arteriovenosum, 1943), **Di Chiro** (types I-III, 1967), **Kendall and Logue** (1977, proving type I is a dural AVF), **Djindjian and Heros** (1977, type IV perimedullary), **Borden** (three-point), **Niimi and Berenstein**, **Bao and Ling** (including Cobb syndrome), **Rosenblum** (intradural versus dural; glomus versus juvenile) YW p.3779.

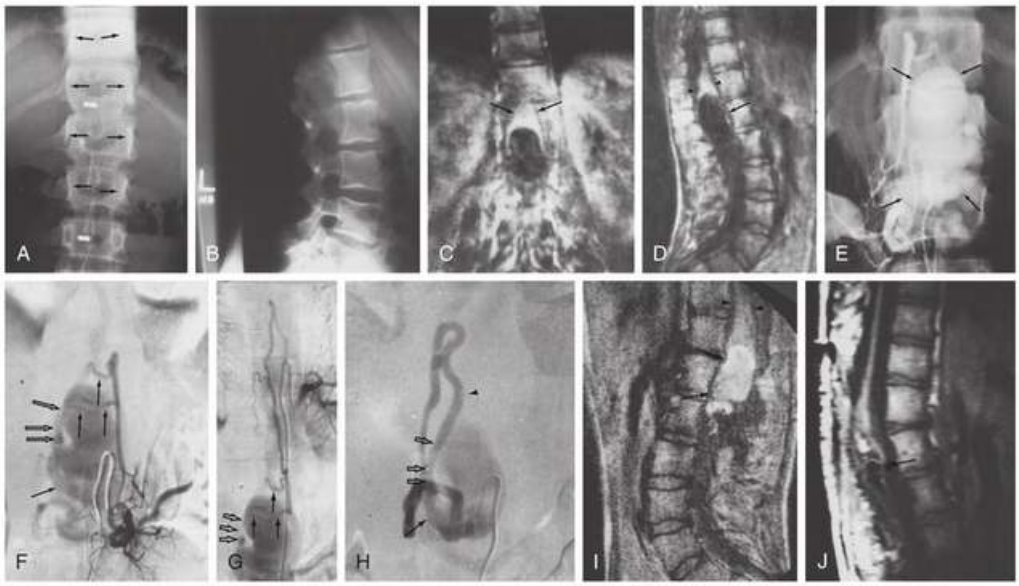


Figure 464.15. A 14-year-old boy with a congenital intradural arteriovenous fistula (AVF) associated with a massive intramedullary aneurysm-varix at the site of the arterial-to-venous transition. Anteroposterior (A) and lateral (B) lumbothoracic spine radiographs reveal medial erosion of the pedicles (A, *arrows*) and scalloping of the posterior aspect of several vertebrae (B). Coronal (C) and sagittal (D) magnetic resonance imaging (MRI) scans (spin echo [SE] 500/40) show the spinal cord *(ars)* splayed around a large intramedullary aneurysm (signal void; D, *arrow*). Selective spinal arteriography (E–H) reveals a huge varix (E, *arrows*) expanding the spinal canal in association with an AVF (F and H, *arrows*). The fistula was supplied by several vessels that converged (H, *arrowhead*) to form a simple AVF (F and H, *arrows*) via a common trunk (F–H, *open arrows*). One week after interruption of the AVF, MRI (SE 500/40) showed high signal in the aneurysm (I, *arrows*), a finding indicative of thrombosis (*ars* show the spinal cord). On MRI 18 months later (J), the thrombosed aneurysm has shrunk to a small focus with a persistent descending vein *(arrow)*. Dilation of the subarachnoid space and the atrophic spinal cord can be seen above the site of the varix. *(From Doppman JL, Di Chiro G, Dwyer AJ, et al. Magnetic resonance imaging of spinal arteriovenous malformations. J Neurosurg. 1987;66(6):830–834.)*

*Reproduced from Youmans & Winn 8e, Fig. 464.15, p. 3808 — Label when you reproduce it: the 14-year-old boy with a **congenital intradural (perimedullary) AVF associated with a massive intramedullary aneurysm-varix** at the arterial-to-venous transition. (A-B) Plain radiographs — **medial erosion of the pedicles and posterior vertebral scalloping**, the chronic bony signature of a high-flow spinal AV lesion. (C-D) MRI — **the cord splayed around a large intramedullary signal-void aneurysm**. (E-H) Selective spinal arteriography — the **huge varix expanding the canal**, the fistula, and the several feeders converging into a common trunk. (I-J) One week and 18 months after interruption of the fistula — **thrombosis of the aneurysm, then shrinkage to a small focus with a persistent descending vein**, with dilation of the subarachnoid space and an atrophic cord above the varix.*

6. Imaging findings that support the classification

- **Arteriography remains the gold standard** and must define **four things**: the **type** of malformation, the **spinal level and configuration** of the fistula or nidus, the **feeding vessels**, and the **normal spinal cord vasculature** YW p.3810.
- **Dural AVF** — nidus **in the intervertebral foramen and lateral spinal canal**; drainage through an arterialised medullary vein into a dilated coronal plexus, **100% rostral**, **0% rapid flow**, **0% associated aneurysm**, **lower half of the spine**; **prolonged venous-phase views of about 15 seconds** are often necessary because the lesion is low flow [YW pp. 3810-3811].
- **Intradural AVM — 80% of nidi lie within the cord**, **rapid flow in 80%**, **associated spinal aneurysm in 44%**, common supply of the malformation and a medullary artery in **100%**, distributed **diffusely** along the spine YW p.3811.
- **MRI** — dilated serpiginous **flow voids**; T2 shows **cord oedema, myelomalacia, infarction and haemorrhage**; Gilbertson found **increased T2 signal in 100% of 66 patients with spinal dural AVFs**, extending an average of **seven levels** and involving the **tip of the conus in 87%** [YW pp. 3806-3807]. Post-gadolinium T1 enhances the **coronal venous plexus and the congested cord**, more profoundly with **delayed imaging** YW p.3807.
- **The two cautions** — "**findings on MRI may be normal or only nonspecifically abnormal** in patients with spinal dural AVFs" YW p.3809, and "it is possible for **intramedullary AVMs to remain radiographically silent on noncontrasted MRI**… in patients with unexplained progressive myelopathy, **postcontrast T1 images are recommended**" YW p.3809.
- **Myelography** — largely superseded, but "injection of contrast into the subarachnoid space identifies **dilated serpentine filling defects**… **a lack of such vessels greatly reduces the likelihood** of the presence of a spinal vascular malformation" YW p.3810.



Figure 464.20. Myelogram of a patient with a spinal dural arteriovenous fistula. The dilated coronal venous plexus is evident on the dorsal surface of the spinal cord. *(From Muraszko KM, Oldfield EH. Vascular malformations of the spinal cord and dura. Neurosurg Clin N Am. 1990;1[3]:631–652.)*

*Reproduced from Youmans & Winn 8e, Fig. 464.20, p. 3810 — Label when you reproduce it: the **myelogram of a spinal dural arteriovenous fistula** — the **dilated coronal venous plexus outlined as serpentine filling defects on the dorsal surface of the spinal cord**. Use it to make the historical and practical point that a negative myelogram (no serpentine vessels) greatly reduces the likelihood of a spinal vascular malformation, but a positive study still requires selective spinal arteriography to establish the type and exact level.*

(c) Spinal arachnoiditis — radiology and treatment [3]

7. Definition, causes and why it matters here

- **Definition** — "**spinal adhesive arachnoiditis (SAA)** refers to **scarring of pial and arachnoid membranes within the thecal sac** and occurs as a **sequela of chronic inflammation**. The severity of disease ranges from **focal adhesions to**

dense scarring as seen in arachnoiditis ossificans" YW p.2604.

- **Causative triggers** — "**infection, history of myelography, subarachnoid hemorrhage, degenerative lumbar disease, previous spine surgery, and intrathecal steroid injection**" YW p.2604.
- **Latency** — "onset of symptoms can be variable and ranges from **only 14 days to up to 44 years** following the initial insult; **delayed onset is typical**, with most symptoms developing **years** after the inciting event. In addition, **many patients with SAA remain asymptomatic despite radiographic findings**" YW p.2604.
- **Frequency** — radiographic evidence of SAA in **16.5% to 35%** of patients who have undergone myelography, but the incidence of **symptomatic** lumbar arachnoiditis after myelography is only about **1%**. Previous lumbar surgery transforms the risk: Laitt reported "a **3% occurrence of arachnoiditis following myelography in patients who did not have a history of lumbar surgery and an 88% occurrence in patients who had previously undergone lumbar surgery**" YW p.2604.
- **Site** — "SAA has a **predilection for the lumbar spine**, although this may simply represent a publication bias… Because of this predilection, patients often initially present with **lumbar radiculopathy and back pain** in addition to the signs and symptoms attributable to a syrinx" YW p.2604.
- **Why it appears in a spinal AVM question** — because **arachnoiditis is one of the four classical causes of syringomyelia** in Youmans' classification: "(3) **spinal arachnoiditis (posttraumatic, postmeningitic)**" YW p.2602 — and because **chronic arachnoid inflammation of the lumbar cistern is the proposed mechanism of filum terminale AVF formation** YW p.3804. Both diseases present as a slowly progressive lumbar/conus syndrome in an older adult, and both are commonly mis-attributed to degenerative stenosis.

7.1 The mechanism of neurological damage

- "Interruption of normal CSF flow in the subarachnoid space" is the final common pathway of syrinx formation and progression in SAA YW p.2604; the condition also causes **cord tethering**, and "cases of **CSF flow impairment and syringomyelocele have been reported as a result of a single arachnoid web**" YW p.2604.

8. Radiology of spinal arachnoiditis

- **The modality** — "SAA has traditionally been diagnosed with **CT myelography**; however, **MRI has supplanted it as the imaging modality of choice**." The sensitivity and specificity of MRI compared with CT myelography have been reported as **92% and 100%** respectively YW p.2604.
- **The classification to reproduce** — "Ross and Delamarter classified the general MRI findings and identified **three anatomic groups**" YW p.2604:

Table 4 · MRI findings associated with lumbar arachnoiditis (Ross and Delamarter grades) — reproduced in full from Youmans & Winn 8e, Table 334.2, p. 2605.

Grade	Findings
1	**Conglomeration of adherent nerve roots residing centrally within the thecal sac**
2	**Peripherally adherent nerve roots and "empty thecal sac" appearance, meningeal thickening**
3	**Soft tissue mass within the spinal canal with obliteration of the subarachnoid space**

- **Associated MRI features** — "syrinxes associated with SAA will exhibit imaging features similar to those mentioned previously. **Additional findings related to arachnoid fibrosis will be noted**" YW p.2604. The general syrinx features on MRI are **cord expansion, T2 hyperintense intramedullary cavity** and, where CSF flow is obstructed, **dorsal displacement or tethering of the cord** YW p.2605.
- **Advanced sequences** — "**constructive interference in steady state (CISS) images** have been developed. CISS images may **better visualize dural thickening, syringomyelia, and microcystic change** than T2-weighted fast spin echo MRI, but conversely may be **less sensitive at detecting 'presyrinx' findings**" YW p.2604.
- **When MRI is not enough** — "imaging findings of SAA may sometimes be **subtle**… a single **arachnoid web** may translate to **very subtle or even absent MRI findings**. In cases of high clinical suspicion and without an alternative explanatory etiology, **myelography may provide additional diagnostic information**" YW p.2604. A **CT myelogram**

demonstrating a contrast block at the level of the webbing is the confirmatory study YW p.2605.

- **Do not forget the differential** — the radiological picture of an arachnoid web with a syrinx must be separated from a **spinal dural AVF**, in which the same sagittal T2 shows **cord expansion, cord T2 hyperintensity and, crucially, serpentine flow voids on the cord surface** with **enhancement of the coronal venous plexus after gadolinium** [YW pp. 3807, 3810].

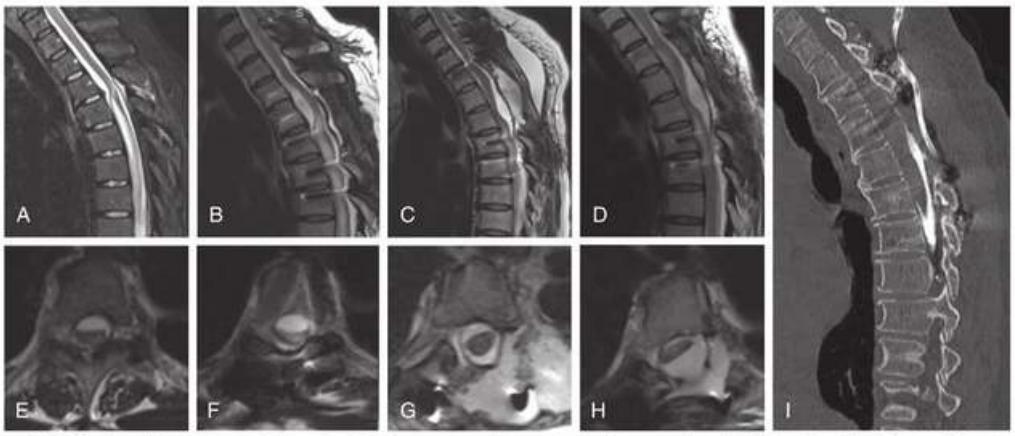


Figure 334.3. Patient originally presented 2 months following a motor vehicle accident with progressive difficultly walking. She had a small facet fracture at T2–T3 on the left that was initially monitored. At the time of her presentation, MRI T2-weighted images of the sagittal (A) and axial (E) spine demonstrated dorsal displacement of the spinal cord with caudal syrinx and T2 signal change throughout the thoracic spine. She underwent exploration of the area where there was a lateral dural defect noted and some arachnoid webbing. This was sectioned and repaired, and because of lateral destabilization, fusion at these levels was performed. She initially recovered but then had recurrence of her symptoms with worsening of the anterior arachnoid webbing and cyst (B and F). A CT myelogram (I) was obtained, and this demonstrated a contrast block at this area. Her spinal cord was found to be circumferentially tethered, with significant arachnoiditis that required a lateral approach to adequately decompress. Given the degree of scarring, placement of a syringoarachnoid shunt was also required. Immediate postoperative imaging shows some improvement (C and G). There was some recurrence of the cyst (D and H), but continued improvement of the dorsal syrinx was demonstrated on images obtained 1 year postoperatively and her symptoms remained stable. She had some initial improvement in both motor strength and sensation that plateaued after 6 months.

*Reproduced from Youmans & Winn 8e, Fig. 334.3, p. 2605 — Label when you look at it: the patient who presented 2 months after a motor vehicle accident with progressive difficulty walking and a small left T2-T3 facet fracture. (A, E) Sagittal and axial T2 MRI — **dorsal displacement of the spinal cord with a caudal syrinx and T2 signal change throughout the thoracic cord**. (B, F) Recurrence with **worsening anterior arachnoid webbing and cyst**. (I) The **CT myelogram showing a contrast block** at that level. (C, G) Immediate postoperative improvement after a **lateral approach for circumferential decompression of the tethered, arachnoiditic cord plus a syringoarachnoid shunt**. (D, H) Residual cyst but continued improvement of the dorsal syrinx at 1 year. Use this figure for the whole of part (c): it shows the MRI signs, the CT-myelographic block, and both arms of treatment.*

9. Treatment of spinal arachnoiditis

9.1 Non-operative

- "Once a patient with SAA becomes symptomatic, **the course is generally progressive**" YW p.2604.
- "Some authors have reported **temporary alleviation of symptoms with oral steroid treatment**" YW p.2604.
- "**Intrathecal administration of hyaluronidase** has been attempted with **encouraging results, but this has not been widely adopted**" YW p.2604.
- "Consideration of **intrathecal steroid** administration has been made **but is limited because of reports of arachnoiditis following spinal steroid administration**" — i.e. the treatment can cause the disease YW p.2604.

9.2 Operative — the two competing strategies

- **Timing** — "surgical treatment is generally **deferred until the patient develops a progressive neurological decline or severe pain**. However, close clinical follow-up and monitoring for worsening are imperative because **stabilization of symptoms following surgery occurs in only 80% of cases at 5- and 10-year follow-up, regardless of degree of radiologic improvement achieved**" YW p.2605.
- **Options** — "**direct lysis of arachnoid adhesions with or without duraplasty** and a variety of **shunting procedures, including syringocavitary, syringosubarachnoid, and lumboperitoneal shunts**" YW p.2605.
- **The case for arachnolysis and duraplasty** — "some authors have advocated that the **primary goal of treatment is**

release of adhesions with duraplasty, citing **improved rates of reoperation and time to clinical recurrence compared with syrinx shunting**… arachnolysis **addresses the underlying disruption of CSF flow and expands the subarachnoid space rather than simply diverting CSF**." Klekamp reported that of 67 patients treated for progressive symptoms, "**97% of patients who had undergone syrinx shunting had recurrence** during follow-up, whereas **78% of patients who had undergone arachnoid release and duraplasty remained stable**" [YW pp. 2605-2606].

- **The meta-analytic support** — Ghobrial's systematic review of 12 studies and 410 patients with primary syringomyelia found that "**arachnolysis was significantly associated with a longer duration until clinically symptomatic recurrence**", whereas **no similar association was found for CSF diversion methods** YW p.2605.
- **The crucial caveat — do not over-dissect a scarred cord** — "**caution should be used when undertaking lysis of arachnoid adhesions because overly aggressive arachnolysis in the setting of severe scarring may lead to neurological worsening**. This is particularly relevant in patients with **postinfectious and postinflammatory arachnoiditis, in whom scarring tends to be severe**." Klekamp's subgroup analysis by severity: "**only 17% of patients with severe scarring stabilized following arachnolysis, compared with 83% of patients with mild scarring**"; Parker found patients with postinfectious arachnoiditis fared worse, with **nearly half worsening after surgery** YW p.2605.
- **The resulting decision rule** — "**the extent of scarring should be considered in the decision algorithm… patients with extensive scarring may be best treated with CSF diversion procedures rather than arachnolysis**" YW p.2605.
- **Shunt results** — "Koyanagi reported that **60% of 15 patients improved following a shunting procedure. However, eight patients required further procedures and only 31% demonstrated clinical improvement**" in the longer term YW p.2605.
- **Anatomical distinction to state explicitly** — "**surgical treatment of lumbar arachnoiditis with arachnolysis should be differentiated from treatment of arachnoiditis in the cervicothoracic spine leading to syringomyelia**" YW p.2604. In the lumbar spine the target is radicular pain and tethering; in the cervicothoracic spine the target is restoration of CSF flow across the block to collapse the syrinx.

9.3 A practical operative sequence (synthesised from the worked case, Fig. 334.3)

- **Exposure** wide enough to reach normal arachnoid above and below the block; a **lateral (or posterolateral) approach** may be required when the cord is **circumferentially tethered** with ventral webbing YW p.2605.
- **Sharp microsurgical arachnolysis** of the web, with **repair of any dural defect** YW p.2605.
- **Expansile duraplasty** to enlarge the subarachnoid space and prevent re-adhesion [YW pp. 2605-2606].
- **Fusion** if the lateral bone removal destabilises the segment YW p.2605.
- **A syringoarachnoid (or syringosubarachnoid) shunt** where scarring is too severe for safe or durable arachnolysis YW p.2605.
- **Serial MRI** for monitoring, recognising that radiological improvement does not guarantee clinical stability YW p.2605.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Spinal dural AVF: male (80%), over 40, lower thoracolumbar, gradual progressive myelopathy (85-95%) with neurogenic claudication (70% activity-exacerbated), no SAH, no bruit, no arm involvement.** Mean age 46.
- **Intradural AVM: either sex, mean age 24, acute onset (37%), SAH in 50%, first symptom SAH in 32%, bruit in 6%, arms involved in 11%.** Children: acute onset in 84%.
- **Foix-Alajouanine = acute deterioration from extreme venous hypertension ± venous thrombosis in a type I dural AVF. It is a true emergency** — relief before thrombosis reverses deficits.
- **Untreated dural AVF: 20% on crutches or non-ambulatory by 6 months; half in a wheelchair or on crutches by 3 years; progressive decline over 2-3 years.**
- **Outcome after treatment correlates directly with preoperative functional grade** — the single argument for early diagnosis.
- **A middle-aged man operated for "lumbar stenosis" who deteriorates acutely after laminectomy has a missed spinal dural AVF until proven otherwise.**
- **Conus medullaris AVM is the only spinal AV lesion producing both upper and lower motor neuron signs.**

- **Spetzler six types: extradural AVF, intradural dorsal AVF, intradural ventral AVF, extradural-intradural AVM, intramedullary AVM, conus medullaris AVM.** Di Chiro I = dorsal dural AVF, II = glomus, III = juvenile/metameric, IV = perimedullary.
- **Anson-Spetzler A/B/C and Merland I/II/III subclassify the ventral (perimedullary) fistula; Hiramatsu's five tiers classify craniocervical junction fistulas (98% radiculomeningeal, 63% present with SAH).**
- **Arachnoiditis is one of Youmans' four causes of syringomyelia** (with Chiari/hindbrain, primary parenchymal, and extramedullary compression).
- **SAA after myelography: 3% if no previous lumbar surgery, 88% if there has been.** Radiographic SAA in 16.5-35% of myelograms; symptomatic in only ~1%.
- **Ross and Delamarter grades: 1 = central conglomeration of roots; 2 = peripherally adherent roots with an "empty thecal sac" and meningeal thickening; 3 = soft tissue mass obliterating the subarachnoid space.**
- **MRI has supplanted CT myelography (sensitivity 92%, specificity 100%), but a single arachnoid web may be MRI-occult — then do a CT myelogram and look for a contrast block.** CISS shows webs and dural thickening best.
- **Arachnolysis with duraplasty beats shunting for durability (97% recurrence after shunt versus 78% stable after arachnolysis) — except when scarring is severe, where only 17% stabilise and CSF diversion is safer.**
- **Only 80% of patients are stable at 5 and 10 years after surgery for syringomyelia, whatever the radiological result** — say this when asked about prognosis.

Pages read for this answer — Youmans & Winn 8e: 2602, 2604, 2605, 2606, 3779, 3780, 3781, 3783, 3799, 3800, 3801, 3803, 3804, 3805, 3806, 3807, 3809, 3810, 3811

Please see the imaging study carried out in a 15-year-old female patient presenting to the emergency in an unconscious status after initial headache. Discuss briefly:

a) Radiological findings. [2]
b) Role of Gamma knife. [2]
c) Role of Endovascular therapies. [2]
d) Surgical nuances. [2]
e) Postoperative care. [2]

LONG | MAY 2024 · Paper III · Q10 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 249 *Pediatric Arteriovenous Malformations* (Wilkinson and Maher), §Presentation, §Natural History, §Mortality, §Diagnostic Decision Making, §Therapeutic Decision Making, §Surgery, §Stereotactic Radiosurgery, §Embolization, §Multimodal Treatment and §Recurrence, pp. 1885-1885.e6 (Figs. 249.1-249.3; **Table 249.1**, p. 1885.e2). Ch. 452 *Therapeutic Decision Making in the Management of AVMs of the Brain* (Morgan), §Focused Irradiation, §Embolization, §Surgery, §Timing of Early Postoperative Radiologic Imaging, §Intensive Care Unit Management After Surgical Resection, §Surveillance Radiology and §Acute Intracranial Hemorrhage and bAVM, pp. 3677-3677.e12 (Figs. 452.1-452.9; **Table 452.1**, p. 3677.e2). Ch. 455 *Microsurgery of Arteriovenous Malformations*, §Imaging, §Microsurgical Resection — Timing of Surgery and General Surgical Technique, §Complications, §Radiosurgery and §Endovascular Therapy, pp. 3695-3715 (Figs. 455.1-455.13; **Tables 455.2-455.5**). Ch. 450 *Pathobiology of True Arteriovenous Malformations*, pp. 3659-3667 (Fig. 450.3, p. 3661; Fig. 450.7, p. 3667). Ch. 300 *Radiosurgery for Intracranial Vascular Malformations*, §AVM Bleeding After Radiosurgery, §Radiation-Related Complications, §Repeat Radiosurgery, §Radiosurgery of Large AVMs and §Radiosurgery-Based Grading Scales, pp. 2349-2353 (Fig. 300.1, p. 2351; **Table 300.1**, p. 2353). Ch. 453 *Adjuvant Endovascular Management of Brain AVMs*, pp. 3679-3683 (Figs. 453.1-453.3).

NOT COVERED IN YOUMANS — answered from the source named below

The examination paper reproduces an imaging study that is not recoverable from the question text supplied, so the actual films cannot be described. What follows therefore (i) states the diagnosis that the stem all but names — a **ruptured brain arteriovenous malformation in an adolescent** — and (ii) gives the systematic radiological reading that earns the two marks whichever modality is printed. The clinical scenario is matched almost exactly by a case Youmans prints in full (Fig. 450.3, p. 3661: a young woman who "presented in a coma with acute right occipital intracerebral hemorrhage with intraventricular and subdural extension", whose CT angiography showed an AVM nidus fed by posterior cerebral artery branches draining through a varix), and that figure is used here in place of the paper's own image.

1. Reading the stem — the diagnosis is in the history

- **A 15-year-old with sudden headache followed by loss of consciousness** is a spontaneous intracranial haemorrhage until proven otherwise, and in this age group the cause is an AVM: "**AVMs are the most common cause of spontaneous brain hemorrhage in children** (excluding the neonatal period)" YW p.3661, and "they are the **most common cause of hemorrhagic stroke in children after the perinatal period**" YW p.1885.e1.
- **Children bleed more than adults.** "In most referral-based population studies, **55% to 85% of children with AVMs present with hemorrhage**. In comparison, approximately **20% to 50% of adults** with AVMs present with hemorrhage. **Even for pediatric AVMs in critical/eloquent areas of the brain, hemorrhage is often the initial presentation**" YW p.1885.e1. Across the modern series tabulated in the chapter the hemorrhagic presentation rate falls from **74%-85% in the 1980s to 57%-63% in the 2000s**, as incidental discovery rises from 0% to 16% YW p.1885.e2.
- **Adolescent girls with an AVM are a recognised higher-risk subgroup** — "one group found that **deep venous drainage, female gender, and small size were associated with hemorrhagic presentation in children**" YW p.1885.e2 .
- **Mortality is higher in children** — "the mortality rate is reported to be **higher in children than in adults**, possibly because AVMs are more prevalent in the **basal ganglia, thalamus, or posterior fossa** in children, and possibly because children **present more frequently with hemorrhage**" YW p.1885.e2.
- **Location differs** — "AVMs are **more likely to be in eloquent locations in children than in adults, particularly in the basal ganglia and thalamus**", and are **more prevalent in the posterior fossa** in children YW p.1885.e2.
- **Structure differs** — "pediatric AVMs… have a **higher occurrence of linear, vein-based malformations**", in contrast with the "compact, spherical nidus" typical of the adult lesion; the paediatric type has a "**configuration perpendicular to the cortex and projecting toward the ventricle**" YW p.1885.e1.
- **Associated aneurysms** — "**between 9% and 29% of AVMs in children are accompanied by associated aneurysms** " YW p.1885.e1.

(a) Radiological findings [2]

2. How to read the films, in order

2.1 Non-contrast CT — the first study

- **What CT can show** — "a noncontrast CT scan may demonstrate the presence of **acute hemorrhage, hydrocephalus, calcification, or areas of encephalomalacia related to previous surgery or rupture**" YW p.3697.
- **The haemorrhage** — describe **site (lobar, deep/basal ganglionic, thalamic, posterior fossa), volume, midline shift, intraventricular extension, subarachnoid or subdural extension, and hydrocephalus**. The matched Youmans case is an "**acute right occipital intracerebral hemorrhage with intraventricular and subdural extension**" in a comatose patient YW p.3661.
- **The clue that it is not a "primary" bleed** — a **lobar haematoma in a normotensive adolescent**, **calcification at the margin of the clot**, **serpiginous vessels at the edge of the haematoma**, and **disproportionate intraventricular blood**

all point to an underlying malformation.

- **Contrast CT** — "a contrast-enhanced CT scan can provide information regarding the **AVM location, nidus, feeding arteries, and draining veins** and is **particularly valuable as a quick study in the setting of a life-threatening hemorrhage before surgical evacuation**" YW p.3697.

2.2 CT angiography

- CTA defines the **nidus, its arterial feeders and its venous drainage** and any **flow-related or intranidal aneurysm**; in the matched case it "demonstrates the nidus of the AVM **supplied by branches of the right posterior cerebral artery and draining via a varix into the straight sinus**" YW p.3661.
- CTA is also the study Ch. 452 recommends **immediately after surgery** to look for residual nidus YW p.3677.e10.

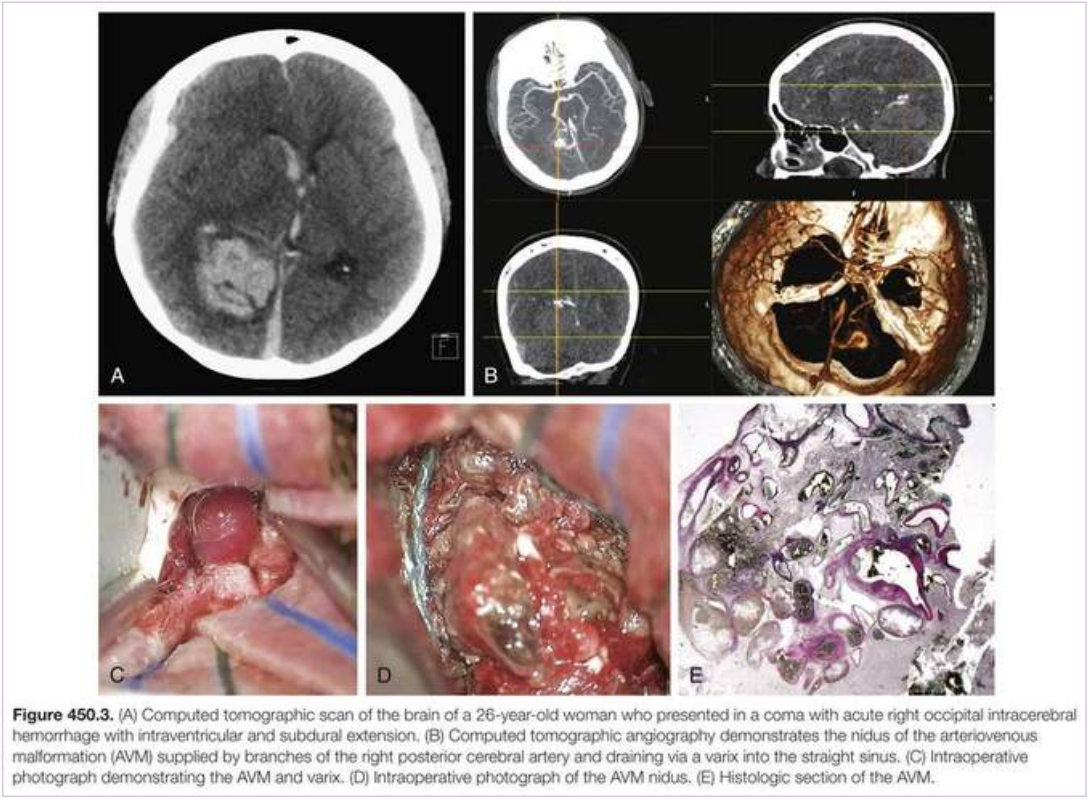


Figure 450.3. (A) Computed tomographic scan of the brain of a 26-year-old woman who presented in a coma with acute right occipital intracerebral hemorrhage with intraventricular and subdural extension. (B) Computed tomographic angiography demonstrates the nidus of the arteriovenous malformation (AVM) supplied by branches of the right posterior cerebral artery and draining via a varix into the straight sinus. (C) Intraoperative photograph demonstrating the AVM and varix. (D) Intraoperative photograph of the AVM nidus. (E) Histologic section of the AVM.

*Reproduced from Youmans & Winn 8e, Fig. 450.3, p. 3661 — Label when you reproduce it: (A) the CT of a young woman who **presented in coma with an acute right occipital intracerebral haemorrhage with intraventricular and subdural extension** — mark the lobar clot, the intraventricular blood and the subdural component. (B) The CT angiogram — mark **the nidus supplied by branches of the right posterior cerebral artery** and **the varix draining into the straight sinus** (i.e. deep venous drainage, Spetzler-Martin venous point = 1). (C) Intraoperative photograph of the AVM and its varix. (D) Intraoperative photograph of the nidus. (E) The histological section. This single case is the template answer to "describe the radiological findings" in a young patient who collapses after a headache.*

2.3 MRI

- "MRI is the **most important imaging modality** after catheter angiography… superior to CT in delineating the **macroarchitectural details of the AVM and defining its exact anatomic relationship to the surrounding brain**" YW p.3698.
- "An AVM typically appears as a tightly packed **'honeycomb' of flow voids** on T1- and T2-weighted images. **Secondary changes in the adjacent brain tissue such as mass effect, edema, and ischemic changes** can also be seen" YW p.3698.
- **The caveat that matters acutely** — "although MRI is sensitive in revealing subacute hemorrhage, **in the setting of acute hemorrhage it is not very useful, as the hematoma obscures all details of the AVM**. We therefore recommend obtaining a **formal cerebral angiogram** in such cases if the clinical history and the imaging characteristics of the hematoma suggest the presence of an AVM" YW p.3698.

2.4 Digital subtraction angiography — the gold standard

- "Cerebral **digital subtraction angiography (DSA) is still considered the 'gold standard'** to establish the diagnosis and to preoperatively assess a patient with an AVM" YW p.3697; in children too, "the 'gold standard' method for AVM diagnosis remains **catheter angiography**" YW p.1885.e2.
- **What DSA must report** YW p.3697:
  - **Size, location and configuration of the nidus (compact versus diffuse).**
  - **Pattern and location of feeding arteries and draining veins.**
  - **Angioarchitectural features associated with increased risk of haemorrhage — feeding artery or intranidal aneurysms, deep venous drainage, venous aneurysm or outflow compromise, perforating feeding vessels, and deep or periventricular location.**
  - **External carotid injections** "should be performed in large-convexity AVMs, particularly with a history of previous surgery, embolization, or hemorrhage, because these lesions may recruit external carotid arterial supply."
- **Timing of DSA after a bleed** — "**vessels that were not visualized on an early angiogram because of compression from a hemorrhage may appear on follow-up DSA several weeks later.** Furthermore, it is important that an angiogram be performed **close to the time of surgery** because AVMs can change in size and configuration over time" YW p.3697.
- **The negative angiogram** — "in children presenting with **intraparenchymal hematoma and a negative noninvasive imaging workup**, angiography may reveal otherwise undetected lesions… even angiography in the setting of a new hemorrhage **may fail to reveal the AVM**. Consequently, in the setting of **unexplained intracranial hemorrhage with a negative angiogram, we recommend repeat angiography after a sufficient period to allow for substantial resolution of the hemorrhage**" [YW pp. 1885.e2-1885.e3].
- **Radiation discipline in a child** — technical modifications to reduce dose include "**automatic capture of radiation data per procedure… tight collimation of the field of view; use of pulsed fluoroscopy; minimization of the air gap between the patient and detector; use of image-hold techniques; and use of age- and sex-specific shielding**", and "**most surveillance regimens include the use of MRI for routine surveillance; repeat catheter angiography is performed only to confirm lesion obliteration**" YW p.1885.e3.

2.5 Functional imaging before treatment

- **PET** quantifies local cerebral function and blood flow with fluorodeoxyglucose and water; PET images can be mapped onto MRI "to estimate the **proximity of functionally active cortical tissue to AVM location**" YW p.3698.
- **Functional MRI** uses blood-oxygen-level change, but "**eloquent located AVMs frequently create false-positive functional MRI mapping results as the increased AVM blood flow mimics activation**" — a caution worth quoting YW p.3698.
- **Magnetoencephalography** is the third modality named YW p.3698.

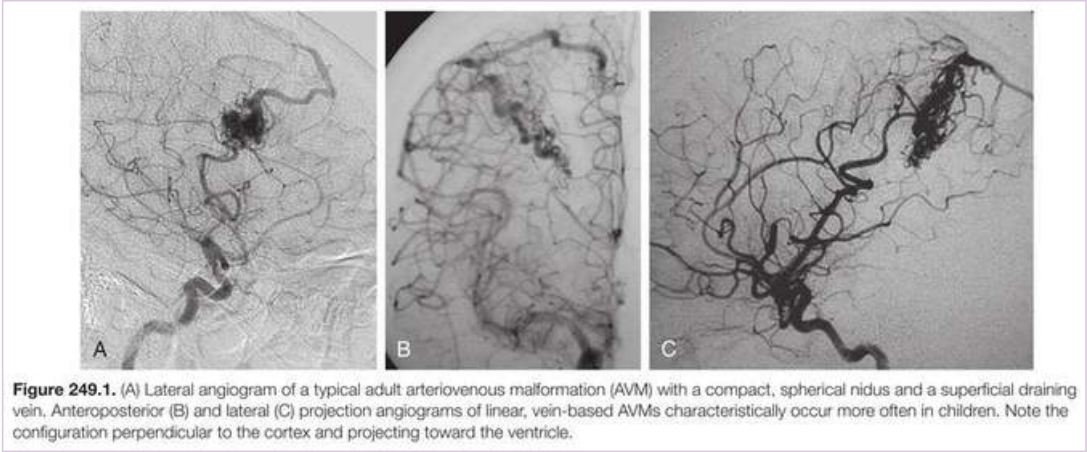


Figure 249.1. (A) Lateral angiogram of a typical adult arteriovenous malformation (AVM) with a compact, spherical nidus and a superficial draining vein. Anteroposterior (B) and lateral (C) projection angiograms of linear, vein-based AVMs characteristically occur more often in children. Note the configuration perpendicular to the cortex and projecting toward the ventricle.

*Reproduced from Youmans & Winn 8e, Fig. 249.1, p. 1885.e1 — Label when you reproduce it: (A) the lateral angiogram of a **typical adult AVM — compact, spherical nidus with a superficial draining vein**; (B and C) AP and lateral angiograms of the **linear, vein-based AVM that characteristically occurs in children**. Mark the feature the caption stresses: the paediatric lesion is **configured perpendicular to the cortex and projects toward the ventricle**. Say in your label why this matters surgically — the vein itself provides a ready-made surgical corridor, so these lesions are particularly suited to microsurgery.*

(b) Role of Gamma Knife [2]

3. What radiosurgery is for, and what it cannot do here

3.1 The mechanism and the indication

- **Mechanism** — "the aim of radiosurgery is **gradual obliteration of the AVM by progressive intimal hyperplasia and progressive nidal thrombosis**", delivered by a **cobalt source (Gamma Knife), a linear accelerator, or the Bragg peak of heavy particles (proton or helium beam)** YW p.3711.
- **Indication** — "**SRS is ideal for small (<3 cm) AVMs located in eloquent or deep-seated areas of the brain where the morbidity of surgical excision would be considered unacceptable.** It is also a good treatment choice for patients whose **age or comorbidities make the risk of general anesthesia unacceptable**" YW p.3711.
- **The physics that sets the 3 cm limit** — "the tolerance of normal brain tissue to withstand damage is severely tested **above 10 Gy**… one must achieve a desired delivery of **at least 20 Gy to the bAVM to induce thrombosis but less than 10 Gy to critical brain**… Therefore expectation of low-risk effective treatment achieving cure by focused irradiation as a single modality is **confined to small-volume bAVMs**" YW p.3677.e4. Ch. 300 states the same limit mechanically: "as the **planned irradiated volume (PIV)** increases, the radiation exposure to the adjacent brain increases because the dose gradient is less steep… It is this general concept that **limits the size of intracranial radiosurgical targets to approximately 3 cm or less in average diameter**" YW p.2351.
- **Dose in children** — "most centers have reported dosing in the range of **18 to 23 Gy and most commonly 20 to 22 Gy**" YW p.1885.e4.

3.2 What it achieves

- **Paediatric series** — "in a report of a **25-year experience with 363 pediatric patients** who had AVMs of a **median Spetzler-Martin grade of III, 80% of whom presented with hemorrhage**, the **overall obliteration rate was 83%, and the cumulative complication rate was 3%. The mean time to obliteration was 32 months** for patients requiring one treatment and **80 months** for those requiring repeat treatment" YW p.1885.e4.
- **International database** — Chen's 539 patients showed a **15-year obliteration rate of 88%** but a **15-year cumulative hemorrhage rate of 14.5%**, with a **7% cyst formation rate and 3% meningioma formation rate at 15 years** YW p.1885.e4. Starke's 357 paediatric patients showed only **63% obliteration at a mean follow-up of 92 months**, with **annual post-SRS hemorrhage rates of 0.8% for unruptured and 1.6% for previously ruptured AVMs** YW p.1885.e4.

- **Children respond as well as adults** — "Chen et al. compared 315 pediatric AVMs treated by SRS to **315 adult AVMs matched by propensity scoring** and found **equivalent outcomes of obliteration in children versus adults**" YW p.1885.e4.
- **Adult benchmarks** — obliteration **79% for AVMs <10 cm³ but only 47% for >10 cm³** (Friedman); **61% overall rising to 83% for <4 cm³** (Pollock); **100% for <4 cm³ and 70% for >3.7 cm** (Steinberg, proton beam) YW p.3711. Starke's multicentre study of 2236 patients gave **obliteration 64.7%, annual post-radiosurgery hemorrhage 1.1%, symptomatic adverse treatment events 10%, permanent neurological morbidity 3%, favourable outcome 60.3%** YW p.3711.

3.3 What it cannot do — the two disadvantages to state

- "**The two main disadvantages of radiosurgery are the latent period until complete obliteration and the lack of certainty of obliteration.** During these periods of delay, which may range from **1 year to several years**, the patient remains at risk for hemorrhage, and **the risk is almost the same as if no treatment had occurred, at least during early follow-up**" YW p.3711.
- "**Radiosurgery is not effective in 10% to 15% of even small AVMs.** Increasing AVM size **reciprocally affects obliteration rate**, and repeated radiosurgery for incompletely obliterated AVMs carries a **worse rate for subsequent obliteration**. **No definitive evidence suggests a reduction in the rate of hemorrhage in patients whose lesion is not completely obliterated**" YW p.3711.
- **The counterweight from Ch. 300** — "later more detailed analyses have concluded that the risk of AVM bleeding is **either unchanged or reduced during this latency interval**"; Maruyama found a **54% reduction in bleeding risk during the latency interval, greatest in those who presented with haemorrhage**, and Karlsson found protection as early as **6 months** after a margin dose of **25 Gy** YW p.2351.

3.4 Radiation-related complications — the paediatric concern

- **Imaging change** — "radiation-induced changes (RICs) typically manifest **6 to 18 months** after radiosurgery as **perinidal T2 signal changes**"; Yen found RICs in **482 of 1426 patients (33.8%)**, of whom **8.6% were symptomatic and only 1.8% had permanent deficits** [YW pp. 3711, 2351]. Ilyas' meta-analysis of 6779 patients: **complete obliteration 54%, radiologic RICs ~35%, symptomatic 9%, permanent symptoms ~4%** — hemiparesis 52%, visual field deficit 28%, diplopia 12.9%, sensory dysfunction 4%, ataxia 4% YW p.3711.
- **Who gets them** — "patients with AVMs in the **thalamus, basal ganglia, and brainstem** are more likely to develop neurological deficits secondary to imaging changes, **especially patients with larger treatment volumes**"; dosimetric predictors are the **12-Gy volume (V12)**, the **10-Gy volume (V10)** and **Dmean20** YW p.2351.
- **Late complications** — cyst formation and diffuse white matter change; in 233 patients followed a median 9.8 years, late complications occurred in **16 (6.9%) at a median of 8.7 years**, symptomatic in **4.7%** [YW pp. 2351-2352].
- **Secondary tumour** — "the development of a radiation-induced tumor after radiosurgery is **exceedingly rare**"; a review of 1837 patients found **no radiation-induced tumors in 11,264 patient-years** YW p.2352. But the paediatric chapter is more cautious: **36 reported cases of SRS-induced neoplasm**, one series reporting a **3.4% risk of radiation-induced tumour more than 15 years after radiosurgery**, and an international study finding **7% cyst formation and 3% meningioma formation at 15 years** YW p.1885.e4.
- **The paediatric balance, in the book's own words** — adoption of radiosurgery in children "lagged behind its initial use in the adult population largely because of concerns regarding the **effects of irradiation on the developing CNS, the longer expected remaining life span, and the consequently increased potential for radiation-induced malignancies in the future**" YW p.1885.e4.

3.5 Choosing radiosurgery in this patient

- "**Stereotactic radiosurgery — favored for eloquent/deep lesions, with or without embolization. Occasionally prior to surgery (volume reduction)**" YW p.1885.e3.
- Quantify the expectation with the **Pollock-Flickinger radiosurgery-based AVM score**, which in the paediatric chapter is given as **(0.1 × AVM volume) + (0.02 × patient age) + (0.3 × AVM location)**, where location scores **0 for frontal or temporal, 1 for parietal, occipital, intraventricular, corpus callosum or cerebellar, and 2 for basal ganglia,**

thalamic or brainstem; "a score **less than 1.0 indicates a greater than 90% chance of an excellent outcome**, and a score **higher than 2.0 indicates only a 40% likelihood**"; the scale "has been validated not only in adults but also in the **pediatric population**" YW p.1885.e4.

- **For large lesions** — the options are **volume-staged SRS (VS-SRS)**, hypofractionation, or embolization plus SRS; VS-SRS in 34 patients achieved obliteration **14% at 3 years, 54% at 5 years and 75% at 7 years**, with **18% bleeding after treatment** and **6% permanent radiation-related complications**; "**VS-SRS reduces the incidence of radiation-related complications in patients with large intracranial AVM**" YW p.2353.
- **Repeat radiosurgery is legitimate** — "repeat AVM radiosurgery has been proven to be a **safe and effective option for the majority of patients with subtotal AVM obliteration**"; actuarial obliteration **77% at 5 years** with **symptomatic adverse radiation effects in 10%**; but "the **complication rate increases with the overall amount of radiation given**" YW p.2352.
- **Subtotal obliteration** (angiographic disappearance of the nidus with a persistent early draining vein) — of 136 patients not re-treated, **66 of 90 having later angiography went on to complete obliteration** and there were **no instances of later intracerebral haemorrhage in 767 patient-years**; "**observation without further AVM treatment is now generally recommended**" [YW pp. 2351-2352].

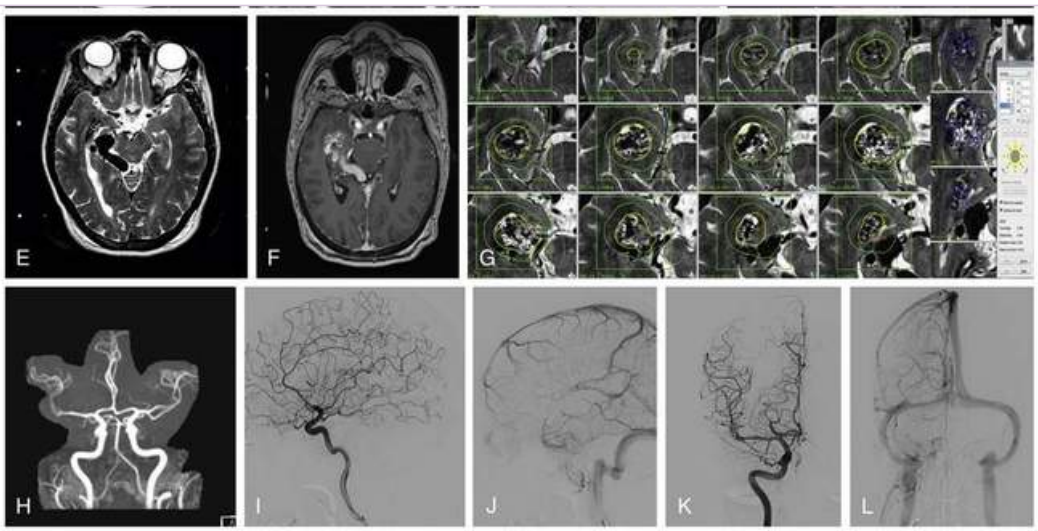


Figure 450.7. (A) Computed tomographic brain scan of a 50-year-old woman with sudden onset of headache and visual disturbance shows acute hemorrhage within the right temporal lobe and thrombosis within a varix. (B) Magnetic resonance angiography suggestive of an underlying arteriovenous malformation (AVM). (C and D) Diagnostic cerebral angiography confirms a choroidal-type AVM with predominant supply from the anterior choroidal artery and secondary supply from anterior temporal and posterior communicating perforators with drainage via a large varix into the internal cerebral vein. (E and F) Stereotactic T2 and T1 images obtained for Gamma Knife radiosurgery. (G) On the day of radiosurgery shot planning the AVM received a marginal dose of 25 Gy. (H) Magnetic resonance angiography obtained at 3 years after radiosurgery suggested obliteration. (I–L) Diagnostic cerebral angiography obtained at 4 years following radiosurgery confirmed AVM obliteration without residual varix or shunt.

*Reproduced from Youmans & Winn 8e, Fig. 450.7, p. 3667 — Label when you look at it: the complete radiosurgical case — (A) CT showing **acute right temporal haemorrhage with thrombosis within a varix**; (B) MR angiography suggesting an underlying AVM; (C-D) diagnostic angiography confirming a **choroidal-type AVM with predominant supply from the anterior choroidal artery** and secondary supply from anterior temporal and posterior communicating perforators, **draining via a large varix into the internal cerebral vein**; (E-F) the **stereotactic T2 and T1 planning images**; (G) the **Gamma Knife shot plan, marginal dose 25 Gy**; (H) **MR angiography at 3 years suggesting obliteration**; (I-L) **catheter angiography at 4 years confirming obliteration without residual varix or shunt**. This is the figure to draw for "role of Gamma Knife" — it shows indication (deep choroidal AVM), planning, dose and the 3-4 year latency to angiographic cure.*

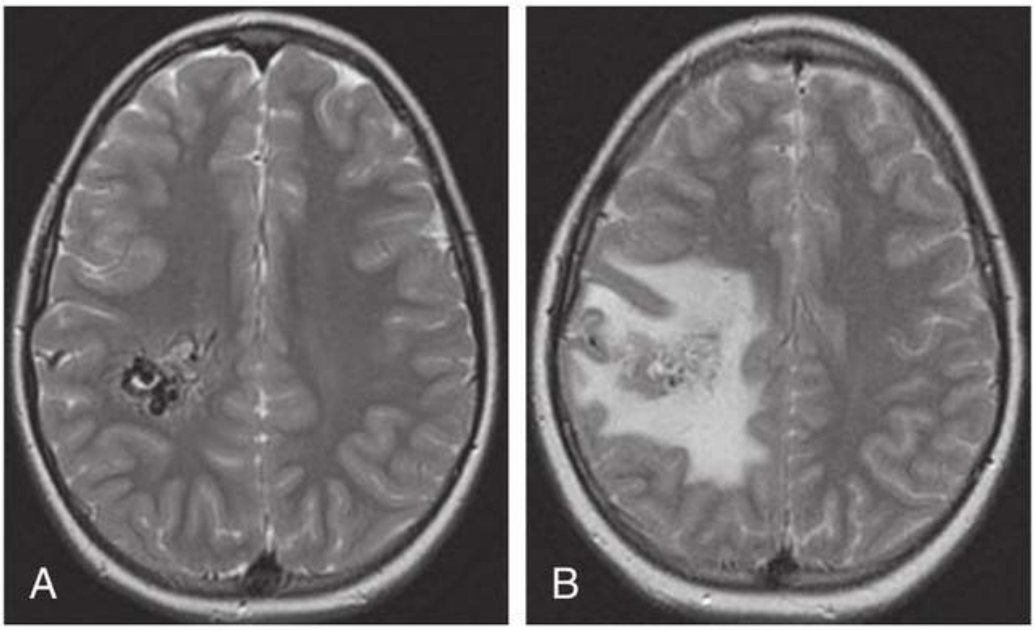


Figure 300.1. An 11-year-old boy with a right frontoparietal arteriovenous malformation (AVM). (A) Axial long-repetition-time magnetic resonance imaging (long-TR MRI) before radiosurgery. (B) Axial long-TR MRI 9 months after radiosurgery. The nidus has decreased in size and there are extensive areas of increased signal surrounding the irradiated AVM.

*Reproduced from Youmans & Winn 8e, Fig. 300.1, p. 2351 — Label when you look at it: (A) axial long-TR MRI of an 11-year-old boy with a right frontoparietal AVM **before** radiosurgery and (B) **9 months after** radiosurgery — "**the nidus has decreased in size and there are extensive areas of increased signal surrounding the irradiated AVM**". Use it to explain radiation-induced change: it appears 6-18 months after treatment, occurs in about a third of patients, is symptomatic in roughly 9% and permanent in about 4%, and correlates with the 12-Gy volume.*

(c) Role of endovascular therapies [2]

4. Four legitimate roles, and one caution

"Currently, endovascular therapy is used in several ways including as **adjuvant embolization before definitive surgical resection or radiation therapy**, as **palliative therapy targeted toward angiographic high-risk features** (feeding artery or intranidal aneurysms) or to **decrease flow in patients presenting with progressive neurological deficits**, and as **curative therapy** (complete AVM occlusion)" YW p.3712.

4.1 Preoperative (adjuvant) embolization — the main indication

- "**Embolization before definitive surgical resection is the main indication for endovascular therapy.** Because of the morbidity associated with embolization, it should be **targeted with the goal of increasing the safety of surgical resection**. Embolization **should not be performed indiscriminately** for the purpose of reduction of blood flow to make the surgery faster or easier for the surgeon" YW p.3712.
- **What to embolize** — "**preoperative occlusion of arterial feeders that are inaccessible during early surgical exposure** can be very helpful. Similarly, preoperative **embolization of perforator supply** to an AVM can greatly increase the safety of surgical resection. In contrast, **embolization of superficial feeders that can be easily controlled at surgery is not necessary**" YW p.3712.
- **Other named indications** — occlusion of a **ruptured proximal feeding artery aneurysm** before resection or

radiosurgery; **staged embolization of large high-flow AVMs** to restore cerebral vascular reactivity and "potentially minimize the risk for postoperative normal pressure perfusion breakthrough"; reduction of flow in eloquent-area AVMs to make them resectable; occlusion of **perforator supply** to make deep AVMs resectable; and occlusion of **dural or transosseous feeders** that "can cause significant bleeding while elevating a craniotomy flap" [YW pp. 3712-3713].

- **Two strategies from Ch. 452** — "**embolization of feeding vessels that are difficult to access by surgery (e.g. posterior cerebral artery) for early proximal control**, and **embolization of the nidus to reduce the effective volume**" YW p.3677.e8.
- **The governance rule** — "**the only unacceptable scenario is that the embolization team, independent of surgical input, decides the extent of embolization**… Indeed, **preoperative embolization can be eliminated without an increase in the overall adverse outcome rate for surgery**" YW p.3677.e8.
- **In a child, there is a specific argument for it** — "a technical concern specific to children is their **smaller blood volume and decreased ability to tolerate blood loss. Consequently, preoperative embolization is occasionally helpful in the pediatric population**" YW p.1885.e3.

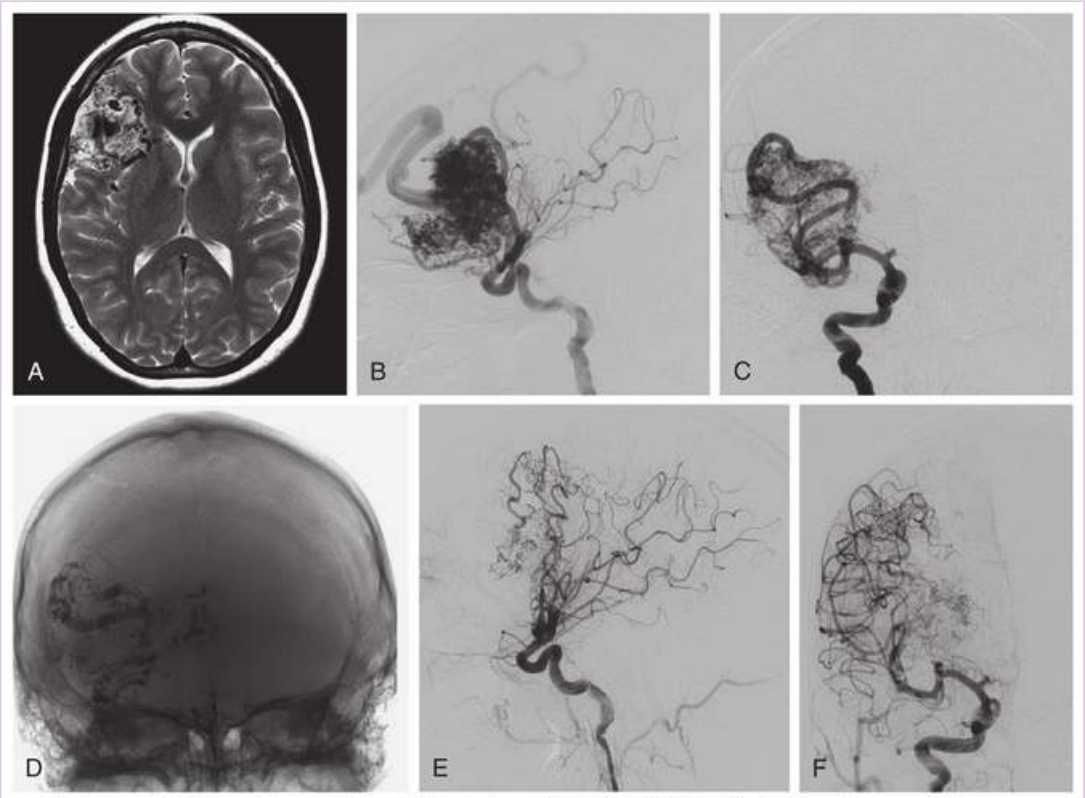


Figure 453.3. Staged preoperative arteriovenous malformation (AVM) embolization. A 30-year-old patient had left-sided ptosis and was found to have a 5-cm right frontal AVM on brain magnetic resonance imaging (A). Catheter angiogram obtained before embolization shows that the AVM is predominantly supplied by superior division feeders of the right middle cerebral artery (B and C). Progressive embolization of the AVM was performed during three staged weekly sessions with the goal of gradual global flow reduction. The *n*-butyl cyanoacrylate glue cast at the end of the third embolization session can be seen on skull fluoroscopy (D). Lateral (E) and anteroposterior (F) common carotid injections show significant reduction in arterial flow to the AVM compared with the preembolization angiogram. The patient subsequently underwent uncomplicated, complete surgical resection of the embolized AVM.

*Reproduced from Youmans & Winn 8e, Fig. 453.3, p. 3682 — Label when you reproduce it: the **staged preoperative AVM embolization** in a 30-year-old — mark on the successive runs the **progressive devascularisation of the nidus across the stages**, the **Onyx cast**, and the residual nidus left for the surgeon. Beside it write the rule of engagement: embolize only those feeders the surgeon cannot reach early (deep perforators, posterior cerebral feeders, dural and transosseous supply), stage the procedure for large high-flow lesions to avoid normal perfusion pressure breakthrough, and never let the extent of embolization be decided without surgical input.*

4.2 Embolization before radiosurgery — largely discredited

- "**Delayed recanalization and reappearance of the portion of the AVM nidus not included in the radiation field** has been known to occur. In fact, **previous embolization has been reported as a negative predictor of successful AVM**

obliteration following radiosurgery. Failure of radiosurgery is particularly common following **particle embolization**, with reported rates of recanalization ranging from **15% to 20%**" [YW pp. 3712-3713].

- Russell's 2018 meta-analysis of 12 studies and 1716 patients "found a clear association of **significantly lower obliteration rates** in AVM treatment with **combined neoadjuvant embolization and SRS compared with SRS alone** "; Zhu's meta-analysis of 6 studies and 2069 patients found obliteration at 3 years of **49.5% with embolization before Gamma Knife versus 70.4% with Gamma Knife alone** YW p.3713.
- **Conclusion to quote** — "given that **there is no definitive evidence that embolization performed before radiosurgery reduces the risk for hemorrhage** during the time period until complete AVM obliteration occurs, **we generally do not recommend the use of embolization for this reason**" YW p.3713.
- The paediatric chapter agrees: embolization before SRS decreases nidus size and allows acceptable dose limits, " **however, there is some evidence that partial preembolization may worsen radiosurgery outcomes by decreasing obliteration rate**" YW p.1885.e4.

4.3 Palliative or partial embolization — probably harmful

- "The issue of whether palliative or partial embolization alters the natural history is unclear. **Most studies have suggested that such embolization does not improve clinical outcomes compared with conservative therapy**" YW p.3713.
- **The numbers** — Miyamoto: annual haemorrhage **2.6% in untreated versus 14.6% in palliatively treated** AVMs, and **25% in those who had embolization alone**. Kwon: of 16 medically treated patients **31% deteriorated and 25% bled**, versus **27.3% deteriorated and 45.5% bled** after partial embolization. Barrow: annual haemorrhage **1% in conservatively treated grade IV-V AVMs versus 10.4% in partially treated** YW p.3713.
- **The counter-evidence** — Laakso's 623 Helsinki patients: annual mortality **3.4% conservative, 1.8% partially occluded, 1.2% totally occluded**, with the benefit of partial occlusion only appearing **5 to 7 years after treatment** YW p.3713. The paediatric chapter warns that "**partial treatment — including the period between embolization and subsequent definitive management — may increase the risk for hemorrhage**" YW p.1885.e5.

4.4 Curative embolization — only in the right hands and the right lesion

- Overall complete obliteration rates are "between **5% and 30%** in most series", rising to **96%** in cases selected with intention to cure; Valavanis and Yasargil reported a **39% cure rate overall but 75% in the 182 AVMs embolized with curative intent**; Saatci's 350 AVMs treated with Onyx gave **51% overall angiographic obliteration**, and by subgroup **98% for grades I-II with 2.5% morbidity and 0.6% mortality** versus **12.5% for grades III-V with 10.9% morbidity and 2.1% mortality**, with a **1.1% recanalization rate at 1 year** [YW pp. 3713-3714].
- **The recommendation** — "an attempt at curative embolization should be considered **only at centers with considerable expertise** in AVM embolization and **only in patients with AVMs that have relatively simple angioarchitecture**, with endovascularly accessible feeding arteries located in deep or critical areas of the brain where surgical resection would carry an unacceptable morbidity, or in patients with **medical comorbidities** that would make surgical resection too risky" YW p.3714.
- **In children** — "reported rates of complete nidus obliteration with embolization alone range widely, from **0% to 67%**. Consequently, although endovascular treatment is used as the **standard of care for definitive treatment of vein of Galen malformations**, it is used **primarily as adjunct therapy for pediatric AVM extirpation**" YW p.1885.e4.
- **Paediatric safety data** — off-label Onyx use in children showed "a **24% rate of complications but only a 2% rate of permanent neurological morbidity**", with **microcatheter-related complications and DMSO-induced pulmonary oedema** described; "cerebral angiography and embolization **can be performed safely in children with a more favorable complication profile than in adults**, no long-term neurologic complications in diagnostic procedures, and a **less than 1% rate of neurologic deficit in treatments**" YW p.1885.e5. Against this, "procedures involving **therapeutic intervention are associated with more than twice the radiation exposure of diagnostic angiography**", and estimates of increased brain malignancy risk from a single angiographic procedure are **1.3 to 4.7 times baseline** depending on age and collimation, with **almost one-third of children undergoing multiple procedures — more than 10 in some cases** YW p.1885.e5.

4.5 The ARUBA caution

- In ARUBA, **62% of the intention-to-treat arm included cases for embolization (32% as the only treatment)**, with only **5% surgery alone and 14% embolization followed by surgery**; "therefore it is likely that **embolization is the major cause of adverse outcomes**. A conclusion that may be drawn is that **the role of embolization in unruptured bAVM is questionable if alternate management options are reasonable**" YW p.3677.e6.
- This patient, however, has **ruptured**, and "**embolization in ruptured bAVM may have a greater role than in unruptured bAVM**… early rebleeding can occur and be a consequence of **intranidal or prenidal aneurysms or venous varix rupture associated with venous stenosis. In such cases, obliteration of the offending aneurysm may be appropriate**" YW p.3677.e7.

(d) Surgical nuances [2]

5. Decision, timing, and the operation itself

5.1 Should this child have surgery?

- "**Current consensus opinion advocates treatment for most pediatric AVMs, except when it would cause unacceptable morbidity, especially in patients who present with hemorrhage**" YW p.1885.e3.
- "**Surgery remains a favored treatment if it can be accomplished safely.** In surgical series in children, **excellent results have been obtained in resection of Spetzler-Martin grades I to III AVMs, with immediate cure rates in most cases and a risk for complications of less than 10%**" YW p.1885.e3.
- "Sanchez-Mejia reported **superior outcomes in children compared with adults** after microsurgical resection and found that the modified Rankin score **improved or remained unchanged after surgery in 94% of children, as opposed to 70% of adults**"; Celli reported an **operative mortality of 2.6% in children versus 8.5% in adults** YW p.1885.e3.
- **The ARUBA/SIVMS results do not apply here** — "the applicability of these studies to the pediatric population is limited inasmuch as **most pediatric AVMs manifest with hemorrhage**, and the **expected long life span of children provides a lifetime of cumulative risk for rupture if AVMs remain untreated**" YW p.1885.e3. Estimated lifetime rupture risk ≈ **105 − age in years** — i.e. about **90% for a 15-year-old** at a 3% annual rate [YW pp. 1885.e2, 3701].

5.2 Timing

- **The general rule** — "AVM surgery is generally an **elective** procedure. In cases of ruptured AVMs that lead to intracranial hemorrhage and **no significant neurological deficits**, our policy is to operate in a **delayed fashion (4-6 weeks)**. During this time period, the risk for early rebleeding is relatively low, yet the delay allows time for **the hematoma to liquefy, the associated surrounding edema to resolve, and the dysautoregulated brain tissue to recover**. In addition, the subarachnoid blood that is frequently found early after hemorrhage **makes it difficult to map the surface anatomy and to identify feeding arteries and draining veins**" YW p.3702.
- **The exception this patient represents** — "**in the setting of life-threatening hemorrhage necessitating urgent surgery, we generally recommend only gentle evacuation of the clot without disturbing the AVM.** Only in the case of **small surface AVMs that can easily be removed with the clot** do we attempt to excise the AVM on an emergency basis" YW p.3702.
- **Do not resect eloquent brain because it is "already lost"** — "significant neurological deficits following AVM rupture **are not necessarily permanent**. Frequently the deficit… occurs as a result of a **hematoma exerting pressure** on critical brain structures **rather than actual destruction of functional neural tissue**. We therefore recommend delaying surgery for several weeks to months to allow such potential recovery to occur" YW p.3702; and "**surgery should not be performed assuming that any loss of function present acutely allows greater freedom for adjacent brain removal**" YW p.3677.e12.
- **Ch. 452's rule for acute ICH** — "the management of acute ICH with bAVM should be determined by the **normal decisions with regard to ICH**. Whether the bAVM is removed at the time of hematoma evacuation should be

CHAPTER 14

Spine: Degenerative Disease, Spinal Tumours & Spinal Surgery

21
QUESTIONS SOLVED

Intramedullary & Intradural Spinal Tumours
6 questions

a) Dumb-bell neurofibromas. [4]
b) Hypothalamic hamartomas. [3]
c) Choroid plexus papillomas. [3]

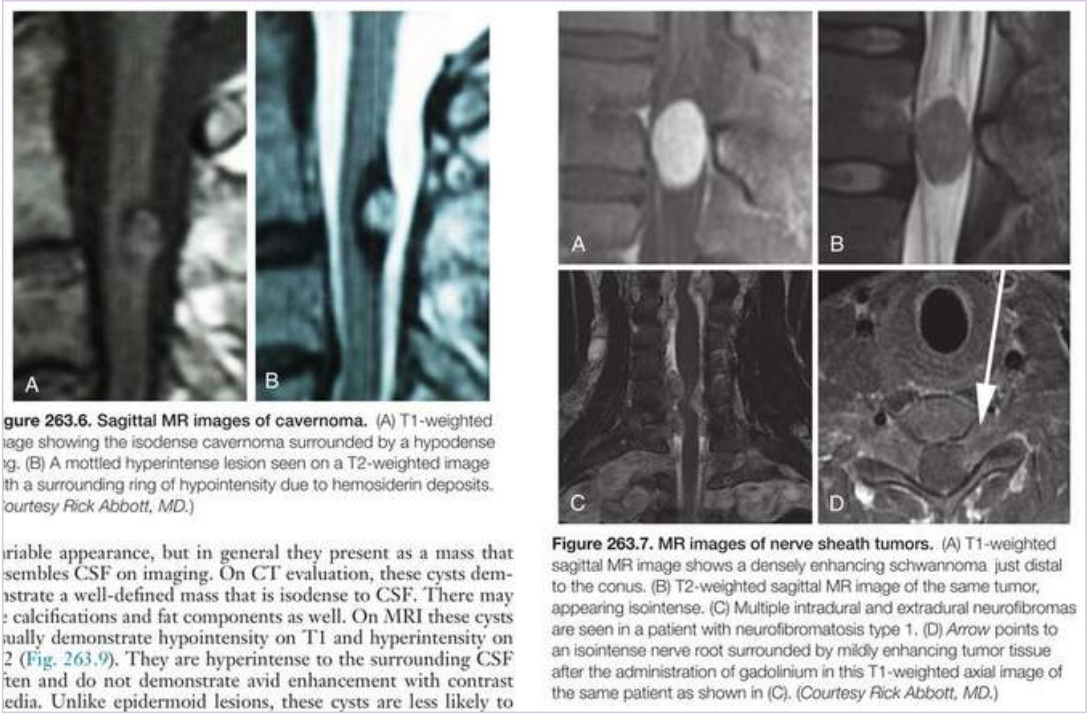
LONG | JUN 2021 · Paper II · Q9 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 327 *Evaluation and Treatment of Benign Intradural Extramedullary Tumors*, §Histology and Gross Pathology, §Epidemiology, §Syndromes, §Surgical Considerations and §Surgery for Dumbbell Tumors and Extradural Nerve Sheath Tumors, pp. 2547-2553 (Fig. 327.1, p. 2552). Supplementary: Ch. 285 *Benign and Malignant Tumors of the Peripheral Nerve*, §Neurofibroma, pp. 2213-2215 (Figs. 285.2 and 285.3, pp. 2214-2215; Fig. 285.10, p. 2221); Ch. 263 *Tumors of the Spine, Spinal Canal, and Spinal Cord in Children*, §Intradural Extramedullary Tumors and §Treatment: Surgery, pp. 1997, 2001-2002, 2006 (Fig. 263.7, p. 2002); Ch. 329 *Evaluation and Treatment of Malignant Primary Spinal Tumors*, §Spinal Malignant Peripheral Nerve Sheath Tumors, pp. 2574-2575 (Fig. 329.3, p. 2574); Ch. 97 *Radiosurgical Treatment for Epilepsy*, §Hypothalamic Hamartomas and §Topologic Classification and Treatment Strategy, pp. 621-623 (Figs. 97.3 and 97.4, pp. 622-623); Ch. 98 *Laser Interstitial Thermal Therapy in Epilepsy*, §Hypothalamic Hamartomas, p. 633 (Fig. 98.3, p. 633); Ch. 235 *Choroid Plexus Tumors*, §Epidemiology, §Pathology, §Clinical Features, §Diagnostic Imaging and §Treatment, pp. 1777-1785 (Figs. 235.2-235.6, pp. 1779-1783; Table 235.1, p. 1782).

(a) Dumb-bell neurofibromas [4]

1. Definition and terminology — fix these first

- **A "dumb-bell" tumour is an intradural-extradural nerve sheath tumour (NST).** Youmans states it plainly: "Spinal schwannomas or neurofibromas can be exclusively intradural or exclusively extradural, or can involve both compartments as **intradural-extradural, or 'dumbbell,' tumors**" YW p.2547.
- **The origin is always the intradural segment of a nerve root.** "In instances in which NSTs have a significant extradural component, whether purely extradural or intradural-extradural dumbbell tumors, **the origin remains the intradural segment of a dorsal or ventral nerve root**" YW p.2551.
- **The waist of the dumb-bell is the dural root sleeve and the neural foramen.** "The key difference is when there is **extended lateral growth through the dural root sleeve into the neural foramen and beyond the dorsal root ganglion into the paraspinal region**, where extradural lesions can grow to impressive size" YW p.2551.
- **Neurofibroma versus schwannoma — the single distinction that earns the mark.** A schwannoma is "well-encapsulated, arising from a **single nerve fascicle**, displacing other uninvolved fascicles as they grow"; a neurofibroma is "less well encapsulated" and presents "as a **diffusely expansile lesion of the involved nerve**. Often, multiple fascicles are involved, making resection impossible without sacrificing the parent nerve" YW p.2547.
- **The pathological rule**: "**The presence of axons within the tumor on gross pathology distinguishes neurofibroma from schwannoma**" YW p.2547. Paediatric texts put it the same way: "Schwannomas have a **thin capsule separating them from surrounding nerve fibers, whereas neurofibromas do not**" YW p.1995.
- **Youmans is explicit that the classic dumb-bell morphology belongs to the neurofibroma**: neurofibromas "are typically described as a **dumbbell-shaped mass extending along the spinal nerve root from the spinal canal into the neural foramen**" YW p.1997.



gure 263.6. Sagittal MR images of cavernoma. (A) T1-weighted iage showing the isodense cavernoma surrounded by a hypodense ig. (B) A mottled hyperintense lesion seen on a T2-weighted image th a surrounding ring of hypointensity due to hemosiderin deposits. ourtesy Rick Abbott, MD.)

riable appearance, but in general they present as a mass that sembles CSF on imaging. On CT evaluation, these cysts demnstrate a well-defined mass that is isodense to CSF. There may calcifications and fat components as well. On MRI these cysts ually demonstrate hypointensity on T1 and hyperintensity on 2 (Fig. 263.9). They are hyperintense to the surrounding CSF ten and do not demonstrate avid enhancement with contrast edia. Unlike epidermoid lesions, these cysts are less likely to

Figure 263.7. MR images of nerve sheath tumors. (A) T1-weighted sagittal MR image shows a densely enhancing schwannoma just distal to the conus. (B) T2-weighted sagittal MR image of the same tumor, appearing isointense. (C) Multiple intradural and extradural neurofibromas are seen in a patient with neurofibromatosis type 1. (D) *Arrow* points to an isointense nerve root surrounded by mildly enhancing tumor tissue after the administration of gadolinium in this T1-weighted axial image of the same patient as shown in (C). (*Courtesy Rick Abbott, MD.*)

Reproduced from Youmans & Winn 8e, Fig. 263.7, p. 2002 — Label when you reproduce it: (A) sagittal T1 with contrast — densely enhancing schwannoma just distal to the conus; (B) T2 sagittal of the same lesion, isointense; (C) multiple intradural and extradural neurofibromas in a patient with neurofibromatosis type 1 — point out the dumb-bell waist at the foramen; (D) axial T1 post-gadolinium — an isointense nerve root surrounded by mildly enhancing tumour, i.e. the "target sign".

2. Histology, immunohistochemistry and molecular basis

- **Cell of origin** — "The cell of origin of a neurofibroma is considered to be a **Schwann cell**, but it is not the predominant cell type in the tumor" YW p.2214.
- **Constituent cells** — neurofibromas "are composed of **Schwann cells, fibroblasts, and nerve fibers admixed with mucopolysaccharides, fluid, and fibrous material**, all of which result in fusiform expansion of the tumor" YW p.1997; peripheral nerve texts add **perineural cells, mast cells and endothelial cells**, with "many axons, compared with a schwannoma" YW p.2214.
- **Light microscopy** — "a neurofibroma has a **myxomatous matrix** and exhibits prominent **mucopolysaccharide staining**. There are numerous **collagen fibrils** in the background, which lead to **intense staining with reticulin**; in contrast, schwannomas do not stain as well because of lack of such fibrils" YW p.2214. Classically the collagen is "arranged in a disorganized fashion, often with an appearance resembling **shredded carrots**" YW p.1997.
- **Immunohistochemistry** — neurofibromas "stain for **S-100 less intensely than schwannomas, and express EMA and CD57**" YW p.1997; peripheral nerve data put it as staining "poorly for **S-100 and Leu-7** antigens" compared with schwannoma YW p.2214. Schwannomas by contrast are compact **Antoni A** areas with **Verocay bodies** and looser **Antoni B** areas, staining for **S-100, vimentin and Leu-7**, and are separated from meningioma by **lack of EMA reactivity** [YW pp. 2547, 1997].
- **Grade** — "Neurofibromas are characterized as **WHO grade I lesions**" YW p.1997.
- **Growth patterns** — "Neurofibromas can assume various growth patterns including **localized, plexiform, and diffuse**. The **diffuse and plexiform forms have a more common growth pattern seen with NF1**" YW p.1997. Grossly they are "**tan-white** and do not contain areas of degeneration such as seen in schwannomas" YW p.1997.

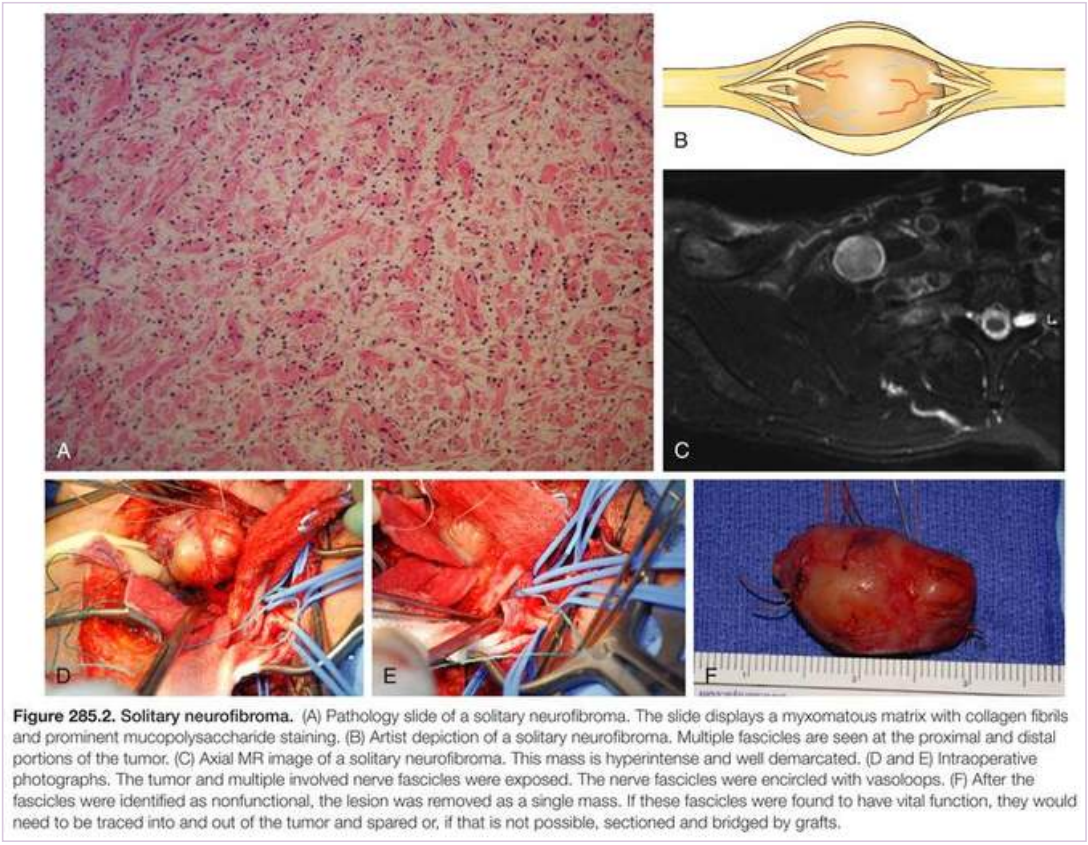


Figure 285.2. Solitary neurofibroma. (A) Pathology slide of a solitary neurofibroma. The slide displays a myxomatous matrix with collagen fibrils and prominent mucopolysaccharide staining. (B) Artist depiction of a solitary neurofibroma. Multiple fascicles are seen at the proximal and distal portions of the tumor. (C) Axial MR image of a solitary neurofibroma. This mass is hyperintense and well demarcated. (D and E) Intraoperative photographs. The tumor and multiple involved nerve fascicles were exposed. The nerve fascicles were encircled with vasoloops. (F) After the fascicles were identified as nonfunctional, the lesion was removed as a single mass. If these fascicles were found to have vital function, they would need to be traced into and out of the tumor and spared or, if that is not possible, sectioned and bridged by grafts.

Reproduced from Youmans & Winn 8e, Fig. 285.2, p. 2214 — Label when you reproduce it: (A) pathology slide — myxomatous matrix, collagen fibrils, prominent mucopolysaccharide staining; (B) artist's depiction — multiple fascicles entering and leaving at the proximal and distal poles (contrast with the single fascicle of a schwannoma); (C) axial MR — hyperintense, well-demarcated mass; (D and E) intraoperative photographs — tumour exposed with the involved fascicles encircled with vessel loops; (F) after the fascicles were shown to be non-functional, the lesion removed as a single mass.

3. Syndromic associations

- **NF1 is the defining association**: "**Neurofibromas occur primarily in patients with neurofibromatosis 1 (NF1)** but can result from sporadic mutations as well" YW p.2547; "Most commonly, neurofibromas are associated with **NF1**" YW p.1997.
- **Genetics** — NF1 is "an **autosomal dominant** syndrome characterized by a mutation in **neurofibromin 1 (NF1)**, the gene coding for neurofibromin on **chromosome 17**, often resulting in **multiple spinal neurofibromas**" YW p.2548. Prevalence **1 in 2500 to 1 in 3000**, i.e. far commoner than NF2 (1 in 50,000) YW p.2548.
- **NF2**, by contrast, is a **chromosome 22 / merlin** disease leading to "**multiple spinal schwannomas, neurofibromas, and spinal meningiomas**" YW p.2548. Other syndromes predisposing to spinal NSTs are **schwannomatosis** (multiple schwannomas without the defining features of NF1 or NF2) and the **Carney complex** (facial pigmentation, cardiac myxomas, endocrine problems and melanotic schwannomas, **10% of which may be malignant**) YW p.2548.
- **Segmental (mosaic, regionalized) NF1** — café au lait spots and neurofibromas restricted to one anatomic region from a **postzygotic NF1 mutation**; "unilateral involvement with **no crossing of the midline**, negative family history, and no systemic stigmata" YW p.2214.
- **Why this matters surgically**: "The IDEM tumors encountered in syndromic patients are usually **neurofibromas**, which makes the potential **sacrifice of the involved nerve root all the more troubling** because the deficits incurred may be followed by further deficits in the future as new tumors become symptomatic" YW p.2548. Recurrence is far higher in neurofibromatosis patients than in sporadic NSTs — **39% versus 11%** YW p.2548.

4. Clinical features and epidemiology

- **NSTs display an equal prevalence in men and women, with a peak incidence in the fourth and fifth decades**, and are uncommon in the very old or very young YW p.2548. Spinal schwannoma incidence is **0.3-0.4 per 100,000** YW p.2548; the commonest intradural spinal tumours overall are meningiomas, followed in varying order by intramedullary ependymomas or NSTs YW p.2548.
- **Presentation** — "As a group, these benign, slow-growing tumors generally present with **pain — either radiculopathy or axial back pain — or focal neurological deficits** attributable to loss of function in involved or collaterally compressed nerve roots, **myelopathy** from spinal cord compression, or **cauda equina dysfunction** from chronic compression" YW p.2548.
- **Spinal deformity and multiplicity are the syndromic red flags** — "patients presenting with **multiple tumors or tumors at a young age** can present with **spinal deformity**. In such cases, suspicion of an underlying syndrome is warranted, and further work-up should include **imaging of the entire neuraxis**" YW p.2548.
- **Compartment rule of thumb** — "Both schwannomas and neurofibromas are **more likely to be purely extradural in the cephalad spine and more likely intradural in the caudal spine**. The propensity for cervical schwannomas to be extradural may be explained by the relatively **shorter intradural course of cervical nerve roots** compared to thoracic and lumbar nerve roots" YW p.2547.
- **Paediatric presentation** — weakness followed by pain is the commonest symptom in children with intradural extramedullary tumours, occurring in roughly **40-50%** and **30-50%** respectively; incontinence follows in about **20%** YW p.1999.

5. Imaging

- **MRI is the modality of choice** — "MRI provides visualization in all three planes and best delineates the relationship of pathology to the spinal cord and nerve roots. Usually these lesions display **avid contrast enhancement**, and meningiomas typically feature a **dural tail**" YW p.2548.
- **Neurofibroma-specific signs** — "unlike schwannomas, [neurofibromas] **infiltrate the nerve root, so there is no clear wall or capsule** separating the tumor from surrounding tissues"; **T1 iso- to hypointense, T2 hyperintense**; a "**string of beads**" sign when several nerve roots are involved; and a typical "**target sign**" on T2 or STIR "due to the nerve root being encased by tumor" YW p.2001.
- **Plain films and CT** — plain radiography "may display **enlarged neural foramina, increased interpediculate distance, vertebral body scalloping, and thinning of the pedicles**, all of which can be attributed to slow tumor growth and reactive bone changes over time" YW p.2548. CT is "well suited for delineating bony anatomy, planning instrumentation, and demonstrating tumor calcification" YW p.2548.
- **Vascular imaging is mandatory for cervical dumb-bells** — "Vascular imaging methods (angiography, magnetic resonance angiography, computed tomographic angiography) may be useful for certain cervical lesions, because they allow **clear delineation of the relationship of pathology to the vertebral artery**. Rarely, preoperative vertebral artery **balloon occlusion testing or embolization and sacrifice** are needed" YW p.2548.
- **Red flags for malignancy (MPNST)** — "larger maximal diameter (**>5 cm**), **irregular lobulated margins, indistinct boundaries** on MRI, and **osteolytic bone destruction** on computed tomography when compared with benign nerve sheath tumors; however, **there are no specific findings on routine imaging alone that can reliably distinguish MPNSTs** from their benign counterparts" YW p.2574.

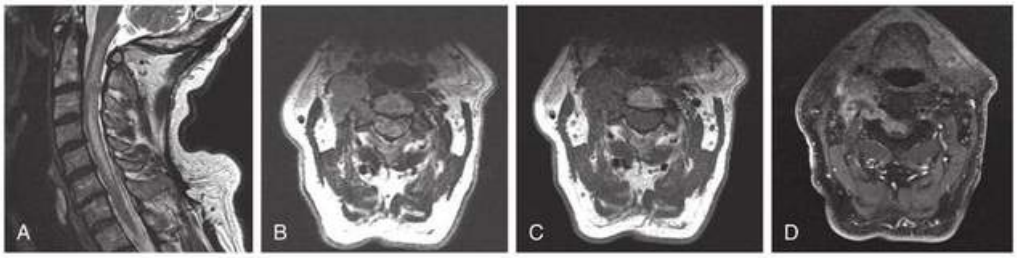


Figure 329.3. Malignant peripheral nerve sheath tumor. A 72-year-old man presented with 2 months of progressive neck pain and paresthesia all along the right side of his body. Subsequent imaging demonstrated an intraspinal lesion at the C2–C3 level. (A) On T2-weighted sagittal magnetic resonance imaging, there was associated cord edema extending multiple segments. (B) Axial T2-weighted image demonstrated significant extraforaminal extension and widening of the right-sided neural foramen. (C and D) T1-weighted axial images showed isointensity to chord parenchyma (C) along with heterogeneous enhancement with contrast administration (D). The patient underwent a right-sided C2–3 facetectomy and C2–4 posterior instrumented fusion for tumor resection. Subsequent pathology returned with a diagnosis of malignant peripheral nerve sheath tumor.

Reproduced from Youmans & Winn 8e, Fig. 329.3, p. 2574 — Label when you reproduce it: a malignant peripheral nerve sheath tumour at C2-C3 with the classic dumb-bell shape. (A) T2 sagittal — cord oedema extending over multiple segments; (B) axial T2 — significant extraforaminal extension with widening of the right neural foramen (the dumb-bell waist); (C and D) axial T1 before and after contrast — isointense to cord, heterogeneous enhancement. Note the treatment: right C2-C3 facetectomy with C2-C4 posterior instrumented fusion.

Table 1 · Schwannoma versus neurofibroma — the comparison the examiner wants — from Youmans & Winn 8e, Ch. 327 §Histology and Gross Pathology, p. 2547; Ch. 285 §Neurofibroma, p. 2214; Ch. 263 §Pathology and §Intradural Extramedullary Tumors, pp. 1997, 2001.

Feature	Schwannoma	Neurofibroma
Frequency among benign NSTs	**Far more common**	Less common
Capsule	Well encapsulated; **thin capsule separates it from nerve fibres**	Not encapsulated; **no plane, diffusely expansile**
Fascicles involved	**Single fascicle**; others displaced	**Multiple fascicles** traverse the tumour
Axons within tumour	Absent	**Present** — the defining gross/histologic distinction
Origin	Obersteiner-Redlich zone (oligodendrocyte→Schwann cell transition), dorsal root more often	Along the spinal nerve root, intradural / extradural / both
Histology	Compact **Antoni A** with **Verocay bodies** + loose **Antoni B**; degenerative change common	**Myxoid matrix**, "shredded carrot" collagen, **reticulin** +, no degeneration; tan-white
Immunohistochemistry	**S-100 ++, vimentin, Leu-7**; **EMA negative** (vs meningioma)	**S-100 weak**, **EMA +, CD57 +**
Syndrome	**NF2**, schwannomatosis, Carney complex	**NF1**
Growth patterns	Solitary, occasionally multiple	**Localised, plexiform, diffuse**
Malignant potential	Low (melanotic schwannoma in Carney ~10%)	**Plexiform NF is the recognised precursor of MPNST**; 3-5% lifetime risk in NF1
Resectability	Fascicle preservation usually possible; parent fascicle "rarely contains functional tissue"	"Usually lack a plane and are **inseparable from their nerve root of origin**"
Recurrence (NF vs sporadic)	11% sporadic	**39% in neurofibromatosis**

6. Operative strategy for a dumb-bell tumour — steps in order

6.1 Preparation

- **Preoperative intravenous steroids** for all patients undergoing surgery for NSTs YW p.2550.
- **Monitoring**: SSEPs and MEPs for any intradural component; "For NSTs involving the **C5-T1 and L2-S4 nerve roots, continuous EMG and evoked EMG monitoring should be considered**" YW p.2550. Evoked EMG "is particularly useful for identifying **efferent motor roots**" YW p.2551. Guo and colleagues used **compound muscle action potential stimulation with a handheld monopolar electrode in 10 patients undergoing resection of cervical dumbbell tumors**, allowing identification and prediction of postoperative nerve root function in all 10 YW p.2549.
- **Positioning**: prone; **Mayfield above T1**; chest bolsters with shoulders tucked for lesions above T6; shoulder abducted 90 degrees and an open-frame table below T6 YW p.2550.

6.2 Sequence — intradural first

- **"We favor intradural exposure first, because resection of the intradural component will decompress the spinal cord and release the neural elements from adhesions to the tumor capsule, avoiding traction injury during manipulation of the extradural tumor component"** YW p.2551.
- **Dural opening**: midline durotomy, then the intradural tumour component is "**transected at the distal dural root sleeve** , then the dural edge is reflected medially to better visualize the epidural space and expose the extradural component" YW p.2551. A **T-shaped durotomy extended along the dural root sleeve** toward the foramen is the specific variant for dumb-bell lesions [YW pp. 2550, 2006].
- **Bone work**: "**Facetectomy is usually performed** to access the foraminal and extraforaminal compartments" YW p.2551 . Extended laminectomy with unilateral complete facetectomy is often required.
- **Extradural resection**: resected en bloc or internally debulked with an ultrasonic aspirator; "it is important to **stay on the tumor capsule** to avoid epidural and foraminal bleeding, as well as the perivertebral venous plexuses" YW p.2551.
- **Delivery**: "Medial tumor should be freed of its medial dural root sleeve attachment, allowing for **free rotation of a cored-out tumor capsule** to deliver the lateral extradural component into the operative field for identification of its efferent attachment, which can then be transected" YW p.2552.
- **Extradural-first is the exception**: "This approach may be favored when there is a **large intraspinal, extradural component that prevents fashioning a durotomy**. In these cases, the dura remains closed during the bloody dissection of the extradural component. The **medial attachment of the extradural tumor should be transected early** to avoid undue traction on intradural elements" YW p.2552.

6.3 Region-specific hazards

- **Cervical** — "blind ventral dissection may endanger the **vertebral artery, which is usually displaced by tumor, not engulfed**"; when the **C1 root is involved, a small craniotomy may be needed** [YW pp. 2551-2552].
- **Thoracic** — "attention must be paid to the **pleural cavity ventrally** and care taken to avoid violating the pleura accidentally, a complication that necessitates **chest tube placement and carries an increased risk of a CSF pleural fistula**"; additional removal of the **transverse process and rib head** may be required as part of a lateral extracavitary approach [YW pp. 2551-2552].
- **Lumbar** — "opening of the **intertransverse membrane** may be required for removing a paraspinal tumour"; a true retroperitoneal approach traverses the psoas and "places the **lumbosacral plexus at risk**" and is limited by the iliac crest [YW pp. 2549, 2551].
- **Sacral** — "extended lateral bone removal may be limited because the **sacroiliac lateral articulation cannot be taken down without significant risk of sacroiliac instability**. Additionally, ventral spinal nerves can exit ventrally. In cases in which presacral extension occurs, a **separate anterior retroperitoneal approach is required with the assistance of a colorectal surgeon**" YW p.2552. "Generally, **bladder and bowel function is preserved if S2-S4 are intact on at least one side**" YW p.2550.

6.4 Staging the operation

- **"A staged approach may be necessary when tumor is encountered outside the neural foramen."** In the free space of the retroperitoneum, extrapleural space or neck soft tissue the extraforaminal component "can grow to a strikingly large size", involving "the **vertebral artery in the neck, the pleural cavity in the thorax, and the psoas and lumbosacral plexus in the retroperitoneum**"; many need a separate incision and the participation of a **vascular,**

thoracic and/or colorectal surgeon YW p.2551.

- **Nevertheless** — "most lesions can be resected through a **single exposure with a posterior or extended posterolateral approach** that allows simultaneous visualization of both intradural and extradural components and allows for placement of posterior spinal instrumentation when needed" YW p.2551.

6.5 Fusion — when and why

- **Biomechanical data** — "whereas **medial facetectomies — even bilaterally performed — do not introduce significant spinal instability, unilateral complete facetectomies can introduce significant instability in the lumbar or cervical spine**" YW p.2550.
- "Expansive open-door laminaplasties and C2 decompressions are associated with **increased risk of cervical kyphosis**, particularly when performed to treat spinal cord tumors" YW p.2550; even "if the facet complex is not violated, **multilevel laminectomies may predispose to cervical kyphosis** and warrant spinal stabilization" YW p.2549.
- **"The issue of whether or not to fuse following facetectomy for dumbbell tumors, however, remains subject to debate"** — an honest sentence worth reproducing YW p.2550.
- **Instrumentation should be planned in the same sitting when anticipated**, and "should be considered even if a minimal midline posterior decompression is performed" where pre-existing deformity or instability is noted; it "may be required in cases involving **junctional levels and reoperations**" YW p.2550.

6.6 Nerve root sacrifice — the judgement call

- "**Preservation of uninvolved ventral nerve roots is particularly important in cervical and lumbosacral regions, whereas dorsal roots can usually be sacrificed without deficit**" YW p.2551.
- "**Neurofibromas usually lack a plane and are inseparable from their nerve root of origin.** In these instances, in the cervical and lumbar spine, **debulking with preservation of anterior rootlets may be best if the nerve root is found to be functional**, whereas roots that are confirmed to be **nonfunctional with intraoperative stimulation can be sacrificed**" YW p.2551.
- "In the upper cervical spine, the surgeon should beware of **spinal accessory nerve rootlets coursing superior and anterior to the denticulate ligament** in a cephalad course" YW p.2551.
- **Division of the denticulate ligament allows further ventral access** YW p.2551.
- **Malignant transformation is the counterweight** — "the rate of progression to malignant peripheral NST is **higher in patients with neurofibromatosis** and remains a concern in instances of subtotal resection, making the decision to **sacrifice functionality for oncologic benefit** all the more challenging" YW p.2548.

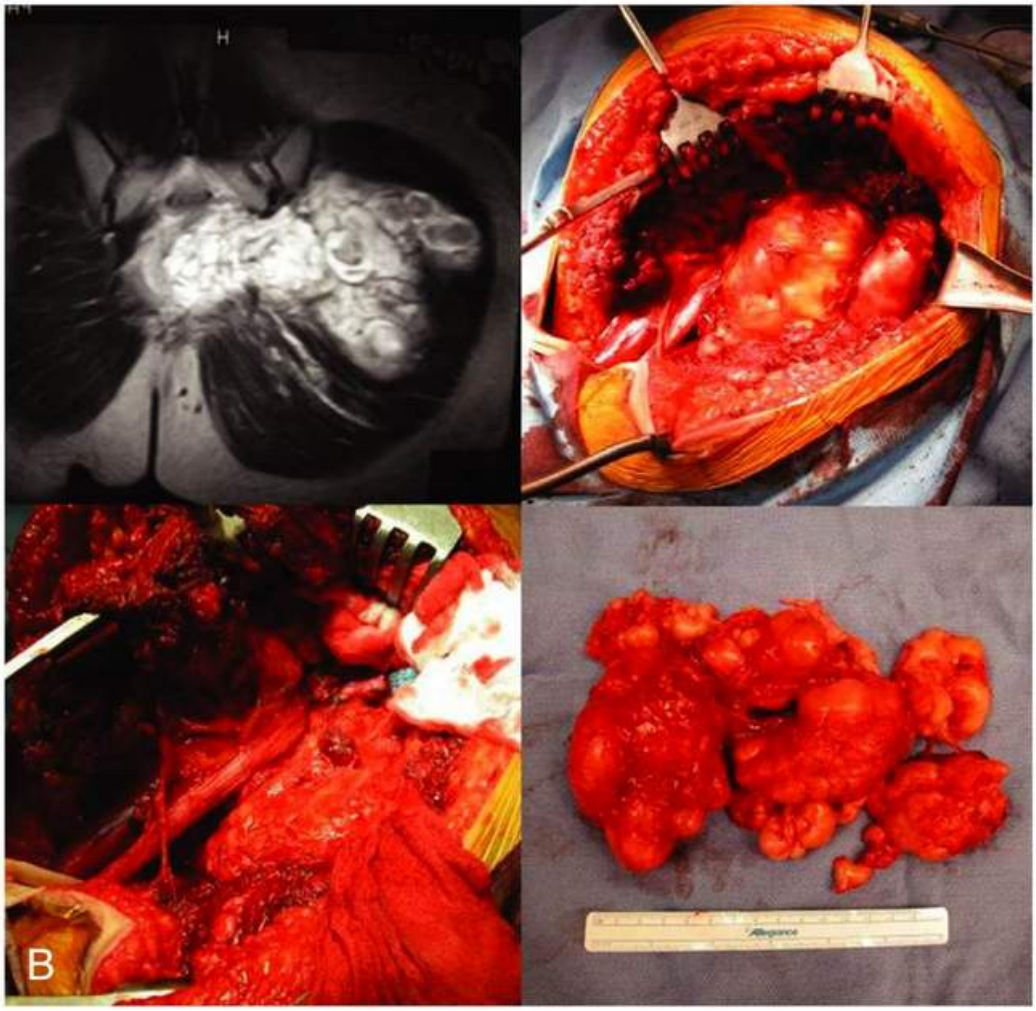


Figure 285.3. Plexiform neurofibroma. (A) Artist depiction of a plexiform neurofibroma. Multiple nodular growths may be seen along the long segment of the nerve. (B) Axial MR image and intraoperative photographs. A plexiform neurofibroma extending along the sciatic nerve was identified. A significant portion of the tumor bulk was removed to decompress the nerve. Often, complete removal of the mass is not possible without significant neurological deficit.

Reproduced from Youmans & Winn 8e, Fig. 285.3, p. 2215 — Label when you reproduce it: (A) artist's depiction of a plexiform neurofibroma — multiple nodular growths along a long segment of the nerve; (B) axial MR image plus intraoperative photographs of a plexiform neurofibroma extending along the sciatic nerve, with a significant portion of the bulk removed to decompress the nerve. State in the label that complete removal is often impossible without major deficit.

7. Malignant transformation — MPNST arising in a dumb-bell neurofibroma

- **Definition** — MPNSTs "are rare soft tissue sarcomas that arise **de novo** from peripheral nerve sheath cells, or as a **degeneration from previously existing plexiform neurofibromas**. They can be found throughout the body, but involve the **spinal nerve roots in 2%-3% of cases**" YW p.2573.
- **Risk** — "The majority of MPNSTs occur in patients with **NF1**, who have a **3%-5% incidence rate** of developing a MPNST. In comparison, the incidence of MPNSTs in the general population is approximately **0.001%**" YW p.2574. **Radiation** is the other major risk factor: **4%-11% of MPNSTs** arise in previously irradiated regions YW p.2574.
- **Premalignant histology** — the NIH consensus overview proposes "**neurofibroma with cytologic atypia or**

hypercellularity" and "**atypical neurofibromatous neoplasm with uncertain biologic potential (ANNUBP)**", the latter requiring at least two of: nuclear atypia, hypercellularity, variable loss of neurofibroma architecture, **loss of CD34**, and high mitotic activity YW p.2214. Markers of progression include **high Ki-67 (MIB-1), loss of S100/SOX10, loss of CD34, loss of the CDKN2A locus at 9p21 and loss of nuclear p16** — none diagnostic alone YW p.2214.

- **Treatment and outcome** — en bloc resection with wide margins plus radiotherapy is the extraspinal standard, "unfortunately, this type of wide resection is often not possible in spinal MPNSTs due to the proximity of critical structures such as dura, other nerves, and major blood vessels" YW p.2574. **2-year local recurrence 60%**; **5-year survival just over 60%** in spinal series, and **16%-52%** across all MPNSTs YW p.2574. Adjuvant radiation improves progression-free but not overall survival; local control needs **≥60 Gy**, limited by cord tolerance YW p.2574. **Malignant triton tumour**, with rhabdomyoblastic differentiation, is ~5% of MPNSTs and has a **5-year survival of only 11%** YW p.2574; **cellular schwannoma** is the benign mimic with **100% 5-year survival** YW p.2574.

8. Adjuvant therapy and outcome for benign dumb-bell NSTs

- **"Generally, chemotherapy and conventional radiotherapy do not have a significant role in the management of spinal NSTs and meningiomas"** YW p.2553.
- **Stereotactic radiosurgery** — Gerszten and coworkers treated **73 patients with 15-20 Gy in a single fraction**, achieving radiographic tumour control in all with only three instances of radiation-induced cord toxicity; Sachdev and colleagues achieved **local control in 102 of 103 lesions**, with symptomatic relief in **91% of meningiomas, 67% of neurofibromas and 86% of schwannomas** YW p.2553. **Caveat**: radiosurgery "may not be suitable for lesions close to the spinal cord or **large dumbbell tumors close to critical subjacent structures**" YW p.2553.
- **Microsurgical gross total resection remains the "gold standard" for isolated IDEM tumors** YW p.2553.
- **Outcome** — ventral lesions and upper thoracic location carry a higher incidence of surgical complications; patient-reported pain, quality of life, general health and disability all improve significantly after resection YW p.2553. **Advanced age and medical comorbidity are independent risk factors for adverse events and non-home discharge** YW p.2553.

(b) Hypothalamic hamartomas [3]

9. Nature, genetics and pathophysiology

- **Definition** — HHs are "rare **congenital heterotopic lesions** that are **intrinsically epileptogenic when closely connected to the mammillary bodies**" YW p.621; elsewhere, "rare **developmental malformations of the ventral hypothalamus**" YW p.633.
- **They are not neoplasms.** "Because these lesions are **not technically neoplasms, removal is not mandatory**, and they can also be treated with **disconnection rather than gross total resection**" YW p.621. This single sentence changes the whole management answer.
- **Intrinsic epileptogenesis is proven** — Paillas and coworkers (Marseille, 1969) first showed the epilepsy could be cured by resecting the HH itself; Munari and colleagues provided **direct stereo-EEG depth-electrode evidence** of epileptic impulse generation within the lesion, reinforced by **ictal SPECT** YW p.621.
- **Histology** — "**GABAergic, interneuron-like, and pacemaker-like phenotypes with characteristic intrinsic firing activity** and large, dispersed, **pyramidal projection-type excitatory cells**"; multiple **BDNF-TrkB signalling pathways** are activated in HH YW p.621.

10. Clinical features

- **Gelastic seizures in the first years of life** are the classic presentation: "Patients classically experience **gelastic seizures during the first years of life**" YW p.621. HHs are "associated with **precocious puberty and gelastic seizures** and are typically associated with **refractory epilepsy**, usually resulting in complex partial seizures or gelastic seizures" YW p.633.

- **Progression to an epileptic encephalopathy** — "In more severe forms of the disease, an epileptic encephalopathy characterized by **drug resistance, various types of seizures with generalization (including drop attacks), cognitive decline, and severe psychiatric comorbidity** develop in affected patients during the following years" YW p.621.
- **Drug resistance from onset** — "Usually the seizures begin **early in life and are often particularly drug resistant from the onset**" YW p.621.
- **False localisation** — "Commonly the seizure semiology suggests the involvement of **temporal or frontal lobe regions** and a phenomenon of **secondary epileptogenesis**" YW p.621. **Gelastic** seizures are formally listed among the motor seizure semiologies in Youmans' classification of seizures YW p.494.
- **Other presentations** — "HHs can also be **asymptomatic** or be associated with **precocious puberty**, neurological disorders (including epilepsy, behavior disturbances, and cognitive impairment), or both" YW p.621.
- **Natural history is unfavourable** — "because of **behavioral symptoms (particularly aggressive behavior) and mental decline**, which occur as a direct effect of the seizures" YW p.621.
- **Anatomical rule linking morphology to epilepsy** — "Symptomatic epilepsy-related HH is observed **only with medium to large sessile HHs that are broadly attached to the tuber cinereum or mammillary body**" YW p.621.

11. Topologic classification (Régis) — the classification the examiner wants

- "**Topologic classification of the lesion based on good high-resolution MRI is a key feature in the decision-making process.** Previous classifications were based on anatomic or surgical considerations. These classifications do not describe the large diversity of these lesions and their therapeutic consequences" YW p.622.
- "As underlined by Palmini and coworkers, **the exact location of the lesion in relation to the interpeduncular fossa and the walls of the third ventricle correlates with the extent of excision, seizure control, and complication rate**" YW p.622.

Table 2 · Topologic classification of hypothalamic hamartoma and the treatment it dictates — reproduced in full from Youmans & Winn 8e, Ch. 97 §Topologic Classification and Treatment Strategy, pp. 622-623 (Fig. 97.4, p. 623).

Type	Topology	Preferred first-line treatment (Youmans)	Reasoning given
I	**Small HH located inside the hypothalamus**, extending more or less into the third ventricle	**GKRS**	"the best candidates for GKRS"; morbidity of microsurgical removal is likely to be high
II	**Small and mainly in the third ventricle**	**GKRS** ("certainly a safer alternative"); open surgery only for very severe recurrent status epilepticus	Endoscopic and transcallosal interforniceal approaches risk **short-term memory worsening, endocrine disturbance (hyperphagia/obesity, low thyroxine, sodium disturbance), thalamic or thalamocapsular infarcts** — even in expert hands
III	**Located in the floor of the third ventricle**	**GKRS preferred**	"extremely close relationship between the **mammillary body, the fornix**, and the lesion"; sessile HH always has some hypothalamic extension
IV	**Sessile, in the cistern**	**Disconnection** (pterional ± orbitozygomatic osteotomy) can be discussed; **GKRS if small**	GKRS simultaneously treats the small associated hypothalamic part frequently visible on high-resolution MRI
V	**Pediculate**	Radiosurgery **or** disconnection via a pterional approach	"rarely epileptic and can be easily cured"; in severe epilepsy a second modality speeds seizure cessation; still look for hypothalamic extension near the mammillary bodies

VI	**Giant**	**Not good candidates for up-front radiosurgery** — "in nearly all cases a combination of several therapeutic modalities should be used"	Radiosurgery targeting only the superior part and leaving the lesion below the floor untreated "has been uniformly disappointing"
Mixed	e.g. II + I	Treat according to the dominant component	—

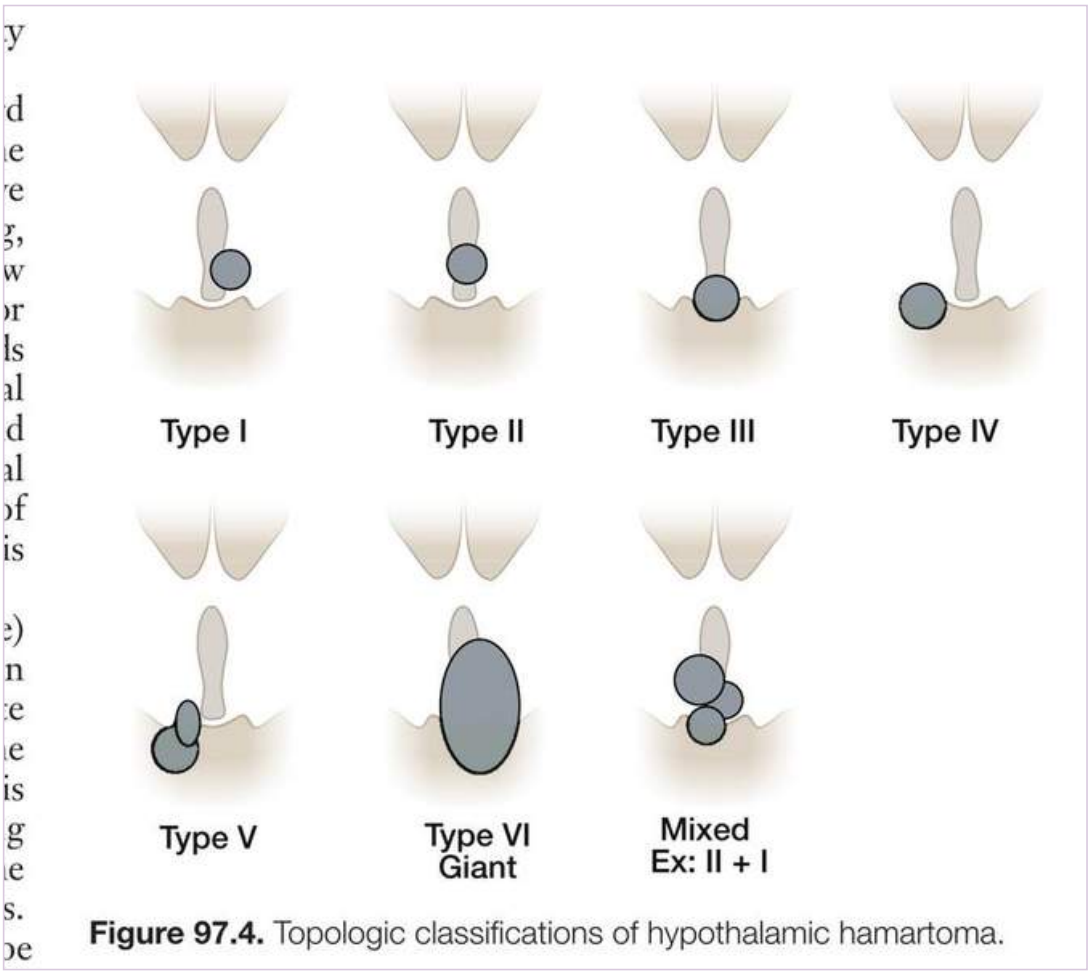


Figure 97.4. Topologic classifications of hypothalamic hamartoma.

Reproduced from Youmans & Winn 8e, Fig. 97.4, p. 623 — Label when you reproduce it: the six topologic types of hypothalamic hamartoma (I intrahypothalamic, II intraventricular, III floor of third ventricle, IV sessile cisternal, V pediculate, VI giant, plus mixed). Mark the mammillary body, the fornix and the floor of the third ventricle on each panel, because those are the structures that determine whether radiosurgery or disconnection is chosen.

12. Management

12.1 Microsurgery and disconnection

- **Microsurgical resection carries a heavy price.** "Microsurgical resection in this critical area is associated with a significant risk for **oculomotor palsy, hemiparesis, and visual field deficits**" YW p.621.
- **Palmini's 2002 audit of expert centres** — "severe surgical complications after microsurgical resection in **7 of 13 patients**", comprising "four **thalamocapsular infarctions with contralateral hemiplegia**, transient **third nerve paresis** in four patients, a **central diabetes insipidus**, and a **nonreversible hyperphagia**"; nevertheless three patients had complete seizure control and the remaining 10 had **>90% reduction** in seizure frequency YW p.621.
- **Delalande's disconnection series (17 patients)** — a second, usually endoscopic, intervention was needed in eight; **47% (8/17) became seizure free**, but permanent complications included one hemiplegia, one hemiparesis, two hyperphagia, one panhypopituitarism, one hypothyroidism and one growth hormone deficiency; transient morbidity was

one meningitis and two diabetes insipidus. "**Only six patients (35%) were seizure free with no permanent deficit**" YW p.622. Delalande observed **no memory deficit** and "a correlation between **completeness of disconnection and control of the seizures**" YW p.622.

- **In Delalande's pterional experience only 2 of 14 patients were seizure free after a single disconnection** — hence Youmans recommends this approach "only in cases of lesions too large for GKRS as the first step of a staged approach", with GKRS performed at **3 months** as the second step YW p.623.

12.2 Radiosurgery

- **Rationale** — "**Radiosurgery is able to circumvent many of the severe neurological risks** inherent in these procedures, while still attaining similar result profiles" YW p.622.
- **Technique** — Leksell 201-source Cobalt-60 Gamma Knife; **multi-isocentric, highly conformal and selective planning with low peripheral doses** because of the optic pathways and hypothalamus; **median dose 17 Gy (range 13-26 Gy)**; lesions generally small (median diameter 9.5 mm, range 5-26 mm); median lesion volume **398 mm³ (28-1600 mm³)**; **special attention to the dose to the mammillary body and fornix**, tailored using a single run of shots with the **4-mm collimator** [YW pp. 622].
- **Results of the prospective Marseille trial (57 patients, median follow-up 71 months)** — by Engel class: **Engel I 39.6%, Engel II 29.2% (I+II 68.8% overall; 75% in anatomic types I-III), Engel III 20%** YW p.622. **28 patients (58.3%) required a second GKRS**; microsurgery was needed in **7 (16.6%)** with large HHs, of whom **28.6%** reached Engel I or II YW p.622.
- **Comorbidity outcome** — "Global psychiatric comorbidity was **cured in 28%, improved in 56%, stable in 8%**, and continued to worsen in 8%. **No permanent neurological side effect was reported (in particular, no memory deficit).** Non-disabling transient **poikilothermia in three patients (6.2%)**; a transient increase in seizure frequency in **eight patients (16.6%)** with a median duration of 30 days (9-90)" YW p.622.
- **Conclusion Youmans draws**: "Based on these results, **radiosurgery can be the first-line intention strategy in patients with small to middle-size HHs of types I to III**" YW p.622.

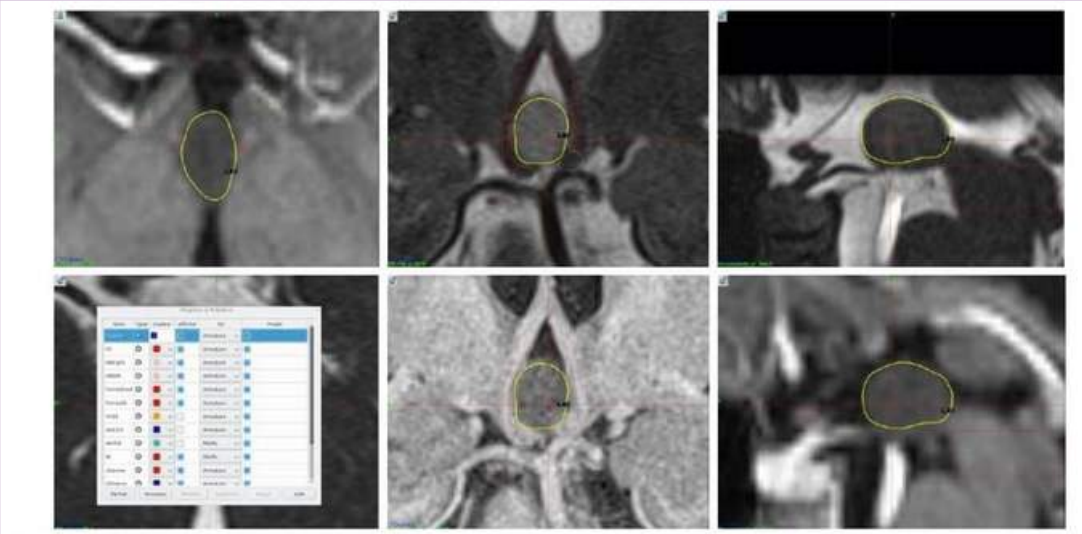


Figure 97.3. Screenshot of the planning station for Gamma Knife radiosurgery during treatment planning for epileptic hypothalamic hamartoma. Different imaging sequences are used to delineate the lesion efficiently. Careful attention is paid to critical structures and the dose received.

Reproduced from Youmans & Winn 8e, Fig. 97.3, p. 623 — Label when you reproduce it: the Gamma Knife planning station screenshot for an epileptic hypothalamic hamartoma. Point out the multiple imaging sequences used to delineate the lesion and the critical structures whose dose is checked — optic pathways, mammillary body, fornix, hypothalamus.

12.3 Other ablative options

- "**Stereotactic radiofrequency thermocoagulation and laser ablation** have been proposed by some authors for lesioning of HH instead of the direct microsurgical approach" YW p.622.
- **MRgLITT** — "**Overall, evidence strongly supports MRgLITT for HH-related epilepsy as a safer and more**

effective approach than traditional surgical interventions"; complication rates for LITT range **2%-5%** (neurological deficit, wound complications, CNS infection) versus **up to 15% after surgical resection**, and hospital stay is significantly shorter with most patients discharged the next day. In centres with less experience, transient neurological deficits have been reported as high as **50%** and permanent deficits as high as **20%** YW p.633.

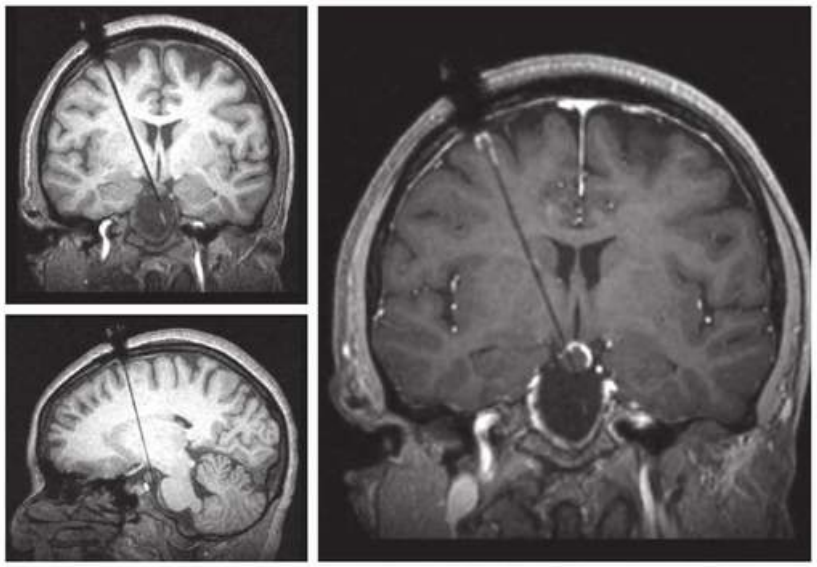


Figure 98.3. Magnetic resonance–guided laser interstitial thermal therapy for hypothalamic hamartoma. *Left* figures demonstrate the lesion and the laser probe. *Right* figure demonstrates the immediate postablation scan.

Reproduced from Youmans & Winn 8e, Fig. 98.3, p. 633 — Label when you reproduce it: MR-guided laser interstitial thermal therapy for hypothalamic hamartoma. Left panels — the lesion and the trajectory of the laser probe; right panel — the immediate post-ablation scan showing the ablation cavity. Label the third ventricle, mammillary bodies and the probe entry trajectory.

12.4 Timing

- **Operate early.** "Consequently we consider it essential to **operate on these young patients as early as possible, whatever the surgical approach being considered (resection or radiosurgery)**", because reversal of behavioural symptoms after radiosurgery "seems to begin **even before complete cessation of the seizures**" and correlates with improvement in background EEG activity YW p.621.

(c) Choroid plexus papillomas [3]

13. Definition, epidemiology and grading

- **Definition** — CPTs are "benign or malignant neoplasms that arise from the **choroid plexus**, which is a specialized tissue that develops along certain segments of the neural tube and is present within each of the four ventricles" YW p.1777.
- **De novo origin** — "Because benign CPTs **rarely convert to malignant phenotypes**, it is believed that both benign and malignant tumors **arise de novo**" YW p.1777.
- **Frequency** — CPPs and CPCs are "uncommon, accounting for **<1% of all brain tumors**", but "**approximately 14% of all brain tumors** diagnosed in utero" YW p.1777; they represent **1.8%-2.9%** of brain tumours in paediatric series, and **14% and 12.8%** of all brain tumours in the first year of life in two series YW p.1777. "**CPPs account for approximately 75% of all CPTs**"; of all choroid neoplasms **29%-39% are CPCs**, with higher incidence in children YW p.1777.
- **Age and site** — male-to-female ratio **1.2:1**, median age at diagnosis **3.5 years**; **supratentorial (lateral and third ventricle) tumours occur mostly in infants, median age 1.5 years**, whereas in adults CPTs occur almost exclusively infratentorially, with **median ages of 22.5 years (fourth ventricle) and 35.5 years (CP angle)** YW p.1777. Laurence's distribution: **50% lateral ventricle, 37% fourth ventricle, 9% third ventricle**, remainder elsewhere YW p.1777.

- **WHO grading by mitotic count** — "CPPs usually have **fewer than 2 mitotic figures per 10 high-power fields**, whereas **aCPPs have more than 2 but fewer than 5**, and **CPCs have more than 5 mitotic figures per 10 high-power fields**" YW p.1778. The **atypical CPP (aCPP), WHO grade II**, was introduced in 2007 and occupies an intermediate position for **Ki-67/MIB1, TP53 positivity and 5-year event-free survival** YW p.1778.

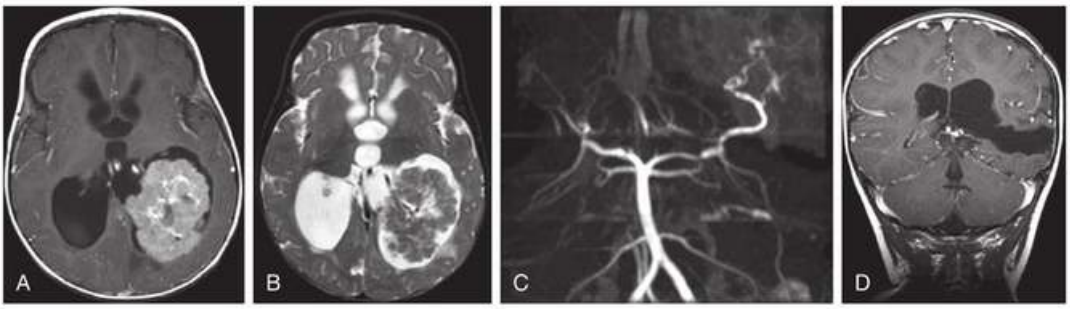


Figure 235.4. A large left ventricular choroid plexus papilloma in an 18-month-old girl. (A) T1-weighted image with gadolinium enhancement. (B) T2-weighted axial image. (C) Magnetic resonance angiogram demonstrating a choroidal artery arising from the posterior cerebral artery and leading to the tumor. (D) Postoperative coronal T1-weighted image. The surgical route was through the temporal lobe to first access the feeding artery before tumor resection. (*From Gupta N. Choroid plexus tumors in children. Neurosurg Clin N Am. 2003;14[4]:621–631.*)

*Reproduced from Youmans & Winn 8e, Fig. 235.4, p. 1781 — Label when you reproduce it: a large left ventricular choroid plexus papilloma in an 18-month-old girl. (A) T1-weighted image with gadolinium enhancement — the lobulated, intensely enhancing intraventricular mass; (B) T2-weighted axial image; (C) **magnetic resonance angiogram demonstrating a choroidal artery arising from the posterior cerebral artery and leading to the tumour** — this is the vessel to ligate first; (D) postoperative coronal T1. State in the label that **the surgical route was through the temporal lobe to first access the feeding artery before tumour resection**, which is the operative principle of the whole chapter.*

14. Pathology

- **Gross** — "the surface of the tumor is similar to the **soft fronds of the choroid plexus**, and the overall shape is approximately globular. The well-differentiated secondary structures result in a **cauliflower-like appearance**" YW p.1777. CPPs "**expand the ventricle rather than invade adjacent brain tissue**"; CPCs have an ill-formed boundary and "**brain invasion is frequently observed**" YW p.1777.
- **Microscopy** — "the prominent **papillary structure** is composed of simple **cuboidal or columnar epithelia**. The internal stroma of these fibrovascular structures consists of connective tissue and small blood vessels"; "choroid epithelial cells **do not contain cilia or blepharoplasts**, as do ependymal cells. **Mitotic figures are rare**" YW p.1778.
- **Three defining features of CPC** — "(1) the **cytologic criteria of malignancy**, such as nuclear atypia, increased nucleus-cytoplasm ratio, and prominent mitotic figures; (2) the **loss of the normal papillary architecture**; and (3) evidence of **brain invasion** with extension of the tumor through the ependymal lining of the ventricle" YW p.1778.
- **Immunohistochemistry** — CPPs "usually express **cytokeratin, vimentin, the calcium-binding protein S100, and podoplanin**" YW p.1778. **Transthyretin (prealbumin)** was believed specific, but **20% of choroid tumours do not express it**; absence of transthyretin-positive cells and **<50% of cells staining heavily for S100** both correlate with poor prognosis YW p.1778. Ki-67/MIB1 is **low in CPPs and significantly higher in CPCs** YW p.1778. **Kir7.1 and stanniocalcin-1** were confirmed as choroid-selective markers; **BAF47/INI1 (SMARCB1) is expressed in most CPCs but not in atypical teratoid/rhabdoid tumours**, which is the practical way to separate the two YW p.1778. Nearly **75% of CPPs are CK7-positive and CK20-negative** — helpful but shared with metastatic breast and lung carcinoma YW p.1778.
- **Genetics** — "Patients with **Li-Fraumeni syndrome** have germline mutations in **TP53** and have an increased likelihood of developing CPTs, particularly CPCs"; germline TP53 mutations occurred in **50% of CPCs but only 5% of CPPs**, and the **R337H** germline mutation was identified in **63% of all CPC cases** in a region of southern Brazil YW p.1779. **MDM2 amplification**, **hSNF2/SMARCB1** mutation, **TWIST1**, and **PDGF receptor β** overexpression (potentially targetable with **imatinib**) are all implicated YW p.1779. The historical **SV40 large T antigen** link is not supported by current epidemiology YW p.1779. Even benign CPPs showed chromosomal aberrations in **32 of 34 cases**; **12q loss** predicts shorter overall survival in CPC YW p.1779.

15. Clinical features

- **The dominant mechanism is raised intracranial pressure** — "related to increased intracranial pressure (ICP) secondary to **obstructive hydrocephalus, CSF overproduction, or both**" YW p.1779. "Historical reports have noted that **hydrocephalus resolves after complete tumor removal**, which suggests that **CSF hypersecretion** was responsible for ventriculomegaly" YW p.1779.
- **Symptoms in infants and young children** — "**nausea/vomiting, irritability, headache, visual difficulty, and seizure** "; the commonest signs are "**macrocephaly, papilledema, and decreased level of consciousness**" [YW pp. 1779-1780].
- **Duration and acuity** — symptoms lasted **2 months in children under 2 years** and **6 months on average in those over 2**; but "the presence of **stupor or coma as the presenting sign in 25% of pediatric patients** suggests a more acute clinical course in some cases. **Rapid decompensation can result either from massive hydrocephalus or from tumoral hemorrhage**" YW p.1780.
- **Hydrocephalus frequency** — present in **78%** of cases at the Hospital for Sick Children and **95%** at Boston Children's YW p.1780; approximately **75% of paediatric patients** present with raised ICP and **40%** with increased head circumference, whereas **68% of adults present with headache and 50% with gait ataxia** YW p.1780.
- **Lateralising signs are uncommon** and "usually related to **asymmetrical ventricular dilatation**" YW p.1780.

16. Imaging

- **Classic features** — "CPPs are **clearly located within the ventricle, are well demarcated from the brain, are lobulated, and often have punctate calcification**... These tumors **enhance homogeneously and intensely** with contrast material, which reflects an excellent blood supply. Papillomas appear **isodense in relation to brain tissue on T1-weighted images**... **T2-weighted images demonstrate intermediate to high signal intensity** with areas of heterogeneous internal signal" YW p.1780.
- **The vascular clue** — "An **enlarged choroidal artery leading into the tumor mass** can sometimes be seen in contrast-enhanced images" YW p.1780; MR spectroscopy shows "a prominent **choline peak and absence of N-acetyl aspartate**", with **myo-inositol specifically increased in CPPs** YW p.1780.
- **CPP versus CPC** — "both aCPP and CPC have been associated with **larger tumor size, greater extent of peritumoral edema, irregular morphology, and tumor necrosis**"; **tumour infiltration beyond the ventricles** suggests malignant pathology; a **lower mean ADC and larger tumour volume** correlate with grade YW p.1780.
- **Differential diagnosis on imaging** — "Cerebellar astrocytomas tend to stain **less homogeneously** and often have cystic areas. **Medulloblastomas** are characterized by a more heterogeneous appearance, although they also stain vividly... and may be confused with fourth ventricular CPPs. **Ependymomas** arise physically in similar locations but tend to **enhance inhomogeneously**. Finally, **meningiomas** can occur in an intraventricular location but are **rare in children**" YW p.1780.

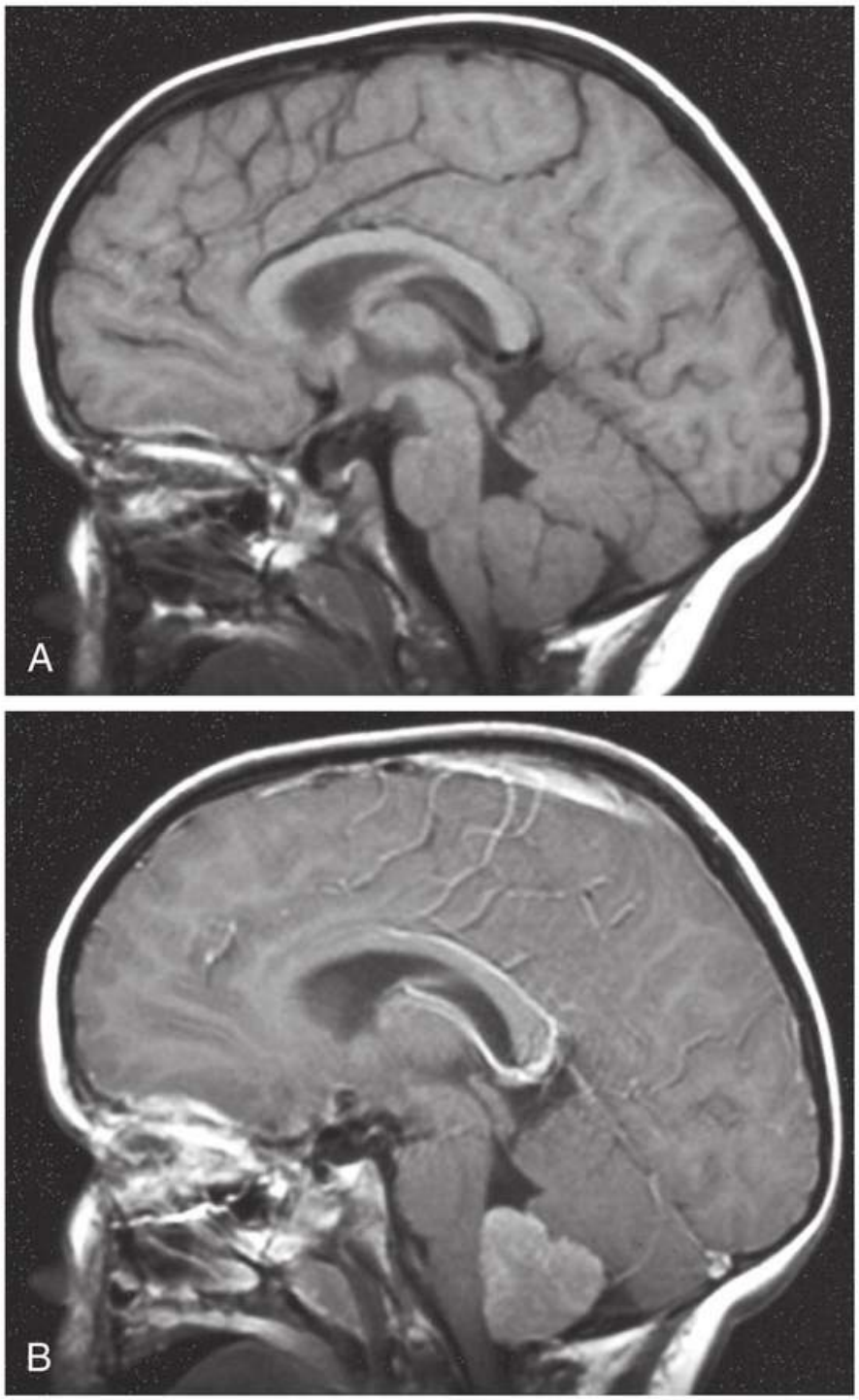


Figure 235.3. A typical choroid plexus papilloma arising in the fourth ventricle. T1-weighted images before (A) and after (B) gadolinium enhancement.

Reproduced from Youmans & Winn 8e, Fig. 235.3, p. 1780 — Label when you reproduce it: a typical choroid plexus papilloma arising in the fourth ventricle — T1-weighted images before (A) and after (B) gadolinium enhancement. Describe: intraventricular location, sharp demarcation from brain, lobulated cauliflower surface, intense homogeneous enhancement, obstructive hydrocephalus.

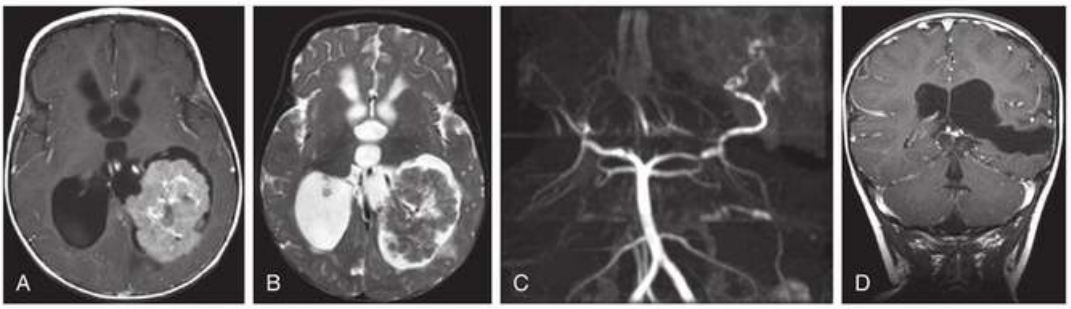


Figure 235.4. A large left ventricular choroid plexus papilloma in an 18-month-old girl. (A) T1-weighted image with gadolinium enhancement. (B) T2-weighted axial image. (C) Magnetic resonance angiogram demonstrating a choroidal artery arising from the posterior cerebral artery and leading to the tumor. (D) Postoperative coronal T1-weighted image. The surgical route was through the temporal lobe to first access the feeding artery before tumor resection. (*From Gupta N. Choroid plexus tumors in children. Neurosurg Clin N Am. 2003;14[4]:621–631.*)

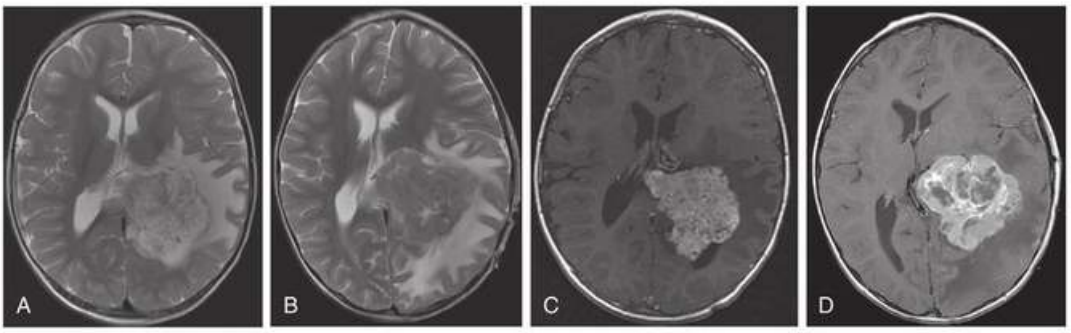


Figure 235.5. Magnetic resonance imaging comparisons of choroid plexus papilloma (CPP) and choroid plexus carcinoma (CPC). (A) T2-weighted axial section. A CPP is accompanied by significant adjacent cerebral edema. Some consistent fine structure is visible inside the tumor. There may be some brain invasion at the lateral edge of the tumor. (B) T2-weighted axial section. This CPC is also accompanied by significant adjacent brain edema. The structure within the tumor is much less defined. There may be brain invasion laterally, but the tumor appears generally distinct from the brain. (C) T1-weighted, gadolinium-enhanced axial section. The CPP enhances nearly uniformly and demonstrates a small lobular structure. The edges are distinct from the surrounding brain. (D) T1-weighted, gadolinium-enhanced axial section. The CPC also enhances brightly but with much less regularity within the tumor. The fine lobules are not visible in the papilloma. There is no clear site of brain invasion.

Reproduced from Youmans & Winn 8e, Fig. 235.5, p. 1781 — Label when you reproduce it: MRI comparison of CPP and CPC. (A and C) CPP — T2 with adjacent cerebral oedema, consistent fine internal structure; T1+Gd enhancing nearly uniformly with a small lobular structure and edges distinct from brain. (B and D) CPC — T2 with much less defined internal structure; T1+Gd enhancing brightly but with much less regularity and no visible fine lobules. This is the figure to use when asked how to tell papilloma from carcinoma.

17. Management

17.1 Hydrocephalus first

- "Because **up to 90% of patients present with symptoms of increased ICP secondary to hydrocephalus**, the initial step is to decide whether **CSF drainage** is required" YW p.1780.
- "In infants **younger than 8 to 10 months** of age, the presence of **open sutures** allows compensation by slow enlargement of the head, and treatment of hydrocephalus can often **wait until the planned surgical date**" YW p.1780.
- "In the presence of a **decline in neurologic function**, an **external ventricular drain should be inserted immediately**, before definitive tumor management. Placement of a ventriculoperitoneal shunt, although an acceptable alternative, **does not allow external CSF drainage and ICP monitoring** in the intraoperative and postoperative setting. Furthermore, the presence of **intraventricular blood and debris after tumor resection may lead to blockage of the shunt**" YW p.1780.
- **Shunt dependency** — "**37% of surviving patients required a CSF shunt**" in the Ellenbogen series; hydrocephalus resolves after resection in a substantial number, but intraventricular haemorrhage, postoperative changes or meningitis increase the chance a shunt is still needed YW p.1780.

17.2 Surgical principles

- **Three steps in every plan** — "(1) **temporary or permanent resolution of hydrocephalus**, (2) **identification of the arterial supply**, and (3) **planning the surgical approach to allow access to the vascular supply and maximal exposure of the tumor**" YW p.1782.
- **The two problems are vascularity and size** — "Piecemeal resection is usually associated with **increased blood loss**. The **most effective strategy is early identification and ligation of the feeding artery**"; where the resection-friendly angle does not expose the feeder, "the surgeon should consider using a **separate approach to coagulate the feeding artery before tumor resection**" YW p.1782.
- **En bloc where possible** — "In general, **en bloc excision is recommended**, although this may not be feasible with very large tumors. If the tumor must be removed in part, then **gradual and gentle coagulation of the fronds** of the tumor allows its manipulation without excessive bleeding and enables **shrinkage of the tumor**" YW p.1782.

Table 3 · Surgical approaches for intraventricular choroid plexus tumours — reproduced in full from Youmans & Winn 8e, Table 235.1, p. 1782.

Tumour location	Surgical approach	Technical considerations
Lateral ventricle	**Transcortical**	For tumours in the **posterior half**, cortical entry **posterior to the angular gyrus and central sulcus** — more challenging in the dominant hemisphere, where language pathways must be avoided. Other options: **superior or middle temporal gyri** for tumours mostly within the temporal horn. For tumours in the **anterior half**, cortical entry through the **frontal lobe**, favouring an **anterolateral** approach. In general, transcortical approaches risk a **ventriculosubdural fistula** — **pial sutures and sealants** may reduce this.
Third ventricle	**Transcallosal**	Exposure is limited, so **early control of the vascular supply is critical**. If supply arises from the anterior choroid plexus, **callosotomy** facilitates identification and division of arteries parallel to the **choroidal fissure**. For tumours **eccentric** within the third ventricle, enter through the **ipsilateral lateral ventricle** and follow the **choroidal fissure** as a corridor.
Fourth ventricle	(a) **Midline posterior fossa craniotomy**; (b) **retrosigmoid craniotomy**	A midline posterior approach **facilitates CSF diversion**. **PICA branches to the brainstem must be identified** to avoid neurovascular injury. The **tonsil can be reflected laterally or upward** for tumours extending through the **foramina of Luschka**. Retrosigmoid may be required if the tumour extends into the **cerebellopontine angle**.

17.3 Paediatric anaesthetic and haematological considerations

- "The primary operative concerns in small children are related to **blood loss, resuscitation, and anesthesia**. The surgical team must be completely familiar with managing fluid replacement and **blood loss that can exceed one or two blood volumes**" YW p.1782.
- "**Tumor vascularity, and not size**, has shown to correlate greatest with the need for intraoperative transfusion"; **age under 4 years** and suspected **malignant pathology** are associated with higher mean blood loss YW p.1782.
- "Several units of blood and blood products should be available **before the procedure starts**. **Adequate intravascular access is crucial**, and a **central catheter** should be considered if peripheral access is limited"; transfusion should begin "**before the development of adverse events such as hypotension and hypoxia**". Note the **physiologic haemoglobin/haematocrit nadir in infants 2 to 6 months of age** YW p.1782.

17.4 Outcome and adjuvant therapy

- **Key concepts, verbatim** — "**Overall and progression-free survival are best with choroid plexus papilloma and**

poorest with choroid plexus carcinoma"; "**Gross total resection significantly affects survival**, and **the role of adjuvant therapy remains unclear**, although **neoadjuvant chemotherapy may facilitate future resections**"; "In children, specific emphasis should be placed on **limiting blood loss and/or having adequate transfusion protocols** given the **hypervascularity** of these tumours" YW p.1777.

- **CPP is curable by surgery alone** — "**The benign tumors can be cured with surgical resection alone**, but the treatment can be associated with increased morbidity related to the **intraventricular location** and their predominance in **very young children**" YW p.1777.
- **Dissemination** — "Although CPCs rarely metastasize from the intracranial or intraspinal compartment, they **can disseminate throughout the CSF pathways**" YW p.1778 — hence craniospinal imaging and CSF cytology in high-grade disease.
- **The value of stromal invasion in a CPP is questionable** — "three of four patients with **CPP and invasion** who underwent **gross total resection were cured without the need for adjunctive therapy**" YW p.1778.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **A dumb-bell tumour's origin is always intradural** — the intradural segment of a dorsal or ventral root; the "waist" is the dural root sleeve at the foramen.
- **Axons inside the tumour = neurofibroma; no axons and a clean capsule around a single fascicle = schwannoma.**
- **Neurofibroma → NF1 (chr 17, neurofibromin); schwannoma → NF2 (chr 22, merlin).** NF1 is 1 in 2500-3000; NF2 is 1 in 50,000.
- **Operate intradural first**, transect at the distal dural root sleeve, reflect the dural edge medially, then take the extradural component — this avoids traction injury to the cord.
- **Unilateral complete facetectomy destabilises; bilateral medial facetectomy does not** — plan the fusion in the same sitting.
- **Bowel and bladder are preserved if S2-S4 are intact on at least one side.**
- **Cervical dumb-bell = get vascular imaging**; the vertebral artery is displaced by tumour, not engulfed. Thoracic dumb-bell = beware the pleura and a CSF-pleural fistula.
- **Recurrence 39% in neurofibromatosis versus 11% sporadic**; NF1 patients carry a 3-5% lifetime risk of MPNST, almost always from a plexiform neurofibroma.
- **Hypothalamic hamartomas are not neoplasms** — disconnection, not excision, is sufficient; gelastic seizures from the first years of life plus precocious puberty is the syndrome.
- **Only medium-to-large sessile HHs broadly attached to the tuber cinereum or mammillary body cause epilepsy.**
- **Régis types I-III are first-line Gamma Knife** (median 17 Gy); type VI (giant) always needs multimodality treatment; MRgLITT complication rate 2-5% versus up to 15% for open resection.
- **Choroid plexus papilloma: <2 mitoses/10 HPF (WHO I); atypical CPP 2-5 (WHO II); carcinoma >5 (WHO III).** CPPs are 75% of all CPTs.
- **The intraventricular, cauliflower-like, intensely and homogeneously enhancing mass in an infant with macrocephaly is a CPP until proved otherwise** — look for the enlarged choroidal artery.
- **Ligate the feeder before you debulk** — vascularity, not size, predicts transfusion; have blood in the room before the incision.
- **Li-Fraumeni/TP53 germline mutation is present in 50% of CPCs but only 5% of CPPs.**

Pages read for this answer — Youmans & Winn 8e: 494, 621, 622, 623, 633, 1777, 1778, 1779, 1780, 1782, 1995, 1997, 1999, 2001, 2006, 2214, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2573, 2574

Dorsal spinal ependymoma:

a) Clinical features. [3]

b) Radiological features. [3]

c) Management. [4]

LONG | DEC 2021 · Paper II · Q10 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 329 *Evaluation and Treatment of Malignant Primary Spinal Tumors*, §Introduction, §Anaplastic Ependymomas and §Malignant Astrocytomas, pp. 2570-2573 (Fig. 329.2, p. 2573; **Table 329.1 — Diagnostic and Therapeutic Considerations in Intramedullary Spinal Cord Tumors**, p. 2571). Supplementary: Ch. 263 *Tumors of the Spine, Spinal Canal, and Spinal Cord in Children*, §Pathology, §Presentation, §Diagnostic Evaluation and §Treatment: Surgery, pp. 1995-2007 (Figs. 263.3 and 263.4, p. 2001); Ch. 327 *Evaluation and Treatment of Benign Intradural Extramedullary Tumors*, §Surgery for Tumors of the Filum Terminale and §Adjuvant Therapy, pp. 2547-2553 (Fig. 327.3, p. 2553); Ch. 167 *Hemangioblastomas*, §Spinal Cord Hemangioblastomas, pp. 1177-1179 (Fig. 167.5, p. 1178); Ch. 208 *Dorsal Root Entry Zone Lesions for Pain*, §Anatomy, p. 1572 (Fig. 208.1, p. 1572); Ch. 297 *Fractionated Radiotherapy for Spine Tumors*, pp. 2317-2319 (Fig. 297.1, p. 2319); Ch. 309 *Electrophysiologic Studies and Monitoring*, pp. 2429-2430; Ch. 316 *Evaluation and Treatment of OPLL*, §Pathologic Features, p. 2478 (Fig. 316.1, p. 2478).

1. Definitions and terminology — fix these first

- **"Dorsal spinal ependymoma" in an exam stem means an intramedullary ependymoma of the thoracic (dorsal) cord** — a glial tumour arising from the ependymal lining of the central canal, sitting **centrally** within the cord. Youmans classifies spinal tumours as **extradural or intradural**, and intradural tumours as **intramedullary or extramedullary** YW p.2570.
- **Ependymoma is the commonest intramedullary tumour of the adult spinal cord.** "In adults, **ependymomas are the most common intramedullary tumor, accounting for 50%-70% of lesions**, with the remaining portion primarily consisting of astrocytomas. **This trend is reversed in younger children, with astrocytomas predominating in those under the age of 10**" YW p.2570.
- **Epidemiology** — primary intradural intramedullary tumours make up **5%-10% of spinal column tumours in adults and about 35% in children**; **primary glial tumours make up more than 80%** of intramedullary tumours YW p.2570. "For intramedullary tumors overall, the average age at presentation has been estimated to be approximately **35-39 years**, with a **slightly higher incidence in males**" YW p.2570. In children, ependymomas "are the minority... comprising only **10% to 15%**" YW p.1996.
- **Grading** — "these lesions are typically of **low-grade histology (WHO grade I or II)**, and are most commonly found as either a **well-circumscribed intramedullary lesion** or, in its **myxopapillary** variety, as a distinct enhancing mass associated with the **filum terminale**" YW p.2572. "**Anaplastic ependymomas (WHO grade III) are rare, accounting for less than 2% of patients with intraspinal ependymomas**" YW p.2572. Grades I (myxopapillary) and II (cellular, clear cell, tanycytic, papillary) are histologically benign; **grade III (anaplastic) is not** YW p.1996.
- **Genetics** — "Though most cases are sporadic, patients with **neurofibromatosis 2** are predisposed to develop ependymomas, and spinal ependymomas in particular are prone to contain **NF2 gene deletions**" YW p.2572. The **NF2 suppressor gene on 22q12.2**, which encodes **merlin**, "has been demonstrated to be **the only tumor driver of spinal ependymomas**, [and] is found in approximately **50% of lesions**" YW p.1996. In vitro modelling shows **erbB-2-dependent pathways** activating downstream tyrosine kinases — a possible future adjuvant target YW p.1996.
- **Filum/myxopapillary variant** — "Forty percent of spinal ependymomas occur in the **filum terminale**. The majority of these are **myxopapillary**, occurring with a slight **male predilection (1.7:1)** with a **mean age at diagnosis of 36.4 years** " YW p.2548. Myxopapillary ependymomas "represent only **13% of all spinal ependymal tumors**" YW p.1996.

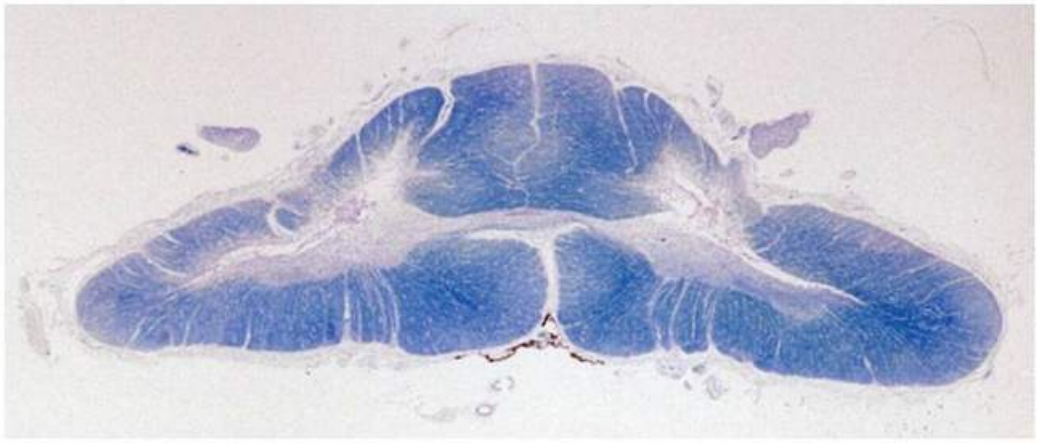


Figure 316.1. Transverse section of the cervical spinal cord. Triangular shape of the spinal cord with severe intrinsic changes, including loss of neurons and cavity formation.

Reproduced from Youmans & Winn 8e, Fig. 316.1, p. 2478 — Label when you reproduce it: transverse section of the cervical spinal cord. Use it to orient the answer — mark the anterior median fissure, the dorsal (posterior) median sulcus, the dorsolateral sulcus, the anterior and posterior horns of grey matter, the dorsal columns, the lateral corticospinal tract and the central canal. The ependymoma arises from the ependyma of the central canal and therefore expands the cord symmetrically from the centre.

(a) Clinical features [3]

2. The symptom sequence

- **Pain is the first and commonest symptom, and it is worse at night.** "As with most other spinal tumors... the most common presentation is **focal back pain, typically localized to the segments directly over the tumor**. Classically, this pain is differentiated from more common forms of back pain in that it will **worsen at night when the patient is lying down due to increased venous engorgement and increased local mass effect of the tumor**" YW p.2570. "Similar to those with spinal astrocytomas, many patients with intramedullary ependymomas present with **back pain that can worsen at night in the recumbent position**" YW p.2572.
- **Dysaesthesia without sensory loss is the ependymoma-specific sign.** "Particular to ependymomas, though, is a **predilection to present with dysesthesias but not sensory loss**. This is thought to stem from the **central location of these tumors, resulting in preferential disruption of crossing spinothalamic fibers**" YW p.2572. This is the sentence that earns the mark.
- **Symmetrical sensory findings point to ependymoma.** In children, "sensory abnormalities trail the motor deficits and are more limited, typically being unilateral. **When the sensory abnormalities are symmetrical, the diagnosis of ependymoma should be suspected**" YW p.1998.
- **Long-tract and segmental deficits** — "deficits of either the sensory or motor tracts are common and occur in **approximately half of patients**. These include signs of **myelopathy and upper motor neuron disease, such as spasticity, hyperreflexia, and extensor plantar signs** on examination" YW p.2570.
- **Sphincter disturbance is late** — "**Bowel and bladder dysfunction are less common, and are typically indicative of more advanced disease**, but can be seen earlier on in lesions located in the conus medullaris" YW p.2570.
- **Tempo** — "Symptoms from intramedullary spinal cord tumors are often **nonspecific and can arise over the course of several years**. Malignant lesions, however, often have a **more rapid progression of symptoms**"; "**anaplastic ependymomas may give rise to symptoms more quickly**" [YW pp. 2570, 2572].

3. Level-specific features for a dorsal (thoracic) lesion

- **The thoracic cord presents insidiously.** "IMSCTs of the thoracic spine have a **more insidious onset**. The first manifestations are usually **pain and progressive scoliosis**. Not uncommonly these children are simply **followed for idiopathic scoliosis** until such time as the degree of scoliosis or the evolution of complaints mandates imaging" [YW pp. 1998-1999].
- **Abdominal pain as a false localiser** — "Younger patients will commonly complain of **abdominal pain**, and this leads to a **gastroenterology referral** prior to their coming to the attention of a pediatric neurosurgeon" YW p.1999.
- **Examination** — "**paraspinal spasm and evidence of myelopathy**. **Sensory findings occur late**, as do **bowel and bladder dysfunction** as the tumor or its cyst extends into the conus" YW p.1999.
- **Conus lesions reverse the sequence** — "When the epicenter of the tumor is in the conus, then the **early manifestations may involve bowel and bladder function**, resulting in a history of **frequent urinary tract infections** and complaints of irregular, problematic bowel habits" YW p.1999.
- **Paediatric presenting complaints, in rank order** (Constantini/Epstein series of 164 children): "**motor regression, which occurred 65% of the time**... followed by **pain (48%), gait abnormality (37%), dysesthesia (32%), and progressive kyphoscoliosis (32%)**. On examination one can expect to find **signs of myelopathy in most patients**" YW p.1998.
- **Hydrocephalus and dissemination** — uncommon with low-grade tumours; "there is a significantly higher incidence in those with high-grade lesions", and malignant lesions "are more likely to develop **disseminated disease by spreading in the subarachnoid space to involve the leptomeninges**" YW p.2570.
- **Grade the deficit formally.** Table 329.1 requires the history to record "**Nature, length, and severity of symptoms; existing neurological deficits and timing of decline; presence of pain, particularly nocturnal back pain; history of any systemic or CNS malignancy; history of any previous craniospinal radiation; family history of CNS tumors or tumor syndromes; history and risk factors for autoimmunity and/or demyelinating disease**" YW p.2571.

Table 1 · Diagnostic and therapeutic considerations in intramedullary spinal cord tumours — reproduced in full from Youmans & Winn 8e, Table 329.1, p. 2571.

Domain	What Youmans says to do
History	Nature, length and severity of symptoms · Existing neurological deficits and timing of decline · Presence of pain, **particularly nocturnal back pain** · History of any systemic or CNS malignancy · History of any previous craniospinal radiation · Family history of CNS tumours or tumour syndromes · History and risk factors for autoimmunity and/or demyelinating disease
Imaging work-up	**Spinal MRI** for primary lesion evaluation · Special consideration to any **asymmetry of spinal cord dilation and infiltrative borders** of the lesion · **Craniospinal imaging** if suspicion for leptomeningeal spread · **CT** for nearby bony anatomy and instrumentation planning · **Systemic cancer screening** (CT chest/abdomen/pelvis and/or PET-CT) · **Vascular imaging in cases of diffuse cord oedema** to rule out dural arteriovenous fistula (Foix-Alajouanine syndrome)
Surgical planning	Plan must take account of patient symptoms, goals of care and health status · **Observation with serial imaging may be appropriate** in some asymptomatic individuals with infiltrative-appearing low-grade lesions · Benefit of aggressive resection is controversial; **consider biopsy and expansile duraplasty** in suspected high-grade lesions · **Attempted gross total resection should be limited to cases in which good planes of dissection are present**
Postsurgical management	Pathological results dictate **multimodal therapy** coordinated with an experienced oncologist and radiation oncologist · **Serial imaging** to monitor for local recurrence

(b) Radiological features [3]

4. MRI — the study of record

- **Sequence protocol** — "At minimum, MRI to investigate a possible spine tumor should include a **T1-weighted sequence, with and without gadolinium enhancement, and a T2-weighted sequence in axial and sagittal planes**. **Anything less will compromise one's interpretation of the imaging.** A **gradient echo** sequence and a **FLAIR**

sequence can add additional information about **hemosiderin deposits** (gradient echo) or **subtle intramedullary lesions** (FLAIR)" YW p.1999.

- **The signature signs of a spinal ependymoma:**
  - **Central location and symmetrical cord expansion.** "**Unlike astrocytomas and gangliogliomas, ependymomas arise centrally and expand the cord symmetrically**" YW p.1999. Youmans states it as a key concept: "**Glial and glial-neuronal IMSCTs are eccentric, whereas ependymomas are centered on axial MRI**" YW p.1995.
  - **A sharp plane with the cord.** "The hallmarks of intramedullary ependymomas are their **central location in the cord and their sharp demarcation from the surrounding parenchyma**, tending to **establish a plane between themselves and the surrounding spinal cord**" YW p.1996.
  - **Signal** — "generally **hypointense on T1-weighted images and hyperintense on T2-weighted and FLAIR images** , and **homogeneously enhance with gadolinium contrast**" YW p.2572. "The majority of **nonmyxopapillary ependymomas are isointense or hypointense on T1**, as opposed to **myxopapillary ependymomas, which are either isointense or hyperintense**" YW p.1999.
  - **Length** — "The size of ependymomas at presentation appears to be the **same as that encountered with intramedullary astrocytomas (four vertebral levels)**" YW p.1999. Compare gangliogliomas, which average **eight** segments YW p.1995.
  - **Enhancement pattern** — of 16 tumours in Kahan's series, **14 enhanced**: "five showed a **heterogeneous** pattern, six showed a **homogeneous** pattern, and three showed only **rim** enhancement", with one minimal and one non-enhancing YW p.1999.
  - **Cysts** — "Almost **two-thirds of these patients had cysts**; eight were **intratumoral**, six were **rostral or caudal to the tumor**, and nine were a **reactive dilation of the central canal**" YW p.1999.
  - **Haemorrhage — the "cap sign".** "**Twenty percent showed evidence of chronic hemorrhage.** Choi et al. found that nearly 20% of their patients had some evidence of hemorrhage, with the majority showing **hemosiderin susceptibility signals capping either the rostral or caudal pole**"; Nemoto found it in **60%** of patients when the phenomenon was first reported YW p.1999.
- **Myxopapillary variant** — "isointense to hyperintense on T1-weighted images and hyperintense on T2"; they "**enhance vividly** with contrast media and commonly have **intratumoral hemorrhage owing to their high vascularity**", producing heterogeneity; "**Hypodense areas on T2-weighted images suggest remote hemorrhage and are highly suggestive of a myxopapillary ependymoma**" YW p.2001. The "classic evolution... is characterized by **chronic remodeling of local bony structures** — expansion of the spinal canal as well as the classically appearing **'scalloped' posterior surfaces of vertebral bodies**" YW p.2001.

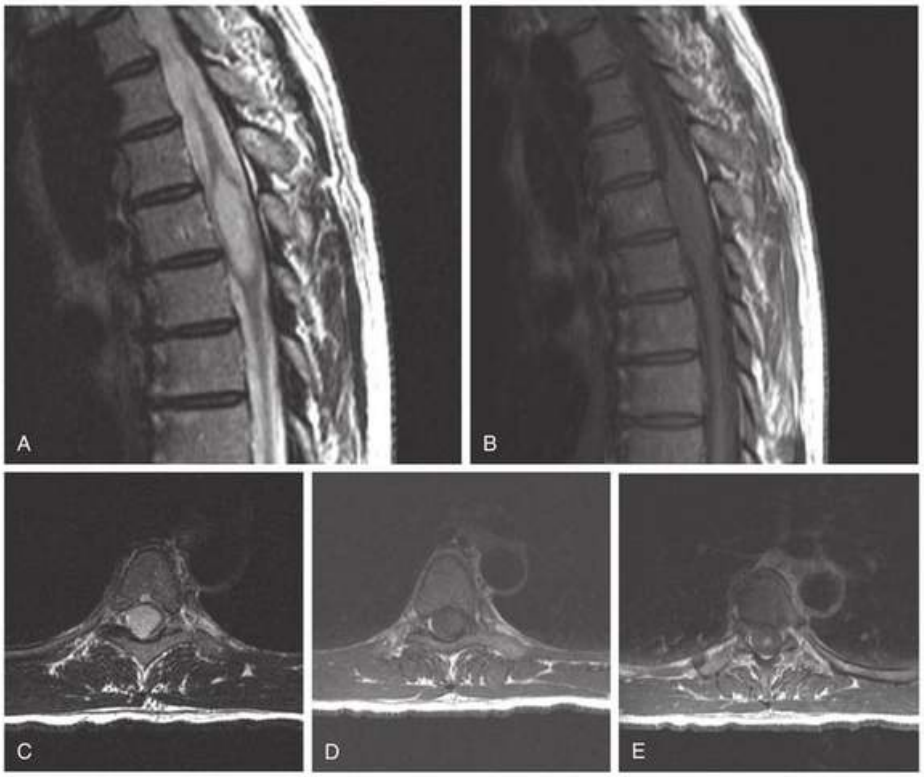


Figure 329.2. Low-grade ependymoma. A 56-year-old woman presented with a 4-year history of occasional right foot paresthesia, worsening balance with increased falls, and chronic constipation and abdominal pain. (A and B) Spinal magnetic resonance imaging revealed the presence of (A) a T2-hyperintense lesion with focal cord expansion centered about the T4–T6 level, which was (B) isointense to cord parenchyma on T1-weighted imaging. (C) Axial T2-weighted sections revealed expansion of the cord and displacement of more normal parenchyma laterally. (D and E) Axial T1-weighted sections with (D) and without (E) contrast demonstrated punctate enhancement in the center of the lesion. Subsequent thoracic laminectomy and biopsy demonstrated the presence of a low-grade ependymoma (World Health Organization grade II).

Reproduced from Youmans & Winn 8e, Fig. 329.2, p. 2573 — Label when you reproduce it: low-grade ependymoma in a 56-year-old woman with 4 years of right foot paraesthesia, worsening balance, falls, chronic constipation and abdominal pain. (A) sagittal T2 — hyperintense lesion with focal cord expansion centred at T4-T6; (B) sagittal T1 — isointense to cord parenchyma; (C) axial T2 — cord expansion with more normal parenchyma displaced laterally; (D and E) axial T1 with and without contrast — punctate central enhancement. Emphasise the CENTRAL epicentre and the symmetrical expansion.

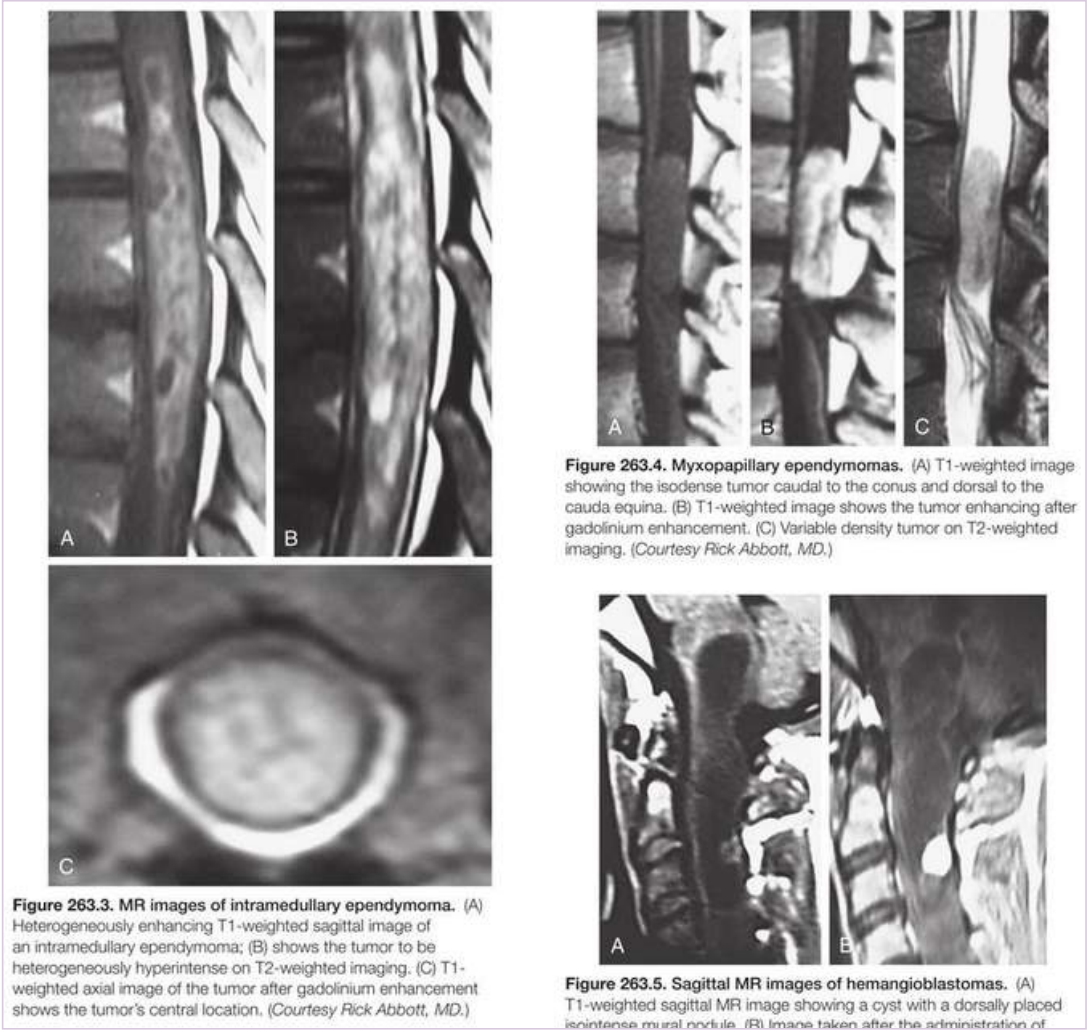


Figure 263.3. MR images of intramedullary ependymoma. (A) Heterogeneously enhancing T1-weighted sagittal image of an intramedullary ependymoma; (B) shows the tumor to be heterogeneously hyperintense on T2-weighted imaging. (C) T1-weighted axial image of the tumor after gadolinium enhancement shows the tumor's central location. (*Courtesy Rick Abbott, MD.*)

Figure 263.4. Myxopapillary ependymomas. (A) T1-weighted image showing the isodense tumor caudal to the conus and dorsal to the cauda equina. (B) T1-weighted image shows the tumor enhancing after gadolinium enhancement. (C) Variable density tumor on T2-weighted imaging. (*Courtesy Rick Abbott, MD.*)

Figure 263.5. Sagittal MR images of hemangioblastomas. (A) T1-weighted sagittal MR image showing a cyst with a dorsally placed isointense mural nodule. (B) Image taken after the administration of

Reproduced from Youmans & Winn 8e, Fig. 263.3, p. 2001 — Label when you reproduce it: MR images of an intramedullary ependymoma. (A) heterogeneously enhancing T1 sagittal; (B) heterogeneously hyperintense on T2; (C) axial T1 after gadolinium showing the tumour's CENTRAL location. This is the axial image that separates ependymoma from astrocytoma.

5. Differential diagnosis on imaging

- **The list is short.** "The interpretation of an MRI series is simplified by the fact that there are only a **limited number of pathologies** that will account for an intramedullary mass lesion within the spinal cord. In children a mass lesion within the spinal cord is probably (**>90%**) an **astrocytoma, ganglioglioma/glial neuronal tumor, or ependymoma. Hemangioblastoma and PNET are remote possibilities**" YW p.1999.
- **When the mass does not match the oedema, think inflammation.** "When the size is subtle or not consistent with the degree of T2 signal hyperintensity (i.e., edema), then one should consider an **inflammatory process such as multiple sclerosis or transverse myelitis**. **Scanning of the brain and a delayed, repeat imaging examination 3 to 6 months later will clarify the situation**" YW p.1999.
- **In adults, Youmans lists the mimics explicitly** — "it is important to rule out the possibility of other lesions that can appear similar to intramedullary spinal tumors on MRI, such as **multiple sclerosis, transverse myelitis, cord infarction, or a dural arteriovenous fistula**" YW p.2571. Table 329.1 mandates **vascular imaging in cases of diffuse cord oedema to exclude a dural AVF (Foix-Alajouanine syndrome)** YW p.2571.
- **Separating ependymoma from astrocytoma preoperatively can be impossible** — "in many instances, it may be **very difficult to distinguish malignant astrocytomas from lower grade astrocytomas or ependymomas based on routine MRI alone**" YW p.2571. The astrocytoma pattern for contrast is "**asymmetrical, focal, fusiform expansion of the cord that typically spans fewer than four vertebral segments**", with **infiltrative margins** in higher grades,

patchy enhancement, haemorrhage and necrosis YW p.2571.

- **Adjunct sequences — DWI** for suspected ischaemic infarct and for intramedullary/extramedullary inclusion cysts; **diffusion tensor tractography** "can demonstrate the **displacement pattern of spinal tracts around a growing tumor**, yet its role in differentiating different tumors from one another and in assisting with presurgical planning is **still being defined**" YW p.1999.
- **CT, plain films and myelography** — "CT scans and plain radiographs are reserved for the evaluation of **associated spinal deformities and instabilities**, and a **myelogram is generally reserved for those situations in which MRI cannot be performed**" YW p.1999.

Table 2 · MRI differentiation of the three intramedullary glial tumours — from Youmans & Winn 8e, Ch. 263 §Diagnostic Evaluation, pp. 1999-2001 and §Key Concepts, p. 1995; Ch. 329 §Malignant Astrocytomas and §Anaplastic Ependymomas, pp. 2571-2572.

Feature	Ependymoma	Astrocytoma	Ganglioglioma
Epicentre on axial MRI	**Central; symmetrical cord expansion**	**Eccentric**	**Eccentric**
Plane with cord	**Sharp demarcation; a plane can be developed** (interface only several cells thick)	**Margins blur into cord parenchyma**; infiltrative	**Infiltrative; no plane**
Mean craniocaudal extent	**4 vertebral segments**	4 segments	**8 segments** (all holocord tumours were gangliogliomas)
T1	Iso- or hypointense (myxopapillary: iso- or **hyper**intense)	>80% hypointense, ~20% isointense	**Mixed intensity** in the majority
T2	Hyperintense	Hyperintense but **inhomogeneous**, unlike oedema	60% homogeneously hyperintense; 40% heterogeneous
Enhancement	**Homogeneous** (14/16 enhance; 5 heterogeneous, 6 homogeneous, 3 rim)	Enhances, and the walls of tumoral cysts enhance too	**Patchy 65%, focal 19%, none 15%**
Cysts	**~2/3** (intratumoral, polar, or reactive central-canal dilatation)	Tumoral and reactive cysts	**46% — commonest of the three**
Haemorrhage	**20%-60%; hemosiderin "cap" at rostral or caudal pole**	Uncommon	Uncommon
Age/frequency	Commonest IMSCT in **adults (50%-70%)**; only 10%-15% in children	Commonest in **children <10 years**; 46% of paediatric series	**Second commonest intraparenchymal tumour in children/young adults**
Syndrome	**NF2 / 22q12.2 merlin deletion in ~50%**	BRAF mutations in grade I-II; **H3F3A K27M** in grade III-IV	—

(c) Management [4]

6. Decision framework

- **The initial management of an IMSCT is almost always surgical** — "because of the obvious desire to **confirm the radiologic impression by histologic assessment of tissue obtained at operation**" YW p.2005.
- **The key difference from astrocytoma**, stated verbatim: "**A key difference for ependymomas, however, is that lower grade lesions can be curable with a gross total resection. More aggressive resection is commonly facilitated by the relatively well-defined dissection planes found around these lesions**" YW p.2572.
- **For high-grade lesions the strategy changes** — "Higher grade lesions are treated similarly to high-grade astrocytomas, with **attempts at the maximal safe resection that the available plane of dissection will allow**. Small case series for anaplastic ependymomas have suggested that **gross total resection is possible in the majority of these**

lesions" YW p.2572.

- **Observation is legitimate in selected cases** — "**Observation with serial imaging may be appropriate in some asymptomatic individuals with infiltrative-appearing, low-grade lesions**" YW p.2571.
- **Preoperative steroids** — "the use of **steroids (e.g., 0.25 mg/kg/day for 3 days) preoperatively to potentially reverse presenting symptoms and increase the tolerance of the spinal cord to surgery. This is presumably due to decrease in vasogenic edema with improved perfusion of the cord surrounding the tumor**" YW p.2005. **Tranexamic acid** is not routine but "may be considered for tumor expected to be especially bloody" YW p.2005.

7. Intraoperative neurophysiology — the single biggest advance

- "The decrease in morbidity of surgery on tumors of the spine and spinal cord seen over the past several decades is **largely the story of the coming of age of intraoperative physiologic monitoring**" YW p.2005. Youmans lists it as a key concept: "**The use of intraoperative physiologic monitoring for resecting IMSCTs results in better outcome**" YW p.1995.
- **D waves are the prognostic parameter.** "In 1998 criteria were reported that could be used to reliably predict permanent postoperative motor deficits. **Changes in D waves were found to be 100% predictive of permanent postoperative loss of motor function**" YW p.2005.
- **The historical comparison** — when a senior surgeon's IMSCT results before and after introducing IOM were matched for preoperative function, histology, tumour location and extent of resection, "there was a **significantly better outcome (P < .0016)** at follow-up in those whose surgery included IOM" YW p.2005.
- **MEPs are considered the gold standard for this operation.** Intraoperative monitoring is "considered the 'gold standard'" for **intramedullary spinal cord tumour resection** YW p.2429, and in high-risk procedures such as **complex deformity correction or intramedullary tumor resection, IONM may prevent devastating neurologic injury** YW p.2455.
- **Surgeons can compare preoperative EMG recordings with patients who lost CMAPs** during IMSCT resection YW p.2430.
- **5-ALA** — "the use of **5-aminolevulinic acid (5-ALA)** for the identification of the tumor margins intraoperatively... provides a clearer distinction between normal and lesional tissue and **may improve the safety of more complete resections**" YW p.2005.

8. Operative steps in order — dorsal midline approach to a thoracic ependymoma

1. **Positioning and localisation.** Prone; "with regard to planning the skin incision, **palpable landmarks of the spine are used; however, when in doubt, lateral radiographs to confirm localization prior to skin incision are used**" YW p.2005.
2. **Midline incision over the spine; remove the lamina and spinous processes dorsal to the tumour.** "When the lamina is intact, a **laminotomy can be considered**" YW p.2005 — this is the osteoplastic option that reduces postlaminectomy kyphosis in children. In adults the standard is "a **multilevel laminectomy over the site of the tumor, and midline durotomy** to expose the posterior aspect of the cord" YW p.2571.
3. **Confirm the exposure with ultrasound before opening the dura.** "The adequacy of the exposure can be confirmed with **ultrasonography before the dura is opened**" YW p.2005; "**Intraoperative ultrasonography can be useful in guiding the amount of necessary exposure and in localizing the tumor**" YW p.2571.
4. **Limit the exposure to the solid tumour.** "In general, **only the solid portion of an intramedullary tumor needs to be removed**, so exposure is initially limited to reflect this unless tumor nodules are suspected within cysts capping the main tumor" YW p.2005.
5. **Open the dura after placing epidural electrodes for monitoring** YW p.2005.
6. **Myelotomy.** "A **myelotomy is performed over the entire length of solid tumor. This relieves the intramedullary pressure that is present and allows for a symmetrical, simultaneous decompression**" YW p.2005. For

ependymoma specifically: "**The approach is almost always midline because this tumor's epicenter is midline. Only in cases in which the tumor has erupted through the pia can a myelotomy be avoided**" YW p.2005. For deep lesions generally, "deeper lesions may require **careful planning of a myelotomy site to minimize the chance of neurological deficit**" YW p.2571.

7. **Biopsy and frozen section.** "On initial exposure, **biopsy specimens of the tumor are taken, and ideally a frozen section** or other microscopic tissue examination is performed to **determine whether or not the tumor is malignant**" YW p.2005.
8. **Develop the plane.** "After exposure the dorsal surface of the tumor is studied to see if a **plane can be developed** between the tumor and the surrounding parenchyma. **The histologic interface between the tumor and normal spinal cord is only several cells thick**, allowing for the development of a plane with only a **low threat of injury** to the surrounding cord. **The most vulnerable fiber tracks are sensory**" YW p.2005.
9. **Deliver the tumour pole first.** "Once the dorsal surface of the tumor has been cleared, **one of the poles is exposed in order to start to lift the tumor from its bed**. If at any point the **mass of the tumor is interfering with its mobilization, there should be no hesitancy to debulk its center**" YW p.2005.
10. **Work stepwise — sides, then ventral surface.** "As the tumor is lifted from its cavity, it is first separated along its **sides** and then along its **ventral surface** in a stepwise fashion" YW p.2005.
11. **The ventral vessels are the danger.** "**Small vessels arising from the anterior spinal artery will usually be encountered along the tumor's ventral surface. They should be cauterized as they enter the tumor.** Care must be taken here, as there is a **risk for disseminated thrombosis, either into the anterior spinal artery or into branches supplying the interior of the spinal cord**" YW p.2005.
12. **Respect the monitor.** "Sometimes a portion of tumor will be **adherent** to the surrounding parenchyma, making the establishment of a plane difficult. **This will become apparent when the recorded potentials begin to deteriorate. Further resection in this event should not proceed unless there is recovery of the potential. Rather, the area is allowed to rest**" [YW pp. 2005-2006].
13. **Haemostasis by tamponade, not cautery.** "**Bleeding after removal of the tumor is controlled by tamponade; cautery is used only when this fails**" YW p.2006; more generally, "**bipolar cautery is recommended only for bleeding that cannot be controlled by tamponade, as its use has a risk of injury to surrounding cord tissue**", and thrombin-soaked Gelfoam held with cottonoids for several minutes is preferred YW p.2005.
14. **Closure.** "After the resection cavity of an intramedullary tumor is dry, the **subdural space is irrigated clear of debris so as to minimize postoperative inflammation in the subarachnoid space. The myelotomy can be left open and the dura is closed primarily. The laminar roof of a laminotomy is then repositioned.** A drain dorsal to the lamina can be left with its catheter **tunneled out through the paraspinal musculature to exit the skin lateral to the incision** when leakage of CSF is of concern... followed by a **watertight fascial stitch using material that will not stretch when in contact with fluids**" YW p.2006.
15. **Expansile duraplasty is the fallback for infiltrative disease** — "When residual bulk disease is known to be left behind, an **expansile duraplasty with a patch graft will allow for subsequent expansion of the cord as the tumor progresses**" YW p.2571.

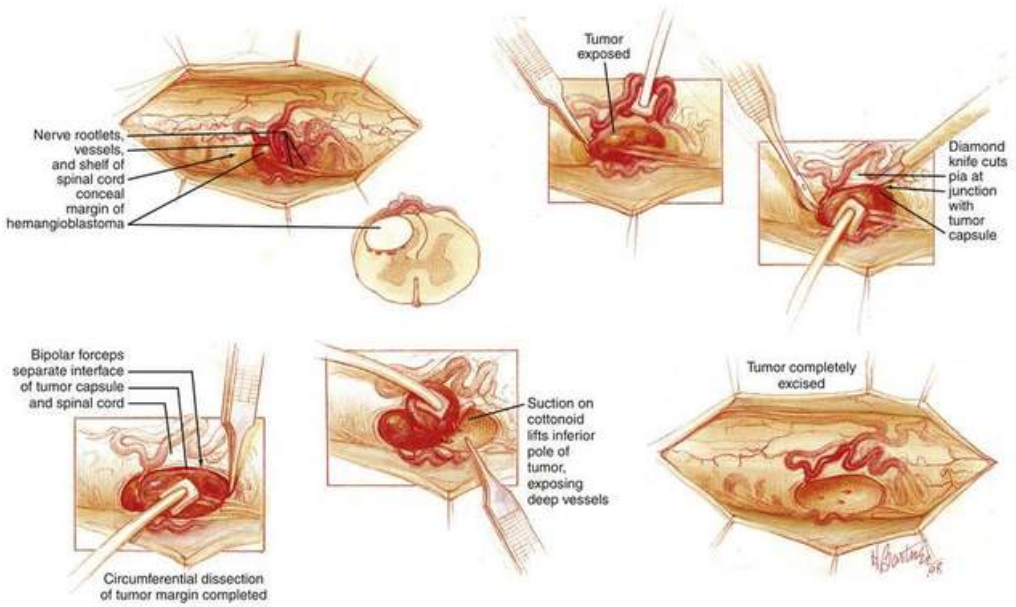


Figure 167.5. Microsurgical resection of spinal cord hemangioblastomas. The intradural portion of the operation for resection of spinal cord hemangioblastomas is shown. Using an operating microscope, the surgeon identifies associated vessels and tumor. The surgeon exposes the tumor by reflecting the overlying vessels with gentle traction. Vessels entering and leaving the tumor are coagulated with bipolar coagulation and sharply divided. The junction between the pia and the tumor capsule is identified and incised with a diamond knife and microscissors. Dissection of the tumor is continued more deeply and circumferentially at the tumor capsule–spinal cord interface with bipolar microforceps. After circumferential dissection of the tumor margin is complete, the surgeon reflects the inferior pole to the hemangioblastoma with gentle suction on a neurosurgical cotton patty (Cottonoid; Codman Neuro, Raynham, MA) to expose the underlying vessels. (*From Lonser RR, Weil RJ, Wanebo JE, DeVroom HL, Oldfield EH. Surgical management of spinal cord hemangioblastomas in patients with von Hippel-Lindau disease. J Neurosurg. 2003;98[1]:106–116.*)

Reproduced from Youmans & Winn 8e, Fig. 167.5, p. 1178 — Label when you reproduce it: the intradural portion of the operation for an intramedullary tumour, drawn for a spinal cord hemangioblastoma but applicable step for step to an ependymoma. Panels: nerve rootlets, vessels and the shelf of spinal cord pia concealing the tumour margin; the diamond knife incising the pia at its junction with the tumour; bipolar forceps separating the tumour capsule-cord interface; circumferential dissection complete, with suction on a cottonoid lifting the inferior pole to expose the deep ventral vessels; tumour completely excised. Label the myelotomy, the tumour-cord interface and the ventral feeding vessels from the anterior spinal artery.

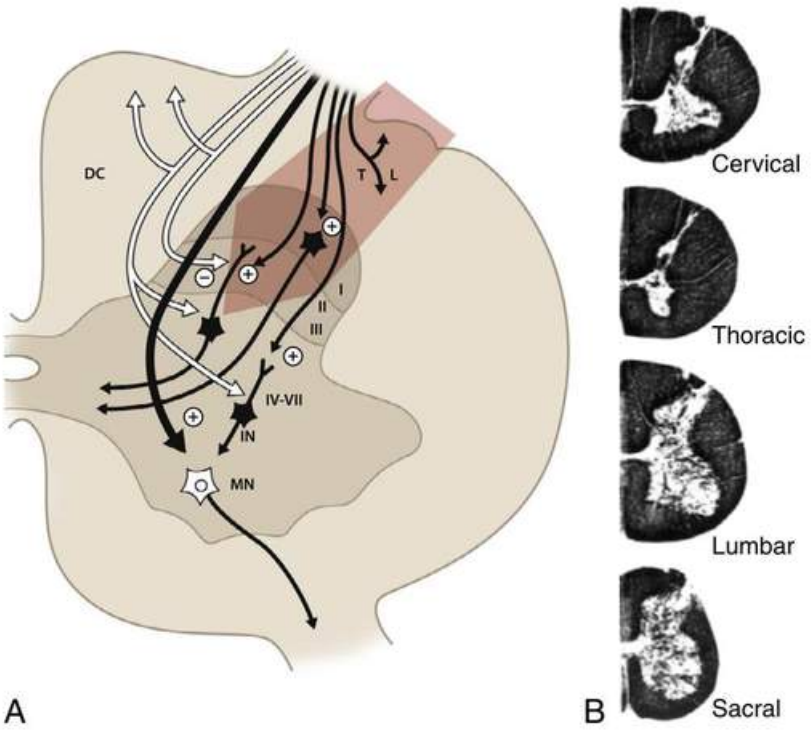


Figure 208.1. Anatomy of the dorsal root entry zone (DREZ). (A) Organization of fibers on transverse section. Most of the fine afferents, which convey excitatory input, enter the dorsolateral sulcus as a lateral bundle in the DREZ and then penetrate the dorsal horn ventrolaterally through the medial part of the tract of Lissauer and the dorsal aspect of the substantia gelatinosa *(sg).* The Ramón y Cajal's recurrent collaterals of the large primary afferent fibers[45] penetrate into the dorsal horn through the ventromedial aspect of the sg to exert inhibitory effects on the dorsal horn neurons.[76] The number of dendrites of the cells of origin of the spino-reticulo-thalamic tract, which will then form the contralateral anterolateral pathways, make synaptic connections with the primary afferents inside the sg layers, so that sg exerts a strong segmental modulating effect on the nociceptive input.[34,82] The microsurgical DREZotomy (MDT) target *(large dark-pink arrow)* includes the lateral bundle of the (nociceptive) fine fibers, the medial (excitatory) part of the tract of Lissauer, and the five dorsalmost layers of the dorsal horn, where the primary afferents terminate and whose neurons become hyperactive if deafferented. MDT attempts to spare most of the large fibers of the medial bundle that reach the dorsal column *(DC).* (B) Variations in shape, width, and depth of the DREZ area according to spinal cord level *(top to bottom):* cervical 7, thoracic 5, lumbar 4, sacral 3. Note that the DREZ is narrow and the dorsal horn is deep at the thoracic level, so DREZ lesioning at this level can be especially dangerous for the corticospinal tract and the dorsal column. *IN,* Interneurons; *MN,* motor neurons.

*Reproduced from Youmans & Winn 8e, Fig. 208.1, p. 1572 — Label when you reproduce it: (A) transverse organisation of the dorsal root entry zone — the dorsolateral sulcus, the lateral (fine, nociceptive) bundle, the medial bundle running to the dorsal columns, the tract of Lissauer, substantia gelatinosa and Rexed laminae I-VII, interneurons and motor neurons. (B) variation of the DREZ with level — cervical 7, thoracic 5, lumbar 4, sacral 3. The examiner's point: **at the thoracic level the DREZ is narrow and the dorsal horn is deep**, so dorsolateral entry there is especially dangerous for the corticospinal tract and dorsal column — which is exactly why a **dorsal midline myelotomy** is used for a dorsal (thoracic) ependymoma.*

9. Adjuvant therapy

- **Low-grade, gross totally resected ependymoma needs nothing further** — GTR is curative for lower-grade lesions YW p.2572.
- **Anaplastic ependymoma** — "In cases of **anaplastic astrocytoma, postoperative radiation therapy is recommended, regardless of whether gross total resection was achieved**, and includes both adults and children. Given the rarity of these lesions, the **benefits of chemotherapy have yet to be elucidated**" YW p.2572.
- **Outcome for anaplastic ependymoma** — "Literature reviews have reported **1- and 2-year overall survival rates of 92% and 82%**, respectively, as well as **5- and 10-year survival rates in the range of 50%-100%**" YW p.2572. "Despite its malignant histology, there are **limited data to suggest that outcomes are significantly better than those in malignant spinal astrocytomas**" YW p.2572.
- **Myxopapillary ependymoma is the exception where radiotherapy has a defined role** — "Adjuvant radiotherapy following surgery has been associated with **significantly improved local control at 10 years (86% versus 46%)** and **progression-free survival at 10 years (75% versus 37%) regardless of whether resection was total or subtotal**. The adjuvant radiotherapy in these instances is **intensity-modulated radiotherapy**, with treatment fields including the **thecal sac, sacroiliac joints, and meningeal sleeves within intervertebral foramina**; **failure to use adjuvant radiotherapy is associated with an increased rate of treatment failure**" YW p.2553.
- **Radiation toxicity is real, especially in children.** "**High-dose radiation of 55 to 60 Gy results in a 6% chance of radiation myelitis, and doses of even 50 Gy can induce spastic quadriplegia**; there are also reports of **alteration in growth of bones in children** undergoing radiotherapy" YW p.2007. In one cohort, "**four of the surviving patients experienced a second malignancy**, and **two had late (6 and 14 years) occurrence of an anaplastic glioma in the irradiated bed**" YW p.2007.
- **The modern conclusion** — "It appears that the **efficacy of aggressive resection (>80%) of IMSCTs matches that of surgery** [followed by radiation]" YW p.2007, so radiotherapy is reserved for high-grade histology, unresectable residual or recurrence.
- **En bloc principle for the filum variant** — "en bloc resection is often preferred and **great care is taken to avoid piecemeal debulking of the lesion, because this has been associated with increased rates of local failure and upward seeding or CSF metastasis**" YW p.2552. The filum "is identified and tested with a **neurostimulator**... then **cauterized above and below the tumor and then divided**, allowing the tumor to be delivered from the thecal sac en bloc" YW p.2552.

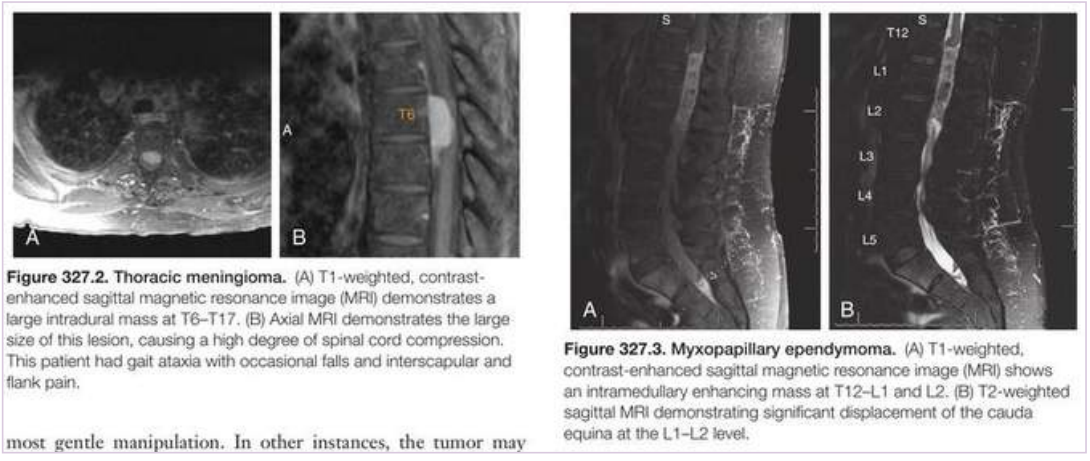


Figure 327.2. Thoracic meningioma. (A) T1-weighted, contrast-enhanced sagittal magnetic resonance image (MRI) demonstrates a large intradural mass at T6–T17. (B) Axial MRI demonstrates the large size of this lesion, causing a high degree of spinal cord compression. This patient had gait ataxia with occasional falls and interscapular and flank pain.

most gentle manipulation. In other instances, the tumor may

Figure 327.3. Myxopapillary ependymoma. (A) T1-weighted, contrast-enhanced sagittal magnetic resonance image (MRI) shows an intramedullary enhancing mass at T12–L1 and L2. (B) T2-weighted sagittal MRI demonstrating significant displacement of the cauda equina at the L1–L2 level.

Reproduced from Youmans & Winn 8e, Fig. 327.3, p. 2553 — Label when you reproduce it: myxopapillary ependymoma. (A) sagittal T1 post-contrast — enhancing mass at T12-L1 and L2; (B) sagittal T2 — significant displacement of the cauda equina at L1-L2. Use it to contrast the filum-terminale variant with the central, symmetrically expanding thoracic intramedullary ependymoma.

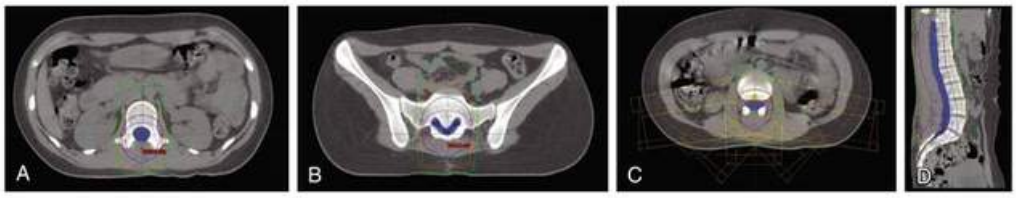


Figure 297.1. (A) Subtotal resection of myxopapillary ependymoma extending from the conus medullaris, filling the thecal sac, and coating the sacral nerve roots in a 17-year-old female patient. (B) Postoperative MR image showing residual nodularity on the conus and enhancement of the nerve roots. (C) Axial slice through the three-dimensional conformal radiation therapy plan showing excellent coverage of the thecal sac and rapid dose falloff anteriorly. (D) Sagittal slice at the isocenter showing a rapid dose falloff anteriorly. The patient underwent oopexy to move the ovaries anteriorly and inferiorly along the round ligament. The patient completed 50.4 Gy in 28 fractions and is disease free with normal hormonal function 3 years after therapy.

Reproduced from Youmans & Winn 8e, Fig. 297.1, p. 2319 — Label when you reproduce it: subtotal resection of a myxopapillary ependymoma extending from the conus medullaris, filling the thecal sac and coating the cauda equina. This is the imaging appearance that mandates adjuvant intensity-modulated radiotherapy, because subtotally resected myxopapillary ependymoma seeds the CSF.

10. Outcomes

- **Extent of resection is the dominant variable.** "It is now known that a **resection of greater than 80% in children with low-grade IMSCTs imparts a >70% 5-year event-free survival rate**, an outcome that at least equals, if not surpasses, that of the other therapies that are available" YW p.2005; Youmans lists it as a key concept: "**Resection exceeding 80% of IMSCTs results in a >70% 5-year event-free survival rate**" YW p.1995.
- **Epstein's series** — GTR in **77%** of patients and subtotal (80%-95%) in another **20%**, with **progression-free survival of 78% in the GTR group and 62% in the subtotal group**; both groups had **60% PFS at 10 years** YW p.2005. Ahmed's 37 children with low-grade lesions: **38% GTR, 92% PFS at 5 and 10 years and 68% at 20 years; overall survival 100% at 5, 10 and 20 years** YW p.2005.
- **Recurrence can be re-operated** — "**Resection of recurrent benign IMSCTs has the same morbidity as primary resection**" YW p.1995.
- **Overall survival for IMSCT surgery** is quoted as "**approximately 70% ± 5% overall 5-year survival rate**" YW p.2010.
- **Contrast with malignant astrocytoma**, so the examiner sees you know the prognostic gulf: "median survival of a little over 1 year and **1-, 2-, and 5-year survival of 67%, 40%, and 23%**" YW p.2572; **leptomeningeal dissemination in 47%-58%** of malignant astrocytomas YW p.2570.

11. Complications and how to avoid them

- **Dorsal column dysfunction** is the price of the midline myelotomy — "the most vulnerable fiber tracks are **sensory**" YW p.2005; hence the near-universal transient proprioceptive loss and gait ataxia after thoracic myelotomy.
- **Anterior spinal artery territory infarction** from cautery of ventral perforators, with the specific hazard of "**disseminated thrombosis, either into the anterior spinal artery or into branches supplying the interior of the spinal cord**" YW p.2005.
- **Postlaminectomy kyphosis/deformity** — laminotomy with replacement of the laminar roof is the preventive measure YW p.2005; retrospective data show expansive laminaplasty and C2 decompression "are associated with **increased risk of cervical kyphosis, particularly when performed to treat spinal cord tumors**" YW p.2550.
- **CSF leak and pseudomeningocele** — watertight dural closure, drain tunnelled laterally through the paraspinal musculature, non-stretching fascial suture, and a probing drain to detect early leakage YW p.2006; where a watertight closure fails, **lumbar drainage for 48-72 hours with a clamping trial before removal**, and **intravenous antibiotics while the drain is in** YW p.2553.
- **Neurological deterioration** — respect the D wave; stop and rest rather than push through a falling potential [YW pp. 2005-2006].
- **Wrong-level surgery** — confirm level with lateral radiograph before incision and with intraoperative ultrasound before durotomy [YW pp. 2005, 2571].

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Ependymoma is the commonest intramedullary tumour of the adult cord (50%-70%); astrocytoma predominates under the age of 10.**
- **Nocturnal back pain localised to the level of the tumour** is the classic first symptom — venous engorgement plus local mass effect on lying down.
- **Dysaesthesia without sensory loss** is peculiar to ependymoma, from disruption of the **crossing spinothalamic fibres** at the central canal. **Symmetrical sensory findings suggest ependymoma.**
- On axial MRI, **ependymoma is CENTRAL and expands the cord symmetrically**; **astrocytoma and ganglioglioma are ECCENTRIC**.
- **The haemosiderin "cap sign"** at the rostral or caudal pole is reported in 20%-60% of spinal ependymomas.
- **The tumour-cord interface is only a few cells thick** — that is why a plane exists and why gross total resection can cure a low-grade lesion.
- **Midline myelotomy over the whole length of solid tumour**, because the epicentre is midline; avoid the myelotomy only if tumour has erupted through the pia.
- **Debulk the centre before mobilising the poles**; separate sides first, then the ventral surface last, where the anterior spinal artery perforators are.
- **Tamponade, not bipolar** — cautery in the resection bed injures cord.
- **Changes in D waves are 100% predictive of permanent motor loss** — stop and let the cord rest.
- **Resection >80% gives >70% 5-year event-free survival**; Epstein achieved GTR in 77%.
- **Myxopapillary ependymoma must come out en bloc** — piecemeal removal seeds the CSF; adjuvant IMRT raises 10-year local control from 46% to 86%.
- **50 Gy can cause spastic quadriplegia and 55-60 Gy carries a 6% risk of radiation myelitis** — a reason to resect rather than irradiate a low-grade lesion.
- **Diffuse cord oedema with an "intramedullary tumour" — do vascular imaging** and exclude a dural AV fistula (Foix-Alajouanine) before you operate.

Pages read for this answer — Youmans & Winn 8e: 1995, 1996, 1998, 1999, 2001, 2005, 2006, 2007, 2010, 2429, 2430, 2455, 2548, 2550, 2552, 2553, 2570, 2571, 2572

a) Classification of Intradural Tumour. [3]
b) Difference between Intradural extramedullary and intramedullary tumour. [3]
c) Draw a labelled diagram of spinal cord at cervical level. [4]

LONG | DEC 2022 · Paper II · Q6 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 311 *Differential Diagnosis of Spinal Disease*, §Differential Diagnosis and **Box 311.1 — Differential Diagnosis of Spinal Disorders**, pp. 2444.e2-2444.e3 (Fig. 311.1, p. 2444.e2). Supplementary: Ch. 327 *Evaluation and Treatment of Benign Intradural Extramedullary Tumors*, §Key Concepts, §Histology and Gross Pathology, §Epidemiology, §Imaging and §Presentation, pp. 2547-2553 (Figs. 327.1-327.3, pp. 2552-2553); Ch. 329 *Evaluation and Treatment of Malignant Primary Spinal Tumors*, §Introduction, pp. 2570-2575 (Figs. 329.1-329.3, pp. 2571-2574; Table 329.1, p. 2571); Ch. 263 *Tumors of the Spine, Spinal Canal, and Spinal Cord in Children*, §Epidemiology, §Pathology and §Diagnostic Evaluation, pp. 1995-2004 (Figs. 263.1-263.8, pp. 2000-2002); Ch. 304 *Spinal Anatomy*, §Spinal Nerves — Gross Anatomy, pp. 2391-2399 (Fig. 304.1, p. 2391); Ch. 208 *Dorsal Root Entry Zone Lesions for Pain*, §Anatomy, p. 1572 (Fig. 208.1, p. 1572); Ch. 316 *Evaluation and Treatment of OPLL*, §Pathologic Features of Spinal Cord Lesions, p. 2478 (Fig. 316.1, p. 2478); Ch. 321 *Evaluation and Treatment of Degenerative Cervical Myelopathy*, §Clinical Evaluation, p. 2519; Ch. 315 *Evaluation and Treatment of Cervical Disk Herniations*, §Myelopathy, p. 2467.

(a) Classification of intradural tumours [3]

1. The framework — two cuts, then histology

- **Cut 1 — the dura. "Spinal tumors are classified as extradural or intradural"** YW p.2570.

- **Cut 2 — the pia.** "**Intradural tumors are further classified as either intramedullary or extramedullary**" YW p.2570.
- **Then the cell of origin.** Within the intramedullary compartment, "**primary glial tumors make up more than 80% of these intramedullary tumors** and include **astrocytomas, ependymomas**, and less common neoplasms such as **gangliogliomas, oligodendrogliomas, and subependymomas**" YW p.2570. Within the intradural extramedullary (IDEM) compartment, "the most common entities encountered are **meningiomas, nerve sheath tumors (schwannomas and neurofibromas), and, at the filum terminale, myxopapillary ependymomas**" YW p.2547.
- **Give the numbers with the classification** — "Primary intradural, intramedullary tumors make up **5%-10% of spinal column tumors in adults and about 35% in children**" YW p.2570; "**Intradural extramedullary tumors of the spinal column account for roughly 25% of all tumors occurring within the spine**" YW p.1995; and "the most common intradural spinal tumors (both intramedullary and extramedullary) are **meningiomas**, followed in varying order by **intramedullary ependymomas or NSTs**, depending on the report" YW p.2548.
- **Overall incidence of intradural spinal tumours** — "**0.74 per 100,000 person-years**, with an incidence of **0.77 per 100,000 in females and 0.70 per 100,000 in males**" in more recent epidemiologic studies (older surveys gave 1.1 per 100,000) YW p.2548.

*Table 1 · Classification of intradural spinal tumours — compartment by compartment, with the histologies Youmans names — from Youmans & Winn 8e, Ch. 311 **Box 311.1**, pp. 2444.e2-2444.e3; Ch. 327 §Key Concepts and §Histology, p. 2547; Ch. 329 §Introduction, p. 2570; Ch. 263 §Pathology, pp. 1996-1997.*

Compartment	Subgroup	Tumours (Youmans' own list)
INTRADURAL EXTRAMEDULLARY (≈25% of all spinal tumours)	**Nerve sheath tumours**	**Schwannoma**, **Neurofibroma** (and malignant peripheral nerve sheath tumour)
	Meningothelial	**Meningioma** (12% of all meningiomas; psammomatous is the commonest spinal subtype; WHO I-III)
	Filum terminale	**Filum terminale (myxopapillary) ependymoma**, **Paraganglioma**
	Congenital / inclusion	**Dermoid, Epidermoid, Lipoma, Teratoma, Neurenteric cyst**
	Other	**Hemangioblastoma, Ganglioneuroma, Arachnoiditis** ; rarely **atypical teratoid/rhabdoid tumour**; **drop metastases** (medulloblastoma, ependymoma)
INTRADURAL INTRAMEDULLARY (5%-10% of spinal tumours in adults, ~35% in children)	**Glial**	**Astrocytoma** (WHO I-IV), **Ependymoma** (WHO I-III)
	Other glial / glioneuronal	**Ganglioglioma, Oligodendroglioma, Subependymoma, Neurocytoma**
	Vascular	**Hemangioblastoma**, cavernous malformation
	Metastasis	Intramedullary **metastasis**
	Rare malignant	**Primary spinal cord melanoma**, anaplastic ganglioglioma, anaplastic oligodendroglioma
EXTRADURAL (for contrast)	Bone / epidural	Metastasis (commonest), myeloma/plasmacytoma, chordoma, chondrosarcoma, osteosarcoma, Ewing sarcoma; benign: osteoid osteoma, osteoblastoma, giant cell tumour, aneurysmal bone cyst, haemangioma, eosinophilic granuloma

2. Classification by age — the second axis the examiner likes

- **Adults**: "**ependymomas are the most common intramedullary tumor, accounting for 50%-70% of lesions**, with the remaining portion primarily consisting of astrocytomas" YW p.2570. IDEM: **meningioma** peaks in the **sixth to eighth**

decade, female predominance **3:1 to 4.2:1**, thoracic predilection YW p.2548; **NSTs** peak in the **fourth and fifth decades** with equal sex distribution YW p.2548.

- **Children**: "**This trend is reversed in younger children, with astrocytomas predominating in those under the age of 10**" YW p.2570. In the Constantini/Epstein series of 242 children, "**46%... had astrocytomas, with 24% being malignant; 36%... had a mixed glial-neuronal tumor**, the majority of which were **gangliogliomas**... **Sixteen percent were ependymomas**" YW p.1996. Youmans' key concept: "**Eighty percent of intramedullary spinal cord tumors (IMSCTs) have a glial or glial-neuronal cell type**" YW p.1995.
- **Paediatric IDEM tumours** are "primarily either **nerve sheath tumors or meningiomas**, but **spinal inclusion cysts (dermoid or epidermoid tumors) and metastatic medulloblastomas** can also be seen. Very rarely, **atypical teratoid or rhabdoid tumors** have been reported as extramedullary tumors" YW p.1995. Annual incidence in children 0-19 years: **nerve sheath tumours 0.27 per 100,000; tumours of the meninges 0.2 per 100,000** YW p.1995.
- **Malignancy is the exception** — "**Although most primary intradural spinal tumors are benign**, the uncommon cases of malignant intradural tumors present unique diagnostic and treatment challenges"; "less than one-third [are] found to be malignant" YW p.2570.

3. Classification by syndrome

- **NF1** — autosomal dominant, **neurofibromin, chromosome 17**, prevalence **1 in 2500-3000**; "often resulting in **multiple spinal neurofibromas**"; the principal source of **MPNST** YW p.2548.
- **NF2** — autosomal dominant, **merlin, chromosome 22**, prevalence **1 in 50,000**; "can lead to **multiple spinal schwannomas, neurofibromas, and spinal meningiomas**" YW p.2548 and predisposes to **ependymomas**, "spinal ependymomas in particular are prone to contain **NF2 gene deletions**" YW p.2572.
- **Schwannomatosis** — "multiple schwannomas **without the defining features of NF1 or NF2**" YW p.2548.
- **Carney complex** — "facial pigmentation, cardiac myxomas, endocrine problems, and **melanotic schwannomas, 10% of which may be malignant**" YW p.2548.
- **von Hippel-Lindau** — "Approximately **25% of hemangioblastomas of the spine are associated with mutations in the VHL gene on chromosome 3p25-26**", autosomal dominant with **90% penetrance**, encoding an **E3 ubiquitin ligase targeting HIF1α** YW p.1996.
- **Li-Fraumeni, Gorlin syndrome and prior radiation** predispose to meningiomas in children YW p.1997; "Younger patients with spinal meningiomas typically are subject to a predisposing factor such as **neurofibromatosis 2 or prior radiation exposure**" YW p.2548.

(b) Intradural extramedullary versus intramedullary tumours [3]

4. The structural difference and how it shows on imaging

- **The definitive radiological rule** — IDEM tumours "are within the CSF spaces of the canal and are therefore most often associated with **sharp CSF interfaces, sometimes known as a 'CSF cap'**. In addition, these tumors **displace the spinal cord within the canal, rather than expanding it as seen with intramedullary lesions**, and they often **expand the involved ipsilateral subarachnoid spaces**" [YW pp. 2001-2002]. That single sentence contains the whole of part (b).
- **Intramedullary lesions expand the cord** — "One expects to see a significant mass when confronting an intramedullary tumor that will **expand the cord's diameter** and stand out on at least one of the sequences" YW p.1999.
- **Within the intramedullary group, the axial epicentre sub-classifies** — "**Glial and glial-neuronal IMSCTs are eccentric, whereas ependymomas are centered on axial MRI**" YW p.1995.

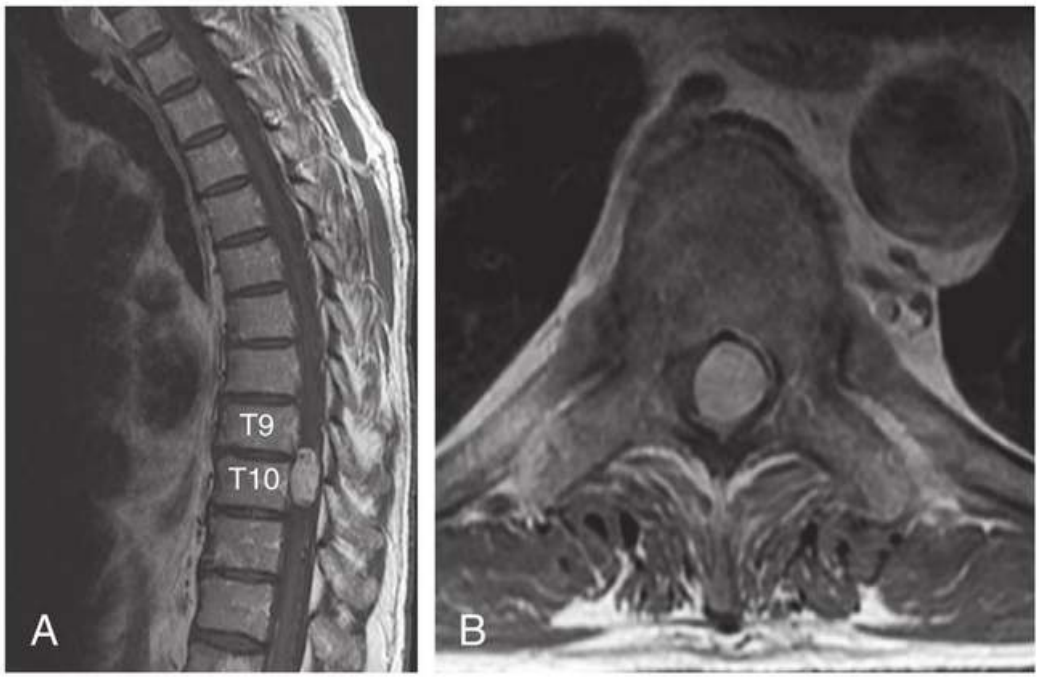


Figure 327.1. Thoracic schwannoma. (A) T1-weighted, contrast-enhanced sagittal magnetic resonance image (MRI) demonstrates a large intradural mass at T9–T10. (B) Axial MRI demonstrates the large size of this lesion, causing a high degree of spinal cord compression. This patient had gait ataxia and left-sided thoracic pain.

Reproduced from Youmans & Winn 8e, Fig. 327.1, p. 2552 — Label when you reproduce it: thoracic schwannoma — the archetypal INTRADURAL EXTRAMEDULLARY tumour. (A) sagittal contrast-enhanced T1 — a large intradural mass at T9-T10; (B) axial MRI showing the size of the lesion and the high degree of spinal cord compression. Point out the CSF cap above and below, and that the cord is DISPLACED, not expanded.

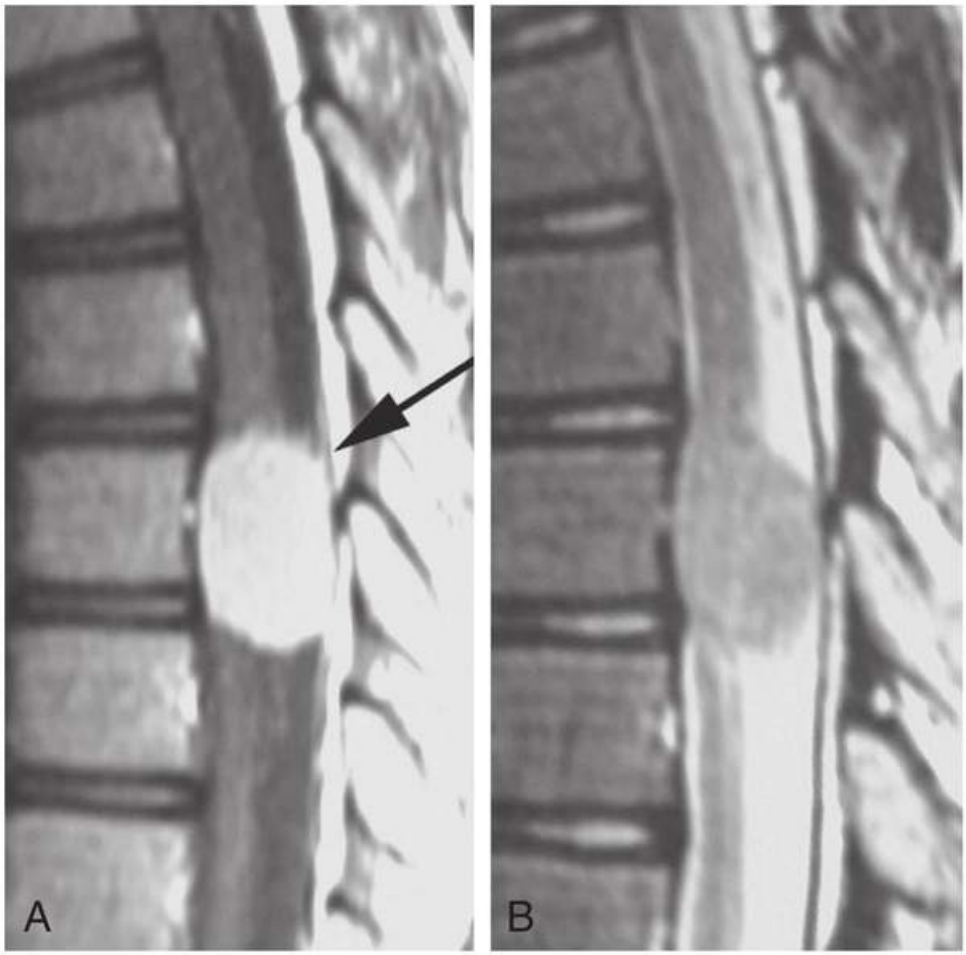


Figure 263.8. Sagittal MR images of intradural meningioma. (A) T1-weighted image showing the tumor to densely enhance after gadolinium enhancement. The *black arrow* points to a small dural tail of enhancement. (B) The same tumor appears isointense on T2-weighted imaging. (*Courtesy Rick Abbott, MD.*)

Reproduced from Youmans & Winn 8e, Fig. 263.8, p. 2002 — Label when you reproduce it: sagittal MR images of an intradural meningioma. (A) T1 after gadolinium — densely enhancing tumour, with the black arrow on a small DURAL TAIL of enhancement; (B) the same tumour isointense on T2. The dural tail is the sign that separates meningioma from nerve sheath tumour.

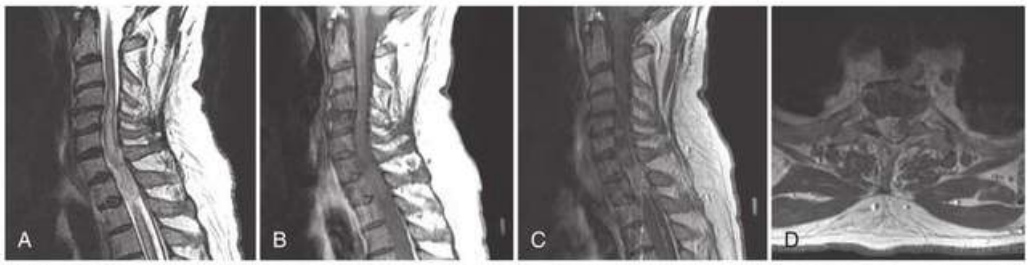


Figure 329.1. High-grade astrocytoma. A 58-year-old man presented with several weeks of back and chest pain as well as worsening right leg weakness. He also reported decreased sensation in his chest and legs. (A) Spinal magnetic resonance imaging was obtained, demonstrating a hyperintense intramedullary lesion on T2-weighted images in the cervical and cervicothoracic lesion that expanded and distorted the cord. (B and C) T1-weighted image (B) demonstrates isoinstense signal characteristics that heterogeneously enhanced in the C7–T1 region with contrast administration (C). (D) Axial T1-weighted image after contrast enhancement showed asymmetrical growth of the cord, with displacement of nonenhancing portions toward the left of the canal. The patient underwent a C5-to-T2 laminectomy and tumor biopsy. Pathology confirmed the presence of a high-grade astrocytoma.

Reproduced from Youmans & Winn 8e, Fig. 329.1, p. 2571 — Label when you reproduce it: high-grade astrocytoma — the archetypal INTRAMEDULLARY tumour. A 58-year-old man with weeks of back and chest pain and worsening right leg weakness. (A) T2 sagittal — hyperintense intramedullary lesion in the cervical and cervicothoracic cord that EXPANDS AND DISTORTS the cord; (B and C) T1 isointense, heterogeneously enhancing at C7-T1 with contrast; (D) axial T1 post-contrast — ASYMMETRICAL growth of the cord with displacement of non-enhancing portions to the left of the canal. Contrast the eccentric expansion here with the central expansion of ependymoma.

Table 2 · Intradural extramedullary versus intradural intramedullary tumours — the comparison table — from Youmans & Winn 8e, Ch. 263 §Diagnostic Evaluation, pp. 1999-2002 and §Key Concepts, p. 1995; Ch. 327 §Key Concepts, §Epidemiology, §Imaging and §Presentation, pp. 2547-2553; Ch. 329 §Introduction and §Malignant Astrocytomas, pp. 2570-2572.

Feature	Intradural EXTRAMEDULLARY	Intradural INTRAMEDULLARY
Position relative to pia	Outside the cord, within the thecal sac	**Within the cord substance**
Share of spinal tumours	~**25%** of all spinal tumours	**5%-10%** in adults, **~35%** in children
Commonest histologies	**Meningioma**, **schwannoma**, **neurofibroma**; **myxopapillary ependymoma** at the filum	**Ependymoma** (adults, 50%-70%), **astrocytoma** (children <10), ganglioglioma, haemangioblastoma
Effect on cord	**Displaces** the cord; widens the ipsilateral subarachnoid space	**Expands** the cord; effaces the subarachnoid space circumferentially
Classic MRI sign	**"CSF cap"** — sharp CSF interface at the poles; **dural tail** for meningioma; **target sign / string of beads** for neurofibroma	**Fusiform cord expansion**; polar/rostral-caudal cysts; **haemosiderin cap** in ependymoma; syrinx
Axial epicentre	Eccentric, lateral or ventral within the canal	**Central** = ependymoma; **eccentric** = astrocytoma/ganglioglioma
Typical presentation	**Radicular or axial pain**, then myelopathy or cauda equina dysfunction from chronic compression; weakness in 40%-50% of children, pain in 30%-50%; **dysaesthesia is unusual**	**Nocturnal back pain** over the segment; motor regression (65% of children); **dysaesthesia (32%)**; progressive **kyphoscoliosis (32%)**; sphincter disturbance late
Bone changes	Enlarged neural foramina, increased interpediculate distance, **vertebral body scalloping**, thinning of pedicles	Canal expansion and posterior vertebral scalloping only with very slow-growing lesions (e.g. myxopapillary ependymoma)
Dumb-bell morphology	**Yes** — nerve sheath tumours grow through the dural root sleeve into the foramen and paraspinal space	No
Surgical plane	Arachnoid plane between cord and capsule; **denticulate ligament division improves ventral access**	Plane only with ependymoma/haemangioblastoma; astrocytoma is infiltrative

Goal of surgery	**Gross total resection**, achievable in **80%-97%** of spinal meningiomas; recurrence 3.7%-14.7%	GTR curative for **low-grade ependymoma**; for astrocytoma, **maximal safe resection**, ≥80% giving >70% 5-year event-free survival
Adjuvant therapy	Generally **none**; radiosurgery for recurrence/syndromic multiplicity; **IMRT has a defined role after myxopapillary ependymoma**	Radiotherapy for anaplastic histology or unresectable residual; chemotherapy of unclear benefit
Monitoring	SSEP/MEP for any intradural component; **EMG for C5-T1 and L2-S4 roots**	SSEP + MEP + **D wave** — changes in the D wave are 100% predictive of permanent motor loss

5. Clinical differences worth spelling out

- **IDEM tumours announce themselves with pain.** "As a group, these benign, slow-growing tumors generally present with **pain — either radiculopathy or axial back pain — or focal neurological deficits** attributable to loss of function in involved or collaterally compressed nerve roots, **myelopathy** from spinal cord compression, or **cauda equina dysfunction** from chronic compression" YW p.2548.
- **In children the sequence for IDEM tumours is weakness then pain** — "**Weakness followed by pain** is the most common symptom in children with intradural, extramedullary tumors, occurring in roughly **40% to 50%** and **30% to 50%**, respectively. There can be a **radicular component** with extramedullary tumors, but **dysesthesia is unusual**" YW p.1999.
- **IMSCTs announce themselves with motor regression and nocturnal pain** — "The most common complaint at presentation is **motor regression, which occurred 65% of the time**... followed by **pain (48%), gait abnormality (37%), dysesthesia (32%), and progressive kyphoscoliosis (32%)**" YW p.1998.
- **Tempo differs** — "Although the pace of evolution is similar for intradural, extramedullary lesions in comparison with IMSCTs, **it seems to be faster for tumors that are outside the dura**" YW p.1999.
- **A classic clinical vignette for IDEM** — "The classical presentation of a spinal meningioma is seen in a **middle-aged to elderly woman with slowly progressive lower extremity weakness or dysfunction resulting from a thoracic meningioma**" YW p.2548.

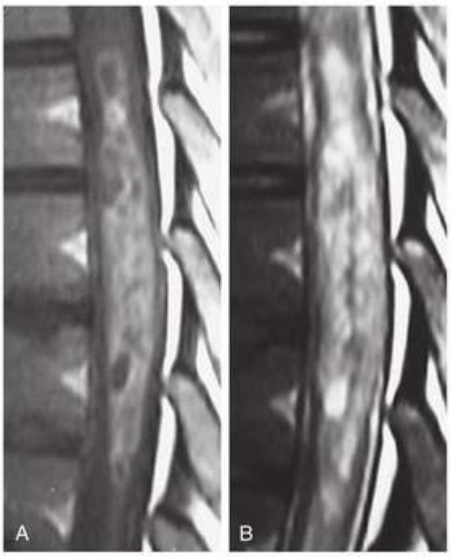


Figure 263.3. MR images of intramedullary ependymoma. (A) Heterogeneously enhancing T1-weighted sagittal image of an intramedullary ependymoma; (B) shows the tumor to be heterogeneously hyperintense on T2-weighted imaging. (C) T1-weighted axial image of the tumor after gadolinium enhancement shows the tumor's central location. (*Courtesy Rick Abbott, MD.*)

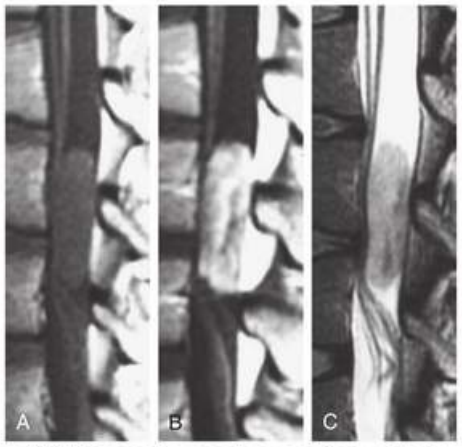


Figure 263.4. Myxopapillary ependymomas. (A) T1-weighted image showing the isodense tumor caudal to the conus and dorsal to the cauda equina. (B) T1-weighted image shows the tumor enhancing after gadolinium enhancement. (C) Variable density tumor on T2-weighted imaging. (*Courtesy Rick Abbott, MD.*)

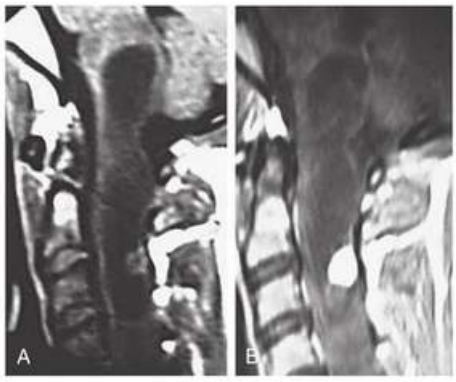


Figure 263.5. Sagittal MR images of hemangioblastomas. (A) T1-weighted sagittal MR image showing a cyst with a dorsally placed isointense mural nodule. (B) Image taken after the administration of

Reproduced from Youmans & Winn 8e, Fig. 263.3, p. 2001 — Label when you reproduce it: (A) heterogeneously enhancing T1 sagittal of an intramedullary ependymoma; (B) heterogeneously hyperintense on T2; (C) axial T1 after gadolinium showing the tumour's CENTRAL location within the expanded cord. This is the image to set beside Fig. 327.1 to teach the intramedullary-versus-extramedullary distinction.

6. Investigations — what to order and why

- **MRI is the modality of choice for both compartments** — "As is the case with most intradural pathology, **magnetic resonance imaging (MRI) is the modality of choice** to evaluate IDEM tumors. MRI provides visualization in all three planes and best delineates the relationship of pathology to the spinal cord and nerve roots" YW p.2548. "There is no question that **MRI of the spine is the diagnostic procedure of choice** when confronted with a patient with signs of a tumor in the spine or spinal canal" YW p.1999.
- **Minimum protocol** — "**T1-weighted sequence, with and without gadolinium enhancement, and a T2-weighted sequence in axial and sagittal planes. Anything less will compromise one's interpretation of the imaging**"; add **gradient echo** (haemosiderin), **FLAIR** (subtle intramedullary lesions) and **DWI** (infarct, inclusion cysts) YW p.1999.
- **CT** — "well suited for **delineating bony anatomy, planning instrumentation, and demonstrating tumor calcification**"; CT myelography is "usually reserved for patients in whom MRI is not possible, allowing identification of the **level of blockage of CSF flow**" YW p.2548.
- **Vascular imaging** — for cervical lesions, "they allow clear delineation of the relationship of pathology to the **vertebral artery**"; "**vascular imaging in cases of diffuse cord edema to rule out dural arteriovenous fistula (i.e., Foix-Alajouanine syndrome)**" [YW pp. 2548, 2571].
- **Craniospinal imaging and systemic screening** when leptomeningeal spread or metastasis is suspected YW p.2571.

- **Image the whole neuraxis if multiple tumours or a young patient** — "suspicion of an **underlying syndrome is warranted**, and further work-up should include **imaging of the entire neuraxis**" YW p.2548.

(c) Labelled diagram of the spinal cord at cervical level [4]

7. The gross organisation you must label first

- **Leptomeninges and the anchoring ligament** — "The spinal cord, like the brain, is **ensheathed in leptomeninges consisting of the pia, arachnoid, and dura** and is **attached to the arachnoid and dural sheath by 20 to 22 paired denticulate ligaments**. **CSF in continuity with the intracranial subarachnoid compartment bathes the cord and its proximal nerve roots**" YW p.2397.
- **Roots and nerves** — "**Thirty-one pairs of ventral and dorsal roots emerge from the spinal cord on each side per level, combining into a mixed spinal nerve**" YW p.2397. There are **8 cervical nerves but only 7 cervical vertebrae**: the **C1 spinal nerve exits above C1** and the **C8 spinal nerve exits below C7** YW p.2399.
- **Enlargements and termination** — the cord "is **40 to 50 cm long and stretches from the foramen magnum to the first or second lumbar vertebral segment**"; "visually the cord is **enlarged in size from C3 to T1 and from L1 to S2, known as the cervical enlargement and lumbar enlargement**" YW p.84. It terminates at the **conus medullaris** and continues as the **internal and external terminal filum**, with the **cauda equina** below and the **dural sac terminating at about S2** YW p.2399. "The **filum terminale**, which is a delicate strand of **non-neurogenic leptomeningeal tissue**, arises from the end of the conus medullaris and attaches distally to the dorsal aspect of the first coccygeal vertebral body. It can **stabilize and tether the lower end of the spinal cord**" YW p.84.
- **Root numbers** — "There are **8 cervical nerves, 12 thoracic nerves, 5 lumbar nerves, 5 sacral nerves, and 1 coccygeal nerve**"; "**all spinal nerves except those associated with the cervical region exit via foramina below their associated vertebral segment**" YW p.84.
- **Rootlet emergence** — "Nerve rootlets protrude from the **dorsolateral and ventrolateral aspect of the spinal cord** and join distally to form **31 pairs of nerves**" YW p.84.

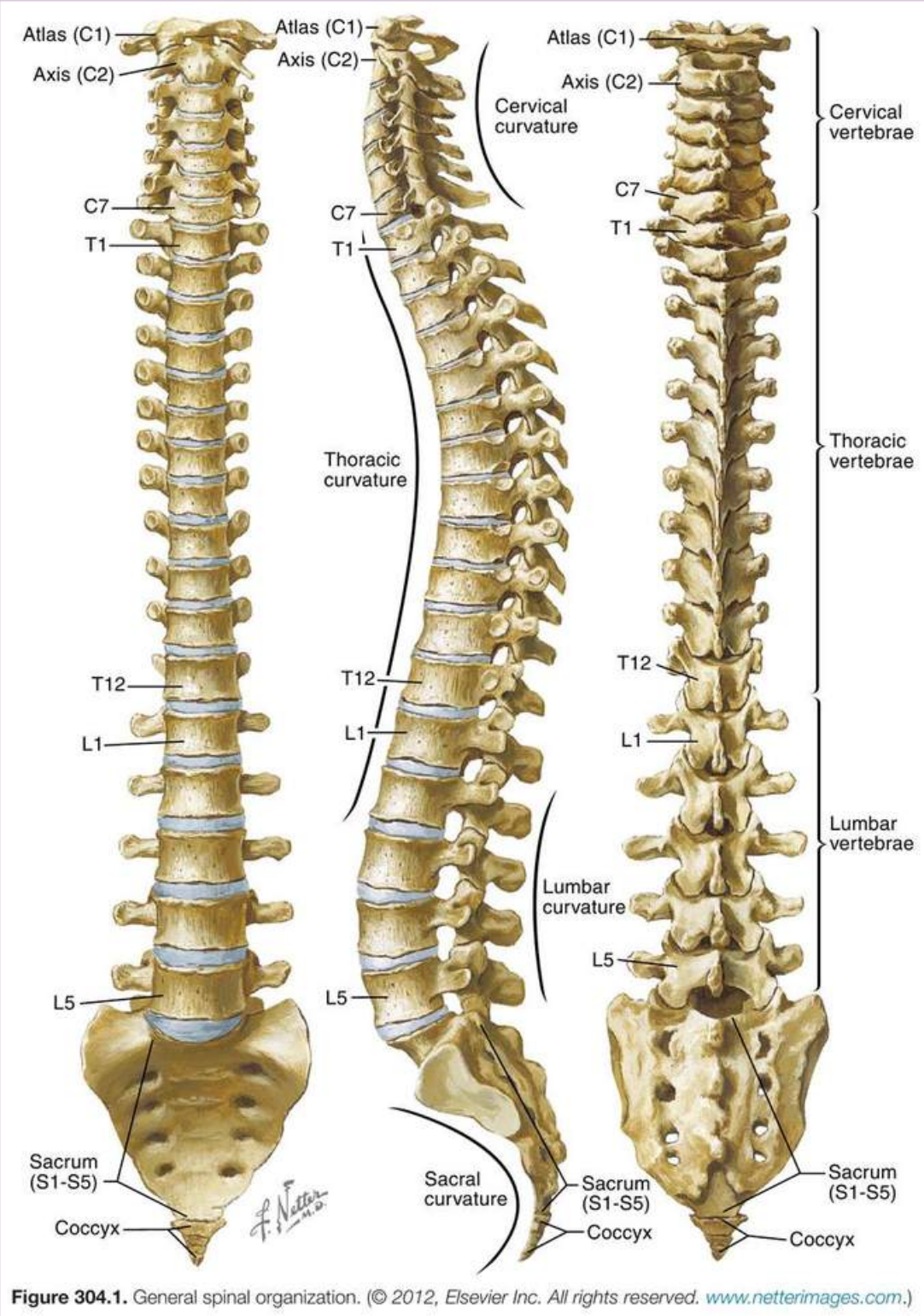


Figure 304.1. General spinal organization. (© 2012, Elsevier Inc. All rights reserved. www.netterimages.com.)

Reproduced from Youmans & Winn 8e, Fig. 304.1, p. 2391 — Label when you reproduce it: general spinal organisation. Label the base of skull, the cervical enlargement, the eight cervical nerve roots (C1 exits above C1, C8 exits below C7), the twelve thoracic roots, the lumbar enlargement, the conus medullaris, the cauda equina, the internal and external terminal filum, the termination of the dural sac and the coccygeal nerve. This is the figure to draw first, then take a transverse cut at C6 for the detail below.

8. The transverse section at a cervical level — what to draw and label

- **The outline and the surface landmarks.** Youmans' own transverse figure of the cervical cord (Fig. 316.1) shows the cord flattened by ventral compression; the healthy outline to draw is oval, wider transversely than sagittally, with (from

the front) the **anterior median sulcus/fissure**, which carries the **anterior spinal artery** YW p.84, (laterally) the **ventrolateral aspect** where ventral rootlets emerge, and (behind) the **dorsolateral sulcus** where dorsal rootlets enter and the **posterior (dorsal) median sulcus** YW p.84.

- **The three concentric tissues.** "**Cross-sections of the spinal cord reveal peripheral white matter, inner gray matter, and a central canal lined with ependymal cells, all surrounded by CSF**" YW p.84 — the ependymal lining of that central canal is the origin of intramedullary ependymoma.
- **Grey-to-white ratio changes with level.** "**Lower levels of the cord have a higher ratio of gray matter to white matter relative to higher levels because lower levels have fewer ascending and descending nerve fibers**" YW p.84.
- **The four subdivisions of grey matter to label.** "The gray matter consists mainly of **cell bodies of neurons and glia** and is divided into the **dorsal horn, intermediate column, lateral horn, and ventral horn column**. The **dorsal horn is found at all levels** and is involved in **somatosensorial and signal transmission to the midbrain and diencephalon**. The **intermediate column and lateral horn** involve **autonomic neurons that innervate organs in the pelvic region**. Lastly, the **ventral horn involves motor neurons that communicate with skeletal muscle**" YW p.84.
- **The dorsolateral sulcus is the structure Youmans names most precisely**, because it is the DREZ: "Most of the **fine afferents, which convey excitatory input, enter the dorsolateral sulcus as a lateral bundle in the DREZ** and then penetrate the dorsal horn ventrolaterally through the **medial part of the tract of Lissauer** and the **dorsal aspect of the substantia gelatinosa**" YW p.1572.
- **Recurrent collaterals** — "**Ramón y Cajal's recurrent collaterals of the large primary afferent fibers penetrate into the dorsal horn through the ventromedial aspect of the substantia gelatinosa to exert inhibitory effects on the dorsal horn neurons**" YW p.1572.
- **The spinothalamic cells of origin** — "The number of dendrites of the **cells of origin of the spino-reticulo-thalamic tract, which will then form the contralateral anterolateral pathways**, make synaptic connections with the primary afferents inside the substantia gelatinosa layers, so that the substantia gelatinosa **exerts a strong segmental modulating effect on the nociceptive input**" YW p.1572.
- **The Rexed laminae to draw inside the dorsal horn**: **I, II, III, IV-VII**, then the **interneurons (IN)** and the **motor neurons (MN)** of the ventral horn — exactly as Youmans labels them YW p.1572.
- **Regional variation matters and is examinable** — "Variations in shape, width, and depth of the DREZ area according to spinal cord level (top to bottom): **cervical 7, thoracic 5, lumbar 4, sacral 3**. Note that **the DREZ is narrow and the dorsal horn is deep at the thoracic level**, so DREZ lesioning at this level can be **especially dangerous for the corticospinal tract and the dorsal column**" YW p.1572. The cervical cord, by contrast, has the **widest DREZ** — which is why cervical DREZotomy and dorsolateral entry are comparatively safer there.

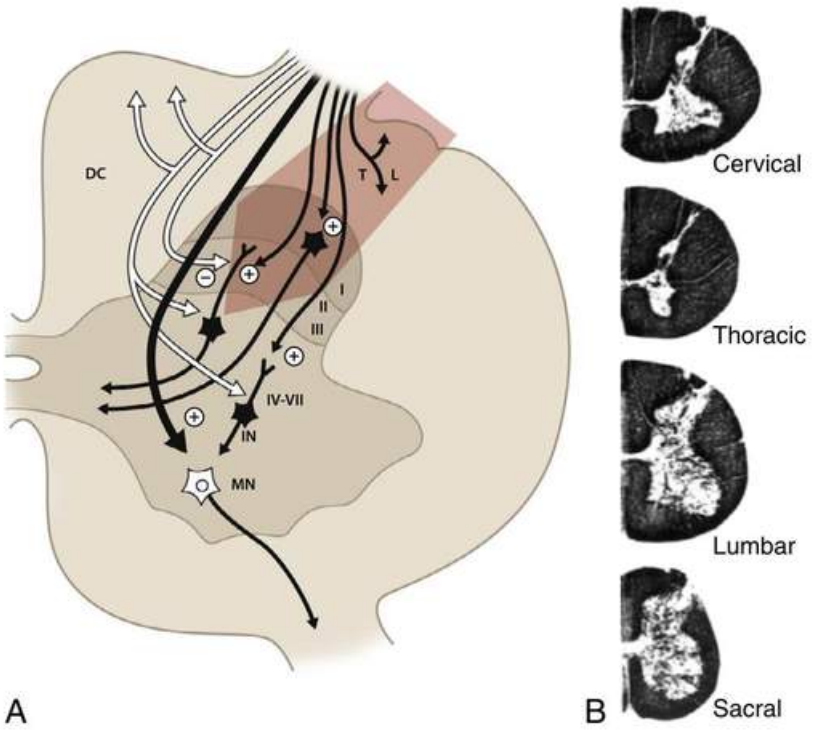


Figure 208.1. Anatomy of the dorsal root entry zone (DREZ). (A) Organization of fibers on transverse section. Most of the fine afferents, which convey excitatory input, enter the dorsolateral sulcus as a lateral bundle in the DREZ and then penetrate the dorsal horn ventrolaterally through the medial part of the tract of Lissauer and the dorsal aspect of the substantia gelatinosa *(sg).* The Ramón y Cajal's recurrent collaterals of the large primary afferent fibers[45] penetrate into the dorsal horn through the ventromedial aspect of the sg to exert inhibitory effects on the dorsal horn neurons.[76] The number of dendrites of the cells of origin of the spino-reticulo-thalamic tract, which will then form the contralateral anterolateral pathways, make synaptic connections with the primary afferents inside the sg layers, so that sg exerts a strong segmental modulating effect on the nociceptive input.[34,82] The microsurgical DREZotomy (MDT) target *(large dark-pink arrow)* includes the lateral bundle of the (nociceptive) fine fibers, the medial (excitatory) part of the tract of Lissauer, and the five dorsalmost layers of the dorsal horn, where the primary afferents terminate and whose neurons become hyperactive if deafferented. MDT attempts to spare most of the large fibers of the medial bundle that reach the dorsal column *(DC).* (B) Variations in shape, width, and depth of the DREZ area according to spinal cord level *(top to bottom):* cervical 7, thoracic 5, lumbar 4, sacral 3. Note that the DREZ is narrow and the dorsal horn is deep at the thoracic level, so DREZ lesioning at this level can be especially dangerous for the corticospinal tract and the dorsal column. *IN,* Interneurons; *MN,* motor neurons.

Reproduced from Youmans & Winn 8e, Fig. 208.1, p. 1572 — Label when you reproduce it: (A) transverse section through the dorsal root entry zone — label the dorsolateral sulcus, the lateral (fine, nociceptive) afferent bundle, the medial bundle continuing into the dorsal column (DC), the tract of Lissauer, the substantia gelatinosa, Rexed laminae I, II, III and IV-VII, the interneurons (IN) and the motor neurons (MN). (B) The four cord outlines by level — cervical 7, thoracic 5, lumbar 4, sacral 3 — showing how the DREZ narrows and the dorsal horn deepens from cervical to thoracic. Use panel B as the template for the cervical cord outline.



Figure 4.4. Overview of the osseous and ligamentous anatomy of the spine. (A) Posterior view of the cervical spine. (B) Lateral view of the cervical spine. (C) Posterior view of the lumbar vertebra. (D) Axial view of a lumbar intervertebral disk. (E) Sagittal view of the lumbar spine. (F) Anterolateral view of the upper cervical spine. (G) Axial view of the spinal cord in the cervical region. (H) Coronal view of the spinal cord in the lumbar region. (I) Posterolateral view of the lumbar spine and the intervertebral foramen. (J) Posterolateral view of the cervical spine. One side of the lamina of C3 and both sides of the lamina and spinous process of C4 were excised. Origin of the anterior spinal artery and posterior spinal artery: (K) Anterior view of the medulla oblongata, spinal cord, and anterior spinal artery. (L) Posterior view of the medulla oblongata, spinal cord, and bilateral posterior spinal arteries. *a.*, Artery; *abd.*, abdominal; *ALL*, anterior longitudinal ligament; *ant.*, anterior; *arti.*, articular; *inf.*, inferior; *lig.*, ligament or ligamentum; *m.*, muscle; *n.*, nerve; *PICA*, posterior inferior cerebellar artery; *PLL*, posterior longitudinal ligament; *post.*, posterior; *proc.*, process; *seg.*, segment; *spin.*, spinous; *sup.*, superior; *trans.*, transverse; *v.*, vein; *VA*, vertebral artery; *vert.*, vertebral. *(D, E, G, and H, Courtesy National Library of Medicine's Visible Human Program, National Institutes of Health, Bethesda, MD.)*

*Reproduced from Youmans & Winn 8e, Fig. 4.4, p. 83 — Label when you reproduce it: the panel you need is **(G) axial view of the spinal cord in the cervical region** — label adipose tissue, lamina, facet joint, superior articular process, intervertebral disc, **grey matter (anterior and posterior horn)**, **spinal cord white matter**, **dorsal root**, **ventral root**, **spinal ganglion** and inferior articular process. Then use **(K) anterior view of the medulla oblongata, spinal cord and anterior spinal artery** to label the **anterior spinal artery**, the **denticulate ligament**, the C1 anterior root, the C2 spinal nerve and both vertebral arteries; and **(L) posterior view** for the **paired posterior spinal arteries** and the accessory nerve. This is the single best cadaveric figure in the book for a labelled cervical cord.*

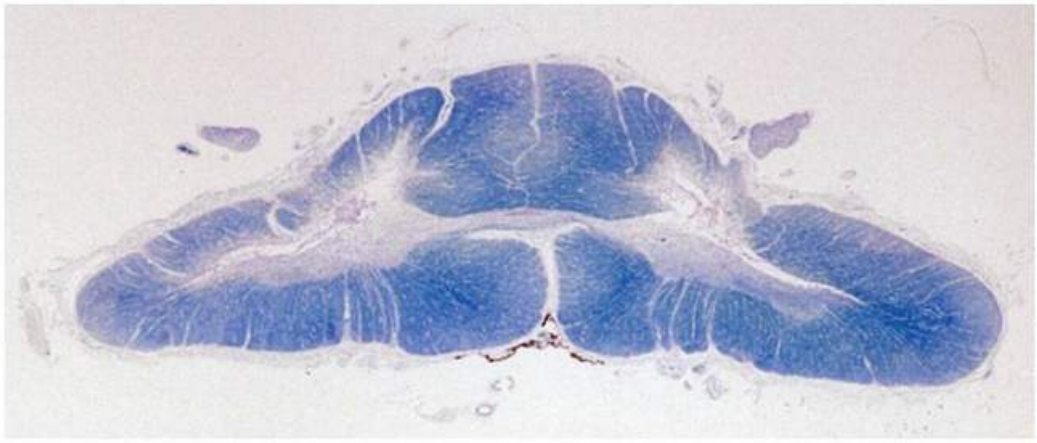


Figure 316.1. Transverse section of the cervical spinal cord. Triangular shape of the spinal cord with severe intrinsic changes, including loss of neurons and cavity formation.

Reproduced from Youmans & Winn 8e, Fig. 316.1, p. 2478 — Label when you reproduce it: transverse section of the cervical spinal cord. Here the cord shows the "triangular" compressed shape with severe intrinsic change — loss of neurons and cavity formation. When you reproduce it as a NORMAL cervical cord, label the anterior median fissure, anterolateral sulcus with ventral rootlets, dorsolateral sulcus with dorsal rootlets, posterior median sulcus, the butterfly grey matter with anterior/lateral/posterior horns and central canal, and then the white columns.

9. The tracts to label, and the clinical statement that justifies each

Youmans names the four tract systems that matter in cervical cord disease and what each does — put these labels on your drawing and annotate them:

- **Corticospinal tract (lateral corticospinal, in the lateral column) — motor** YW p.2467. Cervical myelopathy from its involvement gives "**increased leg rigidity**", "**hyperreflexia below the level of compression with the possible presence of the Babinski reflex or Hoffmann phenomenon and pathologic clonus**" YW p.2467.
- **Spinothalamic tract (anterolateral column) — pain and temperature** YW p.2467, formed by the **contralateral anterolateral pathways** whose cells of origin lie in the dorsal horn and whose fibres **cross in the anterior white commissure** — the anatomical reason a central ependymoma causes dysaesthesia by "**preferential disruption of crossing spinothalamic fibers**" [YW pp. 1572, 2572].
- **Dorsal column (fasciculus gracilis medially, fasciculus cuneatus laterally) — vibration and proprioception** YW p.2467. It receives the **medial bundle** of large myelinated afferents from the DREZ YW p.1572. Its failure produces the "**broad-based, unstable gait**" and positive Romberg of degenerative cervical myelopathy YW p.2519.
- **Spinocerebellar tracts** — "**motor tone and coordination**" YW p.2467; anatomically, "**Dorsal and ventral spinocerebellar tracts transmit information from unconscious proprioception of the lower extremities to the cerebellum**" YW p.84.
- **Youmans' own tract summary, worth quoting verbatim**: "**The dorsal funiculus in the dorsal column, composed of the ascending gracile and cuneate fasciculi, transmits information related to discrimination of simultaneously applied pressure, vibration, position, and conscious proprioception stimuli. In the lateral column, the neospinothalamic tract carries pain, temperature, and crude touch information**" YW p.84.
- **Grey matter — anterior horn cell (alpha motor neuron)** — "The **lower motor neuron component is secondary to alpha motor neuron injury** or nerve root injury when there is concomitant nerve root compression. Patients complain of **dermatomal weakness, tingling, numbness, and decreased fine motor coordination**... **muscle atrophy, focal motor weakness attributable to the involved level, decreased pinprick sensation, and hypoactive reflexes**" YW p.2467. Hand intrinsic atrophy and **flattening of the thenar eminence** are the cervical signs YW p.2467.

- **The lamination point** — Youmans' explanation of why the centre of the cord suffers first: "The pathologic **butterfly pattern of cord ischemia involving the gray and medial white matter** seen in myelopathy further supports a vascular role" YW p.2467. In OPLL, "**gray matter damage is more severe than white matter damage**, however demyelination and axon loss were generally seen, especially in the **posterolateral aspects of the cord**" YW p.2478.
- **Two cross-sectional shapes of the compressed cervical cord** worth adding as an annotation: "the **'boomerang' shape (concave anterior surface with convex posterolateral surfaces)** and the **'triangular' shape (angular lateral surfaces, flat anterior surface)**... In the **boomerang type, the pathology primarily involves gray matter with relative preservation of the white matter tracts**, while the **triangular shape is associated with more widespread degenerative changes, including the lateral corticospinal tracts and posterior columns**" YW p.2478.

10. Measurements to annotate on the drawing

- **Cord diameter** — "in the cervical region, the **average AP diameter of the adult spinal cord is 5 to 6 mm**" YW p.2499.
- **Canal diameter** — "The **normal sagittal cervical canal diameter** has been shown to be approximately **17 to 18 mm**, and a patient is at **high risk for the development of myelopathic changes with a reduction in canal diameter to 13 mm**" YW p.2467.
- **Soft tissue allowance** — "the intracanalicular soft tissue components, such as the posterior longitudinal ligament, dura, and ligamentum flavum, **occupy another 2 mm** of the bony spinal canal. Thus the **minimal spinal canal space required for a noncompressed spinal cord is 10 mm**, which has been set as the threshold value for **absolute cervical spinal stenosis**. **In extension, the spinal canal AP diameter reduces by 2 to 3 mm; therefore 12 to 13 mm is a threshold value for relative stenosis**" YW p.2499.
- **Torg-Pavlov ratio** — "the distance from the midpoint of the posterior aspect of the vertebral body to the nearest point on the corresponding spinolaminar line divided by the AP width of the vertebral body. **The normal Torg-Pavlov ratio is 1; in congenital cervical stenosis, it is 0.8 or less**" YW p.2499.
- **In severe compression the cord can be crushed to 2 mm** — "The diameter of the spinal cord in transverse section is **reduced to 2 mm in some severe cases**" YW p.2478.

11. Blood supply to add to the label list

- **The denticulate ligament divides the cord's circumference** and is the surgical landmark: "**most (96%) spinal cord hemangioblastomas are located posterior to the dentate ligament**", so a **direct posterior approach** is used; tumours **anterior to the dentate ligament** need an anterior or anterolateral approach YW p.1177.
- **Anterior spinal artery** — "At the level of the foramen magnum, before the [vertebral artery] converges to the basilar artery, **one branch from each side converges downward to form the anterior spinal artery, which then courses along the anterior median sulcus of the spinal cord and terminates with the filum terminale**... **The ASA mainly supplies the anterior two-thirds of the spinal cord**" [YW pp. 84-85]. It is reinforced by anterior segmental medullary arteries, "the largest of which is called the **artery of Adamkiewicz**... typically arises from the **left posterior intercostal artery between T9 and L2**" YW p.84.
- **Posterior spinal arteries** — "appear in **pairs** and arise from the **vertebral artery or posterior inferior cerebellar artery**... They **descend along the posterolateral spinal cord** and are reinforced by several posterior segmental medullary arteries... **Posterior spinal arteries supply the posterior third of the spinal cord**" YW p.85.
- **The watershed** — "The thoracic spinal cord between **T4 and T9 is poorly vascularized. This region is termed the critical vascular zone of the spinal cord and corresponds to the narrowest region of the spinal canal**" YW p.84; "The ASA has its **smallest diameter in this region**" YW p.85.
- **Radicular arteries** — "run along with the anterior and posterior roots... and provide blood supply to **nerve roots**... **unlike segmental medullary arteries, radicular arteries do not join the anterior or posterior spinal arteries**" YW p.85.
- **The perforators are the surgical danger** — the ventral perforators enter the ventral surface of an intramedullary tumour and are the site of the most feared complication: "there is a **risk for disseminated thrombosis, either into the**

anterior spinal artery or into branches supplying the interior of the spinal cord" YW p.2005.

- **Venous drainage and pathology** — "Pathologic changes in the venous system are also seen... There are prominent **thick-walled vessels, predominantly venules**, within and around the cysts that are accompanied by **dilated perivascular spaces**. Thus **venous congestion, chronic hypoxia, and subsequent necrosis** play a significant role" in chronic compressive myelopathy YW p.2479.
- **Microvasculature** — in degenerative cervical myelopathy, "chronic cord compression results in **stretching, flattening, and loss of the penetrating branches of the lateral pial arterial plexus**" YW p.2518.

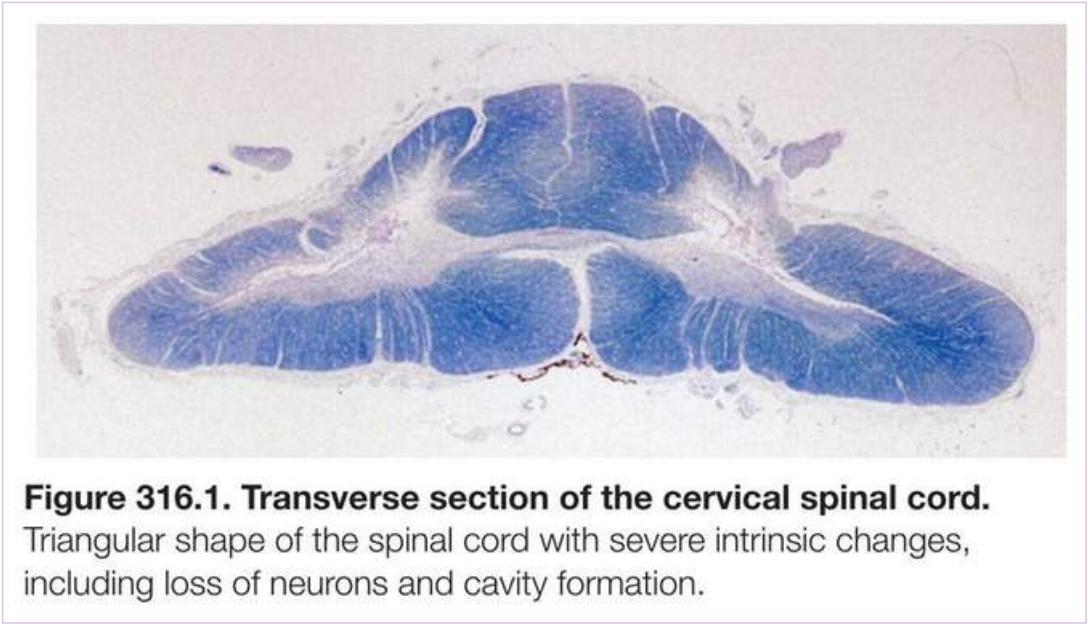


Figure 316.1. Transverse section of the cervical spinal cord.
Triangular shape of the spinal cord with severe intrinsic changes, including loss of neurons and cavity formation.

Reproduced from Youmans & Winn 8e, Fig. 316.1, p. 2478 — Label when you reproduce it: transverse section of the cervical spinal cord — anterior median fissure with the anterior spinal artery, anterolateral sulcus and ventral rootlets, dorsolateral sulcus and dorsal rootlets, posterior median sulcus; the dorsal columns (fasciculus gracilis medially, fasciculus cuneatus laterally), the lateral corticospinal tract, the lateral spinothalamic tract, the central canal and the H-shaped grey matter with its dorsal, lateral and ventral horns.

12. Points that earn extra marks

- **Say why the classification matters operatively.** "The majority of IDEM tumors can be approached via a **straightforward posterior midline incision and laminectomy**" YW p.2547, whereas an intramedullary tumour demands a **midline myelotomy, intraoperative ultrasound, D-wave monitoring** and a plane that may not exist [YW pp. 2005, 2571].
- **Say what changes the plan**: "**More challenging... are those tumors with large extradural components (whether dumbbell tumors or purely extradural tumors), multicompartmental tumors, anteriorly or ventrally situated tumors, malignant or adherent/invasive tumors, tumors whose excision requires extensive bone removal that may require instrumentation, and tumors in which the involved nerve root is functional**" YW p.2548.
- **Name the one intradural tumour that must not be watched** — "Surgery is not undertaken for diagnosis alone, and watchful waiting and serial MRI may be pursued. **Notable exceptions include midline cauda equina lesions (i.e., myxopapillary ependymoma), given a concern for CSF seeding**" YW p.2548.
- **Finish with the outcome figure** — "When gross total resection is achieved, oncologic outcomes for spinal meningiomas are quite good... **low incidence of recurrence — anywhere from 3.7% to 14.7%**. **Complete resection has been reported as achievable in up to 80% to 97% of patients**, with subtotal resection associated with a higher risk of local recurrence" YW p.2553.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Two cuts define the classification**: dura (extradural vs intradural) then pia (extramedullary vs intramedullary). Then histology.
- **IDEM ≈ 25% of spinal tumours; intramedullary 5%-10% in adults and ~35% in children.**
- **Meningioma is the commonest intradural spinal tumour overall**; ependymoma is the commonest intramedullary tumour in adults; astrocytoma in children under 10.
- **The "CSF cap" and cord DISPLACEMENT mean extramedullary; cord EXPANSION means intramedullary.**
- **Central on axial MRI = ependymoma. Eccentric = astrocytoma or ganglioglioma.**
- **Dural tail = meningioma. Target sign / string of beads = neurofibroma. Dumb-bell across the foramen = nerve sheath tumour.**
- **20 to 22 paired denticulate ligaments** anchor the cord; **96% of cord haemangioblastomas lie posterior to the denticulate ligament**.
- **31 pairs of roots; 8 cervical nerves but 7 cervical vertebrae** — C1 exits above C1, C8 below C7.
- **The DREZ is widest cervically (7) and narrowest sacrally (3); the dorsal horn is deepest thoracically** — which is why thoracic dorsolateral entry threatens the corticospinal tract and dorsal column.
- **Cord AP diameter 5-6 mm; normal cervical canal 17-18 mm; absolute stenosis ≤10 mm; relative stenosis 12-13 mm; Torg-Pavlov ratio ≤0.8.**
- **Grey matter suffers before white matter in chronic compression** — the "butterfly pattern of cord ischaemia".
- **Myxopapillary ependymoma at the cauda equina is the one intradural tumour you should not simply watch** — it seeds the CSF.
- **Multiple intradural tumours or a young patient = image the whole neuraxis and look for a syndrome** (NF1 chr 17, NF2 chr 22, schwannomatosis, Carney, VHL 3p25-26).

Pages read for this answer — Youmans & Winn 8e: 84, 85, 1177, 1572, 1995, 1996, 1997, 1998, 1999, 2001, 2002, 2005, 2397, 2399, 2467, 2478, 2479, 2499, 2518, 2519, 2547, 2548, 2553, 2570, 2571, 2572

a) Describe MRC motor grading. [4]
b) Describe the clinical features and management of spinal intramedullary tumours. [6]

LONG | APR 2023 · Paper II · Q5 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 272 *Peripheral Nerve Examination, Evaluation, and Biopsy*, §Motor Examination, p. 2087 (**Table 272.1 — British Medical Research Council Motor Function Grading Scale**, p. 2087). Supplementary: Ch. 284 *Nerve Injuries of the Lower Extremity*, p. 2195 (**Table 284.1 — British Medical Research Council Scale of Muscle Recovery for Entire Nerve**, p. 2195); Ch. 9 *Classification Systems in Neurosurgery*, pp. 133-134; Ch. 329 *Evaluation and Treatment of Malignant Primary Spinal Tumors*, §Introduction, §Malignant Astrocytomas, §Anaplastic Ependymomas and §Rare Malignant Intradural Intramedullary Tumors, pp. 2570-2575 (Figs. 329.1 and 329.2, pp. 2571 and 2573; **Table 329.1**, p. 2571); Ch. 263 *Tumors of the Spine, Spinal Canal, and Spinal Cord in Children*, §Pathology, §Presentation, §Diagnostic Evaluation, §Treatment: Surgery and §Treatment: Alternative and Adjuvant Therapeutics, pp. 1995-2010 (Figs. 263.1, 263.3 and 263.5, pp. 2000-2001); Ch. 167 *Hemangioblastomas*, §Spinal Cord Hemangioblastomas, pp. 1177-1179 (Fig. 167.5, p. 1178); Ch. 309 *Electrophysiologic Studies and Monitoring*, pp. 2429-2430; Ch. 208 *Dorsal Root Entry Zone Lesions for Pain*, p. 1572 (Fig. 208.1, p. 1572); Ch. 321 *Evaluation and Treatment of Degenerative Cervical Myelopathy*, **Table 321.1 mJOA**, p. 2519.

(a) Describe MRC motor grading [4]

1. Origin, status and why it is used

- **The scale is a peripheral nerve classification that has become universal.** "**Peripheral nerve surgery employs a number of well-known classification systems, including the British Medical Research Council (MRC) grading system for muscle strength, which has become universally used in neurologic and neurosurgical practice**" YW p.133.

- **It is a purely descriptive classification** — Youmans lists it with the WHO classification of CNS tumours and the modified Rankin Scale as "**examples of purely descriptive classification systems**", i.e. it categorises without itself directing therapy YW p.134.
- **Source document** — the scale is "**Modified from Medical Research Council. Aids to the examination of the peripheral nervous system, Memorandum no. 45, Her Majesty's Stationery Office, London, 1981**" YW p.2087; the older recovery version derives from "**Medical Research Council. Aids to the Examination of the Peripheral Nervous System [pamphlet]. Memorandum No. 45. London: Her Majesty's Stationery Office; 1976**" and **Seddon H, Peripheral Nerve Injuries, MRC Special Report Series No. 282, 1954** YW p.2195.
- **Where it sits in the examination** — "**Motor testing is perhaps the most objective and reproducible aspect of the neuromuscular examination.** Adhering to the principles outlined earlier, the examiner **compares the involved versus normal extremity with respect to bulk, tone, and strength**. As indicated, **each individual muscle is tested. Strength is rated using the British Medical Research Council system**" YW p.2087.

2. The scale itself

Table 1 · British Medical Research Council motor function grading scale — reproduced in full from Youmans & Winn 8e, Table 272.1, p. 2087 (modified from Medical Research Council, Aids to the Examination of the Peripheral Nervous System, Memorandum no. 45, HMSO, London, 1981).

Grade	Function
5	**Full normal strength**
4	**Full range of motion, active movement against resistance** (**4−** slight resistance; **4** moderate resistance; **4+** strong resistance)
3	**Full range of motion, active movement against gravity only**
2	**Full range of motion, active movement with gravity eliminated**
1	**Muscle contraction but no movement**
0	**No muscle contraction**

- **Note the two details students omit.** First, grades 3, 2 and 1 are all defined against a **full range of motion** — a muscle that moves through only part of its arc is not simply "grade 3". Second, **grade 4 is subdivided 4−, 4 and 4+** because it is the widest and least discriminating grade YW p.2087.

3. The companion scale — MRC recovery grading for a whole nerve

Table 2 · British Medical Research Council scale of muscle recovery for an entire nerve — reproduced in full from Youmans & Winn 8e, Table 284.1, p. 2195 (from MRC Memorandum No. 45, HMSO 1976, and Seddon H, MRC Special Report Series No. 282, 1954).

Grade	Description
M0	**No contraction**
M1	**Return of perceptible contraction in proximal muscles**
M2	**Return of perceptible contraction in proximal and distal muscles**
M3	**All important muscles contract against resistance**[a]
M4	**All synergistic and independent movements are possible**
M5	**Full recovery of all muscles**

[a] "**A grade of 3 for an individual muscle represents only contraction against gravity**" YW p.2195 — this footnote is the source of most confusion and is worth quoting, because M3 for a whole nerve is not the same as grade 3 for one muscle.

- **How the recovery scale is used as an outcome measure** — surgical series report success as "**Louisiana State University Health Sciences Center (LSUHSC) grade 3 or better or British Medical Research Council (BMRC)**

grade 4 or better" YW p.2195; nerve transfers are judged by whether they achieve "**MRC grade M3 strength or [better]**" YW p.2170.

4. How to apply the scale correctly at the bedside

- **Inspect and palpate together.** "When testing a muscle, it is important to **both inspect movement and palpate the muscle being examined. This allows detection of even trace contractions, which may not even result in movement** " — i.e. the difference between grade 0 and grade 1 YW p.2087.
- **Test with and without gravity.** "**Paretic muscles need to be tested both without and with the aid of gravity. To eliminate gravity, special maneuvers may need to be undertaken.** For example, having the patient **supine while testing for lateral abduction of the shoulder will eliminate gravity when testing supraspinatus and deltoid muscles**. Similarly, a supine patient can **rest the arm on the chest wall and then be asked to flex the hand toward the head**, thus allowing the elbow flexors to contract with the effects of gravity minimised" YW p.2087 — this is how you separate grade 2 from grade 3.
- **Record variable strength across the arc.** "**Variable strength over a reduced range of motion is common when patients partially recover. This should be accurately documented**" YW p.2087.
- **Measure the bulk objectively.** "**Muscle atrophy is often obvious during the visual inspection...** When possible, an **accurate assessment of muscle bulk using a tape measure** should be performed. In doing this, the examiner should first **mark the extremity from a fixed bony landmark** to compare comparable areas on the affected and unaffected limbs **during serial examinations**" YW p.2087.
- **Test every muscle when the diagnosis is uncertain, then narrow.** "It is important to **thoroughly test all muscles when the diagnosis remains uncertain**. However, as the lesion becomes better localized, a **more focused motor examination** can be used to isolate the lesion to a single nerve, or even within a segment of the nerve. This is accomplished by **testing sequential muscles innervated by the nerve in question and by confirming the normal examination of a nearby nerve**" YW p.2087.
- **Complicated plexus lesions need the whole map.** "Complicated injuries to the **brachial plexus and lumbosacral plexus** often require a **comprehensive strength assessment of all regional muscles** to provide the best localization" YW p.2087.
- **Exclude the orthopaedic confounder before you grade.** "**Mechanical joint pain or stiffness should be noted during movement, which may warn the clinician of a nonneurological cause of, or contribution to, the patient's inability to move** (e.g., fracture pseudarthrosis, joint dislocation)" YW p.2087 — an MRC grade is invalid if the joint will not move.

5. Limitations, and the scales used instead in spinal cord disease

- **Interrater reliability is the Achilles heel of any descriptive scale.** Youmans discusses "**validity, consistency, and quantification**" as the three properties that matter, where **consistency** "encompasses **interrater reliability and intrarater reliability**" — the probability that independent examiners assign the same case to the same class YW p.134.
- **Grade 4 is too broad**, which is why the **4−/4/4+ subdivision** exists at all YW p.2087.
- **For spinal cord disease, a composite functional scale is used instead.** The **modified Japanese Orthopaedic Association (mJOA) scale** "is scored from **0 (worst function) to 18 (normal function)** and evaluates four domains: **upper limb motor function (5 points), lower limb motor function (7 points), upper limb sensory function (3 points), and sphincter function (3 points)**"; guidelines stratify disease as **severe ≤11, moderate 12-14, mild 15-17** YW p.2519.
- **The Nurick grade** is the older ambulation-based alternative: **0** root signs only; **I** cord signs without walking difficulty; **II** slight difficulty walking not preventing full-time employment; **III** difficulty preventing employment or housework but not requiring help; **IV** able to walk only with help or a frame; **V** chairbound or bedridden YW p.2519.
- **The practical answer**: use **MRC grading for individual muscles and roots**, and **mJOA or Nurick for the myelopathy as a whole** — the examiner will credit you for knowing both belong in the same clerking.

(b) Clinical features and management of spinal intramedullary tumours [6]

6. Epidemiology and histology — the frame for the answer

- **Primary spinal cord tumours account for 2%-8% of all CNS tumours in adults**; the majority are benign, with **less than one-third malignant** YW p.2570.
- **Primary intradural intramedullary tumours make up 5%-10% of spinal column tumours in adults and about 35% in children** YW p.2570.
- **Glial tumours dominate** — "**Primary glial tumors make up more than 80% of these intramedullary tumors** and include **astrocytomas, ependymomas**, and less common neoplasms such as **gangliogliomas, oligodendrogliomas, and subependymomas**" YW p.2570; Youmans states as a key concept "**Eighty percent of intramedullary spinal cord tumors (IMSCTs) have a glial or glial-neuronal cell type**" YW p.1995.
- **Age reverses the histology** — "**In adults, ependymomas are the most common intramedullary tumor, accounting for 50%-70% of lesions**, with the remaining portion primarily consisting of astrocytomas. **This trend is reversed in younger children, with astrocytomas predominating in those under the age of 10**" YW p.2570.
- **Demographics** — "**the average age at presentation has been estimated to be approximately 35-39 years, with a slightly higher incidence in males**" YW p.2570. Paediatric IMSCTs occur at **0.1 to 0.26 per 100,000**; **5.1% of CNS tumours occur within the spinal cord or cauda equina, with 4.2% solely as IMSCTs**, giving roughly **170 to 180 IMSCTs per year in the United States** YW p.1995.
- **Grades of astrocytoma** — "**10%-15% of them are classified as high grade (WHO grade III or IV)**. The majority of these are classified as **anaplastic astrocytomas (WHO grade III)**, but approximately **0.2%-1.5% are glioblastoma multiforme (WHO grade IV)**" YW p.2570.
- **Rare intramedullary entities to name**: gangliogliomas and oligodendrogliomas "**account for only 1%-2% [of] spinal cord tumors**" YW p.2572; **anaplastic ependymoma <2% of intraspinal ependymomas** YW p.2572; only "**a little over 50 cases**" of spinal intramedullary oligodendroglioma are reported YW p.2573; **primary CNS melanoma is 1% of melanomas**, and primary spinal cord melanoma is rarer still, "the majority of these lesions are intramedullary" YW p.2574.

7. Clinical features

7.1 Pain — first, focal, and nocturnal

- "The most common presentation is **focal back pain, typically localized to the segments directly over the tumor**. Classically, this pain is differentiated from more common forms of back pain in that it will **worsen at night when the patient is lying down due to increased venous engorgement and increased local mass effect of the tumor**" YW p.2570.
- In children, "this pain can be **particularly intrusive at night**" YW p.1998.

7.2 Motor and sensory deficits

- "In addition to pain, **deficits of either the sensory or motor tracts are common and occur in approximately half of patients**. These include signs of **myelopathy and upper motor neuron disease, such as spasticity, hyperreflexia, and extensor plantar signs** on examination" YW p.2570.
- **Cervical cord tumours start in the arms** — "Loss of motor function seems initially to be **limited to the upper extremities with progression to involve the legs, bowel, and bladder only late**" YW p.1998.
- **Sensory findings lag and are usually unilateral** — "**Sensory abnormalities trail the motor deficits** and are more limited, typically being **unilateral**. **When the sensory abnormalities are symmetrical, the diagnosis of ependymoma should be suspected**" YW p.1998.
- **Dysaesthesia without sensory loss is the ependymoma marker** — "a predilection to present with **dysesthesias but not sensory loss**... thought to stem from the **central location of these tumors, resulting in preferential disruption of**

crossing spinothalamic fibers" YW p.2572.

7.3 Sphincter and autonomic disturbance

- "**Bowel and bladder dysfunction are less common, and are typically indicative of more advanced disease**, but can be seen earlier on in lesions located in the conus medullaris" YW p.2570.
- Conus lesions reverse the order — early bowel and bladder involvement, "resulting in a history of **frequent urinary tract infections**" YW p.1999.

7.4 Presentation by level (a good structure for the answer)

- **Cervicomedullary junction** — "indications of **brainstem involvement such as nausea and vomiting, history of recurrent upper respiratory tract infections, and the development of a nasal quality in their speech**" YW p.1998.
- **Cervical** — "**neck pain with or without radiation into one or both arms**", nocturnal, plus upper-limb-first weakness YW p.1998.
- **Thoracic** — "a **more insidious onset. The first manifestations are usually pain and progressive scoliosis**. Not uncommonly these children are simply **followed for idiopathic scoliosis**"; **abdominal pain** in young patients sends them to gastroenterology first; examination shows **paraspinal spasm and myelopathy** [YW pp. 1998-1999].
- **Conus/cauda** — bowel and bladder first YW p.1999.

7.5 Paediatric-specific features

- **Presenting complaints in rank order** — "**motor regression, which occurred 65% of the time**... followed by **pain (48%), gait abnormality (37%), dysesthesia (32%), and progressive kyphoscoliosis (32%)**" YW p.1998.
- "Depending on the developmental age of the child, this can present as **alterations of a previously normal gait, increased clumsiness, more frequent falls, or the development of scoliosis**. In younger children, **motor regression** is a commonly reported symptom, where **children who previously had learned to walk or stand subsequently refuse to do so**" YW p.2570.
- "In younger children the parents may report that their child has seemed to **switch hand dominance**; parents of older children note **frequent tripping or falling**" YW p.1998.
- **Diagnostic delay is the rule** — "The onset of symptoms in children harbouring an IMSCT is usually realized **in retrospect, predating the actual diagnosis by months if not a year or more**" YW p.1998.

7.6 Features that signal malignancy

- "**Malignant lesions, however, often have a more rapid progression of symptoms**, with diagnosis typically occurring **months after initial symptoms** occur due to the severity" YW p.2570.
- **Hydrocephalus** — "there is a **significantly higher incidence in those with high-grade lesions**" YW p.2570.
- **Leptomeningeal dissemination** — "Rates of leptomeningeal dissemination as high as **47%-58%** have been reported, and this is associated with **decreased survival**. One study showed that patients with **localized anaplastic astrocytoma had 25-fold increased survival time compared to those with disseminated disease**" YW p.2570.
- **Spontaneous intratumoural haemorrhage** with fluctuating symptoms suggests **oligodendroglioma** YW p.2573; **elevated intracranial pressure from leptomeningeal spread** is also described for that histology YW p.2573.

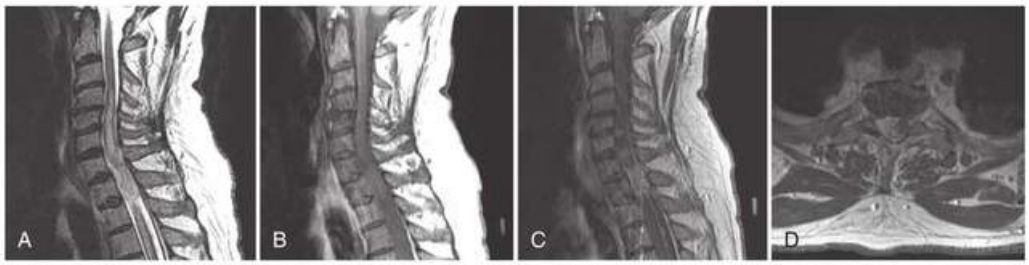


Figure 329.1. High-grade astrocytoma. A 58-year-old man presented with several weeks of back and chest pain as well as worsening right leg weakness. He also reported decreased sensation in his chest and legs. (A) Spinal magnetic resonance imaging was obtained, demonstrating a hyperintense intramedullary lesion on T2-weighted images in the cervical and cervicothoracic lesion that expanded and distorted the cord. (B and C) T1-weighted image (B) demonstrates isointense signal characteristics that heterogeneously enhanced in the C7–T1 region with contrast administration (C). (D) Axial T1-weighted image after contrast enhancement showed asymmetrical growth of the cord, with displacement of nonenhancing portions toward the left of the canal. The patient underwent a C5-to-T2 laminectomy and tumor biopsy. Pathology confirmed the presence of a high-grade astrocytoma.

Reproduced from Youmans & Winn 8e, Fig. 329.1, p. 2571 — Label when you reproduce it: high-grade astrocytoma in a 58-year-old man with weeks of back and chest pain, worsening right leg weakness and decreased sensation in chest and legs. (A) T2 sagittal — hyperintense intramedullary lesion in the cervical and cervicothoracic cord that EXPANDS AND DISTORTS the cord; (B and C) T1 isointense, heterogeneously enhancing at C7-T1 after contrast; (D) axial T1 post-contrast — ASYMMETRICAL growth with non-enhancing portions displaced to the left. He underwent C5-T2 laminectomy and biopsy.

8. Investigations

- **MRI is the cornerstone** — "As with most other spinal tumors, imaging is the cornerstone to further evaluation after a proper history and physical" YW p.2571. The minimum protocol is **T1 ± gadolinium plus T2 in axial and sagittal planes**; "**Anything less will compromise one's interpretation of the imaging**"; add **gradient echo** for haemosiderin, **FLAIR** for subtle lesions, **DWI** for infarct and inclusion cysts YW p.1999.
- **The MRI features by histology** are set out in Table 3 below.
- **Table 329.1 is the checklist to reproduce** — history items, imaging work-up (spinal MRI; attention to asymmetry and infiltrative borders; **craniospinal imaging** if leptomeningeal spread is suspected; **CT** for bony anatomy and instrumentation; **systemic cancer screening with CT chest/abdomen/pelvis and/or PET-CT**; **vascular imaging in diffuse cord oedema to exclude a dural AV fistula, i.e. Foix-Alajouanine syndrome**), surgical planning and postsurgical management YW p.2571.
- **Exclude the mimics** — "it is important to rule out the possibility of other lesions that can appear similar to intramedullary spinal tumors on MRI, such as **multiple sclerosis, transverse myelitis, cord infarction, or a dural arteriovenous fistula**" YW p.2571. In children, "**when the size is subtle or not consistent with the degree of T2 signal hyperintensity (i.e., edema), then one should consider an inflammatory process such as multiple sclerosis or transverse myelitis. Scanning of the brain and a delayed, repeat imaging examination 3 to 6 months later will clarify the situation**" YW p.1999.
- **Angiography for a suspected haemangioblastoma** — "These tumors **markedly enhance on angiography**, showing **feeding arteries coming off the anterior and posterior spinal arteries and large draining veins**... therefore **angiography should be considered for a large tumor resembling a hemangioblastoma. Embolization is not indicated if there is significant risk of interrupting collateral circulation to the cord**" YW p.2000.

Table 3 · MRI signatures of the intramedullary tumours — from Youmans & Winn 8e, Ch. 263 §Diagnostic Evaluation, pp. 1999-2002; Ch. 329 §Malignant Astrocytomas and §Anaplastic Ependymomas, pp. 2571-2573.

Tumour	Epicentre	Length	T1	T2	Enhancement	Cysts / other
Astrocytoma	**Eccentric**	**4 segments** (malignant: **<4** segments, fusiform)	**>80% hypointense**, ~20% isointense	Hyperintense but **inhomogeneous**, unlike oedema	Enhances; **walls of tumoral cysts also enhance**; high grade shows **patchy enhancement, haemorrhage, necrosis**	Tumoral and reactive cysts; **margins blur into cord**

Ependymoma	**Central, symmetrical expansion**	**4 segments**	Iso-/hypointense	Hyperintense, FLAIR bright	**Homogeneous** (14/16 enhance)	**~2/3 have cysts**; **haemosiderin cap** in 20%-60%; sharp plane with cord
Ganglioglioma	**Eccentric**	**8 segments** (all holocord tumours)	**Mixed intensity** in the majority	60% homogeneous, 40% heterogeneous	**Patchy 65%, focal 19%, none 15%**	**Cysts in 46%** — commonest
Haemangioblastoma	Dorsal, often subpial; **96% posterior to the denticulate ligament**	Small (**most ≤1 cm**)	Iso-, hypo- or mixed	Usually hyperintense	**Vivid**; homogeneous when small, heterogeneous when large	**Syrinx/cyst in >50%**; **flow voids in tumours >1.5 cm**; mural nodule on a cyst wall
Cavernous malformation	Intra-axial, ~1 cm	1 segment	Hyperintense centrally with **mixed signal of different-aged blood**	Central hypointensity with small hyperintense areas; **hemosiderin ring larger than on T1**	None significant	**"Target sign"**; may have an associated venous angioma (flow void)
Myxopapillary ependymoma	Conus/cauda/filum	Variable	**Iso- to hyperintense**	Hyperintense	**Vivid**	**Intratumoral haemorrhage**; **T2 hypodensity = remote haemorrhage, highly suggestive**; **posterior vertebral scalloping**

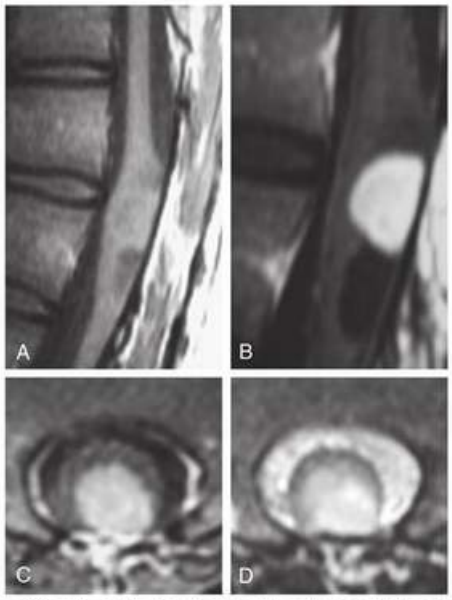


Figure 263.1. Juvenile pilocytic astrocytoma in the midthoracic spinal cord. (A) T1-weighted sagittal MR image showing an isointense tumor and cyst caudal to it. (B) The same tumor after gadolinium enhancement (T1-weighted sagittal MR image). (C) T1-weighted axial MR image of the same tumor showing its eccentricity, and (D) an axial T2-weighted MR image with an inhomogeneous appearance of the same tumor. (*Courtesy Rick Abbott, MD.*)

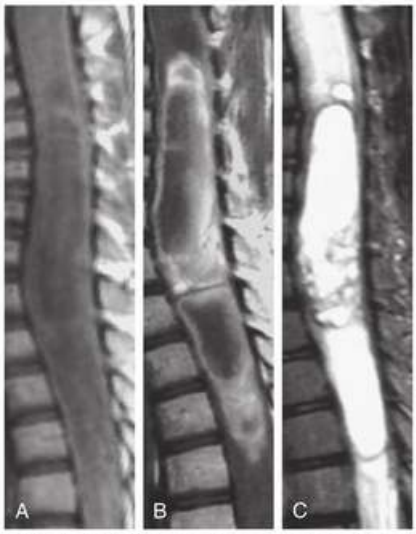


Figure 263.2. Sagittal MR images of a ganglioglioma. (A) T1-weighted image showing a hypodense intramedullary lesion spanning nine levels of the spine. (B) T1-weighted image after gadolinium enhancement. (C) T2-weighted image of the same tumor. (*Courtesy Rick Abbott, MD.*)

will be seen in tumors larger than 1.5 cm. Some can also show extensive, reactive edema.[73] These tumors markedly enhance on angiography, showing feeding arteries coming off the anterior and posterior spinal arteries and large draining veins. In some tumors this information can be helpful in surgical planning; therefore

Reproduced from Youmans & Winn 8e, Fig. 263.1, p. 2000 — Label when you reproduce it: juvenile pilocytic astrocytoma in the midthoracic cord. (A) T1 sagittal — isointense tumour with a cyst caudal to it; (B) the same after gadolinium; (C) axial T1 showing its ECCENTRICITY; (D) axial T2 with the characteristically inhomogeneous appearance. Panel C is the one to point at when asked how astrocytoma differs from ependymoma.

CHAPTER 16

Functional Neurosurgery, Epilepsy, Pain & Movement Disorders

30 QUESTIONS SOLVED

Epilepsy Surgery & Drug-Resistant Epilepsy — 11 questions

Pre-surgical evaluation & surgical approaches in Pediatric epilepsy.

LONG | DEC 2020 · Paper III · Q3 | 10 marks

Also asked as: Epilepsy surgery — also asked as DEC 2021 · Paper III · Q9 (Drug resistant epilepsy: a] Preoperative evaluation [5]; b] Surgical techniques for managing drug resistant epilepsy [5]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 267 *Pediatric Epilepsy Surgery* (S. Ghatan), §Epilepsy and the Developing Brain, §The Path to Pediatric Epilepsy Surgery, §Epilepsy Classification, §Presurgical Evaluation, §Surgical Approaches: Diagnostic and/or Therapeutic, pp. 2039-2045 (Fig. 267.1, p. 2040; Fig. 267.2 — evaluation and surgery protocol, p. 2041; Figs. 267.3-267.4, p. 2043; Figs. 267.5-267.6, pp. 2044, 2046). Supplementary: Ch. 83 *Evaluation of Patients for Epilepsy Surgery*, §Goals of Presurgical Evaluation, §Necessary Techniques for Localisation of the EZ, §Additional Diagnostic Testing, §Invasive Evaluation Techniques, pp. 503-506 (Fig. 83.1, p. 505); Ch. 84 *Magnetic Resonance Imaging for Epilepsy Surgery*, §Structural Cerebral Abnormalities, pp. 508-511, 515 (Figs. 84.1-84.5, pp. 508-511); Ch. 79 *Malformations of Cortical Development*, §Focal Cortical Dysplasias, §Surgery for MCD, pp. 488.e3-488.e7; Ch. 90 *Intracranial Monitoring: Stereo-electroencephalography Recording*, pp. 563-568; Ch. 99 *Hemispheric Disconnection Procedures*, pp. 636-644; Ch. 96 *Palliative Procedures for Drug-Resistant Epilepsy*, pp. 615.e1-615.e10; Ch. 100 *Electrical Stimulation for Epilepsy (VNS, DBS, and RNS)*, pp. 646-665.

(a) Pre-surgical evaluation in paediatric epilepsy [4]

1. Why the child is referred at all — the case that must be made before any test

- **Epilepsy in the developing brain is not a benign waiting game.** Youmans opens the paediatric chapter with the statement that "epileptic encephalopathy, neuronal and synaptic damage, and prevention of maturation because of repeated seizures present great risk to the cognitive and sensorimotor development of the pediatric brain" YW p.2039.
- **Intellectual dysfunction correlates directly with severity of epilepsy, particularly during the first few years of life**; global motor development can be delayed, and focal sensorimotor dysfunction can result from lateralised or regionalised epilepsy YW p.2039.
- **Antiseizure medications themselves carry a burden** — they "can adversely affect systems that include but are not limited to cognitive, visual, hematopoietic, dermatologic, immune, and reproductive" systems, plus a financial burden on the family YW p.2039.
- **Social cost** — ongoing seizures are "synonymous with educational impediments giving way to difficulty with employment and economic productivity," and children with epilepsy are less likely to develop normal social and romantic relationships. **Autism spectrum disorder (ASD) and epilepsy are commonly linked, and the former's severity is exacerbated by the latter**; ADHD, anxiety and depression are well-known psychiatric comorbidities YW p.2039.
- **Mortality is the argument that ends the discussion** — "mortality risk is 90-fold higher in children with medically intractable epilepsy in comparison to their healthy counterparts, and epilepsy is the most common cause of sudden death in children." The **cumulative risk of SUDEP over a childhood/adolescence is 10% over 20 years** and must be weighed in surgical decision making YW p.2039.
- **Epilepsy surgery remains underused in the paediatric population** YW p.2039; parents describe the journey as "a trip around the world" or "five years of hell," and Youmans explicitly recommends a **nurse navigator / "champion"** to shepherd families through insurance, second opinions and peer support [YW pp. 2039, 2040].

2. The entry criterion — definition of drug resistance in children

- **The criterion is identical to that in adults**: "additional medical therapies are unlikely to succeed in controlling seizures if epilepsy is refractory to two or more medications" YW p.2039. Ch. 83 gives the same operational definition — "pharmacoresistant epilepsy, defined as a failure to respond to two or more appropriately chosen and used antiepileptic medications" YW p.503.
- **Expeditious referral to a comprehensive epilepsy centre is critical**, because "with modern diagnostic and therapeutic approaches, many more children are candidates for epilepsy surgery than ever before" YW p.2039.
- **Class I evidence supports surgery over medical therapy in children**: the landmark randomised trial of Wiebe and Engel's early-surgery study in adults have been "augmented with an RCT in pediatric epilepsy surgery by Dwivedi revealing similar results, despite less defined epilepsy networks and more extratemporal and multifocal cases encountered in children" YW p.2042.

3. The goal of the evaluation — two questions, not one

- **Question 1 — where is the epileptogenic zone (EZ)?** "The main goal of epilepsy surgery is the complete resection (or ablation) of the cortical area(s) responsible for the generation of seizures, the epileptogenic zone" YW p.503. Whether conceptualised as a focus or a network, an **anatomo-electro-clinical (AEC) hypothesis** must be formulated before surgery can be planned YW p.503.
- **Question 2 — how much does the EZ overlap eloquent cortex?** "Because the EZ may anatomically overlap with functional (eloquent) cortex, an additional and equally important goal of the presurgical evaluation is determining the extent to which the EZ overlaps with eloquent cortex" YW p.503.
- **The surgical team's task in a child** is "the identification and understanding of epileptogenic networks and their disruption, whether this involves a discrete focus, a zone of onset, a regionalized network, multifocal nodes, and even bilateral onsets" YW p.2042.

4. Classification first — speak the ILAE 2017 language

- **The 2017 ILAE framework has three levels**: (1) **seizure type** — focal, generalised or unknown onset; (2) **epilepsy type** — focal, generalised, combined generalised and focal, unknown; (3) **the specific epilepsy syndrome**. Superimposed are six **aetiologic categories: structural, genetic, metabolic, infectious, immune and unknown**, which are not mutually exclusive YW p.2040.
- **Terminology changes the examiner will test** — *partial* has become *focal*; *simple partial*, *complex partial*, *psychogenic* and *secondarily generalized* have been eliminated; new focal seizure descriptors are automatisms, autonomic, behavioural arrest, cognitive, emotional, hyperkinetic, sensory and focal-to-bilateral tonic-clonic; atonic, clonic, epileptic spasms, myoclonic and tonic seizures may be focal **or** generalised; new generalised types include eyelid myoclonia, myoclonic absence, myoclonic-tonic-clonic, myoclonic-atonic and epileptic spasms YW p.2040.
- **"Developmental and epileptic encephalopathy"** is the new term for the deleterious consequences of seizures at any age YW p.2040.

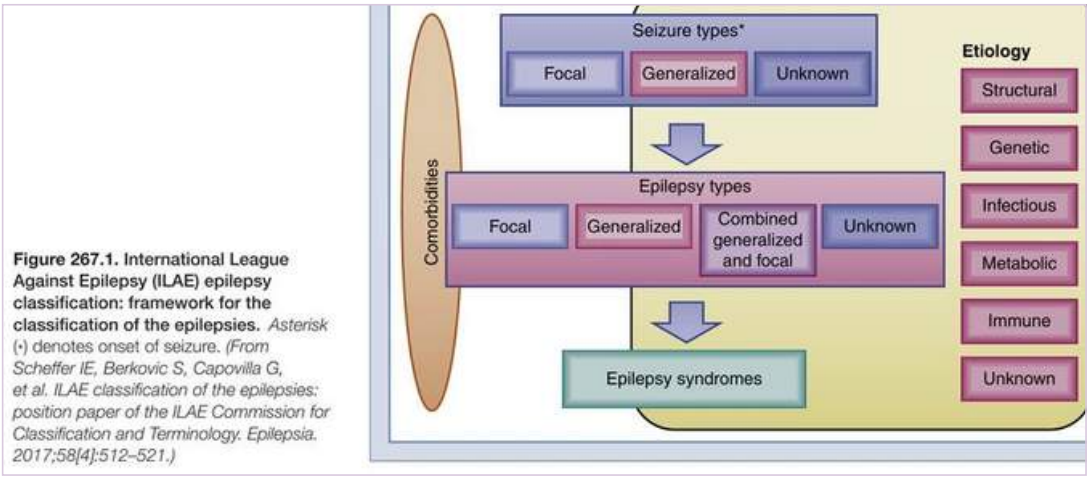


Figure 267.1. International League Against Epilepsy (ILAE) epilepsy classification: framework for the classification of the epilepsies. *Asterisk (•) denotes onset of seizure. (From Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58[4]:512–521.)*

Reproduced from Youmans & Winn 8e, Fig. 267.1, p. 2040 — Label when you reproduce it: the ILAE 2017 three-level framework — seizure types (focal / generalised / unknown onset) feeding into epilepsy types (focal, generalised, combined generalised and focal, unknown), then epilepsy syndromes, with the aetiology column (structural, genetic, infectious, metabolic, immune, unknown) running alongside and comorbidities boxed at the side.

5. Phase I — the four non-negotiable mainstays

Youmans states that "the mainstays for diagnostic testing and establishment of surgical candidacy revolve around the clinical history, video-electroencephalography (video-EEG), MRI, and neuropsychological testing" YW p.2041.

1. **Clinical history** — "requires special attention to the gestational and developmental history, age at onset of seizures, semiology, frequency of seizures, genetic testing, and medication side effects" YW p.2041. In Ch. 83 the aura is singled out: "a clear description of the seizure semiology (symptoms and signs) and in particular the aura, if present, is the most important step in an epilepsy surgery evaluation," to be corroborated by family or witnesses and later compared with recorded seizures YW p.503. Risk factors to elicit: **febrile convulsions, prior head injury, CNS infection**, and a family history of seizures YW p.503.
2. **Video-EEG in a dedicated epilepsy monitoring unit** — "24 hours or longer in duration, requires analysis of both interictal and ictal findings" YW p.2041. It is needed both to **confirm** that the events are epileptic and to generate the electroclinical half of the AEC hypothesis YW p.504. Electrode arrays are tailored to the hypothesis: inferior temporal electrodes for a suspected mesial temporal onset; additional central/parietal electrodes when a somatosensory aura suggests posterior perisylvian involvement; multiple seizures must be recorded when hippocampal atrophy is bilateral YW p.504.
3. **Epilepsy-protocol volumetric MRI (1.5 or 3 T)** — "the standard to assess for malformations of cortical development (MCDs) and other structural epileptogenic abnormalities" YW p.2041. The **HARNESS-MRI protocol** comprises a 3D volumetric T1, a 3D FLAIR and a 2D coronal T2 acquired perpendicular to the long axis of the hippocampus; gadolinium is needed only if tumour, vascular lesion or active infection is suspected, and **an epilepsy-trained neuroradiologist must read it**, because expert reading yields significantly more focal lesions YW p.503. Thin (1–3 mm) slices perpendicular to the hippocampal long axis are essential YW p.508.
4. **Formal, age-appropriate neuropsychological testing** to establish a baseline of cognitive function — "essential in the presurgical evaluation of a child" [YW pp. 2041-2042].

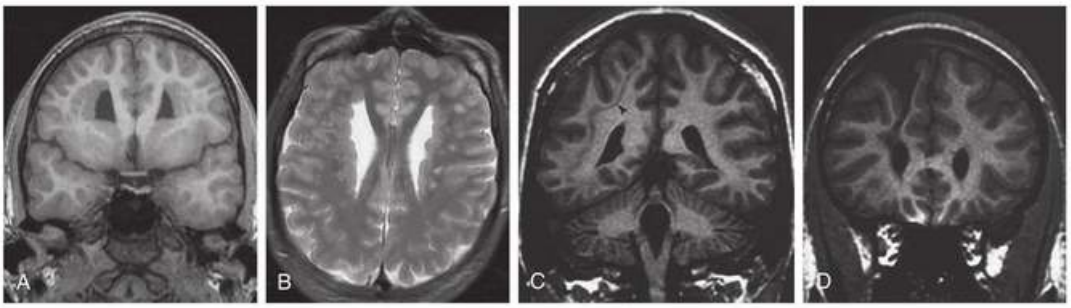


Figure 84.3. Malformations of cortical development, group II. Coronal T1-weighted image (A) and axial T2-weighted image (B) showing extensive bilateral subependymal nodular gray matter heterotopia. (C) Coronal T1-weighted image showing extensive band heterotopia in the right cerebral hemisphere. (D) Coronal T1-weighted image showing schizencephaly that extends to the right ventricle.

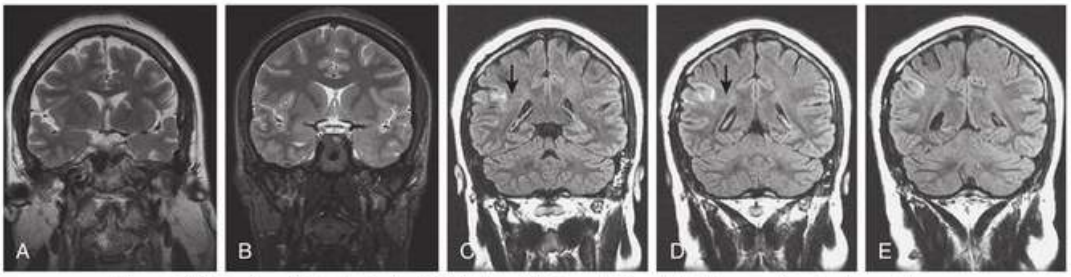


Figure 84.4. Focal cortical dysplasia (FCD). (A and B) Coronal T2-weighted images showing hypoplasia of the left temporal pole and loss of gray-white matter differentiation, in keeping with presence of FCD. (C to E) Type II FCD: coronal T2-weighted fluid-attenuated inversion recovery images showing funnel track hyperintensity (C and D, *arrows*) extending from the cortex of the right supramarginal gyrus to the ventricle.

Reproduced from Youmans & Winn 8e, Fig. 84.4, p. 510 — Label when you reproduce it: focal cortical dysplasia on MRI — (A, B) coronal T2 showing hypoplasia of the left temporal pole with loss of grey-white differentiation (type I pattern); (C-E) coronal T2-FLAIR showing the "funnel" / transmantle track of hyperintensity running from the cortex of the right supramarginal gyrus to the ventricle, the signature of type II FCD. Describe: cortical thickening, blurring of the grey-white junction, transmantle sign, T2/FLAIR hyperintensity, T1 hypointensity.

6. Second-tier (still non-invasive) tests — what each one adds and when

- **FDG-PET** — in use since the 1980s; statistical post-processing and PET-MRI co-registration add value. Some groups achieve equivalent outcomes after anterior temporal lobectomy in **MRI-negative but PET-positive** patients provided the hypometabolism is concordant with the electroclinical data; the Cleveland practice is nonetheless to explore PET-positive/MRI-negative patients invasively. In lesional cases PET adds prognostic rather than localising value YW p.504.
- **Ictal SPECT / SISCOM** (subtraction ictal SPECT co-registered with MRI) — in use since the 1990s, "most helpful in patients with focal epilepsy who have normal MRI findings, and in patients with FCD." It typically shows **multiple areas of hyperperfusion** that must be read as a distributed cortical-subcortical network, and the pattern is useful in designing an invasive implantation YW p.504.
- **MEG / magnetic source imaging (MSI)** — principally localises **interictal** epileptiform activity; correlates with intracranial epileptiform abnormalities and with resection outcome; is "especially good at detecting epileptiform discharges in opercular regions"; also provides **non-invasive functional localisation** of sensorimotor and language cortex YW p.504.
- **MRI post-processing** — voxel-based morphometric analysis (VBM) to unmask subtle neocortical lesions, especially FCD; machine-learning surface-based automated FCD detection in MRI-negative epilepsy; automated hippocampal volumetry for subtle hippocampal sclerosis. "The goal of these postprocessing techniques is to convert a nonlesional MRI examination into a lesional one" [YW pp. 504-505].
- **fMRI** — defines eloquent cortex relative to the putative EZ and "is replacing the Wada test at many epilepsy centers" for lateralisation and sublobar localisation of language; **EEG-fMRI** combines EEG temporal resolution with MRI spatial resolution to separate generator from propagation YW p.505.
- **Paediatric caveat on Wada** — "Wada or sodium amytal testing for memory is typically not tolerated in younger

children or those with other developmental comorbidities, such as ASD or developmental delay," and fMRI-based memory paradigms are being developed for children. "In general, if seizures localize to the mesial temporal lobe in a child, we feel that the risk to memory and cognitive decline with resective surgery is outweighed by the risk posed by intractable seizures" YW p.2042.

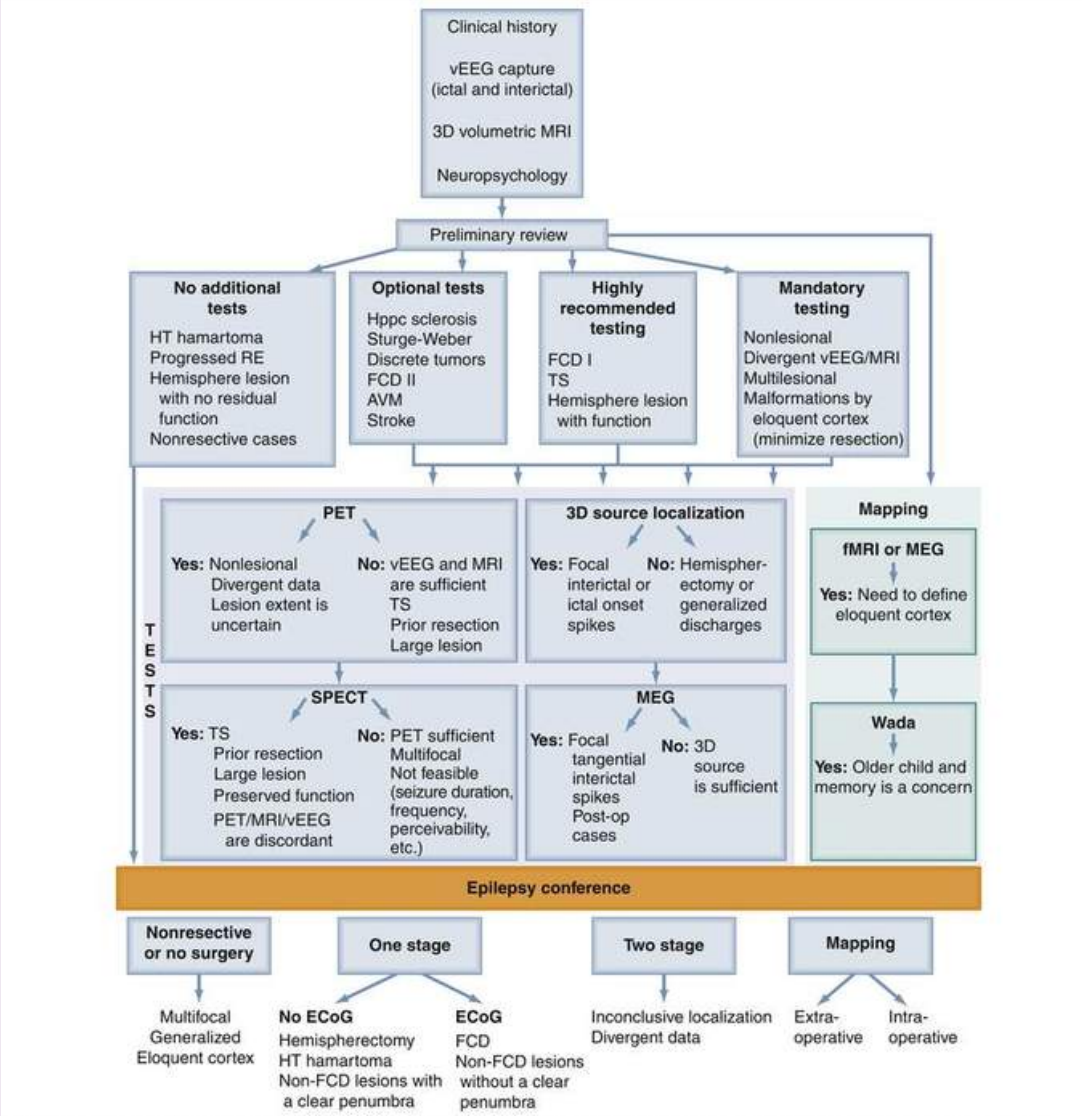


Figure 267.2. Evaluation and surgery protocol for children with epilepsy. *AVM,* Arteriovenous malformation; *3D,* three-dimensional; *ECoG,* electrocorticography; *FCD,* focal cortical dysplasia; *fMRI,* functional magnetic resonance imaging; *Hppc,* hippocampal; *HT,* hypothalamic; *MEG,* magnetoencephalography; *PET,* positron emission tomography; *RE,* Rasmussen encephalitis; *SPECT,* single-photon emission computed tomography; *TS,* tuberous sclerosis; *vEEG,* video-electroencephalography. *(From Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014;55:507–518.)*

Reproduced from Youmans & Winn 8e, Fig. 267.2, p. 2041 — Label when you reproduce it: the paediatric evaluation-and-surgery protocol — the four Phase I mainstays (clinical history, ictal and interictal video-EEG, 3D volumetric MRI, neuropsychology) feeding a preliminary review, then the four branches (no additional tests / optional tests / highly recommended tests / mandatory testing) with their example pathologies, then the second-tier tests (PET, SPECT, MEG, fMRI, Wada, 3D source localisation, mapping), the epilepsy conference, and finally the surgical limbs (one-stage, two-stage, mapping, non-resective/no surgery).

7. The patient management conference (PMC) — where the hypothesis is made

- **Composition** — epileptologists, epilepsy neurosurgeons, neuroradiologists, neuropsychologists and specialists in the relevant functional modalities YW p.504.
- **Purpose** — "to integrate the anatomic and electroclinical data... into a clear presurgical AEC hypothesis," ensuring the data are viewed from multiple expert perspectives and decisions are reached by consensus YW p.504.
- **Two outcomes** — if the data converge on a high-probability EZ, a surgical strategy is proposed directly (e.g. right hippocampal sclerosis plus a concordant right mesial temporal electroclinical syndrome needs nothing further); if they

do not converge, and especially if the MRI is normal, further testing or invasive monitoring follows YW p.504.

- **In children the conference also plans communication** — families "are updated regularly with clear and concise explanations, and guided through test results, hypotheses, and options," and the team must give "an honest estimate of the safety and efficacy of the surgical approach... emphasizing that the risks of longstanding epilepsy dwarf the risks of surgery" YW p.2042.

8. Phase II — invasive evaluation: indications and choice of method

Indications for invasive monitoring YW p.505:

1. The MRI shows **no lesion** (MRI-negative), or shows a lesion **discordant** with the electroclinical hypothesis, and the non-invasive data remain inconclusive.
2. Functional mapping of eloquent cortex with respect to the EZ and the proposed resection boundaries is required.
3. Multiple lesions are present and only some are seizure-generating YW p.488.e7.

Crucially — "crucial to the success of any intracranial evaluation is the formulation of a defined and testable presurgical hypothesis, without which one is merely embarking on a 'fishing expedition' in the brain, an approach that needs to be avoided as it rarely, if ever, leads to a successful surgical intervention" YW p.505.

Table 1 · Subdural grid (SDG) versus stereo-EEG (SEEG) in the paediatric invasive evaluation — compiled from Youmans & Winn 8e, Ch. 83 pp. 505-506, Ch. 89 p. 551, Ch. 90 pp. 563-568 and Ch. 267 pp. 2042-2043.

Feature	Subdural grids and strips	Stereo-EEG (SEEG)
Principle	Extraoperative recording from contiguous cortical surface, localising the EZ with respect to functional cortex	3D spatio-temporal sampling of an anatomo-electro-clinical hypothesis; "not merely a depth-electrode technique but a methodology"
Access	Craniotomy (grids) or burr holes (strips)	2.0–2.5 mm twist-drill holes, frame-based (Leksell/Talairach) or robot-assisted (ROSA)
Great strength	**Contiguous coverage → detailed functional mapping**, especially language; the sole remaining indication for choosing SDG over SEEG	Precise recording from **deep** structures — mesial temporal, insula/operculum, cingulate, interhemispheric, posterior orbitofrontal; bilateral and multilobar sampling easy
Great weakness	Most cortex is buried in sulci and remote from the electrodes; poor sampling of mesial temporal, insular, posterior orbitofrontal and interhemispheric cortex; multilobar/bihemispheric sampling difficult	Limited contacts in cortex → contiguous functional mapping not achievable; must be supplemented by fMRI, DTI or awake craniotomy
Best candidates	Cortical surface lesion; mapping-dominant indications	MRI-negative; deep or difficult-to-cover EZ; re-operation after failed surgery; periventricular nodular heterotopia; suspected insular/temporal-plus epilepsy
Worst outcomes	No lesion on MRI, non-specific histopathology, sublobar or multilobar resections	Incorrect pre-implantation hypothesis → inadequate placement and erroneous interpretation
Morbidity	Greater risk of symptomatic haemorrhage, infection, permanent neurological sequelae than SEEG	Total morbidity 2.5% in a 200-patient/2663-electrode series; hemorrhage 0.4–2.9%, infection 0.2–0.4%, mortality ~0.2–1%

- **SEEG practice in children** — robot-assisted stereotactic navigation "has transformed epilepsy monitoring owing to its safety, minimally invasive nature, and utility in electroclinical diagnosis"; **symmetrical bilateral implantations** are used deliberately when anatomo-electroclinical data are non-concordant or when a neuromodulatory rather than ablative therapy is anticipated, and "rather than being dismissed as a 'fishing expedition,' symmetrical bilateral implantations are meant to increase the utilization of epilepsy surgery" in children previously excluded [YW pp. 2042-2043]. Stimulation through the electrodes maps eloquent cortex and reproduces the child's habitual seizures YW p.2043.
- **Grids/strips/depths in children** — used "when laterality of seizures has been established"; a large craniotomy with a comprehensive montage, a tailored dural patch to avoid mass effect and a watertight seal with vertex exit; mapping in the PICU/EMU; **second-stage operation at 1–2 weeks** with electrode removal and resection or disconnection. Extraoperative mapping is preferred in children, "who are less likely to tolerate an awake craniotomy" [YW pp.

2042-2043].



Figure 267.3. Stereo-electroencephalography (sEEG) placement. Anterior skull radiograph demonstrating near symmetrical sEEG placement in a child with nonlesional, multifocal epilepsy. A biopsy had previously been performed in the right frontal lobe, thereby necessitating an extra right frontal electrode. Rather than being viewed as a "fishing expedition," such an electrode montage allows for delineation of epileptogenic networks that can be targeted with resection, ablation, or a neuromodulatory approach. *(From Kwon CS, Schupper AJ, Fields MC, et al: Centromedian thalamic responsive neurostimulation for Lennox-Gastaut epilepsy and autism. Ann Clin Transl Neurol. 2020;7[10]:2035–2040.)*

*Reproduced from Youmans & Winn 8e, Fig. 267.3, p. 2043 — Label when you reproduce it: near-symmetrical bilateral SEEG in a child with non-lesional multifocal epilepsy — anterior skull radiograph showing the bolt/electrode array (note the extra right frontal electrode required because of a previous right frontal biopsy). Explain that this montage delineates epileptogenic *networks* that can then be resected, ablated or neuromodulated.*

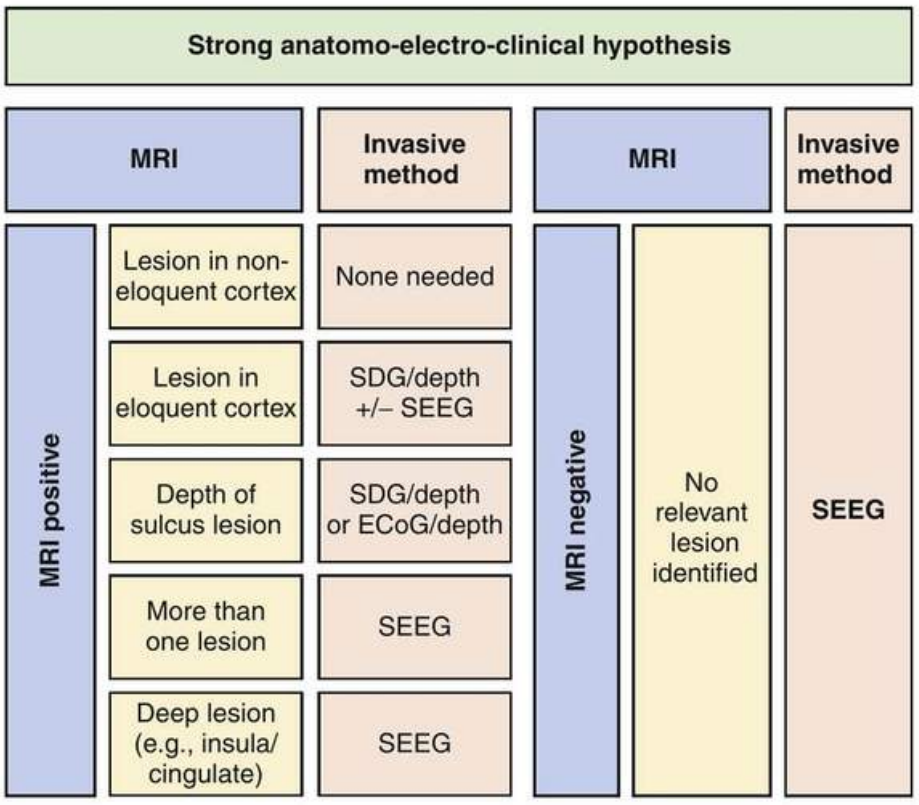


Figure 83.1. Indications for invasive evaluation and choice of the method. *ECoG,* Electrocorticography; *SDG,* subdural grid; *SEEG,* stereo-electroencephalography.

Reproduced from Youmans & Winn 8e, Fig. 83.1, p. 505 — Label when you reproduce it: the decision tree for invasive evaluation — a strong AEC hypothesis at one pole, then the branch points (MRI-negative vs lesional, need for contiguous language mapping vs deep/multilobar sampling), leading to subdural grid implantation on one arm and SEEG on the other. This is the figure to draw when asked "how do you choose between grids and SEEG?"

9. Paediatric-specific pitfalls to state explicitly

- **Consent is by proxy** — "treatment decisions are made by parents or guardians on behalf of the child in their care, and not by the surgical candidates themselves" YW p.2039.
- **Tolerance of the hospital stay** — children with behavioural issues or ASD may need extra medical and safety measures; a child-friendly environment with family involvement "is crucial to the overall success of surgery." Paradoxically, invasive monitoring makes surgery *simpler* in the uncooperative child, because general anaesthesia covers both diagnostic and therapeutic stages YW p.2040.
- **Myelination and MRI timing** — before 6 months myelination is incomplete and immature white matter is isointense with cortex, but the FCD white matter is almost always hyperintense on T2; **contrast between grey and white matter is maximal before myelination begins**, so if seizures start before 6 months, scan immediately. Between 6 and 18 months contrast falls and FCDs are least visible; **a "negative" scan should be repeated at 30 months**, when myelination is largely complete YW p.510.
- **Not all lesions are equally epileptogenic** — an encephaloclastic lesion such as a perinatal infarct is far less epileptogenic than an FCD, and the EZ of an FCD may extend beyond the visible margins, at times to the contralateral hemisphere; conversely in polymicrogyria or periventricular nodular heterotopia only a small component of the lesion may be epileptogenic [YW pp. 503-504].

(b) Surgical approaches in paediatric epilepsy [6]

10. The armamentarium — four families, none mutually exclusive

Youmans is emphatic: "the surgical armamentarium against epilepsy includes resection, disconnection, focal thermal ablation, and neuromodulation, none of which should be considered mutually exclusive," and "no one approach to epilepsy should be considered exclusive: techniques can be used in combination to minimize invasiveness and side effects, as weapons in an armamentarium against epilepsy" [YW pp. 2039, 2042].

Table 2 · The paediatric surgical armamentarium — indication, representative outcome and principal morbidity, from Youmans & Winn 8e Ch. 267 pp. 2042-2045, Ch. 79 pp. 488.e7, Ch. 96 pp. 615.e3-615.e9, Ch. 99 pp. 643-644 and Ch. 100 pp. 653-663.

Family	Procedure	Typical paediatric indication	Outcome
Resection	Lesionectomy / tailored corticectomy	Type II FCD, DNET, ganglioglioma, cavernoma, tuber	Cure rates approach **75%** at short-term follow-up when electroclinical and structural data are concordant
Resection	Anteromedial temporal lobectomy / SAH	Hippocampal sclerosis, temporal DNET	Engel I **66% at 10 years** (adult data)
Resection	Multilobar / posterior quadrant resection	Perinatal stroke, extensive MCD	Variable; guided by intracranial monitoring
Disconnection	Functional hemispherotomy (vertical parasagittal, transsylvian keyhole, peri-insular)	Rasmussen encephalitis, hemimegalencephaly, Sturge-Weber, perinatal infarct/porencephaly, HHE	Seizure-free **75–90%** in modern series; **HME only 40–60%**; porencephaly ~95%
Disconnection	Corpus callosotomy (anterior / complete / posterior)	Atonic drop attacks, Lennox-Gastaut, Rasmussen, infantile hemiplegia	**80–100% reduction in drop attacks**; meta-analysis 88.2% seizure control after total, 58.6% after anterior alone
Disconnection	Multiple subpial transection	EZ in motor, sensory or language cortex; Landau-Kleffner	MST alone: Engel I–III in **75%**; with resection 82%
Ablation	MR-guided LITT	Hypothalamic hamartoma with gelastic seizures, PVNH, deep FCD, tubers, MTS	Engel I **40–60%** for mesial temporal; excellent for hamartoma
Ablation	Gamma Knife / stereotactic radiosurgery	Hypothalamic hamartoma, callosotomy	Engel I 39.6% for MTLE radiosurgery
Neuromodulation	VNS	Generalised or multifocal epilepsy; non-lesional; LGS	<10% seizure-free; ~50% responder rate improving over years
Neuromodulation	DBS (ANT, centromedian)	Multifocal, generalised, LGS	ANT median reduction 41% at 1 yr, 56% at 2 yr, 69% at 5 yr
Neuromodulation	RNS (cortical or CM thalamic)	Multifocal/bilateral onset, eloquent-cortex onset, LGS, Rasmussen	Median reduction 44% at 1 yr, 53% at 2 yr, 66.5% at 6 yr

11. Focal resection and lesionectomy — the archetype

- **The commonest paediatric surgically-remediable epilepsies arise from structural abnormalities of childhood** YW p.2043.
- **The archetypal single-stage case is the hypothalamic hamartoma with gelastic seizures**, "effectively treated via stereotactically guided selective laser ablation (also known as laser interstitial thermal therapy [LITT]) and minimally invasive endoscopic and transcallosal/transventricular approaches" YW p.2043.
- **Malformations of cortical development are the most commonly seen lesions in most paediatric surgical series** and are "the most common cause of intractable pediatric epilepsy"; MCDs are found in **30% of cortical resections** [YW pp. 2043, 488.e7].

- **Type II FCD** — "well-localized seizures secondary to type II cortical dysplasias can be approached via a single-stage craniotomy and excision of the epileptogenic zone, when separate from eloquent cortical areas, but successful seizure control correlates with extent of resection of the radiographically apparent dysplastic region" YW p.2043.
- **Type I FCD** — "generally diffuse, multilobar, and MR negative, and surgery is associated with poorer outcomes by standard neurosurgical methods of excision, disconnection, or ablation"; a **neuromodulatory approach** may be preferred YW p.2043. Outcome in FCD type I is worse than type II "because FCD type I is usually more extensive and its margins are more difficult to define, so surgical resection may be subtotal" YW p.488.e7.
- **Numbers to quote** — surgical treatment of FCD gives cure in **>50%**, with approximately **70% achieving a good outcome (Engel class I and II)**; resection of glioneuronal tumours such as gangliogliomas gives seizure freedom in **58% to 86%** YW p.488.e7. Complete resection yields **70% seizure freedom versus 22% after incomplete resection**; in children with cortical malformations followed 10 years, **83% favourable with complete resection versus 11% with incomplete** YW p.576.
- **Better outcome predictors** — shorter seizure duration, absence of generalised seizures, younger age, total resection YW p.488.e7.
- **Tuberous sclerosis** — "a leading genetic disorder seen in pediatric epilepsy surgical series"; tubers "represent overgrowth of atypical giant astrocytes and groups of large vacuolated giant cells, and the perituberal cortex appears to be electrographically and structurally implicated in epilepsy mechanisms." SEEG is "an ideal tool for intracranial monitoring in patients with multiple tubers." Surgical resection of one or more epileptogenic tubers gives **seizure freedom in 53% to 68%** and good outcome in **64% to 92%**. **Not all tubers are equally epileptogenic** — only those producing the refractory seizures need excision [YW pp. 2043-2044, 488.e7]. Worse outcome is associated with younger age at seizure onset, a history of infantile spasms and bilateral focal interictal discharges YW p.488.e7.
- **Vascular lesions** — cavernous malformations are common and epileptogenic in children; risk factors for epilepsy include **cortical (rather than subcortical) location, temporal localisation, multiple cavernomas, cavernoma volume, hemosiderin-ring volume and male sex**. Youmans advocates "removal of the lesion and the hemosiderin ring and early intervention," with adjunctive invasive monitoring in longstanding intractability because adjacent cortical and allocortical structures often become independently epileptogenic YW p.2044.
- **Perinatal stroke** — "up to two-thirds may develop epilepsy after perinatal strokes and hypoxic or ischemic injury, and 25% of those will develop intractable epilepsy"; options range from focal to multilobar resection, disconnection and hemispherotomy, "most effectively guided by intracranial electrode monitoring" YW p.2044.
- **Intraoperative ECoG** is favoured by some centres to guide single-stage resection YW p.2043; it "allows for the resection of lesional tissue while also allowing for real-time feedback regarding resection of the surrounding epileptogenic cortex," with >90% seizure freedom reported for ganglioglioma and low-grade tumours resected under ECoG guidance YW p.575.



ıure 267.3. Stereo-electroencephalography (sEEG) icement. Anterior skull radiograph demonstrating near symmetrical EG placement in a child with nonlesional, multifocal epilepsy. A psy had previously been performed in the right frontal lobe, thereby cessitating an extra right frontal electrode. Rather than being wed as a "fishing expedition," such an electrode montage allows delineation of epileptogenic networks that can be targeted with ection, ablation, or a neuromodulatory approach. *(From Kwon CS, hupper AJ, Fields MC, et al: Centromedian thalamic responsive urostimulation for Lennox-Gastaut epilepsy and autism. Ann Clin nsl Neurol. 2020;7[10]:2035–2040.)*

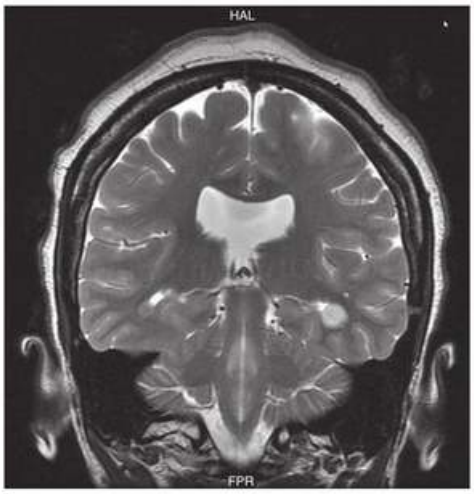


Figure 267.4. Laser interstitial thermal therapy for a periventricular nodular heterotopia (PVNH). This 17-year-old underwent stereo-electroencephalography (sEEG) monitoring with symmetrical implantation of electrodes to map seizure onsets, distinguish between hemispheric predominance, and potentially localize to frontal, temporal, occipital, and/or PVNH onsets. Seizures were predominantly seen in the left PVNH, which was subjected to laser interstitial thermal therapy with the Neuroblate System (Monteris Medical).

Reproduced from Youmans & Winn 8e, Fig. 267.4, p. 2043 — Label when you reproduce it: LITT of a left periventricular nodular heterotopia in a 17-year-old after bilateral symmetrical SEEG — show the depth-electrode trajectory, the heterotopic nodule at the ventricular margin, and the thermal ablation zone. Say in the caption that SEEG first proved the PVNH (rather than frontal, temporal or occipital cortex) carried the onset, and that LITT then treated a target that open surgery could not reach safely.

12. Disconnection 1 — hemispherotomy

- **Definition** — hemispheric disconnection procedures are "a group of surgical interventions for chronic epilepsy that are used as alternatives to anatomic hemispherectomy," whose common denominator is "the disconnection of the cortex of one hemisphere from the contralateral hemisphere and from the deeper structures of the basal ganglia" YW p.636.
- **Evolution** — anatomic hemispherectomy (Dandy 1928; Krynauw 1950) → **Rasmussen's functional hemispherectomy** → **hemispherotomy** (Schramm's transsylvian keyhole; Delalande's vertical parasagittal), i.e. "resection of brain tissue has been largely replaced by disconnection" YW p.636.
- **Why the change** — anatomic hemispherectomy produced hydrocephalus in **52%** of 27 Montreal cases, superficial cerebral haemosiderosis in 33%, and deaths; Rasmussen's functional technique reduced the raised-ICP complication rate **from 35% to 7%** while giving the same seizure-free rate (83% vs 85%) YW p.636.
- **Paediatric indications** — "holohemispheric dysfunction and the plasticity of the developing brain make functional hemispherotomy a safe, effective, and occasionally indicated technique"; the classic diseases are **Rasmussen encephalitis, extensive structural injury from early childhood stroke, hemimegalencephaly and Sturge-Weber syndrome**, all "curable through a hemispheric disconnection achieved using intraventricular disruption of the descending outputs of the temporal, parietal, and frontal lobes, a frontal disconnection, complete corpus callosotomy, and insular topectomy" YW p.2044.
- **Aetiology distribution** (Schramm's 110 cases) — infarct/ischaemia/porencephaly 54, Rasmussen encephalitis 15, hemimegalencephaly 12, cortical dysplasia/migration disorders 10, hemiatrophy of unclear cause 7, Sturge-Weber 6, post-encephalitic/HHE 6 YW p.637.
- **Timing** — children with holohemispheric malformations or HME and continuous unilateral seizures "may be operated on very early (in my group at 4 months)"; in Rasmussen encephalitis one should accept "earlier surgery and earlier motor loss... and not wait until the disease process has destroyed the hemisphere" [YW pp. 637-638].
- **Contraindications** — "hemispheric deafferentation is contraindicated if the presurgical evaluation cannot demonstrate that all typical ictal activity originates from the affected hemisphere." Bilateral EEG activity is seen in up to **75%** but may be propagated; 77% of patients with suspected bilateral disease were still seizure-free or had only minor events. Mental retardation is **no longer** a contraindication [YW pp. 638-639].

- **Unavoidable side effects to consent for** — complete **hemianopia**, loss of fine pincer movement of thumb and index finger and of fine foot movement; possible gait deterioration; severe aphasia if language transfer from a dominant hemisphere is incomplete YW p.639.
- **Complications** — incomplete disconnection (2–30%), blood loss, electrolyte disturbance, coagulopathy, diabetes insipidus/SIADH, contralateral hemisphere swelling, transient fever up to 10 days that must be distinguished from bacterial meningitis, dysphagia, movement disorders, subdural hygroma/haematoma, hydrocephalus (shunt rates 8–30%, highest in HME), and mortality "around 1%, rarely 2%" in modern series YW p.644.
- **Outcome** — modern series report **75–90% seizure freedom**; hemispherotomy techniques gave **85.7% Engel class I** versus 66.1% for the Rasmussen technique and 60.7% for hemicorticectomy/hemidecortication; HME does worst (40–60%), Sturge-Weber best (80–100%), porencephaly 95% in the Bonn paediatric series. **Behaviour improved in 57%, IQ improved in 38% and declined in 9%, schooling improved in 40%** [YW pp. 643-644].
- **Rasmussen caveat** — a long-term study showed "only a palliative effect from hemispherotomy/hemispherectomy in RE, with only 22% of patients achieving seizure freedom at 10 years postoperatively, and considerable morbidity with speech and motor deficits"; Ghatan's group used immunotherapy + VNS + RNS in two children with lasting benefit and no progression of deficits YW p.2044.

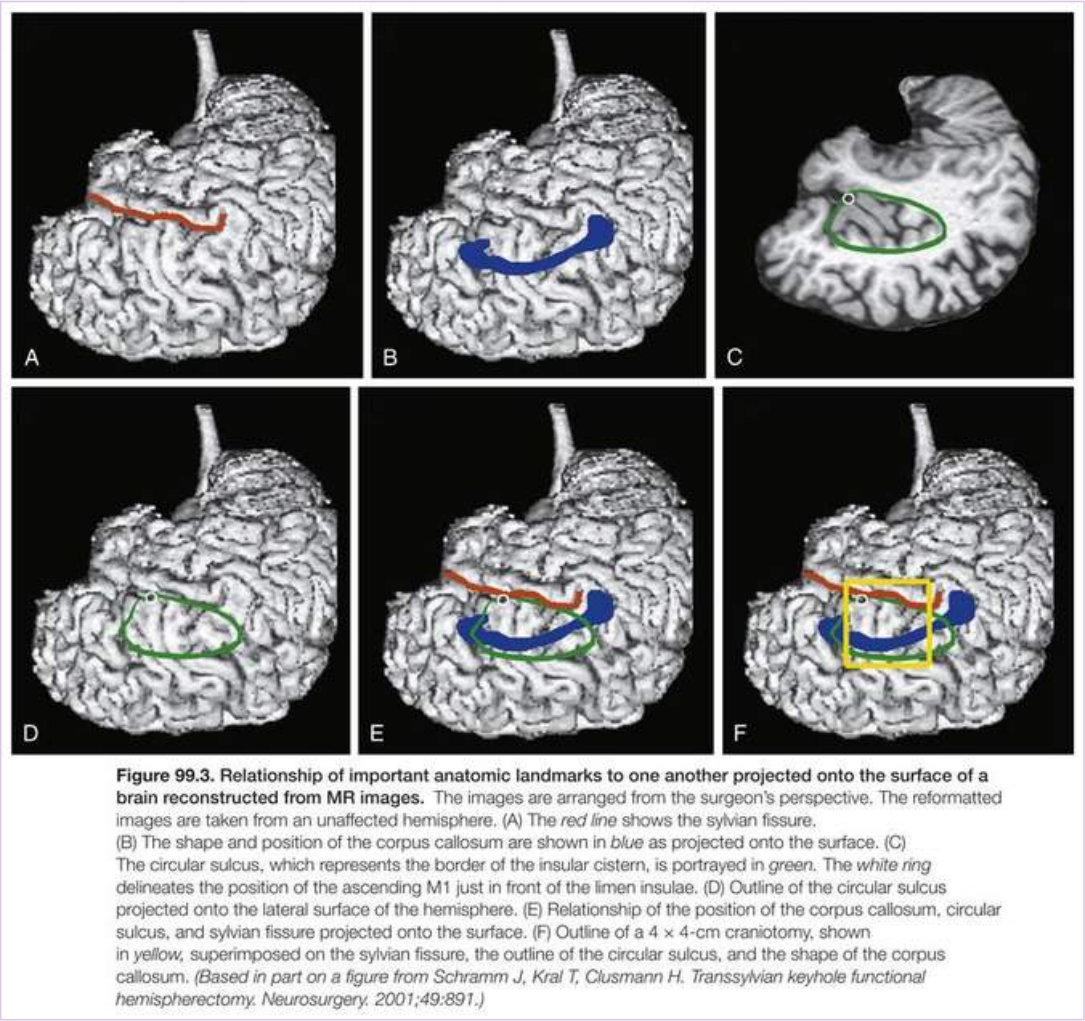


Figure 99.3. Relationship of important anatomic landmarks to one another projected onto the surface of a brain reconstructed from MR images. The images are arranged from the surgeon's perspective. The reformatted images are taken from an unaffected hemisphere. (A) The *red line* shows the sylvian fissure. (B) The shape and position of the corpus callosum are shown in *blue* as projected onto the surface. (C) The circular sulcus, which represents the border of the insular cistern, is portrayed in *green*. The *white ring* delineates the position of the ascending M1 just in front of the limen insulae. (D) Outline of the circular sulcus projected onto the lateral surface of the hemisphere. (E) Relationship of the position of the corpus callosum, circular sulcus, and sylvian fissure projected onto the surface. (F) Outline of a 4 × 4-cm craniotomy, shown in *yellow*, superimposed on the sylvian fissure, the outline of the circular sulcus, and the shape of the corpus callosum. *(Based in part on a figure from Schramm J, Kral T, Clusmann H. Transsylvian keyhole functional hemispherectomy. Neurosurgery. 2001;49:891.)*

Reproduced from Youmans & Winn 8e, Fig. 99.3, p. 640 — Label when you reproduce it: the landmarks of hemispheric disconnection projected on a 3D MR reconstruction from the surgeon's view — (A) sylvian fissure in red; (B) outline of the corpus callosum in blue; (C) circular sulcus of the insula in green with the white ring marking the ascending M1 in front of the limen insulae; (D-E) their relationship to one another; (F) the 4 × 4 cm craniotomy in yellow superimposed on all three.

13. Disconnection 2 — corpus callosotomy in children

- **Rationale** — "the foundational premise behind transection of corpus callosum is prevention of seizure propagation to the contralateral hemisphere"; first described by van Wagenen and Herren in 10 patients in 1940 YW p.615.e1.

- **Paediatric indication** — "used primarily in the setting of atonic seizures"; best results in **atonic seizures (80–100% reduction in drop attacks)**, also Lennox-Gastaut syndrome, Rasmussen encephalitis and infantile hemiplegia [YW pp. 2044, 615.e2].
- **Technique at Ghatan's centre** — "division of the corpus callosum is done through a small vertex craniotomy... the lateral position with the head tilted 45 degrees toward vertical, to allow gravity to gently create space in the interhemispheric fissure, and completely section the callosum in an extraventricular fashion, finding and maintaining the plane between the leaves of the septum pellucidum." **A complete callosotomy is usually performed, with minimal long-term morbidity and significant relief of atonic seizures** [YW pp. 2044-2045].
- **Variants** — posterior callosotomy "to spare prefrontal connectivity with good results at 4-year follow-up"; endoscopic and LITT callosotomy YW p.2045.
- **Complications** — approach-related 2.4–6% (epidural or subdural haematoma, meningitis, deep venous thrombosis); disconnection syndromes — acute callosal disconnection in up to 89% after extended callosotomy, supplementary-motor-area-like syndrome with paresis of the non-dominant leg, incontinence and reduced spontaneous speech, apraxia of the non-dominant hand, split-brain syndrome; symptomatic disconnection syndromes in 45–80%, **adults more than children** [YW pp. 615.e3-615.e4].

14. Ablation — LITT, radiofrequency and radiosurgery

- **LITT principles** — MRgLITT provides real-time thermal feedback, unlike radiofrequency, in which "thermal damage relies on tissue conduction and is difficult to control... Radiofrequency is thus a 'blind' approach"; "thermal spread is software-controlled by MRgLITT and allows temperature control beyond the tip of the probe" YW p.630.
- **Mesial temporal LITT technique** — the probe is inserted **via an occipital approach along the long axis of the hippocampus into the amygdala**, avoiding vasculature, choroid plexus and the ventricle; ablation starts most anteriorly at the amygdala and the catheter is withdrawn in stages. **Sparing of the mesial temporal head is associated with failure, and extending the ablation posteriorly is counterproductive** YW p.630.
- **Outcome** — 12-month Engel class I in **40–60%**; lower than open ATL but with better neuropsychological profile (object recognition and naming preserved even in the dominant hemisphere), lower complication rates, shorter stay, and it does not preclude later open surgery. Commonest complication is a visual field deficit, usually **octantanopsia (up to 37.5%)** [YW pp. 630-631].
- **Paediatric LITT** — "preliminary results for LITT in focal epilepsy from other, less common sources in children, such as mesial temporal sclerosis, are variable, but we and others have used LITT with good results for periventricular nodular heterotopias in children in whom access to dominant temporal or periatrial onset zones would be prohibitively invasive." LITT for tubers has had "mixed results" with limited follow-up [YW pp. 2043-2044].

15. Neuromodulation in the child

- **VNS** — "some class I evidence exists to show that VNS is useful for some children with generalized or multifocal epilepsy. For parents, a reversible technique without implications of resection or disconnection is favorable." Factors associated with response are **age at onset >12 years and non-lesional epilepsy**, with **less than 10% achieving seizure freedom** YW p.2045. Several large analyses "failed to show a benefit of VNS in reducing SUDEP risk in children" YW p.2045.
- **DBS** — "limited data exist to highlight the experience in children"; **centromedian (CM) and anterior thalamic (ANT) nuclei** are the usual targets, mostly for generalised epilepsy, with mixed results. Ghatan's group used a directional lead in bilateral CM with good results in a 17-year-old with multifocal epilepsy after failed temporal lobectomy but "generally have not favored an open-loop system, given the advantages of a responsive rather than tonic treatment strategy" YW p.2045.
- **RNS** — "ideally, a surgical approach that is minimally invasive, maximally effective, and modifiable with time, patient-specific needs, and technologic advances should be chosen for a child... RNS appears to fulfill this promise." Its attractions in the immature brain are inherent plasticity, the safety of a closed-loop responsive rather than tonic system, chronic recordings and biomarkers, and revisability. **Regional networks, extratemporal localisation and temporal-plus epilepsy — all more prevalent in children — may be better served by influencing a network than by disconnecting or ablating tissue** YW p.2045.

- **Lennox-Gastaut syndrome** — affects up to **10% of childhood epilepsies**; triad of multiple intractable seizure types, cognitive impairment and generalised slow spike-and-wave on EEG; most cases are acquired with prior brain injury, West syndrome or other pathology. "A neuromodulatory approach can potentially offer hope where ablative surgeries would fail. We have seen early success with RNS when we have attempted to influence a wider network through the CM nucleus of the thalamus" YW p.2045.
- **Autism with refractory epilepsy** — a well-established link between aberrant behaviour and epilepsy severity; Ghatan's group reports "tangible gains in behavior and cognition with better seizure control," with **reduction in emergency visits and hospitalisations by 90% and better than 50% seizure control in 63% of patients at >1 year** YW p.2045.

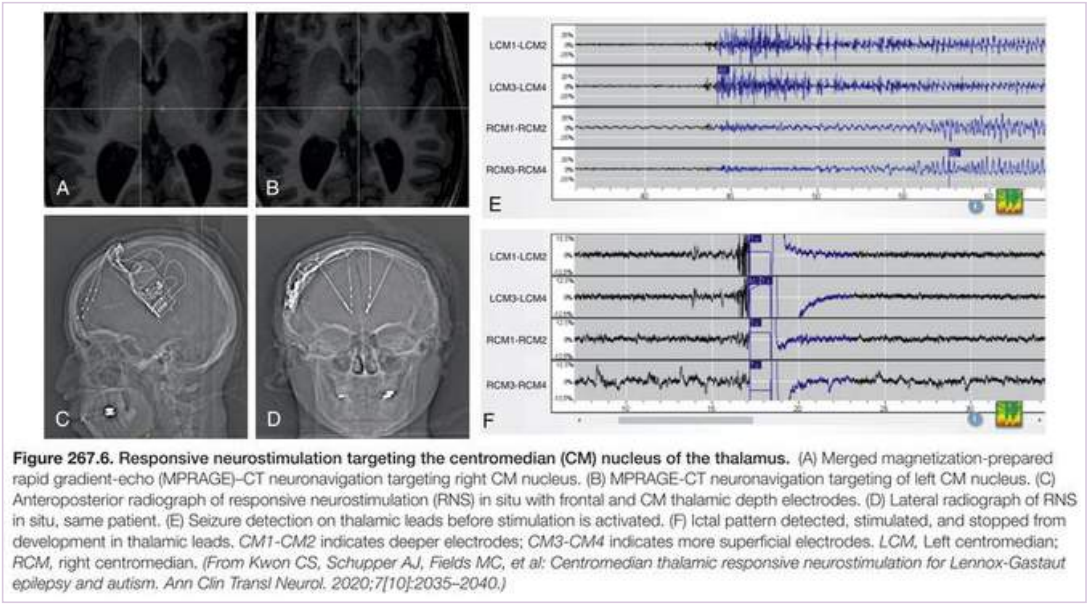


Figure 267.6. Responsive neurostimulation targeting the centromedian (CM) nucleus of the thalamus. (A) Merged magnetization-prepared rapid gradient-echo (MPRAGE)–CT neuronavigation targeting right CM nucleus. (B) MPRAGE-CT neuronavigation targeting of left CM nucleus. (C) Anteroposterior radiograph of responsive neurostimulation (RNS) in situ with frontal and CM thalamic depth electrodes. (D) Lateral radiograph of RNS in situ, same patient. (E) Seizure detection on thalamic leads before stimulation is activated. (F) Ictal pattern detected, stimulated, and stopped from development in thalamic leads. *CM1-CM2* indicates deeper electrodes; *CM3-CM4* indicates more superficial electrodes. *LCM,* Left centromedian; *RCM,* right centromedian. *(From Kwon CS, Schupper AJ, Fields MC, et al: Centromedian thalamic responsive neurostimulation for Lennox-Gastaut epilepsy and autism. Ann Clin Transl Neurol. 2020;7[10]:2035–2040.)*

Reproduced from Youmans & Winn 8e, Fig. 267.6, p. 2046 — Label when you reproduce it: responsive neurostimulation targeting the centromedian nucleus of the thalamus — (A, B) merged MPRAGE-CT neuronavigation targeting right and left CM; (C, D) AP and lateral radiographs of the RNS generator in situ with frontal and CM thalamic depth leads; (E) seizure detection on the thalamic leads before stimulation is enabled; (F) an ictal pattern detected, stimulated and aborted.

16. Outcome data and the take-home message

- **Class I evidence** supports epilepsy surgery over medical therapy in adults **and** children (Wiebe; Engel's early-surgery trial; Dwivedi's paediatric RCT) YW p.2042.
- "A prospective population-based longitudinal study found lasting seizure freedom and many children being weaned from antiseizure medications when referred early in the course of their epilepsy," although a systematic review showed "a shrinking success rate in terms of seizure freedom at 10-year follow-up" YW p.2042.
- **In simple concordant cases surgical cure rates approach 75% at short-term follow-up** YW p.2043.
- **The conclusion Youmans wants stated** — "surgical treatment of FCD should be considered early in the course, not as a desperate last choice only after all medical management of seizures has failed" YW p.488.e7, and "the risks of longstanding epilepsy dwarf the risks of surgery" YW p.2042.

17. Points that earn extra marks

- Quote the **90-fold mortality risk** and the **10%/20-year SUDEP figure** early — they are the single most persuasive numbers in the paediatric answer YW p.2039.
- Name the **HARNESS-MRI protocol** (3D T1 + 3D FLAIR + 2D oblique coronal T2) rather than saying "epilepsy protocol MRI" YW p.503.
- Say explicitly that **Wada is often not feasible in children** and that fMRI memory paradigms are being developed YW p.2042.
- Use the phrase **"anatomo-electro-clinical hypothesis"**; it is the organising idea of the whole evaluation [YW pp. 503, 563].

- Remember that **the trajectory, not just the target, is the SEEG "target"**: "the SEEG electrode 'target' can be conceived as the entire trajectory of a specific electrode and not only its most distal end" YW p.563.
- Know the **paediatric MRI timing rule** (scan before 6 months; repeat at 30 months if negative) YW p.510.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Two failed, appropriately chosen, adequately dosed ASMs = drug-resistant epilepsy** — the same criterion in a child as in an adult, and the trigger for referral, not a reason to wait [YW pp. 503, 2039].
- **The four Phase I mainstays are history, video-EEG, epilepsy-protocol 3D MRI and neuropsychology** — everything else is second-tier and hypothesis-driven YW p.2041.
- **A normal MRI does not exclude surgery**: equally good outcomes are achievable in MRI-negative patients with a careful, thorough presurgical methodology YW p.504.
- **SEEG is now the preferred invasive method**; the sole remaining indication for subdural grids is the need for contiguous functional mapping, particularly of language YW p.506.
- **Never implant without a testable AEC hypothesis** — an implantation without one is a "fishing expedition" that rarely succeeds and only exposes the child to risk YW p.505.
- **Type II FCD = single-stage craniotomy and excision; Type I FCD = diffuse, multilobar, MR-negative, poorer outcomes — consider neuromodulation** YW p.2043.
- **Extent of resection is everything in FCD**: 70% seizure-free with complete resection versus 22% with incomplete resection YW p.576.
- **Hemispherotomy has replaced hemispherectomy**: same seizure outcome, shorter operation, less blood loss, hydrocephalus rate down from 52% to single figures [YW pp. 636, 644].
- **Callosotomy is for drop attacks** — 80–100% reduction; it is palliative, never curative, and complete section carries the highest rate of disconnection syndromes [YW pp. 615.e2-615.e3].
- **In children, neuromodulation is not a last resort** — it is reversible, network-level, modifiable with growth, and RNS in the CM nucleus is the emerging answer for Lennox-Gastaut and multifocal epilepsy YW p.2045.
- **Refer early**: early resection of epileptogenic lesions yields better long-term results than resection deferred to later childhood or adolescence, and long-term cognitive function improves post-operatively, especially in FCD type I YW p.488.e7.

Pages read for this answer — Youmans & Winn 8e: 488.e7, 503, 504, 505, 506, 508, 510, 563, 575, 576, 615.e1, 615.e2, 615.e3, 615.e4, 630, 631, 636, 637, 638, 639, 643, 644, 2039, 2040, 2041, 2042, 2043, 2044, 2045

Drug resistant epilepsy:
a) Preoperative evaluation. [5]
b) Surgical techniques for managing drug resistant epilepsy. [5]

LONG | DEC 2021 · Paper III · Q9 | 10 marks

Also asked as: Epilepsy surgery — also asked as OCT 2025 · Paper III · Q7 (Drug resistant epilepsy [DRE]: definition, evaluation and treatment options) and DEC 2020 · Paper III · Q3 (Pre-surgical evaluation & surgical approaches in Pediatric epilepsy).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 83 *Evaluation of Patients for Epilepsy Surgery* (S.A. Thompson, I.M. Najm), §Goals of Presurgical Evaluation, §Clinical Approach, §Necessary Techniques for Localisation of the EZ, §Additional Diagnostic Testing, §Invasive Evaluation Techniques, §Conclusion, pp. 503-506 (Fig. 83.1, p. 505). Supplementary: Ch. 81 *Antiseizure Medications: Principles of Clinical Use*, §Antiepileptic Drug Efficacy, p. 497; Ch. 80 *Diagnosis and Classification of Seizures and Epilepsy*, §Seizure and Epilepsy Classification, pp. 491-495 (Table 80.2, p. 491; Fig. 80.2, p. 493.e2); Ch. 84 *MRI for Epilepsy Surgery*, pp. 508-518 (Figs. 84.1-84.5); Ch. 86 *Magnetoencephalography/MSI*, pp. 523-533 (Table 86.1, pp. 526-527); Ch. 87 *Wada Testing*, pp. 537-541; Ch. 89 *Intracranial Monitoring with Subdural Grids and Strips*, pp. 551-552 (Fig. 89.1, p. 551); Ch. 90 *Intracranial Monitoring: SEEG*, pp. 563-568 (Figs. 90.2-90.4, pp. 565-566); Ch. 94A *Anteromedial Temporal Lobectomy*, pp. 596-601; Ch. 94B *Selective Amygdalohippocampectomy*, pp. 602-604; Ch. 95 *Resections for Extratemporal Epilepsy*, pp. 605-613; Ch. 96 *Palliative Procedures*, pp. 615.e1-615.e10; Ch. 98 *LITT in Epilepsy*, pp. 630-635; Ch. 99 *Hemispheric Disconnection Procedures*, pp. 636-644; Ch. 100 *Electrical Stimulation for Epilepsy*, pp. 646-665 (Figs. 100.2, 100.5, 100.7); Ch. 101 *Epilepsy Surgery: Outcomes and Complications*, pp. 667-667.e16 (Box 101.1, p. 667.e2).

(a) Preoperative evaluation of drug-resistant epilepsy [5]

1. Definitions — fix these before anything else

- **Epilepsy** — "classically defined as at least two unprovoked seizures occurring >24 hours apart," now also "one unprovoked seizure with at least a 60% risk for recurrent seizure" over the next 10 years [YW pp. 492, 497].
- **Drug-resistant (pharmacoresistant, refractory, intractable) epilepsy** — "the failure of two adequately selected and dosed AEDs" YW p.497. Ch. 83 phrases it as "a failure to respond to two or more appropriately chosen and used antiepileptic medications" YW p.503.
- **The evidence behind the number (Kwan and Brodie, Glasgow cohort) — 47% became seizure free on the first AED, a further 13% on the second, and only 3.7% on the third**; after a third drug the chance of seizure freedom is **1% or less**, and these rates have proved durable on long-term follow-up YW p.497.
- **Scale of the problem** — epilepsy affects **1% of the world's population** and **30% to 40% of cases are refractory to medical therapy**; only 10–50% of medically refractory patients are candidates for resective surgery, and fewer than 10% achieve seizure freedom with VNS YW p.646.
- **The consequence** — "it is then important to consider surgical therapy once the diagnosis of drug-resistant epilepsy is reached, as suggested by a practice parameter endorsed by multiple professional societies" YW p.497. Drug-resistant epilepsy "has a less than 5% chance of being successfully treated with medications alone. Exploring candidacy for epilepsy surgery is thus a necessity in this patient population" YW p.667.
- **The ERSET threshold** — "the Early Randomization Surgery for Epilepsy Trial (ERSET) established unsatisfactory seizure control with medical therapy at 2 years as sufficient to warrant referral to epilepsy surgery," replacing the old 5-year dogma YW p.615.e1.

2. The cortical zones — the conceptual map the examiner wants

- **Epileptogenic zone (EZ)** — "the area of cortex necessary to be removed or disconnected to render the patient seizure free"; its complete resection or ablation is the main goal of surgery [YW pp. 495, 503].
- **Irritative zone** — "the area of cortical tissue that generates" interictal epileptiform discharges; IEDs are a measurement of this zone and are useful for **regionalising** rather than localising the focus YW p.502.e5. MEG, being predominantly an interictal tool, "identifies an irritative zone" YW p.527.
- **Symptomatogenic zone** — auras, lateralising signs and ictal semiology "all reflect the symptomatogenic zone. It does not imply that the seizure starts in this location; rather, that this region is the first nonsilent area of the brain to be affected" YW p.605.
- **Functional deficit zone** — "the area of the brain that shows abnormal functioning in the interictal period as a result of a structural lesion, the functional consequences of the persisting epileptic condition, or both" YW p.515; it is what neuropsychology, interictal PET and the interictal EEG background measure.
- **Epileptogenic lesion** — the structural abnormality on MRI; it is neither necessary nor sufficient for the EZ.
- **Eloquent cortex** — mapped by fMRI, MEG, cortical stimulation or awake craniotomy; the second, equally important goal of the evaluation is to define the overlap between EZ and eloquent cortex YW p.503.

Table 1 · The cortical zones of the presurgical evaluation and the test that defines each — compiled from Youmans & Winn 8e, Ch. 95 p. 605, Ch. 82 p. 502.e5, Ch. 83 p. 503, Ch. 84 p. 515, Ch. 80 p. 495 and Ch. 86 p. 527.

Zone	Definition in Youmans	Defined by
Symptomatogenic zone	"The first nonsilent area of the brain to be affected" by the discharge	Aura, ictal semiology, lateralising signs
Irritative zone	"The area of cortical tissue that generates" interictal epileptiform discharges	Interictal scalp EEG, MEG/MSI, interictal ECoG
Seizure onset zone	The cortex from which the ictal discharge actually begins	Ictal video-EEG, ictal SEEG/ECoG, ictal SPECT
Epileptogenic lesion	The structural abnormality; "finding a lesion on MRI is not necessary for defining the EZ"	Epilepsy-protocol MRI, post-processing, 7T

Functional deficit zone	"The area of the brain that shows abnormal functioning in the interictal period as a result of a structural lesion, the functional consequences of the persisting epileptic condition, or both"	Neuropsychology, interictal FDG-PET, interictal EEG slowing, examination
Epileptogenic zone	"The area of cortex necessary to be removed or disconnected to render the patient seizure free"	Inferred from the convergence of all the above; proved only by post-operative seizure freedom
(Eloquent cortex)	The functional cortex whose overlap with the EZ must be defined	fMRI, MEG, DTI, cortical/SEEG stimulation, awake craniotomy, Wada

3. Phase I, step 1 — history and semiology

- **The aura is the highest-yield single item.** "A clear description of the seizure semiology (symptoms and signs) and in particular the aura, if present, is the most important step in an epilepsy surgery evaluation," and an account from a witness should be obtained and later compared with recorded events YW p.503.
- **Risk factors to elicit** — febrile convulsions, prior head injury, CNS infection, family history of seizures (a genetic basis is relevant to some focal epilepsies) YW p.503.
- **Semiology is classified independently of EEG.** The semiologic seizure classification divides events into **subjective (aura)**, **objective (seizure)** and **asymptomatic (EEG-only)**; auras are auditory, autonomic, gustatory, olfactory, psychic, somatosensory, vestibular or visual; objective seizures are motor (simple: clonic, epileptic spasm, myoclonic, tonic, tonic-clonic, versive; complex: automotor, hypermotor, gelastic/dacrystic) or non-motor (dyscognitive — dialeptic, amnestic, aphasic, akinetic; autonomic) YW p.494.
- **A worked example from the book** — "epigastric aura → automotor seizure → (left or right) head versive seizure → generalized tonic-clonic seizure" with the lateralising sign *figure of 4*; "based on history alone, this patient has a more than 90% likelihood of having right temporal lobe epilepsy!" YW p.495.
- **Lobe-by-lobe semiology (Table 80.2)** should be reproduced in the answer: frontal — olfactory/autonomic aura, simple motor (tonic, clonic, myoclonic, asymmetric tonic, versive), hypermotor, automotor, gelastic, dialeptic, aphasic; temporal — abdominal/rising epigastric aura, fear, olfactory (noxious), gustatory (metallic), auditory, psychic (déjà vu, jamais vu), visual illusions (macropsia/micropsia), autonomic (heart racing), automotor seizures, postictal dysphasia, apnoeic seizures, tachycardia/bradycardia-asystole; parietal — somatosensory aura in 94%, disturbance of body image, complex visual illusions, tonic/focal motor, head deviation, postictal Todd paresis; occipital — visual aura in 73%, elementary visual hallucinations, flashing colours, ictal blindness 28%, eye pulling and nystagmus, contralateral head and eye deviation; insular — somatosensory aura including **pain**, viscerosensitive constriction/suffocation/choking, multimodal olfactory-gustatory-viscerosensory-auditory, panic, dyspnoea, hypersalivation, speech apraxia and automatisms YW p.491.

4. Phase I, step 2 — the two highest-yield tests

Youmans names them unambiguously: "In our opinion the two most important and highest-yield techniques for the localization of the EZ are **high-resolution MRI and video-EEG monitoring**. If the history is concordant, the findings of these studies may be sufficient to formulate a presurgical hypothesis and propose a surgical strategy" YW p.503.

A. High-resolution MRI

- **HARNESS-MRI protocol**: 3D volumetric T1, 3D FLAIR, and a 2D coronal T2 acquired perpendicular to the long axis of the hippocampus (the last being optimal for hippocampal sclerosis). Gadolinium only if tumour, vascular lesion or active infection is suspected. An epilepsy-programme neuroradiologist must report it YW p.503.
- **The yield depends entirely on who reads it and how**: in a large surgical cohort "the sensitivity of nonexpert reader reports of standard MRI for focal lesions was 39%, and the sensitivity of expert reads was 50%. However, the yield almost doubled to 91% with epilepsy protocol MRI. In particular, **hippocampal sclerosis was missed in 86% of cases with standard MRI protocols**" [YW pp. 492-493].
- **Hippocampal sclerosis** — atrophy on coronal T1 and increased signal on T2/FLAIR, with temporal horn dilatation, atrophy of the parahippocampal gyrus, ipsilateral fornix and mammillary body, and of the thalamus and caudate. Visual inspection by an expert detects it in **80–90%**; manual volumetry raises detection to **75–90%**; quantitative techniques

added new detections in **28%** of a 203-patient 3T cohort. **A second pathology (dual pathology) is present in 8–22%, most often FCD** YW p.508.

- **Not all lesions are equally epileptogenic** — a perinatal infarct is far less epileptogenic than an FCD; the EZ of an FCD may extend beyond its visible margins, even contralaterally; conversely only a small component of a polymicrogyria or periventricular nodular heterotopia may be epileptogenic. Hippocampal sclerosis is the most predictive lesion for the EZ, **except in "temporal-plus" epilepsy** where the network extends beyond the temporal lobe [YW pp. 503-504].
- **A lesion is helpful but not required** — "finding a lesion on MRI is not necessary for defining the EZ, and an apparently normal MRI result does not exclude a patient from epilepsy surgery. Indeed, similarly good surgical outcomes may be achieved in MRI-negative patients if a careful and thorough presurgical methodology is used" YW p.504.

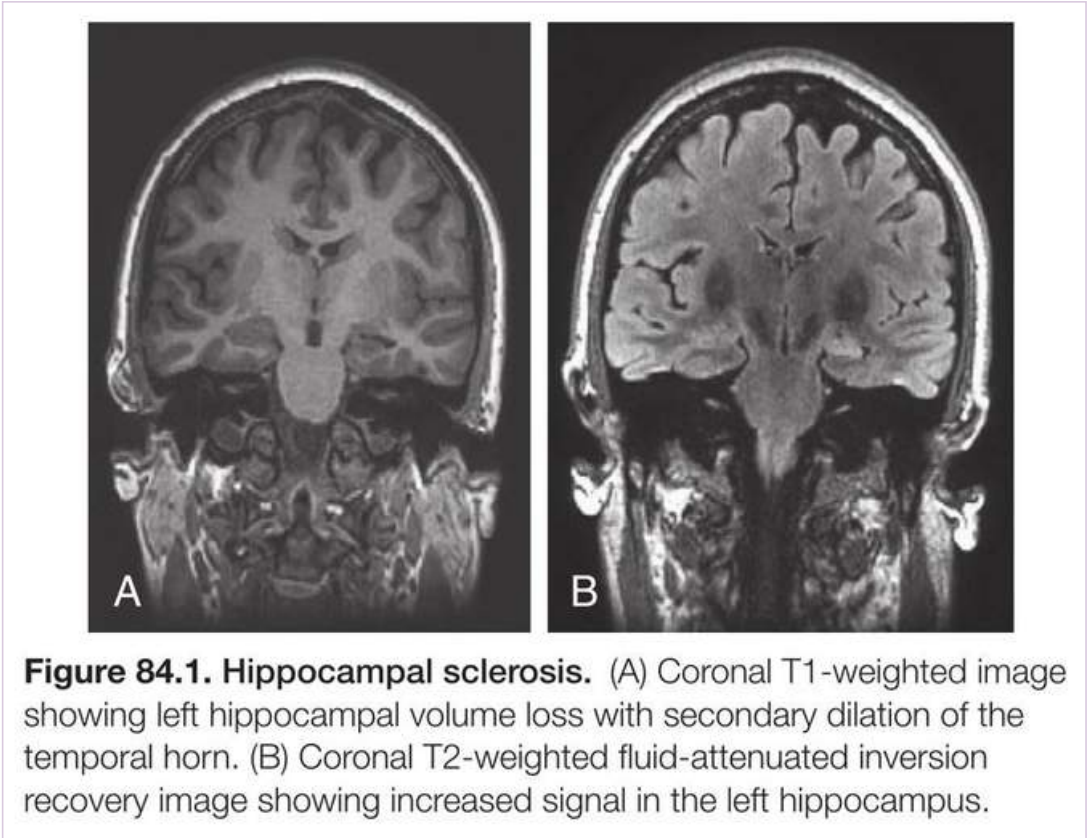


Figure 84.1. Hippocampal sclerosis. (A) Coronal T1-weighted image showing left hippocampal volume loss with secondary dilation of the temporal horn. (B) Coronal T2-weighted fluid-attenuated inversion recovery image showing increased signal in the left hippocampus.

Reproduced from Youmans & Winn 8e, Fig. 84.1, p. 508 — Label when you reproduce it: hippocampal sclerosis — (A) coronal T1 showing left hippocampal volume loss with secondary dilation of the temporal horn; (B) coronal T2-FLAIR showing increased signal in the left hippocampus. In the viva, describe the four associated features: temporal-horn dilatation, atrophy of the parahippocampal gyrus, atrophy of the ipsilateral fornix and mammillary body, and atrophy of the thalamus and caudate.

B. Prolonged video-EEG in a dedicated epilepsy monitoring unit (EMU)

- Required "to confirm the diagnosis of epilepsy and to generate the electroclinical component of the presurgical hypothesis, through analysis of EEG (both interictal and ictal) and seizure semiology" YW p.504.
- **Electrode placement is hypothesis-driven, not routine**: add inferior temporal electrodes for suspected mesial temporal onset; add central and parietal electrodes when a hemibody somatosensory aura implicates posterior perisylvian cortex YW p.504.
- **How many seizures?** In a concordant case (e.g. olfactory aura, automotor seizures, right hippocampal sclerosis) **one or two right-temporal seizures suffice**; with bilateral hippocampal atrophy, record **multiple** seizures because of independent bitemporal onsets — with the caveat that true lateralisation may not be achievable during the EMU stay at all YW p.504.
- **Yield** — capturing habitual seizures during a presurgical EMU evaluation under medication withdrawal is **70% to 80%** YW p.493.

5. Phase I, step 3 — the second-tier tests

1. **FDG-PET** — in use since the 1980s; statistical post-processing and PET/MR co-registration improve it. Some centres accept equivalent ATL outcomes in **MRI-negative/PET-positive** temporal cases provided the hypometabolism is concordant; Najm's group still explores those patients invasively. In lesional cases PET adds prognostic information and delineates propagation networks YW p.504.
2. **Ictal SPECT / SISCOM** — used since the 1990s; "most helpful in patients with focal epilepsy who have normal MRI findings, and in patients with FCD," in whom the EEG is often non-localising. It typically shows **multiple** hyperperfused areas to be read as a distributed cortical-subcortical network, and the pattern helps design the SEEG implantation YW p.504.
3. **MEG/MSI** — localises interictal spikes; correlates with intracranial epileptiform abnormalities and, more importantly, with resection outcome; is "especially good at detecting epileptiform discharges in opercular regions"; also gives non-invasive sensorimotor and language localisation. Resting-state connectivity may localise even without spikes YW p.504. **MEG detects spikes in 47% of patients who have no EEG spikes** YW p.527.
4. **MRI post-processing** — voxel-based morphometry for subtle FCD; machine-learning surface-based automated FCD detection in MRI-negative epilepsy; automated hippocampal volumetry. "The goal of these postprocessing techniques is to convert a nonlesional MRI examination into a lesional one, which greatly advances the AEC hypothesis and informs the surgical strategy" [YW pp. 504-505].
5. **fMRI** — maps eloquent cortex relative to the EZ; "is replacing the Wada test at many epilepsy centers" for language lateralisation and sublobar localisation; **EEG-fMRI** resolves the generator source from its propagation regions and corresponds better to the region of seizure onset than EEG or MEG alone YW p.505.
6. **Neuropsychological assessment** — establishes a profile of strengths and weaknesses across sensory, motor, perceptual-motor, intellectual, memory, executive, personality, affective, social and quality-of-life domains against normative data; "of particular concern in temporal lobe surgery are losses of memory function, including the rare but disabling condition of global amnesia, as well as the more common material-specific memory losses" — verbal in the dominant and visuospatial in the non-dominant temporal lobe YW p.667.e14.
7. **Wada (intracarotid amobarbital) test** — determines hemispheric language dominance and hemispheric memory capacity, "a crude, reversible analog of the proposed resection." Reserve it for patients at risk of post-operative amnesia, or when EEG/MRI/neuropsychology are discordant [YW pp. 537, 541].

6. The patient management conference and the AEC hypothesis

- The conference "should include epileptologists, epilepsy neurosurgeons, neuroradiologists, neuropsychologists, and specialists in other relevant diagnostic modalities"; its format "ensures that the data are considered from multiple expert perspectives, and fosters an approach to decision making and planning by consensus" YW p.504.
- **If the data converge**, a surgical strategy is proposed directly; **if they do not**, especially with a normal MRI, further testing or invasive monitoring is needed YW p.504.
- **In approximately 70% of surgical epilepsy patients** the epilepsy type and the anatomic location of the EZ can be established during a Phase I evaluation; **in 20% to 30% invasive monitoring is necessary** YW p.495.

7. Phase II — invasive evaluation

Indications YW p.505:

1. MRI shows no lesion, or a lesion discordant with the electroclinical hypothesis, and non-invasive data are inconclusive.
2. Functional mapping of eloquent cortex with respect to the EZ and the proposed boundaries is required.

Subdural grids and strips

- Two array types: linear **strips** (e.g. 1 × 6) and rectangular **grids** (12 to 120 contacts, e.g. 10 × 12); platinum-iridium discs **3.97 mm in diameter** with **1 cm centre-to-centre** spacing embedded in Silastic YW p.551.
- Placed via craniotomy (grids) or burr holes (strips); cables tunnelled through a separate stab incision several centimetres away with a purse-string suture for strain relief; the bone flap loosely approximated to accommodate post-operative

mass effect; **electrodes left in for 5–10 days** with intravenous antibiotics and a short course of steroids YW p.551.

- **The stated benefit** is "the contiguous coverage of cortical surfaces, which is especially favorable for detailed functional mapping." **The stated limitation** is that "the majority of cortex is buried within sulci and thus remote from the subdural electrodes," with inadequate sampling of mesial temporal, insular, posterior orbitofrontal and interhemispheric regions, and difficulty with multilobar or bihemispheric sampling YW p.505.
- **Outcome-based candidate selection** (Bulacio series): best results in patients with clear cortical lesions (especially tumours), lobar resections, and when the grid was placed mainly for mapping; **worst results in MRI-negative patients, non-specific histopathology, and sublobar or multilobar resections** YW p.505.

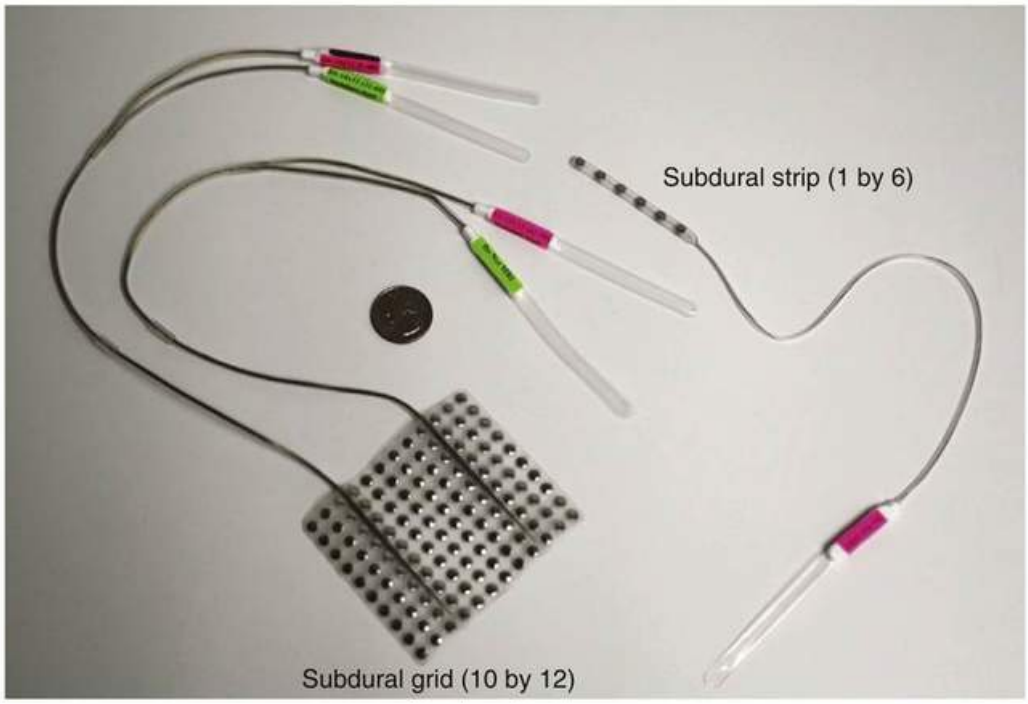


Figure 89.1. Subdural grid and strip electrodes. A standard 10 × 12 subdural electrode grid *(lower left)* and a 1 × 6 subdural electrode strip *(upper right)* created using platinum-iridium electrodes measuring 3.97 mm in diameter and with a center-to-center interelectrode distance of 1 cm. (*A grid electrode is custom made at the Cleveland Clinic, Cleveland, OH.*)

Reproduced from Youmans & Winn 8e, Fig. 89.1, p. 551 — Label when you reproduce it: subdural grid and strip electrodes — a standard 10 × 12 grid and a 1 × 6 strip made of platinum-iridium discs 3.97 mm in diameter with 1 cm centre-to-centre inter-electrode distance, embedded in Silastic. State in the caption why contiguous surface coverage favours functional mapping but under-samples sulcal, mesial and insular cortex.

Stereo-EEG (SEEG)

- Developed by **Talairach and Bancaud in France in the 1950s**; the first implantation was on **3 May 1957**; the term *stereo-electroencephalography* was coined in **1962** and the first tailored corticectomies followed in **1960** [YW pp. 506, 563].
- **SEEG is not merely a depth-electrode technique but a methodology based on AEC analysis, which aims to describe the 3D spatial-temporal organisation of the EZ**; implantation must be individualised on a rational hypothesis accounting for the primary organisation of epileptiform activity and the networks of propagation YW p.506.
- **Specific indications favouring SEEG over grids** YW p.506: (1) deep or difficult-to-cover EZ — mesial temporal, opercular-insular, cingulate, interhemispheric, posterior orbitofrontal; (2) failure of a previous subdural evaluation, where further grids carry adhesion-related risk and the same anatomical limitations; (3) periventricular nodular

heterotopia.

- **The one disadvantage** — "the main disadvantage of the SEEG method is the relatively limited capability for cortical functional mapping in comparison to the SDG method... the need for function mapping of eloquent cortex, especially language areas, remains the sole indication for selecting SDG over SEEG" YW p.506.
- **Technique** — 2.0–2.5 mm twist-drill holes, orthogonal (Cartesian) trajectories preferred for hodologic, volumetric, resection-planning, safety and accuracy reasons; oblique trajectories reserved for posterior orbitofrontal cortex, dorsal frontal and parietal areas (where skull curvature causes deflection), skull defects and the insula. **Implantations exceeding 15 depth electrodes are rare and likely excessive** [YW pp. 564, 566-567].
- **Results** — in 200 patients with 2663 electrodes, SEEG localised the EZ in **154 (77%)**; 134 (87%) of those underwent SEEG-guided resection; of 90 with ≥12 months' follow-up, **61 (67.8%) were Engel class I**; the commonest pathology was **FCD type 1 (61.1%)**; total morbidity **2.5%** YW p.568.

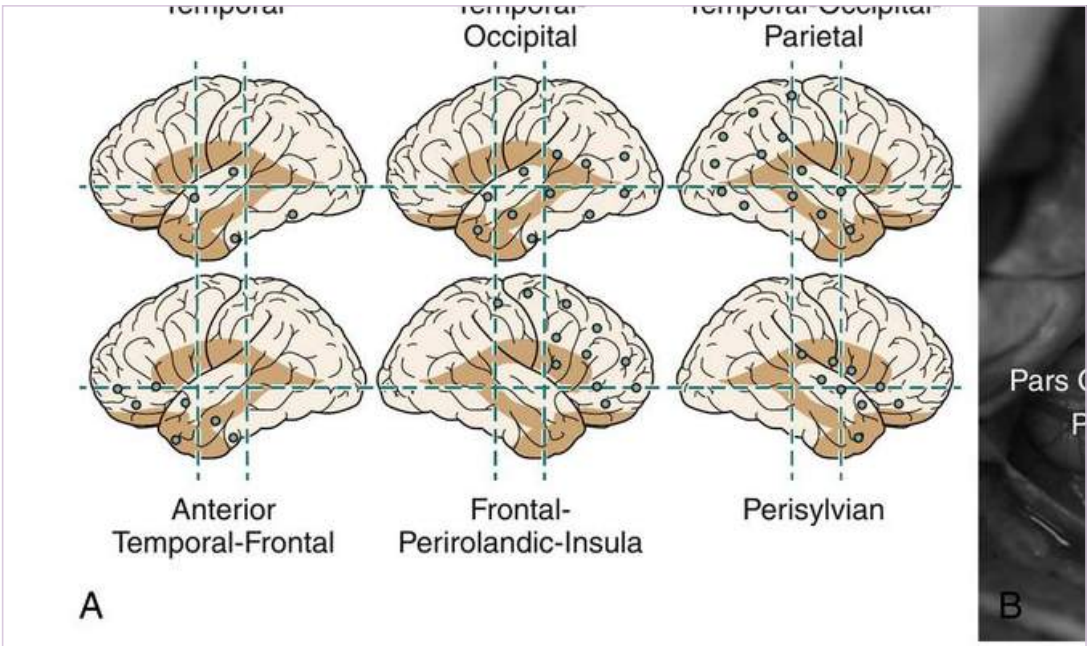


Figure 90.2. Patterns of stereo-electroencephalography (SEEG) implantation. orthogonal electrode entry points *(circles)* normally applied in perisylvian exploration perisylvian space, the configuration also allows mapping of the intrasylvian spaces a *Pars Triang,* pars triangularis; *Pars Operc,* pars opercularis; *Pre-C,* pre-central gyrus temporale; *Supra-Marg,* supra-marginalis.

Reproduced from Youmans & Winn 8e, Fig. 90.2, p. 565 — Label when you reproduce it: patterns of SEEG implantation — the named montages (temporal; temporal-occipital; temporal-occipital-parietal; anterior temporal-frontal; frontal-perirolandic-insula; perisylvian) and, in the lower panel, the hypothetical orthogonal entry points for a perisylvian exploration labelled pars orbitalis, pars triangularis, pars opercularis, precentral gyrus, postcentral gyrus, supramarginal gyrus, planum polare and planum temporale.

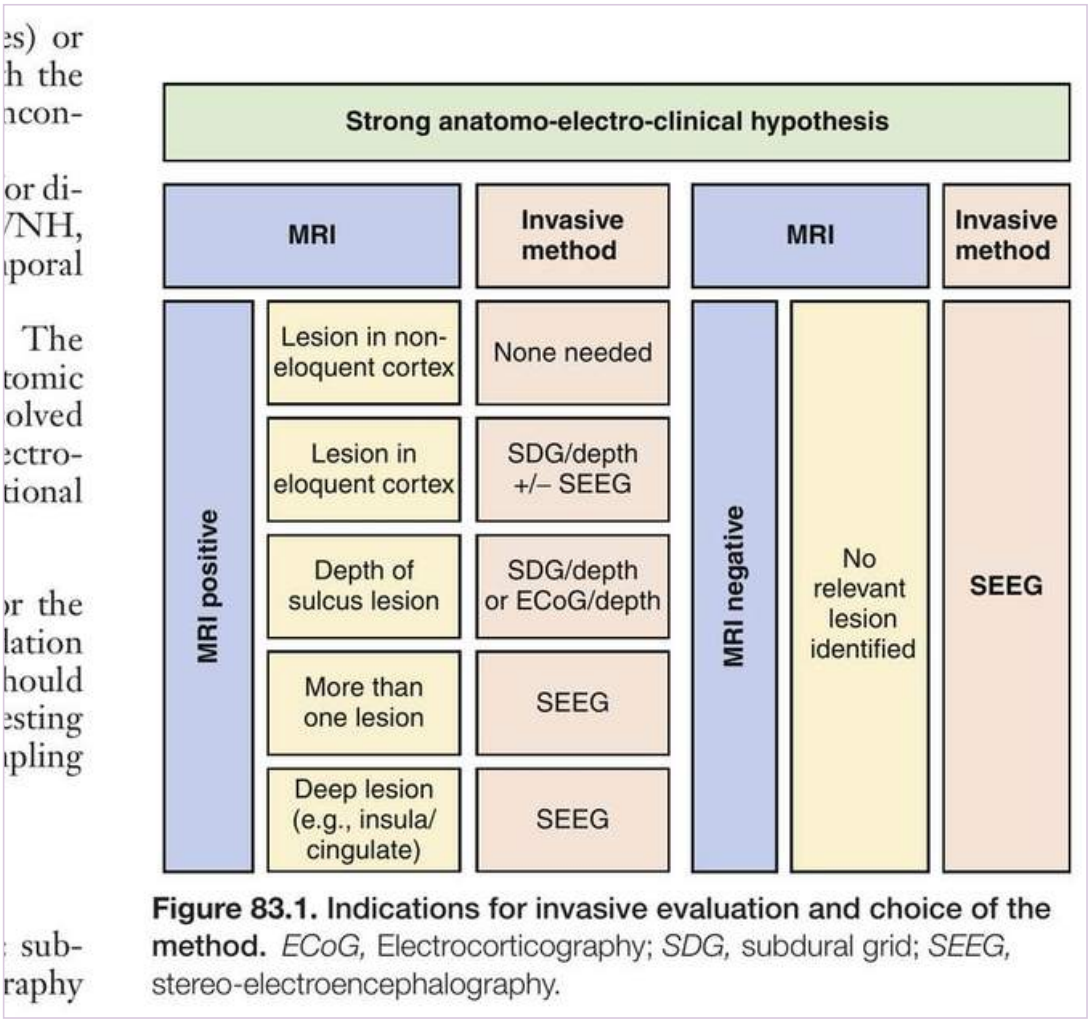


Figure 83.1. Indications for invasive evaluation and choice of the method. *ECoG,* Electrocorticography; *SDG,* subdural grid; *SEEG,* stereo-electroencephalography.

Reproduced from Youmans & Winn 8e, Fig. 83.1, p. 505 — Label when you reproduce it: the algorithm for choosing the invasive method — strong AEC hypothesis at the top, then the branch points (MRI-negative or discordant lesion; deep/multilobar sampling required; contiguous language mapping required) leading to SEEG on one limb and subdural grid implantation on the other.

8. How the result is expressed — outcome scales

- **Engel Epilepsy Surgery Outcome Scale** — Class I: free of disabling seizures (IA completely seizure free since surgery; IB non-disabling simple partial seizures only; IC some disabling seizures but free for at least 2 years; ID generalised convulsions with AED discontinuation only). Class II: rare disabling seizures ("almost seizure free") IIA–IID including nocturnal seizures only. Class III: worthwhile improvement. Class IV: no worthwhile improvement (IVA significant seizure reduction, IVB no appreciable change, IVC seizures worse) YW p.667.e2.
- **ILAE outcome classification (Table 101.1)** — 1: completely seizure free, no auras; 2: only auras; 3: 1–3 seizure days per year; 4: 4 seizure days per year to 50% reduction of baseline; 5: <50% reduction to 100% increase; 6: >100% increase in baseline seizure days YW p.667.
- **Caveat Youmans states** — the Engel "seizure-free" category lumps IA with IB–ID, so truly seizure-free patients cannot be separated unless subcategories are reported; class III "worthwhile improvement" is ambiguous and interpreted variably YW p.667.e1.

Table 2 · The two outcome classifications side by side — the Engel Epilepsy Surgery Outcome Scale reproduced in full from Youmans & Winn 8e, Box 101.1, p. 667.e2, and the proposed ILAE outcome classification from Table 101.1, p. 667.

Engel class	Definition	ILAE outcome	Definition
IA	Completely seizure free since surgery	**1**	Completely seizure free; no auras

IB	Non-disabling simple partial seizures only since surgery	**2**	Only auras; no other seizures
IC	Some disabling seizures after surgery, but free of disabling seizures for at least 2 years	**3**	1–3 seizure days per year ± auras
ID	Generalised convulsions with antiepileptic drug discontinuation only	**4**	4 seizure days per year to 50% reduction of baseline seizure days ± auras
IIA	Initially free of disabling seizures but has rare seizures now	**5**	<50% reduction of baseline seizure days to 100% increase ± auras
IIB	Rare disabling seizures since surgery	**6**	>100% increase of baseline seizure days ± auras
IIC	More than rare disabling seizures since surgery, but rare seizures for the last 2 years		*A "seizure day" is a 24-hour period with one or more seizures, including status epilepticus; baseline is the seizure-day frequency in the 12 months before surgery, corrected for drug reduction during the diagnostic evaluation*
IID	Nocturnal seizures only		
IIIA	Worthwhile seizure reduction		
IIIB	Prolonged seizure-free intervals amounting to more than half the follow-up period, but not less than 2 years		
IVA	Significant seizure reduction		
IVB	No appreciable change		
IVC	Seizures worse		

(b) Surgical techniques for managing drug-resistant epilepsy [5]

9. The classification of operations

Table 3 · Classification of operations for drug-resistant epilepsy, with the principal indication and representative outcome from Youmans & Winn 8e (Ch. 94A pp. 596-601; Ch. 94B pp. 602-604; Ch. 95 pp. 605-613; Ch. 96 pp. 615.e1-615.e10; Ch. 98 pp. 630-635; Ch. 99 pp. 636-644; Ch. 100 pp. 646-665; Ch. 101 pp. 667.e1-667.e16).

Class	Operation	Principal indication	Representative outcome
Curative — resective	Anteromedial temporal lobectomy	Mesial temporal lobe epilepsy with hippocampal sclerosis	Engel I in **66% at 10 years**; multicentre seizure-free 67.9%
	Selective amygdalohippocampectomy (transsylvian, transcortical, subtemporal)	MTLE where lateral neocortex should be spared	Seizure freedom **60–90% at 3–6 years**, equivalent to ATL
	Lesionectomy / tailored corticectomy under ECoG	Cavernoma, DNET, ganglioglioma, FCD, tuber	>90% seizure free for ganglioglioma/low-grade tumour under ECoG
	Frontal resection	Frontal lobe epilepsy	Engel I ~**45–55%**, falling to ~27% at 5 years
	Occipital resection	Occipital lobe epilepsy	Engel I/II **26–92%**; new visual field deficit in 42–75%
	Parietal resection	Parietal lobe epilepsy	Engel I/II **53–82%**; seizure freedom 39.5–57.5%

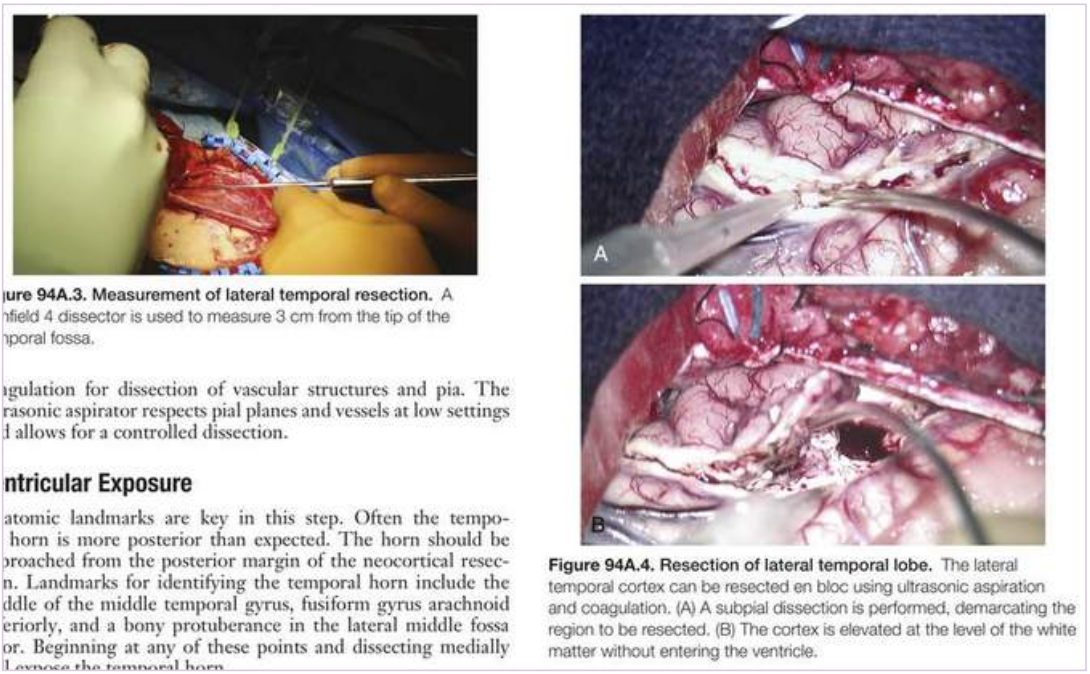
	Multilobar / posterior quadrant resection	Extensive MCD, perinatal infarct	Variable, guided by intracranial EEG
Curative — disconnective	Hemispherotomy (transsylvian keyhole, vertical parasagittal, peri-insular window)	Unihemispheric disease: Rasmussen, HME, Sturge-Weber, porencephaly, HHE	**75–90%** seizure free; HME only 40–60%
Curative — ablative	MRg-LITT	MTS, hypothalamic hamartoma, PVNH, deep FCD, insular epilepsy	Engel I **40–60%** for MTLE
	Stereotactic radiosurgery (Gamma Knife)	MTLE, hypothalamic hamartoma, radiosurgical callosotomy	MTLE: seizure remission **52%** vs 78% after open surgery (randomised ROSE trial); hypothalamic hamartoma: Engel I **39.6%**, Engel I+II 68.8%
Palliative — disconnective	Corpus callosotomy (anterior / complete / posterior)	Atonic drop attacks, Lennox-Gastaut	**80–100%** reduction in drop attacks
	Multiple subpial transection	EZ within motor, sensory or language cortex; Landau-Kleffner	Engel I–III in **75%** when MST alone
Palliative — neuromodulation	Vagus nerve stimulation	Multifocal, generalised, non-lesional; failed resection	16% at 3 months → 30%/41%/41% at 1/2/3 years
	DBS of anterior nucleus of thalamus	Focal epilepsy with or without secondary generalisation	40.4% blinded; 41%/56%/69% at 1/2/5 years
	Responsive neurostimulation	1–2 foci, bilateral mesial temporal, eloquent-cortex onset	41.5% blinded; 44%/53%/66.5% at 1/2/6 years

10. Anteromedial temporal lobectomy — the reference operation

- **Historical line** — Horsley 1890; Penfield's 1950s series of 68 patients with ≥50% seizure reduction in 40 of 51 anterolateral resections; Bailey and Gibbs' 1951 cortical ECoG-guided psychomotor epilepsy surgery; Penfield and Baldwin's 1952 concept of "incisural sclerosis"; Falconer's en bloc hippocampal resection; Crandall's depth electrodes identifying hippocampal ictal onset; **Spencer's 1984 modification**, which increased access to medial structures while limiting resection to the anterior inferior temporal pole and preserving the superior temporal gyrus YW p.596.
- **Extent of lateral resection** — "the classical standard temporal lobectomy resection of the lateral temporal neocortex is between **4 and 5.5 cm on the dominant side and between 5.5 and 6.5 cm on the nondominant side**, as measured posteriorly from the temporal tip." Spencer's group recommends **sparing the STG regardless of side** and limiting the inferior lateral resection to **3 cm** YW p.597.
- **Extent of medial resection** — a prospective trial in 70 patients found **69% seizure freedom at 1 year with resection extended to the superior colliculus versus 38% with partial hippocampectomy**; Schramm's RCT found no difference between 2.5 cm and 3.5 cm mesial resection YW p.597.
- **Language mapping rule** — "the probability of finding language in the anterior 3 cm of the middle and inferior temporal gyri is low. The STG has robust language representation along its length"; map if the dominant-side resection will extend beyond 3 cm posteriorly on the lateral surface or must include the STG YW p.597.
- **Meyer's loop** — the anterior bundle of the optic radiation "runs forward and laterally toward the roof of the temporal horn before curving 2 cm from the temporal pole" and is affected in **up to 90% of temporal lobectomies**, causing the contralateral superior quadrantanopia ("pie in the sky") YW p.596.
- **Key landmark** — the **inferior choroidal point (velum terminale)** marks four things: the anterior fornix, the uncal sulcus, the origin of the choroidal fissure behind the hippocampal head, and the junction of the pes and body of the hippocampus; the midbrain lies medial to it YW p.596.
- **Twelve critical steps (Box 94A.1)** — (1) head in pins, extended 50°, rotated 20–30°, vertex down 10°; (2) expose ≥5 cm of temporal and orbitofrontal lobe; (3) resect 3–3.5 cm of middle and inferior temporal cortex, preserving the temporal horn, lowest ultrasonic aspirator settings; (4) open the temporal horn dissecting inferior to superior along the

fusiform gyrus, bring in the microscope; (5) resect the anterior uncus exposing the ICA then superiorly to the knee of the MCA, all dissection subpial, leaving the tentorial arachnoid undisturbed; (6) find the choroid plexus and choroidal point and draw the imaginary MCA-choroidal line; (7) staying below that line, resect the amygdala and divide the occipitotemporal fasciculus posteriorly; (8) complete the anterior uncal resection, divide the intralimbic gyrus, expose midbrain arachnoid; (9) elevate the pes hippocampi and coagulate PCA perforators; (10) elevate the fimbria off the thalamus and divide the parahippocampal arachnoid; (11) elevate the hippocampal body to the collateral eminence and tail; (12) preserve the posterior inferior temporal branch of the PCA YW p.598.

- **Complications** — mortality **0.1–0.5%**; upper quadrantanopia the commonest deficit (usually unreported by the patient); naming errors; temporalis wasting; frontalis palsy; problems with semantic processing; diplopia; hemiparesis (anterior choroidal artery injury); fourth nerve palsy avoided by preserving the arachnoid above the tentorium [YW pp. 599, 601].
- **Predictors of failure** — rapid seizure spread from the onset zone, non-lesional MRI, PET-EEG discordance, and a history of generalised tonic-clonic seizures YW p.601.



Reproduced from Youmans & Winn 8e, Fig. 94A.4, p. 599 — Label when you reproduce it: en bloc resection of the lateral temporal neocortex — (A) subpial dissection demarcating the region to be resected, with the superior temporal sulcus as the superior limit and the middle fossa floor as the inferior limit; (B) the cortex elevated at the level of the white matter without entering the ventricle. Note the 3 cm posterior limit measured with a Penfield 4 from the anterior middle fossa floor.

11. Selective amygdalohippocampectomy

- **Four corridors**: **transcortical** (Niemeyer 1958, originally through the middle temporal gyrus; later variants through inferior and superior temporal gyri), **transsylvian** (Wieser and Yaşargil 1982), **transsulcal** and **subtemporal** (Hori 1993) [YW pp. 602, 604].
- **Trade-off** — transcortical approaches preserve much cortex but transgress cortex and some temporal stem; **the transsylvian approach preserves all superficial temporal cortex but requires transecting a large segment of the temporal white matter stem**; the subtemporal approach "avoids any disruption of the anterolateral temporal cortex... and also allows excellent access to the mesial temporal lobe without transgression of the temporal stem," through a **2 cm keyhole craniotomy** at the middle fossa floor entering the collateral sulcus YW p.602.
- **Evidence** — no randomised trials exist, but "almost every direct comparison study has shown equivalent seizure-freedom rates (60%–90% at 3–6 years of follow-up) between SAH and ATL in adult patients." Most cognitive-outcome studies slightly favour SAH; the most consistent finding is **a smaller decline in verbal memory in dominant-lobe SAH than ATL** (43% of dominant ATL patients worsened versus 31% of SAH patients in Clusmann's series) [YW pp. 603-604].

12. Extratemporal resections

- **Frontal lobe epilepsy** is the second commonest focal epilepsy. Seizure-freedom rates are "approximately 50%... [and] do not reach the same threshold as that of TLE (approximately 70%)"; Jeha's 70 patients fell from 55% at 1 year to **27% at 5 years**; Englot's meta-analysis of 21 studies gave an overall **45.1%**. Predictors of recurrence: negative MRI, extrafrontal pathology, generalised ictal EEG, incomplete resection YW p.607.
- **Occipital lobe epilepsy** — Engel I/II ranges **26–92%**; the dominant issue is visual field loss. In Kun Lee's 26 patients only one of 18 with normal preoperative fields remained normal; Binder found **42.4%** with new or worsening deficits; a recent study found **61.5%**, and some data suggest the risk is **as high as 75%** [YW pp. 608-610].
- **Parietal lobe epilepsy** — Engel I/II **53–82%**, seizure freedom **39.5–57.5%**; about a quarter of patients in the Binder and Kasowski series also underwent MSTs because the focus extended into functional cortex [YW pp. 610-611].
- **General principle** — "seizures do not respect lobar boundaries, but spread to adjacent cortex and along white matter pathways. In order to render a patient seizure free, the location of seizure onset and regions of fast spread generally need to be removed" YW p.605.

13. Disconnection procedures

- **Hemispherotomy** — three techniques: disconnection via an **opercular window**, the **transsylvian keyhole** approach (4 × 4 or 4 × 5 cm craniotomy above the sylvian fissure; four steps — transsylvian exposure of the circular sulcus, temporomesial disconnection through the temporal stem, complete opening of the lateral ventricle, then frontobasal/posteromediobasal disconnection with paramesial callosotomy), and **vertical parasagittal (dorsal transcortical subinsular) hemispherotomy** (3 × 5 cm parasagittal frontal craniotomy; transcortical access to the ventricle; paramedian callosotomy including the posterior column of the fornix; lateral transection between thalamus and striatum; resection of the posterior gyrus rectus with lateral extension of the transection) [YW pp. 636, 639-642].
- **Advantages over hemispherectomy** — shorter operative time, much less blood loss (transfusion rate 8%), fewer intraoperative complications, lower hydrocephalus/shunt rate (3–5.2% for keyhole vs 8–30% for others) [YW pp. 636, 641-642].
- **Corpus callosotomy** — craniotomy midpoint just anterior to the coronal suture on the non-dominant side; interhemispheric dissection identifying callosomarginal then pericallosal arteries; callosotomy **begins 3 cm posterior to the genu**, proceeds ventrally to the septal leaves and then anteriorly to the anterior commissure; a complete section needs a larger or second craniotomy; posteriorly, beware the internal cerebral veins and vein of Galen below the splenium and the fornices below the callosum [YW pp. 615.e2-615.e3].
- **Multiple subpial transection (Morrell)** — rationale is Mountcastle's vertical columnar organisation: horizontal fibres mediate synchronisation and spread while vertical fibres mediate function, so **transections 5 mm apart, 4 mm deep, perpendicular to the long axis of the gyrus** abolish synchronisation while preserving function. Permanent complication rate **5–7%** in Morrell's 100 patients; overall paresis 25.4% of which 75% transient [YW pp. 615.e5-615.e9].

14. Ablative and neuromodulatory options

- **LITT** — occipital trajectory along the hippocampal long axis into the amygdala; ablate anterior first and withdraw in stages; sparing the mesial temporal head predicts failure; extending posteriorly is counterproductive; **12-month Engel I 40–60%**, better neurocognitive profile than open surgery, commonest complication octantanopsia (up to 37.5%) [YW pp. 630-631].
- **VNS** — coiled leads on the **left** vagus nerve connected to a subclavicular generator; afferents reach the nucleus of the solitary tract, which projects to thalamus, amygdala, anterior cingulate and frontoparietal cortex. Two RCTs (EO3, EO5): high stimulation gave 24.5% vs 6.1% and 27.9% vs 15.2% reduction. Efficacy improves with time: **16% at 3 months, 30% at 1 year, 41% at 2 and 3 years** [YW pp. 653-654].
- **DBS of the anterior nucleus of the thalamus (SANTE)** — 110 patients, 5 V, 90 µs, 145 Hz, 1 min on / 5 min off; final blinded month **40.4% vs 14.5%** reduction (P = .0017); open label **41% at 1 year, 56% at 2 years, 69% at 5 years**; 50% responder rate 43% → 54% → 68%. Only **16% seizure free for ≥6 months** in 5 years. FDA approval 2018 [YW pp. 659-660].

- **Responsive neurostimulation (RNS)** — 191 patients, one or two depth or strip leads at the seizure onset zone; blinded reduction **41.5% vs 9.4%** (P<.01); **44% at 1 year, 53% at 2 years, 60% at 3 years, 66.5% at 6 years**; responder rate 64.6% at 6 years; particularly useful for **multiple or bilateral onset zones and eloquent-cortex onset**; continuous ECoG allows long-term ambulatory monitoring which "may lead to resective (or ablative) surgery in some patients not thought to be candidates" [YW pp. 661-663].

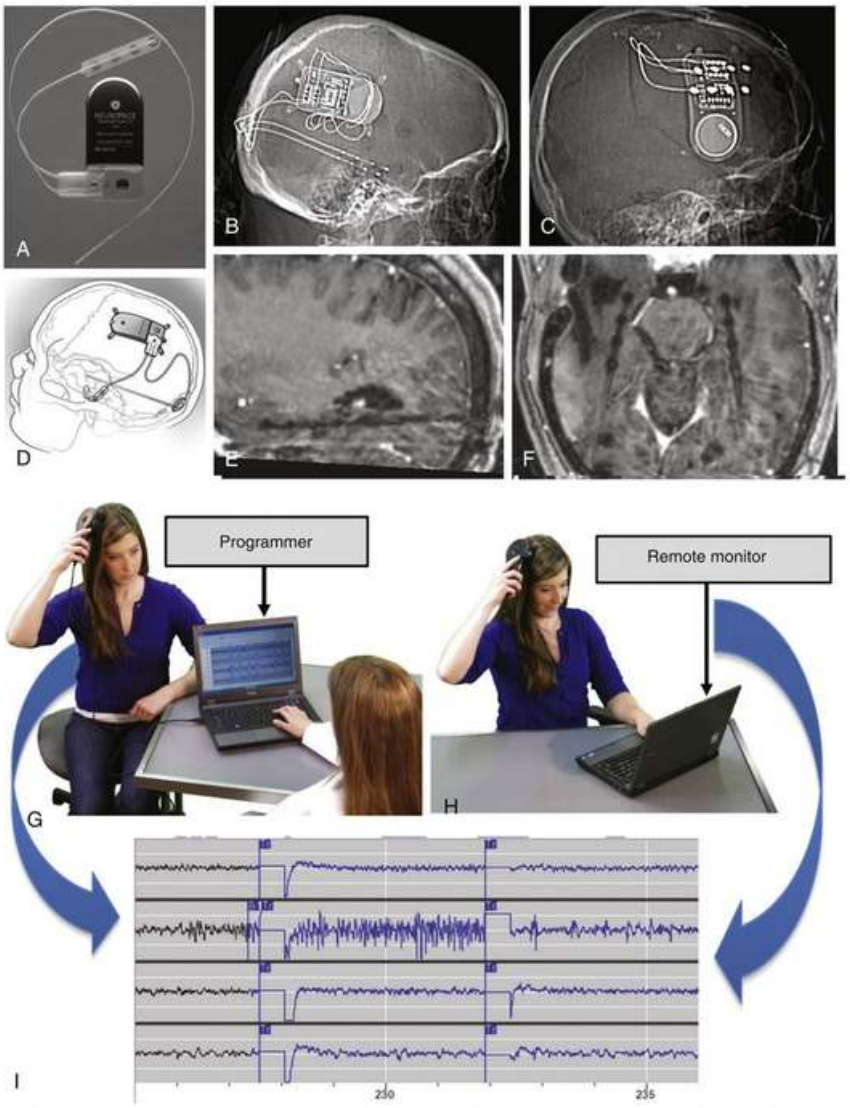


Figure 100.7. RNS System (NeuroPace, Inc.) for the treatment of epilepsy. The RNS System is depicted in (A) and (D). The system consists of an implanted pulse generator with a primary battery cell to which are attached one or two electrode arrays, which can be either depth electrode arrays or surface strip arrays. (B) Lateral radiograph showing the pulse generator implanted into the skull after craniectomy of a window of bone sized to the generator; in this case two hippocampal depth arrays are present, implanted via an occipital approach. (C) Lateral radiograph of pulse generator overlying two 4-contact surface arrays implanted over the left inferior frontal gyrus (Broca region). Lateral (E) and axial (F) magnetic resonance imaging (MRI) of bilateral hippocampal depth electrode arrays. In this case brain MRI of RNS System depth electrodes—which is not approved by the US Food and Drug Administration—was performed because of a non-surgically related neurological condition for which MRI was necessary. The RNS System performs continuous electrocorticography; the stored electrocorticogram (I) is downloaded telemetrically to the programmer's computer (G), and changes in the stimulation program are uploaded telemetrically. Similarly the electrocorticogram is downloaded to the patient's computer (H) for uploading via the Internet to the patient data management system, where it can be scrutinized by the physician and manufacturer's technical experts, and simulations of seizure detection can be performed for optimization in advance of the patient's visit with the programmer. The effect of responsive electrical stimulation is shown in the electrocorticogram (I). Each line depicts the recording from the 4-contact electrodes. In the second line down an electrographic seizure is detected and triggers a stimulation *(blue line)*, during which recording is flat because the amplifier is blanked to prevent saturation. The first stimulation is ineffective, and the electrographic seizure continues. However, after a second detection and stimulation *(second blue line)* the seizure activity is abrogated.

Reproduced from Youmans & Winn 8e, Fig. 100.7, p. 662 — Label when you reproduce it: the RNS System — (A, D) cranially implanted pulse generator with one or two depth or subdural strip arrays; (B) lateral radiograph with two hippocampal depth arrays implanted by an occipital approach; (C) lateral radiograph of the generator over two 4-contact strips across the left inferior frontal gyrus; (E, F) MRI of bilateral hippocampal depth arrays; (G, H) programmer and patient remote monitor; (I) the electrocorticogram showing a detected electrographic seizure, an ineffective first stimulation and a second detection-plus-stimulation that aborts the discharge.

15. Points that earn extra marks

- **Give the Kwan and Brodie numbers** (47% / 13% / 3.7% / <1%) — they convert "drug-resistant epilepsy" from a definition into an argument YW p.497.
- **Quote the MRI sensitivity data** (39% non-expert, 50% expert, 91% with epilepsy protocol; hippocampal sclerosis missed in 86% on standard protocols) [YW pp. 492-493].
- **Name the ERSET 2-year threshold** for referral YW p.615.e1.
- **State that 70% are resolved by Phase I and 20–30% need invasive monitoring** YW p.495.
- **Say that SEEG is now the preferred invasive method** and that language mapping is the only remaining reason to choose grids YW p.506.
- **Never omit the Engel classification with its four classes and the class I subcategories** YW p.667.e2.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Drug-resistant epilepsy = failure of two appropriately chosen, adequately dosed drugs** — not five, not ten, and not "after 10 years of trying" [YW pp. 497, 503].
- **After the third drug fails, the chance of seizure freedom is ≤1%** — that single number justifies the whole surgical pathway YW p.497.
- **Video-EEG plus epilepsy-protocol MRI, read with a concordant history, settle roughly 70% of surgical candidates** [YW pp. 495, 503].
- **A normal MRI is not a contraindication**; it is an indication for post-processing, PET, SISCOM, MEG and, usually, SEEG YW p.504.
- **Hippocampal sclerosis is the most predictive lesion for the EZ — except in "temporal-plus" epilepsy** [YW pp. 503-504].
- **The symptomatogenic zone is where the seizure first becomes non-silent, not where it starts** YW p.605.
- **Implant only to test a defined, falsifiable AEC hypothesis** — anything else is a fishing expedition YW p.505.
- **Spare the superior temporal gyrus** in temporal lobectomy unless it is proven ictal; language runs its whole length YW p.597.
- **Meyer's loop turns 2 cm from the temporal pole** — hence the superior quadrantanopia in up to 90% of temporal lobectomies YW p.596.
- **Palliative does not mean useless**: callosotomy abolishes drop attacks in 80–100%, and RNS/ANT-DBS reduce seizures by ~50–70% with continuing improvement over years [YW pp. 615.e2, 654, 660].
- **Report outcomes with Engel class I subcategories or the ILAE 1-6 scale** — "seizure free" without a subcategory is uninterpretable [YW pp. 667, 667.e1-667.e2].

Pages read for this answer — Youmans & Winn 8e: 491, 492, 493, 494, 495, 497, 502.e5, 503, 504, 505, 506, 508, 515, 527, 537, 541, 551, 563, 564, 566, 567, 568, 596, 597, 598, 599, 601, 602, 603, 604, 605, 607, 608, 610, 611, 615.e1, 615.e2, 615.e3, 615.e5, 615.e9, 630, 631, 636, 639, 641, 642, 646, 653, 654, 659, 660, 661, 663, 667, 667.e1, 667.e2, 667.e14

a) Discuss focal cortical dysplasia classifications. [5]
b) Discuss diagnostic workup and management of FCDs. [5]

LONG | JUN 2022 · Paper II · Q7 | 10 marks

Also asked as: Epilepsy — also asked as MAY 2024 · Paper III · Q2 (a] Focal cortical dysplasia classifications [2]; b] Diagnostic work up of a suspected case of FCD [4]; c] Treatment of FCD [4]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 79 *Malformations of Cortical Development* (H.B. Sarnat, G.G. Heuer, P.B. Crino), §Classification of Malformations of Cortical Development, §Focal Cortical Dysplasias, §Surgery for Malformations of Cortical Development, pp. 488.e1-488.e7 (Table 79.2, p. 488.e3; Figs. 79.1-79.4, pp. 488.e3-488.e4). Supplementary: Ch. 84 *Magnetic Resonance Imaging for Epilepsy Surgery*, §Malformations of Cortical Development, §Focal Cortical Dysplasias, §Age and Imaging of FCD, §Structural MRI post-processing and 3DMMI, pp. 508-518 (Figs. 84.2-84.4, pp. 509-510; Figs. 84.9-84.10, pp. 515-516); Ch. 91 *Intraoperative Electrocorticography and Strategy in Tailored Lesionectomies*, §Focal Cortical Dysplasias, pp. 573-577 (Box 91.1, p. 575; Tables 91.1-91.2, p. 577); Ch. 83 *Evaluation of Patients for Epilepsy Surgery*, pp. 503-506; Ch. 90 *Intracranial Monitoring: SEEG*, pp. 563-570; Ch. 95 *Resections for Extratemporal Epilepsy*, pp. 605-613; Ch. 98 *LITT in Epilepsy*, §Focal Cortical Dysplasia, Insular Epilepsy, and Tuberous Sclerosis, pp. 631-633; Ch. 267 *Pediatric Epilepsy Surgery*, pp. 2043-2045.

(a) Focal cortical dysplasia — classifications [5]

1. Where FCD sits — the parent classification of malformations of cortical development

- **Definition of the parent group** — MCDs are "a heterogenous group of disorders that are characterized by abnormal cerebral cortical cytoarchitecture," spanning "a spectrum of disorders from subtle microdysgenesis affecting a small area of the cortex to devastating lissencephaly." The **unifying feature is the high association with intractable epilepsy** and often with cognitive disability, autism or pervasive developmental disorder YW p.488.e1.
- **Timing of cortical formation** — "the formation of the normal cerebral cortex extends from weeks 8 to 26 of human gestation," from neuroepithelial progenitors in the ventricular zone; excitatory glutamatergic neurons migrate radially inside-out along radial glia from layer VI to layer II, while **inhibitory GABAergic interneurons arise in the ganglionic eminence and migrate tangentially**, comprising about **20% of mature cortical neurons** YW p.488.e1.
- **Three mechanistic groups** (Barkovich; Table 79.2) YW p.488.e3:

1. **Disorders of cellular proliferation** — microcephaly; macrocephaly; cortical tubers of tuberous sclerosis complex; **focal cortical dysplasia with balloon cells**; hemimegalencephaly; and, as neoplastic proliferations, dysembryoplastic neuroepithelial tumour, ganglioglioma and gangliocytoma.
2. **Disorders of neuroblast migration** — lissencephaly; heterotopia; and the congenital muscular dystrophies (congenital muscular dystrophy, muscle-eye-brain disease, Walker-Warburg syndrome).
3. **Disorders of cortical organisation** — polymicrogyria and schizencephaly.

- **The radiological (Ch. 84) restatement of the same three groups** puts type IIa and IIb FCD (Taylor dysplasia without and with balloon cells) in **group I**, and **type I FCD plus mild MCD in group III** [YW pp. 508-509].

Table 1 · Classification of malformations of cortical development — reproduced in full from Youmans & Winn 8e, Table 79.2, p. 488.e3.

Group	Subgroup	Condition
Disorders of cellular proliferation	Abnormal proliferation	Microcephaly
		Macrocephaly
		Cortical tubers (tuberous sclerosis complex)
		Focal cortical dysplasia with balloon cells
		Hemimegalencephaly
	Abnormal proliferation — neoplastic process	Dysembryoplastic neuroepithelial tumour
		Gangliogliomas
		Gangliocytoma

Disorders of neuroblast migration	—	Lissencephaly
		Heterotopia
	Muscular dystrophy	Congenital muscular dystrophy
		Muscle-eye-brain disease
		Walker-Warburg syndrome
Disorders of cortical organisation	—	Polymicrogyria
		Schizencephaly

2. The FCD classification itself — the answer the examiner wants

Definition — "FCDs are regions of cerebral cortex in which tissue architecture and lamination are abnormal. They represent a principal cause of epilepsy in infancy and childhood." Neuropathologic criteria were endorsed by an **ILAE Commission on Neuropathology** YW p.488.e6. Youmans notes the scheme "delineates three broad categories that reflect a spectrum of pathologic severities," further subdivided into **Ia, Ib, Ic, IIa, IIb and III** [YW pp. 488.e3-488.e4].

Two fundamental types are recognised, plus a third associated category YW p.488.e6:

- **FCD type I** (formerly type Ia) — "characterized by microcolumnar or radial lamination but with **morphologically normal neurons**."
- **Ia** — abnormal **radial (columnar)** cortical lamination.
- **Ib** — abnormal **tangential (horizontal, 6-layered)** lamination.
- **Ic** — a combination of Ia and Ib.
- No gene mutation has yet been clearly associated with type I [YW pp. 488.e4, 488.e6].
- **FCD type II** — "also has abnormal lamination, although not usually microcolumnar, but neurons are excessively large (**megalocytic**) and abnormal in shape (**dysplastic**) — the most characteristic feature."
- **IIa** — large **dysmorphic neurons** without balloon cells.
- **IIb** — dysmorphic neurons **plus balloon cells**, which are morphologically similar to the giant cells of tuberous sclerosis. "Balloon cells also occur in the FCD IIb subtype but not in FCD type IIa or in FCD type I" YW p.488.e6.
- **FCD type III** — "either type I or II associated with **another principal lesion**" YW p.488.e6:
- **IIIa** — with **hippocampal sclerosis**.
- **IIIb** — with a **cortical tumour** (typically DNET or ganglioglioma).
- **IIIc** — with a **vascular malformation**.
- **IIId** — with an **infarct, porencephalic cyst or other lesion** acquired in early life.

Three facts to state after the list YW p.488.e6:

1. **All FCDs are congenital lesions.**
2. **All are highly epileptogenic** — "indeed seizures are the presenting clinical symptom."
3. **Type I is less well documented than type II** because no genetic basis has been found and because MRI often shows no lesion at the site of the EEG focus, so type I is "inappropriately called 'nonlesional'."

A separate, lesser entity — mild malformation of cortical development (mMCD), in which histopathology shows only minimal abnormality; "mild MCD was always located in the temporal lobe," most often manifesting as lobar hypoplasia and atrophy (29%), and "it is very difficult to distinguish mild MCD from type I FCD" on imaging YW p.509.

3. Genetics and molecular pathology — where the marks are now

- **FCD type II is a postzygotic somatic mutation of the mTOR pathway.** "FCD type II is much better understood from a genetic perspective because it is a postzygotic somatic mutation that involves component genes of the mTOR signaling pathway" — **PI3K, AKT3, DEPDC5** and **MTOR** itself, both germline and somatic [YW pp. 488.e4, 488.e6].
- **Size depends on timing** — "the size and extent of the lesion depends on timing of the earliest expression of the somatic

mutation within the **33 mitotic cycles** of periventricular neuroepithelium; the earlier the onset, the larger is the lesion, so early onset may produce hemimegalencephaly" [YW pp. 488.e6-488.e7].

- **FCD type II and hemimegalencephaly are genetically the same disorder** — "it is now also confirmed that FCD type II and HME are the same disorder genetically," sharing the same neuronal cytomegaly, dysplasia and abnormal cortical architecture YW p.488.e7.
- **Tuberous sclerosis complex** — mutations in **TSC1 (hamartin)** or **TSC2 (tuberin)**, both modulators of mTOR, which "governs cell size and proliferation." Cortical tubers are focal areas of disorganised lamination containing **giant cells morphologically similar to balloon cells of FCD IIb**; **the number of tubers does not vary with mutation type, patient age, or necessarily neurological phenotype**. TSC is "more complex because in addition to the somatic mutation of the TSC1 and TSC2 genes, it also is an autosomal dominant mendelian trait" [YW pp. 488.e3, 488.e7].
- **Epigenetic subtyping** — "subtypes of FCD II can be further distinguished by genomic DNA methylation patterns" YW p.488.e7.
- **Why type I blurs the grey-white junction** — "this blurring is due to an excessive number of heterotopic neurons in the U-fiber layer just beneath the cortex, which also form complex synaptic plexuses within this layer that can integrate with the overlying cortex and join epileptic networks" YW p.488.e6.
- **The excitatory/inhibitory ratio principle** — "epileptogenesis of each MCD depends in large part on the ratio of excitatory and inhibitory synaptic input to individual neurons," mediated in part by the extracellular proteoglycan **keratan sulfate**, which repels immature glutamatergic axons and facilitates GABAergic ones. This explains why polymicrogyria is highly epileptogenic whereas Down syndrome, in which the ratio shifts toward GABA, has a low epilepsy risk, and why about **40% of infants with alobar or semilobar holoprosencephaly do not have epilepsy** despite severe cortical architectural abnormality [YW pp. 488.e1, 488.e6].

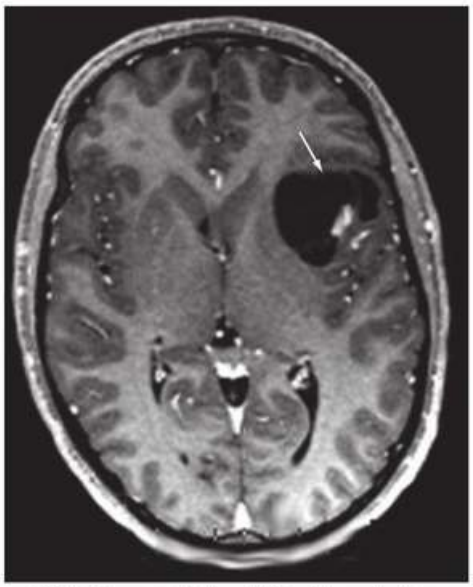


Figure 79.2. MR image depicting a left frontal ganglioglioma *(arrow).* T1-weighted image after administration of intravenous gadolinium.

Several autosomal recessive and X-linked forms of type lissencephaly exist, resulting from mutations in *LIS1*, *DCX*, *AR* or *RELN* genes.[85-88] These genes are believed to be involv in important cell processes, such as movement of the neuro nucleus or dynamic changes in the neuronal cytoskeleton, t are required for neuronal progenitor cells to migrate prope from the ventricular zone into the cortical plate. *LIS1* mutatio are seen in isolated lissencephaly and in association with Mill Dieker lissencephaly syndrome as part of a contiguous ge deletion syndrome. Over the past 5 years, mutations in a numb of genes linked to cytoskeletal regulation and transport have be linked to lissencephaly, including a variety of tubulin isofor and dynein.

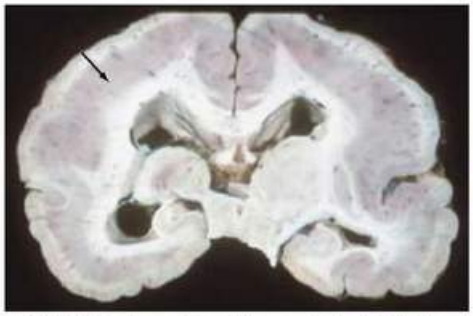


Figure 79.4. Unfixed specimen of lissencephaly. Note thickened cortex *(arrow)* and absence of cortical gyri.

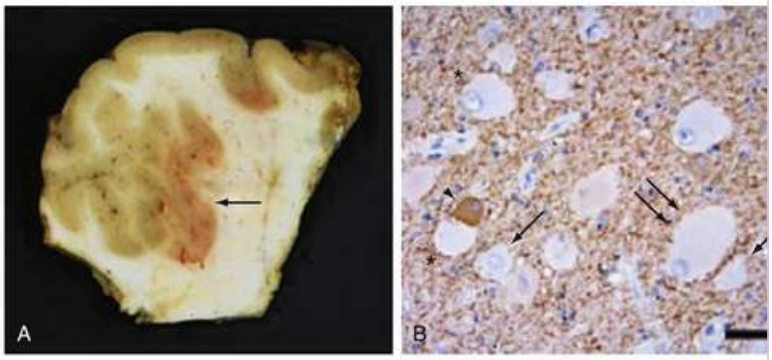


Figure 79.3. Histopathology of Palmini type II cortical dysplasia. (A) Fresh specimen demonstrates thickened cortex *(arrow).* (B) Balloon cells *(double arrows),* dysmorphic neurons *(single arrows* and *asterisk),* and glial cells *(arrowhead;* labeled with glial fibrillary acidic protein).

Reproduced from Youmans & Winn 8e, Fig. 79.3, p. 488.e4 — Label when you reproduce it: histopathology of Palmini type II cortical dysplasia — (A) fresh specimen with the arrow on the thickened cortex; (B) balloon cells (double arrows), dysmorphic neurons (single arrows and asterisk) and glial cells (arrowhead, labelled with glial fibrillary acidic protein). State that the balloon cell defines IIb and that dysmorphic neurons alone define IIa.

Table 2 · The FCD classification at a glance — histology, genetics, imaging, typical site and surgical prognosis; compiled from Youmans & Winn 8e, Ch. 79 pp. 488.e4-488.e7, Ch. 84 pp. 509-510 and Ch. 91 pp. 576-577.

Type	Histology	Genetics	MRI	Typical site / age	Surgical outcome
Ia	Abnormal radial (microcolumnar) lamination; normal neurons	None identified	Often "non-lesional"; lobar/sublobar hypoplasia and atrophy, subcortical white-matter volume loss with T2/FLAIR hyperintensity, cortical thickness preserved, mild grey-white blurring	Posterior temporal / parieto-occipital; seizures begin in early infancy; learning disability, behavioural disorder, autistic spectrum	Poorer — diffuse, multilobar, MR-negative, margins hard to define, subtotal resection common

Ib	Abnormal tangential (6-layer) lamination; normal neurons	None identified	As Ia; associated with hippocampal sclerosis in >70% and the commonest FCD to accompany developmental tumours	Temporal lobe	Poorer, as above
Ic	Ia + Ib	None identified	As above	Temporal	Poorer
IIa	**Dysmorphic (megalocytic) neurons**, no balloon cells	Somatic/germline mTOR pathway — PI3K, AKT3, DEPDC5, MTOR	Cortical thickening, grey-white blurring, T2/FLAIR hyperintensity	Extratemporal, frontal predilection	Better — discrete, single-stage resection feasible
IIb	Dysmorphic neurons + **balloon cells**	Same mTOR pathway; genetically identical to hemimegalencephaly	As IIa plus the **transmantle / "funnel track"** sign from cortex to ventricle; "often better delineated" than IIa though the two cannot be distinguished on MRI	Extratemporal, frontal predilection	Best of the FCDs
IIIa	Type I or II + **hippocampal sclerosis**	—	Hippocampal atrophy and T2 hyperintensity plus temporal-pole blurring	Temporal	Depends on completeness of the dual resection
IIIb	Type I or II + **cortical tumour** (DNET, ganglioglioma)	Shared mutations with MCD; tau upregulation	Multicystic wedge-shaped cortical mass (DNET) or cyst with mural nodule (ganglioglioma)	Temporal in 70%	Seizure freedom 58–86% after tumour resection
IIIc	Type I or II + **vascular malformation**	—	"Popcorn" cavernoma on GRE/SWI; flow voids of AVM	Any	Good after lesion + haemosiderin-ring resection
IIId	Type I or II + **infarct, porencephaly or other early lesion**	—	Encephalomalacia lined by grey matter	Any	Depends on extent

(b) Diagnostic workup and management of FCD [5]

4. Clinical presentation — what brings the patient

- **Seizures are the presenting symptom of every FCD** YW p.488.e6. FCDs are "a frequent cause of epilepsy in infants

and children" YW p.488.e1 and "malformations of cortical development... are the most commonly seen lesions in most pediatric surgical series" YW p.2043.

- **Type I phenotype** — "children with FCD type I often have learning disabilities, cognitive deficits, behavioral disorders, and possibly even autistic spectrum disorder. The typical focus of FCD type I is in the **posterior temporal or parieto-occipital area**, and seizures usually begin in early infancy" YW p.488.e6.
- **Type II phenotype** — extratemporal, with a **predilection for the frontal lobe**, presenting with focal motor, hypermotor or asymmetric tonic seizures that can be very frequent [YW pp. 510, 605].
- **MCDs are the most common cause of intractable paediatric epilepsy**; 70% to 90% of patients with TSC, HME or lissencephaly have seizures, and MCDs are found in **30% of cortical resections** YW p.488.e7.

5. Step 1 — epilepsy-protocol MRI, read properly

- Use the **HARNESS-MRI** protocol — 3D volumetric T1, 3D FLAIR and a 2D coronal T2 perpendicular to the hippocampal long axis; gadolinium only if a tumour, vascular lesion or infection is suspected; and have it read by a neuroradiologist active in an epilepsy programme, because expert reading materially increases lesion detection YW p.503.
- **Type I FCD on MRI** — "can be completely cryptogenic. In this subtype, common findings are **hypoplasia or atrophy at a lobar or sublobar level**. They are frequently associated with subcortical white matter volume loss, which has an increased signal on T2-weighted images and T2-weighted FLAIR images and a decreased signal on T1-weighted images. **Cortical thickness is usually preserved**, although there can be mild blurring at the junction between gray and white matter." Type I is most often temporal, **associated with hippocampal sclerosis in more than 70% of cases**, and is the FCD most commonly associated with developmental tumours YW p.510.
- **Type II FCD on MRI** — "characterized by **increased cortical thickness and blurring of the junction between gray and white matter** on T1- and T2-weighted images. The subcortical area can show an increased signal on T2-weighted and FLAIR images and a decreased signal on T1-weighted images. **This abnormality creates a 'funnel' track between the cortex and the ventricle, which is typical of type II FCDs and explains why the condition is also termed transmantle dysplasia.**" Other findings are abnormal gyration and sulcation with increased T2 signal of the affected cortex (which remains hypointense relative to the underlying white matter) YW p.510.
- **IIa cannot be distinguished from IIb on MRI**, "although type IIb is often better delineated." Type II, in contrast with type I, "often occurs in extratemporal areas, with a predilection for the frontal lobe" YW p.510.
- **Suspect a tumour instead** if the structural MRI shows mass effect, cystic components or calcification — repeat with gadolinium YW p.510.
- **Age and imaging — the single most examinable practical rule** YW p.510:
- **Adults** (myelination complete) — T2, T1 and T1 inversion recovery are all suitable for assessing blurring and cortical thickness.
- **Infants <6 months** — myelination is incomplete and immature white matter can appear isointense to cortex on T1 and T2; however **in FCD the white matter almost always looks hyperintense relative to the dysplastic area on T2**. Because "the contrast between cortex and white matter is maximal before myelination begins, if seizures start before 6 months of age, a scan should be obtained immediately."
- **6 to 18 months** — grey-white contrast diminishes during myelination and **FCDs are least visible**.
- **A "negative" MRI should be repeated at 30 months**, when myelination is largely complete.
- **Ultra-high-field imaging** — 7T "has been demonstrated to detect increased foci of epileptogenic potential" and "has also been useful in detecting cortical dysplasias, vascular malformations, and polymicrogyria"; FLAIR and gradient-echo at 7T improve sensitivity. Drawbacks include nausea, light flashes, metallic taste and noise, and clinical relevance must be interpreted against electrophysiological concordance [YW pp. 508, 510].

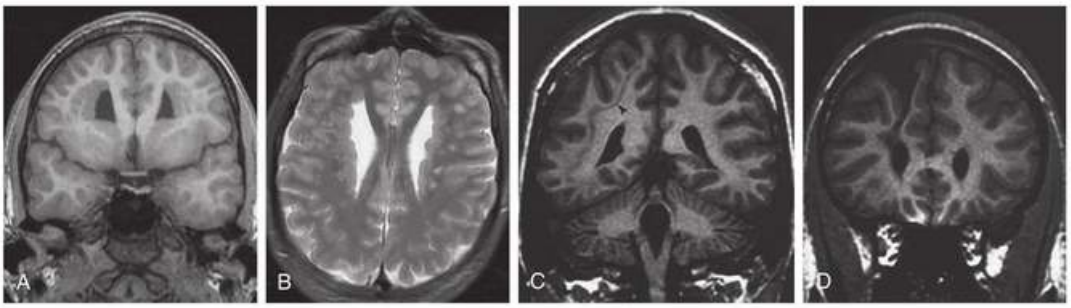


Figure 84.3. Malformations of cortical development, group II. Coronal T1-weighted image (A) and axial T2-weighted image (B) showing extensive bilateral subependymal nodular gray matter heterotopia. (C) Coronal T1-weighted image showing extensive band heterotopia in the right cerebral hemisphere. (D) Coronal T1-weighted image showing schizencephaly that extends to the right ventricle.

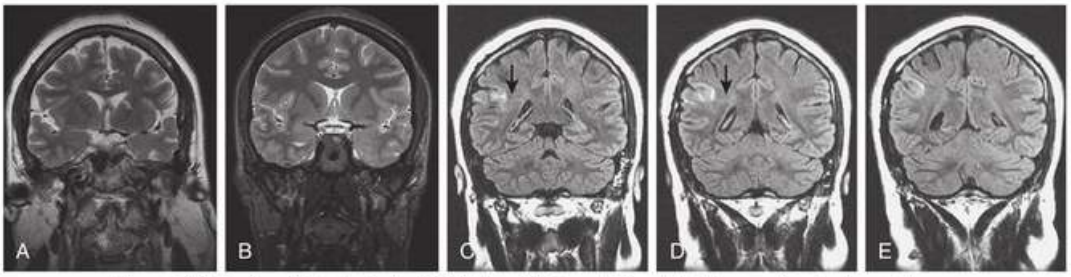


Figure 84.4. Focal cortical dysplasia (FCD). (A and B) Coronal T2-weighted images showing hypoplasia of the left temporal pole and loss of gray-white matter differentiation, in keeping with presence of FCD. (C to E) Type II FCD: coronal T2-weighted fluid-attenuated inversion recovery images showing funnel track hyperintensity (C and D, *arrows*) extending from the cortex of the right supramarginal gyrus to the ventricle.

*Reproduced from Youmans & Winn 8e, Fig. 84.4, p. 510 — Label when you reproduce it: focal cortical dysplasia on MRI — (A, B) coronal T2 showing hypoplasia of the left temporal pole with loss of grey-white differentiation, the type I pattern; (C-E) coronal T2-FLAIR showing the **funnel-track (transmantle) hyperintensity** running from the cortex of the right supramarginal gyrus to the ventricle, the signature of type II FCD (arrows). Name the four MRI signs of type II: cortical thickening, grey-white blurring, T2/FLAIR subcortical hyperintensity, and the transmantle sign.*

6. Step 2 — MRI post-processing to convert "non-lesional" into "lesional"

- **Voxel-based morphometric analysis (VBM)** "has been widely used as a postprocessing tool for the localization of subtle neocortical lesions, especially FCD," and is "especially helpful when combined with MSI localization"; a recent study used VBM prospectively "to identify subtle FCD, increasing the diagnostic yield of MRI in the presurgical evaluation" YW p.504.
- **Automated FCD detection** "using surface-based measures and machine learning algorithms is possible in MRI-negative epilepsy" YW p.504.
- **Morphometric map output** — the junction image and the extension image displayed beside the T1 and a high-resolution FLAIR; data from the identified region "can then be manually segmented, registered with structural MRI, and exported into neuronavigation systems for targeted recordings with depth electrodes" YW p.515.
- **The stated goal** — "to convert a nonlesional MRI examination into a lesional one, which greatly advances the AEC hypothesis and informs the surgical strategy" YW p.505.
- **3D multimodality imaging (3DMMI)** — combining structural, functional and electrophysiological data in a single rendering "changed some aspect of management in 43 (80%) of 54 cases" in a prospective study, and improves outcomes in the difficult cases such as non-lesional extratemporal epilepsy (Engel class I in 17 of 22 patients in Murphy's series) YW p.515.

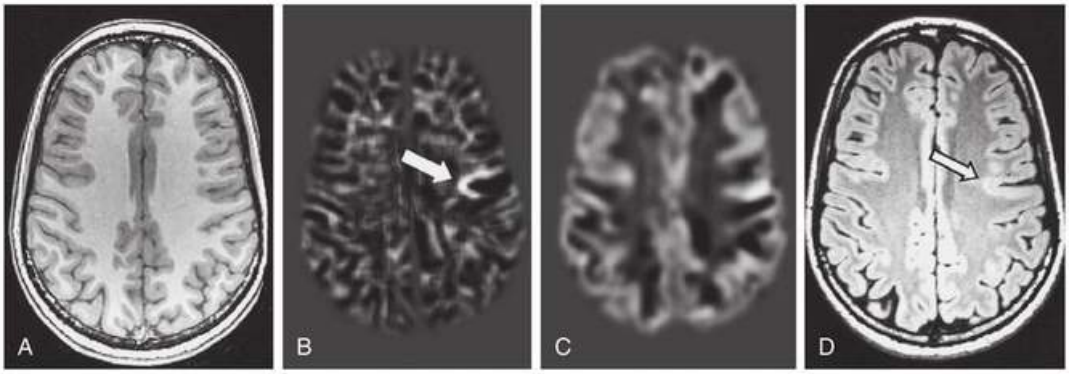


Figure 84.9. Axial view of magnetic resonance postprocessing, demonstrating a left frontal area of focal cortical dysplasia. (A) T1-weighted image. (B) Junction image (*arrow* indicates lesion). (C) Extension image. (D) High-resolution fluid-attenuated inversion recovery image (*arrow* indicates lesion). (*From Wellmer J, Parpaley Y, Von Lehe M, et al. Integrating magnetic resonance imaging postprocessing results into neuronavigation for electrode implantation and resection of subtle focal cortical dysplasia in previously cryptogenic epilepsy. Neurosurgery. 2010;66[1]:187–194.*)

Reproduced from Youmans & Winn 8e, Fig. 84.9, p. 515 — Label when you reproduce it: MRI post-processing demonstrating a left frontal focal cortical dysplasia — (A) T1-weighted image; (B) junction image with the arrow on the lesion; (C) extension image; (D) high-resolution FLAIR with the arrow on the lesion. This is the figure to show when asked "what do you do with a non-lesional MRI?"

7. Step 3 — electrophysiology and functional imaging

- **Video-EEG in the EMU** with hypothesis-driven electrode supplementation, analysing interictal and ictal EEG together with semiology YW p.504.
- **Interictal EEG cannot subtype the lesion** — "EEG and intraoperative electrocorticography (ECoG) including depth electrodes are useful in localizing the epileptogenic focus but **cannot distinguish the types and subtypes of FCD**. Stereo-electroencephalography (SEEG) may show some distinction, however, and demonstrate lesions not evident with MRI" YW p.488.e6.
- **Characteristic ECoG patterns** in FCD are continuous spikes and polyspikes and paroxysmal fast activity YW p.573.
- **Ictal SPECT (SISCOM)** — "most helpful in patients with focal epilepsy who have normal MRI findings, and **in patients with FCD**. In many such patients, the EEG can be nonlocalizing" YW p.504. Functional imaging "that shows hypoperfusion and hyperperfusion of a cortical region, and ictal single-photon emission computed tomography... are useful in some patients in identifying abnormal foci not apparent with standard sequences of MRI in FCD type I and in MRI lesions in FCD type II and also in helping predict postoperative prognosis for seizure relapse" YW p.488.e6.
- **FDG-PET** — hypometabolism may be the only marker in an MRI-negative FCD; PET/MRI co-registration and statistical post-processing increase yield YW p.504. In children, "the use of FDG-PET, diffusion tensor images, and magnetic source images has significantly improved lesion detection and localization, helping identify FCD, tuberous sclerosis, hemimegalencephaly, mesial temporal sclerosis, neoplasms, Rasmussen encephalitis, perinatal infarction, and Sturge-Weber syndrome" YW p.515.
- **MEG/MSI** — detects interictal spikes in **47% of patients who have no EEG spikes**; a VBM-plus-MSI combination is specifically endorsed for FCD [YW pp. 504, 527].
- **fMRI and DTI** — define eloquent cortex and white-matter tracts relative to the dysplasia, particularly when the lesion is perirolandic or perisylvian YW p.505.
- **Neuropsychological testing** — baseline cognitive profile and the functional deficit zone; essential in children [YW pp. 2041-2042].

8. Step 4 — invasive monitoring: when and which

- **Indication** — FCD is the archetypal reason for a Phase II study, because the MRI may be negative (type I) and the EZ may extend beyond the visible margins (type II): "the EZ related to an FCD may well extend beyond its margins, at times even into the contralateral hemisphere" [YW pp. 503-504].
- **SEEG** is the method of choice when the lesion is deep, multilobar, bilateral, MRI-negative or in a re-operation; it "may show some distinction" of FCD subtype and "demonstrate lesions not evident with MRI" [YW pp. 488.e6, 506].

- **Practical numbers** — in the 200-patient/2663-electrode SEEG series, the EZ was localised in **77%**, 87% of those underwent SEEG-guided resection, **67.8% achieved Engel I**, and **the commonest pathology was FCD type 1 (61.1%)** ; total morbidity 2.5% YW p.568.
- **Subdural grids** are chosen only when contiguous functional mapping, especially of language, is the dominant requirement; they under-sample sulcal, mesial, insular and interhemispheric cortex [YW pp. 505-506].
- **Intraoperative ECoG** has been shown to "significantly improve FCD resection in both children and adults and is equivalent to subdural grid implantation for the identification of boundaries without the risks conferred with subdural grid placement" YW p.576.

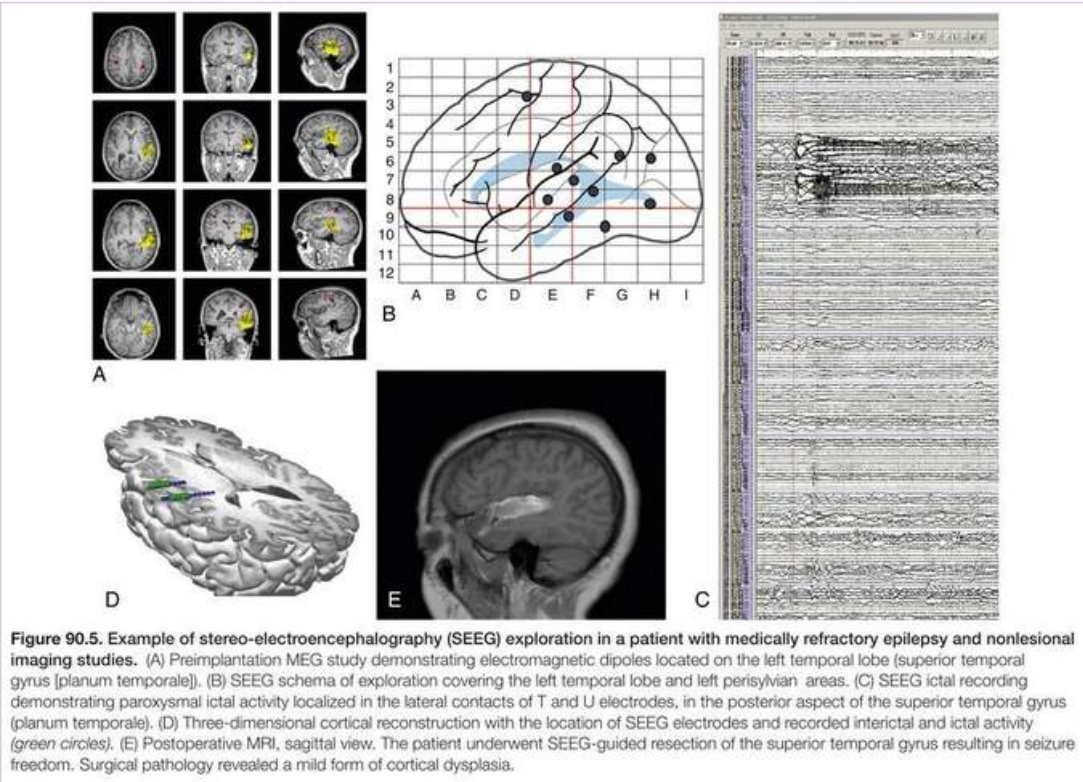


Figure 90.5. Example of stereo-electroencephalography (SEEG) exploration in a patient with medically refractory epilepsy and nonlesional imaging studies. (A) Preimplantation MEG study demonstrating electromagnetic dipoles located on the left temporal lobe (superior temporal gyrus [planum temporale]). (B) SEEG schema of exploration covering the left temporal lobe and left perisylvian areas. (C) SEEG ictal recording demonstrating paroxysmal ictal activity localized in the lateral contacts of T and U electrodes, in the posterior aspect of the superior temporal gyrus (planum temporale). (D) Three-dimensional cortical reconstruction with the location of SEEG electrodes and recorded interictal and ictal activity *(green circles)*. (E) Postoperative MRI, sagittal view. The patient underwent SEEG-guided resection of the superior temporal gyrus resulting in seizure freedom. Surgical pathology revealed a mild form of cortical dysplasia.

Reproduced from Youmans & Winn 8e, Fig. 90.5, p. 569 — Label when you reproduce it: SEEG exploration in a patient with medically refractory, MRI-negative epilepsy — show the orthogonal and oblique depth electrodes, the sampling of lateral, intermediate and deep cortex along each trajectory, the ictal recording localising the onset, and the tailored SEEG-guided resection with the postoperative MRI. Emphasise that the electrode "target" is the whole trajectory, not just its tip.

9. Management — medical

- **Antiseizure medication first, but expect failure.** "Treatment of epileptogenic FCD involves surgical resection as well as antiseizure medications" YW p.488.e1; drug resistance is declared after two appropriately chosen, adequately dosed agents [YW pp. 497, 503].
- **Drug choice is governed by general principles** — sodium-channel, calcium-channel, GABAergic, glutamatergic and carbonic-anhydrase mechanisms; rational polytherapy combines **different** mechanisms, since two drugs with similar mechanisms increase side effects more than they increase efficacy and were associated with more emergency visits and admissions in a database study [YW pp. 497, 499].
- **mTOR-pathway biology raises the prospect of targeted therapy**, since FCD II, HME and TSC all converge on mTOR [YW pp. 488.e4-488.e7]. @@NOTCOV I searched Youmans Ch. 79 (§Focal Cortical Dysplasias, pp. 488.e6-488.e7), Ch. 81 (§Antiepileptic Drug Selection, pp. 498-500) and Ch. 267 (pp. 2043-2044) for a recommendation on mTOR inhibitors (everolimus/sirolimus) as antiseizure therapy in TSC and FCD; the book describes the mTOR pathway in detail but does not give a treatment recommendation or trial data for mTOR inhibitors in epilepsy.@@ @@GUIDE International Tuberous Sclerosis Complex Consensus Group (Northrup & Krueger), 2013 and subsequent — adjunctive everolimus is an accepted antiseizure therapy in TSC-associated refractory focal epilepsy; this is named as the source for that single point, which Youmans does not carry.@@

10. Management — surgical: the principles

- **Surgery is the definitive treatment, and it should be early.** "Surgical treatment of FCD should be considered early in the course, not as a desperate last choice only after all medical management of seizures has failed" YW p.488.e7. "Early resection of epileptogenic lesions yield[s] better long-term results than resection that is deferred until later childhood or adolescence," and long-term cognitive function improves post-operatively, "especially in FCD type I" YW p.488.e7.
- **The four operative options** for MCD-associated epilepsy YW p.488.e7: (1) **simple lesionectomy**; (2) **lesionectomy plus resection of the surrounding epileptic focus**; (3) **resection of the lesion plus the mesial temporal structures** (necessary in longstanding epilepsy where the mesial structures have been recruited); (4) **hemispherectomy / hemispherotomy** for hemispheric disease.
- **Completeness of resection is the single dominant variable.**
- In a cohort of **149 FCD patients, seizure freedom was achieved in 70% with complete resection versus only 22% with incomplete resection** YW p.576.
- A **10-year follow-up in children with cortical malformations showed a favourable outcome in 83% with complete resection versus 11% with incomplete resection** YW p.576.
- "Type I FCD and mMCD are proposed to have significantly lower durable seizure improvement compared with type II FCD, primarily caused by an increased rate of incomplete resection" YW p.576.
- **Overall FCD surgical outcome** — "surgical treatment of FCD results in a cure in only >50% of patients, with approximately **70% having a good surgical outcome (Engel class I and II)**" YW p.488.e7. Series-level Engel class I rates range from **39.3% to 70%** (Chang 2011, n = 143: 70.0%; Cossu 2013, n = 240: 61.0%; Fauser 2015, n = 211: 66.0%; Kim 2009, n = 166: 56.6%; Widdess-Walsh 2005, n = 97: 63.0%; Choi 2004, n = 150: 39.3%) YW p.577.
- **Predictors of a better outcome** — "shorter duration of seizures, absence of generalized seizures, younger patient age, and total resection" YW p.488.e7.
- **Type-specific strategy** YW p.2043:
- **Type II** — "well-localized seizures secondary to type II cortical dysplasias can be approached via a single-stage craniotomy and excision of the epileptogenic zone, when separate from eloquent cortical areas, but successful seizure control correlates with extent of resection of the radiographically apparent dysplastic region."
- **Type I** — "generally diffuse, multilobar, and MR negative, and surgery is associated with poorer outcomes by standard neurosurgical methods of excision, disconnection, or ablation. In these cases, depending on electroclinical diagnosis, a **neuromodulatory approach can be considered**."
- **Type III** — "represent pathologic changes associated with structural abnormalities such as benign tumors, vascular malformations, or inflammatory changes," best treated by staged approaches (SEEG or subdural electrodes) tailored to semiology and video-EEG.

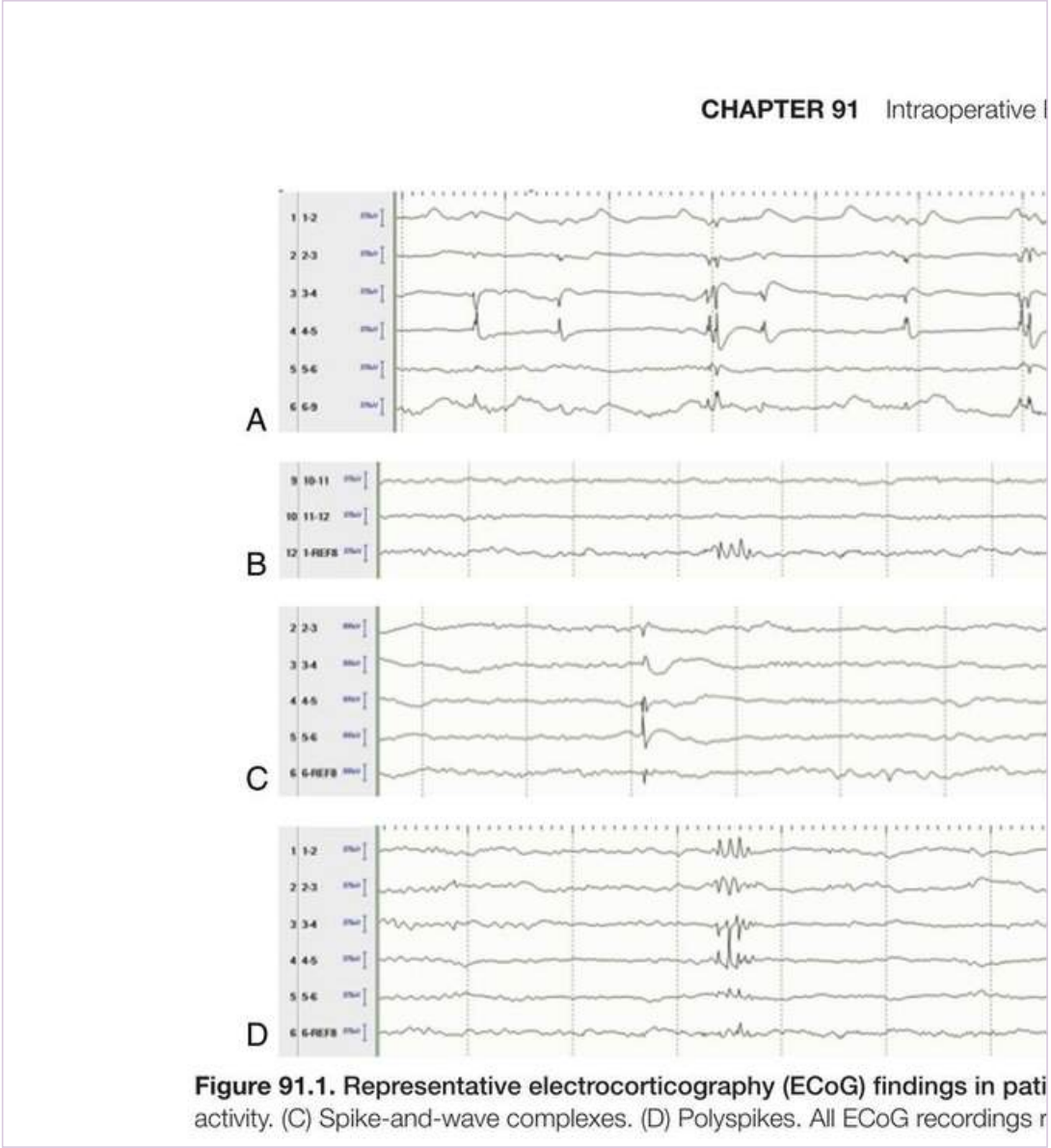


Figure 91.1. Representative electrocorticography (ECoG) findings in pati
activity. (C) Spike-and-wave complexes. (D) Polyspikes. All ECoG recordings r

Reproduced from Youmans & Winn 8e, Fig. 91.1, p. 573 — Label when you reproduce it: representative electrocorticography in FCD — (A) continuous spikes and polyspikes; (B) paroxysmal fast activity. These are the two ECoG signatures that guide a tailored lesionectomy and that tell the surgeon the resection margin has not yet been reached.

11. Management — operative technique and adjuncts

- **Topectomy and tailored lesionectomy** — "the subpial dissection technique is utilized in topectomy. Removal of epileptogenic gray matter proceeds to the bottom of the sulcus, avoiding damage to other neighboring vessels... Unnecessary resection of the underlying white matter is avoided to maintain the integrity of projection and association fibers." Haemostasis with topical agents and minimal electrocautery YW p.575.
- **Conditions treatable by lesionectomy (Box 91.1)** — subcortical/periventricular heterotopia, polymicrogyria, **focal cortical dysplasia**, DNET/low-grade glioma, hamartoma, NF1, Sturge-Weber syndrome, tuberous sclerosis, lissencephaly YW p.575.
- **ECoG guidance** — "ECoG allows for the resection of lesional tissue while also allowing for real-time feedback regarding resection of the surrounding epileptogenic cortex"; >90% seizure freedom was reported for ganglioglioma and low-grade tumours resected under ECoG guidance, and the same benefit has been reproduced in cavernous malformations, FCD and gliosis YW p.575. The caveat is that ECoG "has also been demonstrated to result in more extensive resections than needed for seizure control" YW p.577.
- **Awake mapping / functional mapping** when the dysplasia abuts motor, sensory or language cortex YW p.575.

- **Multiple subpial transection** when the EZ lies within eloquent cortex and cannot be resected — the transection disrupts the horizontal fibres that synchronise and spread the discharge while preserving the vertical functional columns YW p.615.e4.
- **Hemispherotomy** for hemimegalencephaly — "HME is often treated with hemispherectomy; both functional and anatomic methods have been described. HME may be associated with a worse outcome compared with other forms of MCD," though "in well-characterized cases, seizure freedom was achieved in more than 60% of HME cases" YW p.488.e7. Youmans elsewhere gives **40–60%** seizure freedom for HME, the lowest of all hemispherotomy aetiologies, with a higher risk of bleeding, incomplete disconnection and shunting YW p.644.

12. Management — minimally invasive and palliative options

- **MR-guided laser interstitial thermal therapy (LITT)** — "although complete surgical resections enable higher cure rates, the deep and eloquent location of some FCDs can make this surgically challenging." In the first series including FCD, **only about 40% were seizure free**, "much lower than the percentage achieved with open surgical resection"; across series, seizure-freedom rates for FCD range from **50% to 100%**. "MRgLITT for FCD is thus an evolving field, but it does offer a relatively low morbidity option in patients in whom the risk associated with operation is high and those in whom the FCD is deep-seated or adjacent to eloquent locations" YW p.631.
- **Radiofrequency thermocoagulation and stereotactic radiosurgery** are the older minimally invasive options; radiofrequency "does not provide the real-time feedback on tissue coagulation that MRgLITT offers... Radiofrequency is thus a 'blind' approach" YW p.630.
- **Corpus callosotomy and VNS** — "in addition to surgical resections, other options for treatment of epilepsy associated with MCD include corpus callosotomy and vagal nerve stimulation. These options have been used in patients in whom the seizure focus was in eloquent areas, was bilateral, or could not be defined, or in patients who were always poor surgical candidates. Although these treatments rarely result in cure, they can result in significant reduction in seizure frequency" YW p.488.e7.
- **Responsive neurostimulation and laser ablation** — "newer surgical approaches, including responsive neurostimulation and laser ablation, are attractive, but trials will be needed to demonstrate efficacy" YW p.488.e7. In practice, RNS is already being used in children with diffuse type I dysplasia and in TSC refractory to resection [YW pp. 2043-2044].

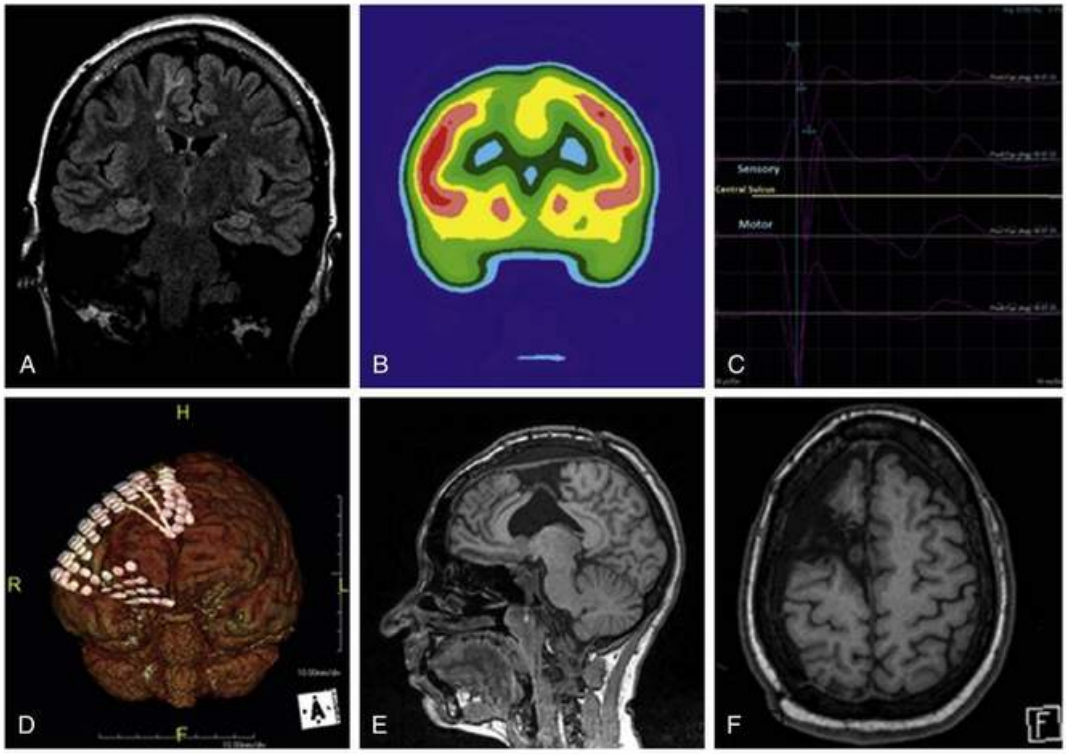


Figure 95.1. Lesional frontal epilepsy. Images in a 43-year-old woman with a history of generalized tonic-clonic seizures since age 3. (A) MRI shows a fluid-attenuated inversion recovery (FLAIR) hyperintensity in the medial portion of the right frontal lobe. (B) Fluorodeoxyglucose–positron emission tomography (FDG-PET) shows reduced uptake of the radioisotope in the same region. (C) Intraoperative mapping of the central sulcus using grid electrodes. (D) Postoperative three-dimensional reformatted CT scan showing grid placement. (E and F) Sagittal and axial postoperative MRI shows resection cavity. Pathologic evaluation revealed focal type IIb cortical dysplasia. Patient developed supplementary motor area (SMA) syndrome postoperatively; however, she ultimately had a full recovery and was seizure free.

Reproduced from Youmans & Winn 8e, Fig. 95.1, p. 606 — Label when you reproduce it: lesional frontal epilepsy due to type IIb FCD in a 43-year-old — (A) FLAIR hyperintensity in the medial right frontal lobe; (B) FDG-PET showing reduced uptake in the same region; (C) intraoperative mapping of the central sulcus with grid electrodes; (D) postoperative 3D CT showing grid placement; (E, F) sagittal and axial postoperative MRI showing the resection cavity. The patient developed an SMA syndrome that fully recovered and became seizure free — the complete multimodal workup of an FCD in one figure.

13. Points that earn extra marks

- **Always give the three types with all their subtypes, and say what defines each** — normal neurons in I, dysmorphic neurons in II, balloon cells only in IIb, a second principal lesion in III YW p.488.e6.
- **Say that all FCDs are congenital and all are highly epileptogenic** YW p.488.e6.
- **Name the mTOR pathway genes** — PI3K, AKT3, DEPDC5, MTOR, TSC1, TSC2 — and say that FCD II and hemimegalencephaly are genetically the same disorder [YW pp. 488.e4, 488.e7].
- **Give the transmantle sign its second name** (funnel track) and say it is typical of type II YW p.510.
- **Give the age-and-imaging rule** — scan before 6 months, least visible at 6–18 months, repeat at 30 months YW p.510.
- **Quote the completeness-of-resection numbers** — 70% vs 22%, and 83% vs 11% at 10 years YW p.576.
- **Explain why type I does worse than type II** despite the milder histology: it is more extensive and its margins are harder to define, so resection is more often subtotal YW p.488.e7.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Type I = abnormal lamination, normal neurons; Type II = dysmorphic megalocytic neurons ± balloon cells; Type III = FCD plus a second principal lesion** — memorise the letters (Ia radial, Ib tangential, Ic both; IIa no balloon cells, IIb balloon cells; IIIa hippocampal sclerosis, IIIb tumour, IIIc vascular malformation, IIId other acquired lesion) YW p.488.e6.
- **Balloon cells are found only in FCD IIb** — and look exactly like the giant cells of a tuberous sclerosis tuber [YW pp. 488.e3, 488.e6].
- **FCD type II and hemimegalencephaly are the same genetic disease**; the earlier the somatic mTOR mutation within the 33 mitotic cycles, the bigger the lesion [YW pp. 488.e6-488.e7].
- **The transmantle ("funnel track") FLAIR hyperintensity from cortex to ventricle is pathognomonic of type II FCD**; IIa and IIb cannot be told apart on MRI YW p.510.
- **Type I FCD is "non-lesional" only because we scan badly** — use VBM, machine-learning surface analysis, 7T, PET and SISCOM to convert a negative MRI into a positive one [YW pp. 504-505, 515].
- **In an infant, scan before 6 months if you can; if the scan at 6–18 months is negative, repeat it at 30 months** YW p.510.
- **EEG and ECoG localise but cannot subtype FCD** — only histology can, and SEEG may hint at it YW p.488.e6.
- **Completeness of resection is the whole game**: 70% seizure freedom with complete resection versus 22% with incomplete YW p.576.
- **Type I FCD does worse than type II** — not because the histology is worse but because the lesion is more extensive and the margins are indistinct YW p.488.e7.
- **Type I FCD accompanies hippocampal sclerosis in more than 70% of cases** — look for dual pathology before every temporal resection YW p.510.
- **Operate early**: cognitive outcome as well as seizure outcome is better, and FCD surgery should never be a "desperate last choice" YW p.488.e7.

Pages read for this answer — Youmans & Winn 8e: 488.e1, 488.e3, 488.e4, 488.e6, 488.e7, 497, 499, 503, 504, 505, 506, 508, 509, 510, 515, 527, 568, 573, 575, 576, 577, 605, 615.e4, 630, 631, 644, 2041, 2042, 2043, 2044

a) Newer anti epileptic drugs. [5]
b) Surgical management of epilepsy. [5]

LONG | DEC 2022 · Paper III · Q9 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 81 *Antiseizure Medications: Principles of Clinical Use* (P. Landazuri, S. Lhatoo), §Overview of AED History, Mechanism and Efficacy, §When to Start AED Therapy, §AED Selection, §Parenteral AEDs, §AED Polytherapy, §Special Considerations for AEDs and Women, §When and How to Stop AED Therapy, pp. 496-501 (Fig. 81.1 — AEDs stratified by generation, p. 496; Table 81.1 — AEDs by mechanism of action, p. 497; Table 81.2 — AEDs by metabolism/excretion, p. 498). Supplementary: Ch. 80 *Diagnosis and Classification of Seizures and Epilepsy*, pp. 491-495 (Box 80.1, p. 492; Fig. 80.1, p. 493); Ch. 83 *Evaluation of Patients for Epilepsy Surgery*, pp. 503-506; Ch. 94A *Anteromedial Temporal Lobectomy*, pp. 596-601 (Box 94A.1, p. 598); Ch. 94B *Selective Amygdalohippocampectomy*, pp. 602-604; Ch. 95 *Resections for Extratemporal Epilepsy*, pp. 605-613; Ch. 96 *Palliative Procedures for Drug-Resistant Epilepsy*, pp. 615.e1-615.e10; Ch. 98 *Laser Interstitial Thermal Therapy in Epilepsy*, pp. 630-635; Ch. 99 *Hemispheric Disconnection Procedures*, pp. 636-644; Ch. 100 *Electrical Stimulation for Epilepsy (VNS, DBS, and RNS)*, pp. 646-665; Ch. 101 *Epilepsy Surgery: Outcomes and Complications*, pp. 667-667.e16.

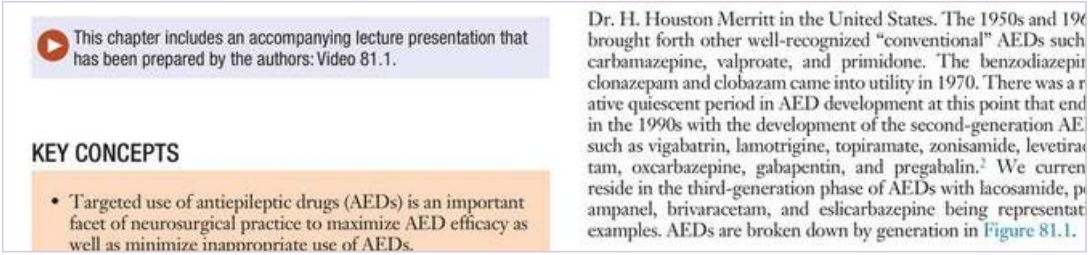
(a) Newer antiepileptic (antiseizure) drugs [5]

1. The generational framework — the organising idea

- **The history in one paragraph** — potassium bromide (Locock, 1857) was the only AED until **phenobarbital** (Hauptmann, Germany, 1912); **phenytoin** followed in 1938 (Merritt, USA); the 1950s and 1960s added **carbamazepine, valproate and primidone**; **clonazepam and clobazam** arrived in 1970. There was then "a relative quiescent period in AED development at this point that ended in the 1990s with the development of the **second-generation AEDs** such as vigabatrin, lamotrigine, topiramate, zonisamide, levetiracetam, oxcarbazepine,

gabapentin, and pregabalin. **We currently reside in the third-generation phase of AEDs with lacosamide, perampanel, brivaracetam, and eslicarbazepine** being representative examples" YW p.496.

- **The most important single statement about the newer drugs** — "**AED stratification by generation is unfortunately not associated with improved efficacy with newer generations, but it is generally associated with improved patient tolerability**" YW p.498. And again: "efficacy among AEDs varies minimally, while newer AEDs do appear to be better tolerated" YW p.499.
- **And a caution about all of them** — "current commercially available AEDs, without exception, have only antiseizure properties and thus do not prevent the development of epilepsy" YW p.496.
- **There are now more than 20 FDA-approved seizure medications**, which is "a welcome scenario on the one hand and a potentially bewildering apothecarial situation on the other" [YW pp. 496, 498].


This chapter includes an accompanying lecture presentation that has been prepared by the authors: Video 81.1.

KEY CONCEPTS

- Targeted use of antiepileptic drugs (AEDs) is an important facet of neurosurgical practice to maximize AED efficacy as well as minimize inappropriate use of AEDs.

Dr. H. Houston Merritt in the United States. The 1950s and 196 brought forth other well-recognized "conventional" AEDs such carbamazepine, valproate, and primidone. The benzodiazepir clonazepam and clobazam came into utility in 1970. There was a r ative quiescent period in AED development at this point that end in the 1990s with the development of the second-generation AE such as vigabatrin, lamotrigine, topiramate, zonisamide, levetira tam, oxcarbazepine, gabapentin, and pregabalin.[2] We curren reside in the third-generation phase of AEDs with lacosamide, p ampanel, brivaracetam, and eslicarbazepine being representat examples. AEDs are broken down by generation in Figure 81.1.

Reproduced from Youmans & Winn 8e, Fig. 81.1, p. 497 — Label when you reproduce it: antiepileptic drugs stratified by generation against year of introduction — 1st generation (bromide, phenobarbital, ethosuximide, phenytoin, benzodiazepines, carbamazepine, valproate); 2nd generation (felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin); 3rd generation (lacosamide, rufinamide, vigabatrin, perampanel, eslicarbazepine, brivaracetam, cannabidiol/Epidiolex). Note the plateau between the 1970s and 1990s and the steep rise thereafter.

Table 1 · The three generations of antiepileptic drugs — from Youmans & Winn 8e, Fig. 81.1, p. 496 and §Overview of AED History, p. 496.

Generation	Drugs	Era
First (conventional)	Bromide, phenobarbital, ethosuximide, phenytoin, benzodiazepines (clonazepam, clobazam), carbamazepine, valproate, primidone	1857–1970
Second	Felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin, vigabatrin	1990s
Third	Lacosamide, rufinamide, perampanel, eslicarbazepine, brivaracetam, cannabidiol (Epidiolex — listed as a brand to distinguish it from the non-FDA-approved supplement)	2000s onward

2. Mechanisms of action — how the newer drugs work

- **The fundamental principle** — "the actual mechanism of AEDs is at the level of cellular ion channels and the neurotransmitters that affect such channels... In a seizure, there is sustained and abnormal synchronization among neurons that gives rise to the seizure. Thus, modulating those ion channels is the mechanism by which AEDs work" YW p.496.
- **Sodium channel** — the classic mechanism (phenytoin, carbamazepine), shared by the newer **lamotrigine, zonisamide, lacosamide, rufinamide, eslicarbazepine, oxcarbazepine, topiramate and felbamate** [YW pp. 496-497].
- **GABA / chloride** — benzodiazepines act at the GABA receptor "which increases the frequency of Cl– channel opening, thus hyperpolarizing the neuron... This reduces neuronal firing and seizure-related spontaneous and coordinated neuronal synchronization." **Crucially, "the benzodiazepine's target GABA receptor becomes internalized during prolonged seizures and subsequent status epilepticus, which can explain tachyphylaxis and diminished effectiveness of benzodiazepines in prolonged status epilepticus after the first 24 to 48 hours"** YW p.496. **Vigabatrin and tiagabine** are the newer GABAergic drugs.
- **Glutamate — the AMPA story** — "glutamate is the primary excitatory neurotransmitter that acts via both NMDA and AMPA receptors. Acute cerebral injury can cause increased NMDA/AMPA receptor activation, which then subsequently causes increased neuronal hyperexcitability with an increased likelihood of focal epilepsy. Indeed, both

imaging and pathologic studies have suggested increased NMDA receptor density in epileptogenic tissue. Therefore, AEDs that diminish this pathway may be of antiseizure potential. **This has resulted in the development of the AMPA-blocking AED perampanel that is in current clinical use**" YW p.496.

- **SV2A — the unique mechanism** — "**levetiracetam (and its new counterpart brivaracetam) has a unique mechanism that affects the synaptic vesicle 2A (SV2A) receptor without direct ion effects**" YW p.496.
- **Multi-mechanism drugs** — "many AEDs, including valproate, exert influence over multiple ion channels" YW p.496; topiramate and zonisamide add **carbonic anhydrase inhibition**.

Table 2 · Antiepileptic drugs stratified by mechanism of action — reproduced in full from Youmans & Winn 8e, Table 81.1, p. 497.

Mechanism	Drugs
Sodium channel	Carbamazepine, eslicarbazepine, felbamate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide, topiramate, valproate, zonisamide
Calcium channel	Ethosuximide, gabapentin, lamotrigine, oxcarbazepine, pregabalin, phenobarbital, phenytoin, topiramate, valproate, zonisamide
GABA	Benzodiazepines, phenobarbital, carbamazepine, gabapentin, pregabalin, tiagabine, topiramate, vigabatrin, valproate
Glutamate	Carbamazepine, felbamate, oxcarbazepine, phenobarbital, topiramate
Carbonic anhydrase	Topiramate, zonisamide
Other (SV2A, AMPA, slow inactivation of Na)	Brivaracetam, carbamazepine, lacosamide, levetiracetam, perampanel, phenytoin

3. Metabolism and excretion — why it decides the choice in a neurosurgical patient

- "Consideration of AED metabolism is of great utility when patients have either preexisting renal or hepatic issues" YW p.498.
- **Patients with renal failure have more AED choices than those with hepatic failure.** "Still, often the preferred choice for either situation is levetiracetam. Levetiracetam is excreted through the kidneys, making it a good choice for those in hepatic failure. For those in renal failure, levetiracetam remains a good choice (in adjusted dosing or immediately following dialysis) as it is unchanged when renally excreted" YW p.498.

Table 3 · Antiepileptic drugs stratified by metabolism / excretion — reproduced in full from Youmans & Winn 8e, Table 81.2, p. 498.

Route	Drugs
Hepatic	Benzodiazepines, carbamazepine, eslicarbazepine, ethosuximide, felbamate, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, rufinamide, tiagabine, topiramate, valproate, zonisamide
Renal	Gabapentin, levetiracetam, pregabalin, vigabatrin

4. Evidence — the head-to-head trials

- **SANAD (Standard and New Antiepileptic Drug trial)** — "a nonblinded randomized trial comparing carbamazepine, lamotrigine, oxcarbazepine, gabapentin, and topiramate. In short, SANAD suggested that **lamotrigine was better tolerated** than the other medications, with **lamotrigine and carbamazepine being the most efficacious** in terms of seizure control" YW p.499.
- **Zonisamide versus carbamazepine** — "zonisamide was **noninferior** to carbamazepine" YW p.499.
- **Levetiracetam versus carbamazepine or valproate** — "trends that while levetiracetam was better tolerated, both carbamazepine and valproate may be **minimally more efficacious** from a seizure perspective" YW p.499.
- **VA elderly study (gabapentin vs carbamazepine vs lamotrigine)** — "gabapentin and lamotrigine were better tolerated. The efficacy results were interesting in that there was a trend toward carbamazepine being more effective, but when combined with tolerability, **lamotrigine may be an optimal choice**" YW p.499.
- **Caveat** — "the following discussion regarding AED selection refers to **focal epilepsy only**, as generalized epilepsy involves a slightly different approach" YW p.499.

5. Dosing philosophy — "the optimal dose is a concept rather than a number"

- "Essentially, one should use the **lowest AED dose possible for a patient to be seizure free**" YW p.498.
- **Median daily dose of the first AED in patients who became seizure free** — "carbamazepine 600 mg, sodium valproate 1000 mg, and lamotrigine 187.5 mg." "As such, it is reasonable to target a lower dose and expect seizure freedom. In typical clinical practice, it is likely a best practice to begin with a low or medium-low dose" YW p.498.
- **Efficacy expectations (Kwan and Brodie)** — 47% seizure free on drug 1, 13% on drug 2, 3.7% on drug 3, and **≤1% thereafter**; hence **drug-resistant epilepsy is defined as failure of two adequately selected and dosed AEDs** YW p.497.

6. Drug-by-drug notes the examiner will probe

- **Levetiracetam** — "often used because of its relative simplicity as it lacks drug-drug interactions and has an intravenous (IV) formulation. **The key levetiracetam adverse effect to remember is agitation, which can present as newly acquired mood lability and irritability**" YW p.499. It is renally excreted, non-enzyme-inducing (an advantage in brain tumour patients on chemotherapy), has "no demonstrated adverse effects" and "the best safety profile in pregnancy," and is a second-line status epilepticus agent at **60 mg/kg (max 4500 mg)** [YW pp. 382, 499, 1107].
- **Brivaracetam** — levetiracetam's "new counterpart," also acting at SV2A, available intravenously [YW pp. 496, 499].
- **Lamotrigine** — "an excellent AED... but its **long titration period (because of the risk for Stevens-Johnson syndrome when titrated quickly)** and interaction with valproate can make this a challenging choice in the neurosurgical patient" YW p.499. Hormonal contraception **lowers** lamotrigine levels and can precipitate seizures YW p.500.
- **Perampanel** — the AMPA-receptor blocker, developed directly from the glutamate hypothesis of post-injury epileptogenesis YW p.496.
- **Lacosamide** — third-generation sodium-channel drug with an intravenous formulation, widely used in neurosurgical practice [YW pp. 496, 499].
- **Eslicarbazepine, rufinamide, zonisamide, topiramate** — sodium-channel drugs; topiramate and zonisamide additionally inhibit carbonic anhydrase (relevant because **carbonic anhydrase inhibitors raise the threshold of the amobarbital anaesthetic effect in the Wada test**) [YW pp. 497, 539].
- **Vigabatrin, tiagabine, gabapentin, pregabalin** — GABAergic/calcium-channel second-generation drugs; gabapentin, pregabalin and vigabatrin are **renally cleared** [YW pp. 497-498].
- **Cannabidiol (Epidiolex)** — the newest agent on the generational chart; Youmans is careful to list it "as a brand to distinguish from supplement cannabidiol, which is not FDA approved for the treatment of epilepsy" YW p.496.
- **Enzyme-inducers to avoid where possible** — phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine; "the use of enzyme-inducing AEDs may be a disadvantage in some cases, particularly cases in which levels of other concurrent medications used by the patient may be compromised by enzyme induction" [YW pp. 499-500].
- **Valproate in the neurosurgical patient** — "it is relevant to remember that it can lead to **increased bleeding and platelet dysfunction**, two factors particularly relevant during EEG monitoring with intracranial electrodes." On the positive side, it has an IV formulation and there is "some suggestion that valproate coupled with temozolomide treatment may increase survival in glioblastoma," although "it should not be expected to be any more effective from a seizure-control standpoint" than levetiracetam YW p.499.
- **Phenytoin** — "may cause cardiovascular side effects, is an enzyme inducer, and has a less attractive side-effect profile in the long term. There are often better options" YW p.499. Long-term phenytoin causes **hyperostosis**, which may alter planning of a callosotomy craniotomy YW p.615.e2.

NOT COVERED IN YOUMANS — answered from the source named below

I searched Ch. 81 §AED Selection and §Specific AED Concerns in Common Neurosurgical Practice (pp. 498-500), Ch. 80 (pp. 491-495) and Ch. 267 (p. 2039) for a systematic, drug-by-drug adverse-effect table for the second- and third-generation agents. Youmans gives adverse effects only for the drugs that matter in neurosurgical practice — levetiracetam (agitation, mood lability, irritability), lamotrigine (Stevens-Johnson syndrome on rapid titration), valproate (bleeding, platelet dysfunction, teratogenicity, lower offspring IQ), phenytoin (cardiovascular effects, enzyme induction, hyperostosis) and lorazepam (sedation). It does not tabulate the class-specific toxicities of the remaining newer drugs.

GUIDELINE UPDATE

Standard pharmacology references (e.g. ILAE/NICE prescribing guidance) — the newer-drug toxicities a DrNB candidate is still expected to name are: **vigabatrin** — irreversible concentric visual field constriction requiring perimetry; **topiramate** — word-finding difficulty, paraesthesiae, renal stones, weight loss, acute angle-closure glaucoma; **zonisamide** — renal stones, oligohidrosis, weight loss; **felbamate** — aplastic anaemia and hepatic failure (restricted use); **perampanel** — dose-related aggression and hostility (black-box warning); **lacosamide** — PR-interval prolongation and dizziness; **gabapentin/pregabalin** — sedation, weight gain, peripheral oedema; **carbamazepine/oxcarbazepine/eslicarbazepine** — hyponatraemia, and HLA-B*1502-linked SJS/TEN in South-East Asian populations; **cannabidiol** — transaminitis, particularly with concomitant valproate. This block is marked because Youmans does not carry it.

7. Intravenous ("parenteral") options — a neurosurgical necessity

- **Older-generation IV drugs**: barbiturates, phenytoin, valproate, lorazepam, midazolam, diazepam. **Newer-generation IV drugs: levetiracetam, lacosamide and brivaracetam** YW p.499.
- **Three typical neurosurgical scenarios**: acute seizure cessation, status epilepticus, and the nil-by-mouth portion of care YW p.499.
- **Acute seizure (<5 minutes)** — lorazepam 2–4 mg IV; midazolam if there is no IV access YW p.499.
- **Status epilepticus** — practically defined as "at least 5 minutes of continuous clinical or electrographic seizure activity or alternatively as recurrent seizures without return to baseline" YW p.497. **First line: lorazepam 4 mg IV** (VA Cooperative Trial; 2016 convulsive status guidelines); if no IV access, **midazolam 10 mg IM**. **Second line: no difference among fosphenytoin 20 mg/kg (max 1500 mg), valproate 40 mg/kg (max 3000 mg) and levetiracetam 60 mg/kg (max 4500 mg)** YW p.499.
- **A randomised comparison of IV phenytoin versus levetiracetam** found both well tolerated, with levetiracetam trending toward fewer major and more minor side effects YW p.499.
- **Non-convulsive status** must be suspected in the encephalopathic neurosurgical patient — **11% to 21% of patients in various ICUs have non-convulsive seizures**, and up to **21% of neuro-ICU patients have electrographic seizures** YW p.498.

8. Rational polytherapy, women, and stopping

- **Polytherapy** — "when two AEDs with similar mechanisms are selected, the side-effect potential may increase while improved seizure control benefits may be relatively small," and a database study showed patients on two same-mechanism AEDs "were more likely to visit the emergency department or be admitted" YW p.499. Combine **different** mechanisms.
- **Women of childbearing age** — "multiple AED registries in pregnancies have conclusively shown that **valproate is one of the most teratogenic of the AEDs in a dose-dependent manner**. Furthermore, children who are maternally exposed to valproate in utero have been shown to have **lower IQs** compared with children exposed to carbamazepine, phenytoin, or lamotrigine. Conversely, **lamotrigine and levetiracetam may be the most optimal choices for women during pregnancy**" YW p.499.
- **Contraception interactions** — enzyme-inducing AEDs (phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine) "can increase metabolism of the estrogen and progesterone components of hormonal birth control,

which can cause unexpected contraception failure. Conversely, **hormonal birth control can decrease serum levels of lamotrigine**, which instead causes a concomitant increase in seizures" YW p.500.

- **When AEDs are NOT useful** YW p.498: (1) **provoked seizures** — alcohol withdrawal seizures occur 6–48 hours after the last drink and are generalised tonic-clonic; phenytoin is ineffective, benzodiazepines work acutely; (2) **seizure prophylaxis in a seizure-naïve brain tumour patient** — "guidelines from both the neurology and neurosurgical literature recommend against this still common practice," yet 34% of never-seizing patients continue AEDs; (3) **prevention of post-traumatic epilepsy** — trials "have not shown that AEDs prevent the development of epilepsy in the adult or pediatric population," although one showed a decrease in seizures in the first week, hence the guideline that "anticonvulsants can decrease the incidence of posttraumatic seizures only within the first 7 days."
- **Stopping** — after acute symptomatic seizures "seizure medications started in the acute phase should not be continued beyond the first 3 months"; for the brief prophylactic course sometimes given after craniotomy, "a phased withdrawal over 2 to 3 weeks is reasonable." The 1991 MRC randomised withdrawal study in 1013 patients seizure-free ≥2 years showed **79% remained seizure free if treatment continued versus 59% if it was stopped** YW p.500.

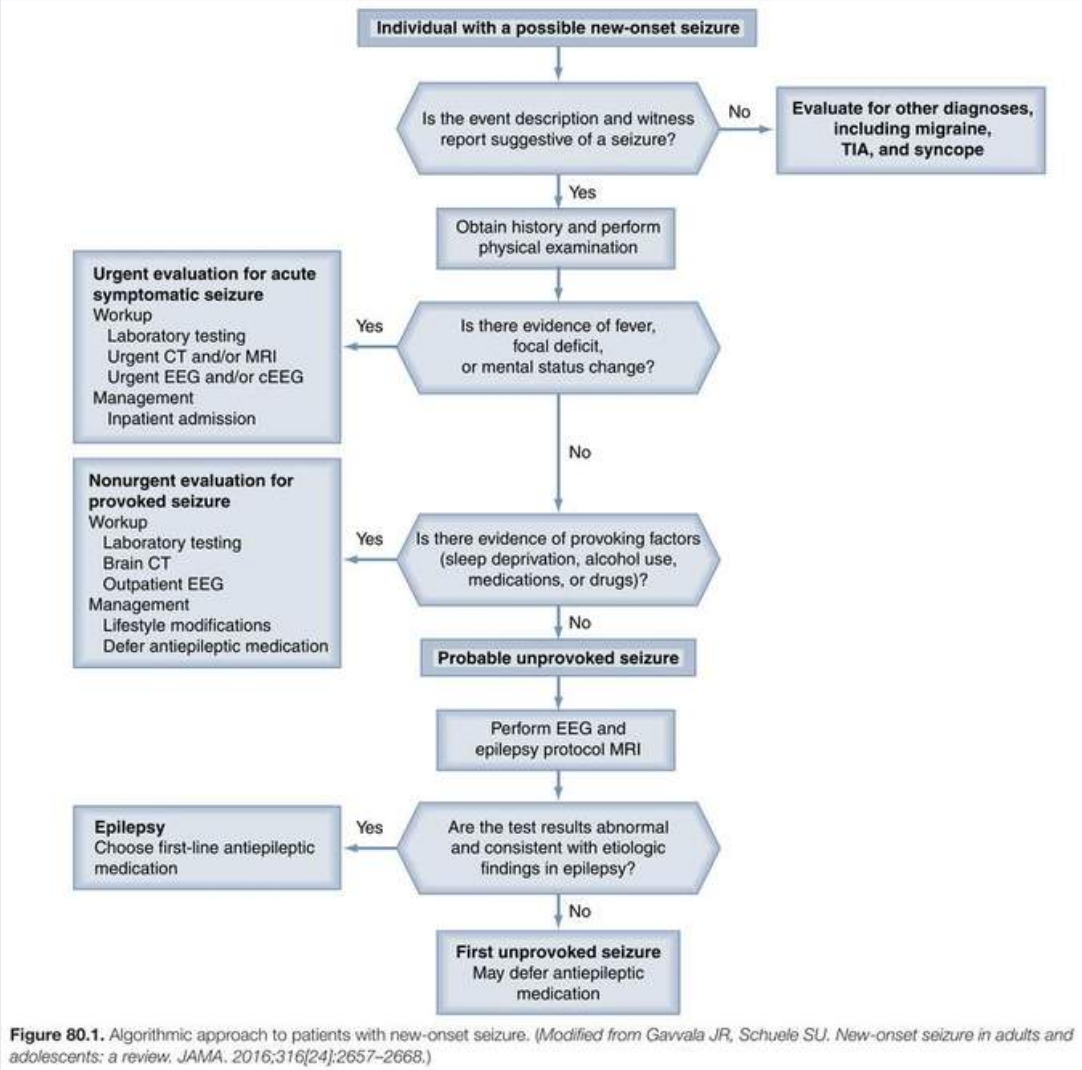


Figure 80.1. Algorithmic approach to patients with new-onset seizure. (*Modified from Gavvala JR, Schuele SU. New-onset seizure in adults and adolescents: a review. JAMA. 2016;316[24]:2657–2668.*)

Reproduced from Youmans & Winn 8e, Fig. 80.1, p. 493 — Label when you reproduce it: the algorithm for a new-onset seizure — is the description suggestive of a seizure (if not, evaluate for migraine, TIA, syncope)? → history and examination → fever, focal deficit or altered mental status (urgent workup: labs, urgent CT/MRI, urgent EEG/cEEG; admit) → provoking factors such as sleep deprivation, alcohol, drugs (non-urgent workup; lifestyle modification; defer AED) → probable unprovoked seizure → EEG and epilepsy-protocol MRI → abnormal and consistent with an epilepsy aetiology = epilepsy, start a first-line AED; normal = first unprovoked seizure, AED may be deferred.

(b) Surgical management of epilepsy [5]

9. When to operate — the gateway

- **Drug-resistant epilepsy = failure of two appropriately chosen, adequately dosed AEDs** [YW pp. 497, 503]; thereafter the chance of medical seizure freedom is ≤1% YW p.497 and "drug-resistant epilepsy has a less than 5% chance of being successfully treated with medications alone" YW p.667.
- **ERSET set the practical threshold at 2 years** of unsatisfactory control as sufficient to warrant referral, replacing the old 5-year rule YW p.615.e1.
- **Two randomised trials have shown the superiority of resective surgery over medical therapy** in adults with temporal lobe epilepsy and of focal resection in children YW p.667.e1.
- **Four classic criteria for offering surgery** YW p.615.e1: (1) seizures not controlled by maximally tolerated doses of correct anticonvulsants; (2) seizures interfere with psychological and intellectual development, employment or social performance; (3) all potentially epileptogenic areas have matured and there is no tendency to spontaneous regression; (4) the patient is strongly motivated to cope with an exhaustive diagnostic regimen and a lengthy operation.

10. Classification of operations — the framework to open with

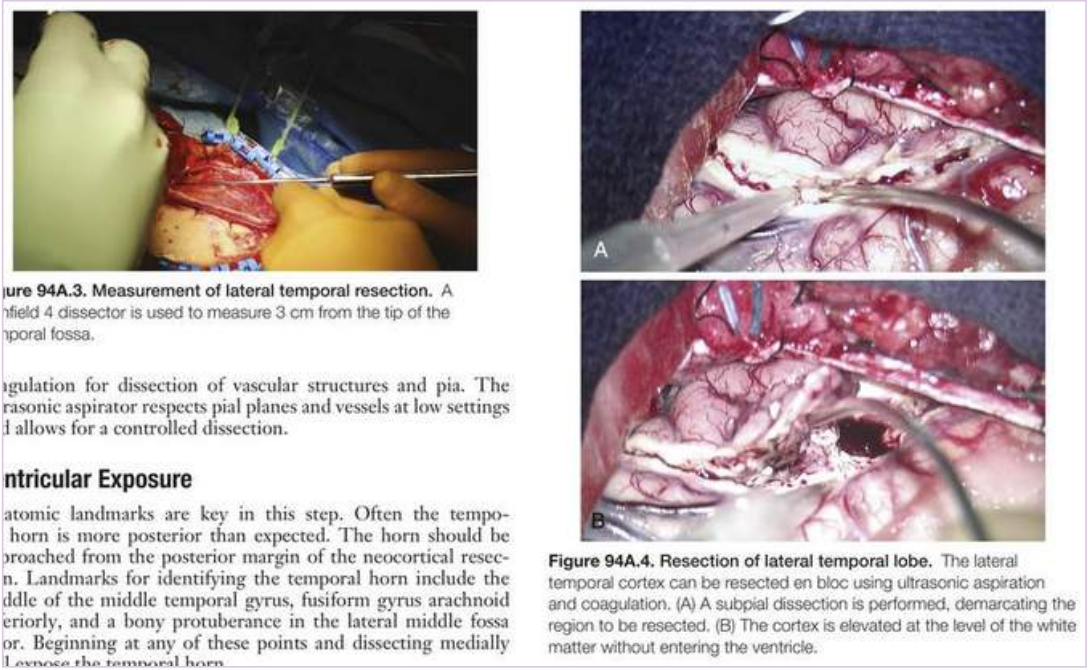
Table 4 · Surgical management of epilepsy — the complete menu, with indication and outcome, compiled from Youmans & Winn 8e Ch. 94A pp. 596-601, Ch. 94B pp. 602-604, Ch. 95 pp. 605-613, Ch. 96 pp. 615.e1-615.e10, Ch. 97 pp. 617-627, Ch. 98 pp. 630-635, Ch. 99 pp. 636-644, Ch. 100 pp. 646-665 and Ch. 101 pp. 667.e1-667.e16.

Intent	Category	Operation	Indication	Outcome
Curative	Resection — temporal	Anteromedial temporal lobectomy	MTLE with hippocampal sclerosis	Engel I **66% at 10 years**; multicentre seizure-free **67.9%**
		Selective amygdalohippocampectomy (transsylvian / transcortical / subtemporal)	MTLE where lateral neocortex should be spared	**60–90%** seizure freedom at 3–6 years; less verbal-memory decline
	Resection — extratemporal	Frontal resection	FLE	Engel I **45–55%**, falling to 27% at 5 years
		Occipital resection	OLE	Engel I/II **26–92%**; new field deficit 42–75%
		Parietal resection	PLE	Engel I/II **53–82%**
		Multilobar / posterior quadrant	Extensive MCD, perinatal infarct	Variable
	Resection — lesional	Lesionectomy ± tailored corticectomy under ECoG	Cavernoma, DNET, ganglioglioma, FCD, tuber	**>90%** seizure free for ganglioglioma/low-grade tumour under ECoG guidance; extratemporal resections overall **45.1%** seizure free
	Disconnection	Hemispherotomy	Rasmussen, HME, Sturge-Weber, porencephaly, HHE	**75–90%**; hemispherotomy 85.7% class I vs Rasmussen technique 66.1% vs hemicorticectomy 60.7%
	Ablation	MRg-LITT	MTS, hypothalamic hamartoma, PVNH, deep FCD, insula	Engel I **40–60%** in MTLE
	Ablation	Gamma Knife radiosurgery	MTLE, hypothalamic hamartoma, radiosurgical callosotomy	MTLE seizure remission **52%** vs 78% for open surgery; hypothalamic hamartoma Engel I **39.6%**, Engel I+II 68.8%
Palliative	Disconnection	Corpus callosotomy	Atonic drop attacks, Lennox-Gastaut, Rasmussen, infantile hemiplegia	**80–100%** reduction in drop attacks; total 88.2% vs anterior 58.6% seizure control

Disconnection	Multiple subpial transection ± resection	EZ in motor, sensory or language cortex; Landau-Kleffner	MST alone Engel I–III **75%**; with resection 82%
Neuromodulation	Vagus nerve stimulation	Multifocal, generalised, non-lesional, failed resection	16% at 3 months → **30% / 41% / 41%** at 1/2/3 years
Neuromodulation	DBS of anterior nucleus of thalamus (SANTE)	Focal epilepsy ± secondary generalisation	**40.4%** blinded → 41% / 56% / 69% at 1/2/5 years
Neuromodulation	Responsive neurostimulation	1–2 foci, bilateral mesial temporal, eloquent-cortex onset	**41.5%** blinded → 44% / 53% / 66.5% at 1/2/6 years

11. Temporal lobe surgery — the reference operation

- **Anteromedial temporal lobectomy (Spencer modification, 1984)** — lateral neocortical resection **4–5.5 cm on the dominant and 5.5–6.5 cm on the non-dominant side** from the temporal tip in the classic operation, but Spencer's group spares the superior temporal gyrus regardless of side and limits the inferolateral resection to **3 cm**, because "the probability of finding language in the anterior 3 cm of the middle and inferior temporal gyri is low. The STG has robust language representation along its length" YW p.597.
- **Positioning** — head rotated contralaterally ~50°, extended 30° until the sylvian fissure is parallel to the table, vertex dropped 10° so the temporal region is parallel to the ground with the malar eminence the highest point YW p.597.
- **The key landmark** — the **inferior choroidal point (velum terminale)**, which marks the anterior fornix, the uncal sulcus, the origin of the choroidal fissure and the pes/body junction of the hippocampus; the midbrain lies medial to it YW p.596. The **MCA–choroidal line** is the superior limit of amygdala resection [YW pp. 598-599].
- **Extent of medial resection** — resection to the cerebral peduncle gave 38% seizure freedom versus **69% when extended to the superior colliculus** in a prospective trial of 70 patients; Schramm's RCT found no difference between 2.5 and 3.5 cm YW p.597.
- **Visual fibres** — Meyer's loop "runs forward and laterally toward the roof of the temporal horn before curving **2 cm from the temporal pole**"; it is affected in **up to 90%** of temporal lobectomies, producing the contralateral superior quadrantanopia YW p.596.
- **Complications** — mortality **0.1–0.5%**; upper quadrantanopia (usually unreported by the patient), naming errors, temporalis wasting, frontalis palsy, semantic processing deficits, diplopia (fourth nerve, avoided by preserving arachnoid above the tentorium), hemiparesis from anterior choroidal artery injury [YW pp. 599, 601].
- **Selective amygdalohippocampectomy** — four corridors (transcortical, transsylvian, transsulcal, subtemporal). Seizure freedom is equivalent to ATL at **60–90% over 3–6 years**; the consistent advantage is **a smaller decline in verbal memory after dominant-lobe surgery** (43% of ATL patients worsened versus 31% of SAH patients in Clusmann's series) [YW pp. 602-604].



ure 94A.3. Measurement of lateral temporal resection. A nfield 4 dissector is used to measure 3 cm from the tip of the mporal fossa.

gulation for dissection of vascular structures and pia. The rasonic aspirator respects pial planes and vessels at low settings l allows for a controlled dissection.

ntricular Exposure

atomic landmarks are key in this step. Often the tempo- horn is more posterior than expected. The horn should be proached from the posterior margin of the neocortical resec- n. Landmarks for identifying the temporal horn include the ddle of the middle temporal gyrus, fusiform gyrus arachnoid eriorly, and a bony protuberance in the lateral middle fossa or. Beginning at any of these points and dissecting medially l expose the temporal horn.

Figure 94A.4. Resection of lateral temporal lobe. The lateral temporal cortex can be resected en bloc using ultrasonic aspiration and coagulation. (A) A subpial dissection is performed, demarcating the region to be resected. (B) The cortex is elevated at the level of the white matter without entering the ventricle.

Reproduced from Youmans & Winn 8e, Fig. 94A.4, p. 599 — Label when you reproduce it: en bloc resection of the lateral temporal neocortex — (A) subpial dissection demarcating the region to be removed, with the superior temporal sulcus as the superior limit and the middle fossa floor as the inferior limit; (B) the cortex elevated at the level of the white matter without entering the ventricle. Mark the 3 cm posterior limit measured with a Penfield 4 dissector from the anterior middle fossa floor.

12. Extratemporal resections and the network principle

- **The governing idea** — "epilepsy is a network disorder. Seizures do not respect lobar boundaries, but spread to adjacent cortex and along white matter pathways. In order to render a patient seizure free, the location of seizure onset **and regions of fast spread** generally need to be removed" YW p.605.
- **Frontal** — second commonest focal epilepsy; the frontal lobe is **35–45% of cortical volume** and much of it is buried ventromedially where scalp and even convexity electrodes fail; seizure-freedom rates are approximately 50% versus 70% for temporal [YW pp. 605, 607]. Medial approaches need a bicoronal incision and an interhemispheric route; **the falx stops at the superior border of the cingulate gyrus**, and the pericallosal and callosomarginal arteries must be protected; SMA syndrome must be distinguished from direct motor cortex injury, because the latter recovers poorly [YW pp. 606-607].
- **Occipital** — visual field deficit is the limiting factor; new or worsening deficits in **42.4% to 75%** [YW pp. 609-610]. Preserve subcortical visual projections; in dominant-hemisphere occipital plus mesial temporal resections, preserve the connection between the language-dominant temporal lobe and the contralateral occipital lobe or the patient develops **alexia without agraphia** YW p.608.
- **Parietal** — MRI is the most useful test (lesions in 95% of Binder's series); about a quarter of patients also need MSTs where the focus enters functional cortex [YW pp. 610-611].
- **ECoG-guided tailored lesionectomy** — the subpial technique with resection of epileptogenic grey matter to the bottom of the sulcus, sparing underlying white matter to preserve projection and association fibres YW p.575.

13. Disconnection procedures

- **Hemispherotomy** — "hemispheric disconnection procedures are a group of surgical interventions for chronic epilepsy that are used as alternatives to anatomic hemispherectomy," whose common denominator is "the disconnection of the cortex of one hemisphere from the contralateral hemisphere and from the deeper structures of the basal ganglia" YW p.636. Three modern techniques: disconnection through an **opercular window**, the **transsylvian keyhole** approach, and **vertical parasagittal (dorsal transcortical subinsular) hemispherotomy**. Advantages over hemispherectomy: shorter operation, much less blood loss, fewer intraoperative complications, lower hydrocephalus rate YW p.636.
- **Corpus callosotomy** — non-dominant-side craniotomy with the midpoint just anterior to the coronal suture;

callosotomy begins **3 cm posterior to the genu**, proceeds ventrally to the septal leaves then anteriorly to the anterior commissure; a complete section needs a larger or a second craniotomy; the internal cerebral veins and vein of Galen guard the splenium and the fornices lie just beneath the callosum [YW pp. 615.e2-615.e3].

- **Multiple subpial transection (Morrell)** — based on Mountcastle's vertical columnar organisation and Sperry's mica-plate experiments: **transections 5 mm apart and 4 mm deep, perpendicular to the long axis of the gyrus**, with the hook kept vertical and reversed in the depths of a sulcus, disrupt horizontal synchronising fibres while preserving vertical functional columns [YW pp. 615.e4-615.e7].

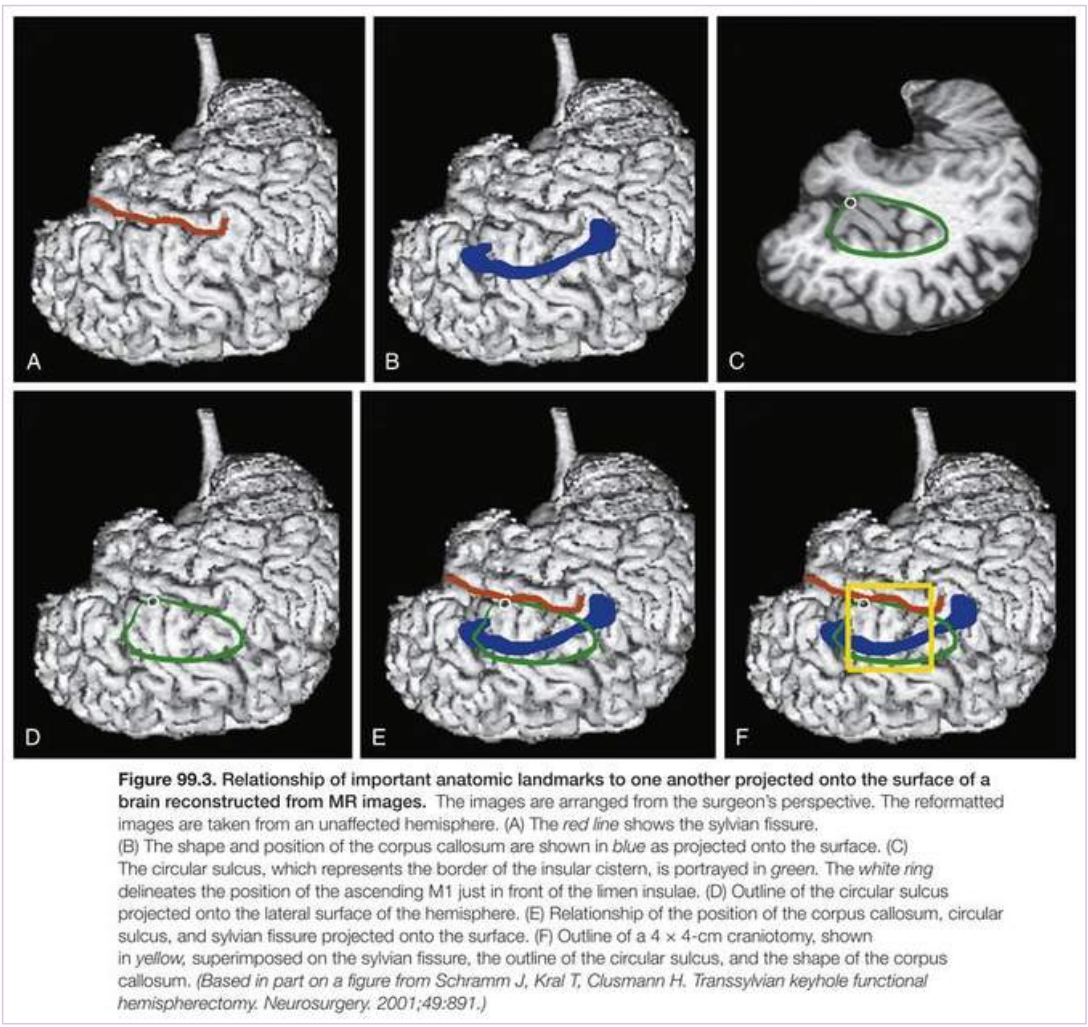


Figure 99.3. Relationship of important anatomic landmarks to one another projected onto the surface of a brain reconstructed from MR images. The images are arranged from the surgeon's perspective. The reformatted images are taken from an unaffected hemisphere. (A) The *red line* shows the sylvian fissure. (B) The shape and position of the corpus callosum are shown in *blue* as projected onto the surface. (C) The circular sulcus, which represents the border of the insular cistern, is portrayed in *green*. The *white ring* delineates the position of the ascending M1 just in front of the limen insulae. (D) Outline of the circular sulcus projected onto the lateral surface of the hemisphere. (E) Relationship of the position of the corpus callosum, circular sulcus, and sylvian fissure projected onto the surface. (F) Outline of a 4 × 4-cm craniotomy, shown in *yellow*, superimposed on the sylvian fissure, the outline of the circular sulcus, and the shape of the corpus callosum. *(Based in part on a figure from Schramm J, Kral T, Clusmann H. Transsylvian keyhole functional hemispherectomy. Neurosurgery. 2001;49:891.)*

Reproduced from Youmans & Winn 8e, Fig. 99.3, p. 640 — Label when you reproduce it: the anatomical landmarks of hemispheric disconnection projected on a 3D MR reconstruction, arranged from the surgeon's perspective — (A) the sylvian fissure in red; (B) the corpus callosum in blue; (C) the circular sulcus of the insula in green with the white ring on the ascending M1 just in front of the limen insulae; (D) the circular sulcus on the lateral surface; (E) all three together; (F) the 4 × 4 cm craniotomy in yellow superimposed on them.

14. Ablative surgery

- **MRg-LITT** — the probe is placed via an **occipital trajectory along the long axis of the hippocampus into the amygdala**; ablation begins anteriorly and the catheter is withdrawn in stages. "Sparing of the mesial temporal head was associated with treatment failure... Furthermore, extending the ablation posteriorly is counterproductive." Engel I at 12 months **40–60%**; the trade-off is "a lower rate of seizure freedom compared with open resection... in exchange for reduced complication rates, reduced morbidity, and shorter hospital stay," with preservation of naming and object recognition even in the dominant hemisphere. Commonest complication: **octantanopsia in up to 37.5%** [YW pp. 630-631].
- **Why LITT displaced radiofrequency** — "radiofrequency thermal damage relies on tissue conduction and is difficult to control... Radiofrequency is thus a 'blind' approach," whereas "thermal spread is software-controlled by MRgLITT

and allows temperature control beyond the tip of the probe" YW p.630.

- **Stereotactic radiosurgery** — in the randomised NIH multicentre trial comparing Gamma Knife with open surgery for mesial temporal lobe epilepsy, **open surgery was superior: 16 of 27 (52%) SRS-treated patients achieved seizure remission versus 21 of 27 (78%) after open surgery**; reported morbidities were visual field deficits, headache, nausea, vomiting and depression, and neurocognitive change appeared similar to ATL [YW pp. 667.e16-667.e17]. For **hypothalamic hamartoma**, Gamma Knife gave **Engel class I in 39.6% and Engel I+II in 68.8%** in the Marseille series, with doses above 17 Gy to the margin giving better remission than doses below 13 Gy, although LITT now achieves 80–90% seizure reduction in the same lesion [YW pp. 622, 667.e16]. Gamma Knife is also used for **stepwise anterior callosotomy at a 60 Gy marginal dose at the 50% isodose** YW p.627.

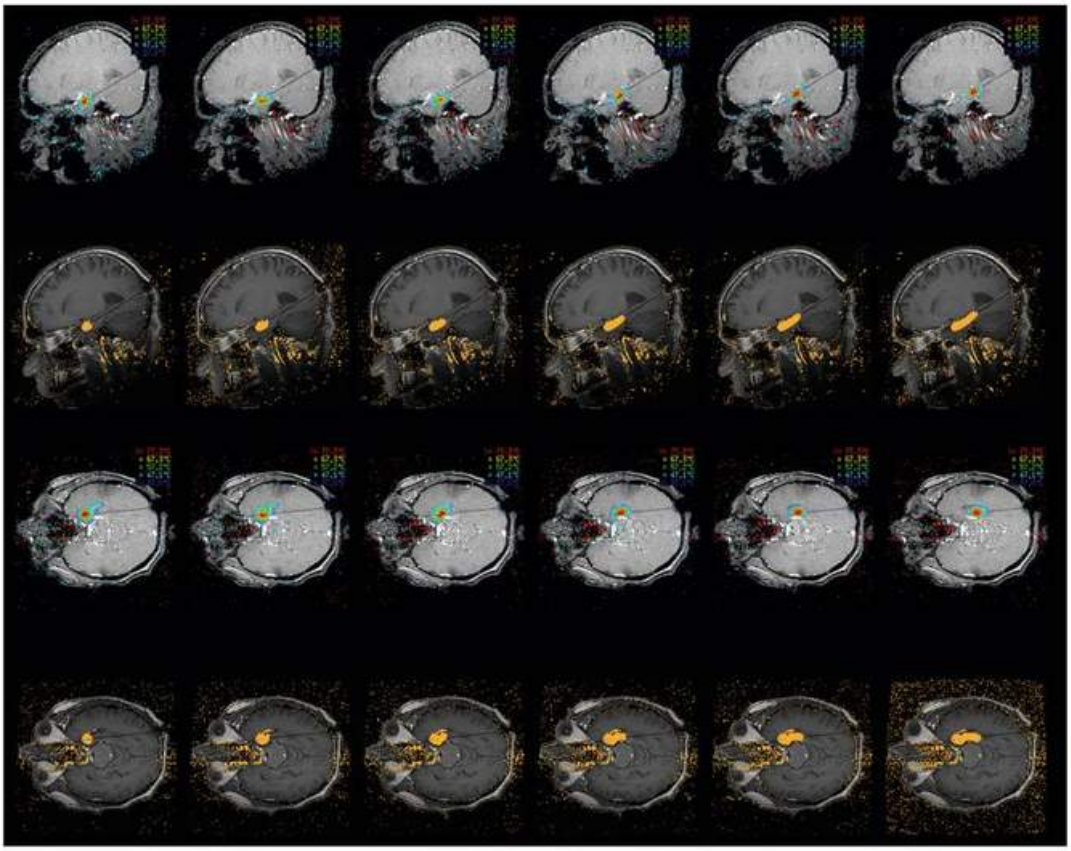


Figure 98.2. Magnetic resonance–guided laser interstitial thermal therapy for mesial temporal sclerosis.

Reproduced from Youmans & Winn 8e, Fig. 98.2, p. 631 — Label when you reproduce it: MR-guided laser interstitial thermal therapy for mesial temporal sclerosis — show the occipital entry, the bolt and fibre trajectory along the long axis of the hippocampus into the amygdala, the real-time thermal damage estimate overlay, and the post-ablation contrast-enhanced ablation cavity. Say that the amygdala and hippocampal head must be included or the ablation fails, and that extending posteriorly is counterproductive.

15. Neuromodulation

- **VNS** — coiled leads on the **left vagus nerve**, generator below the clavicle. Sensory afferents project to the **nucleus of the solitary tract**, which projects to thalamus, amygdala, anterior cingulate and frontoparietal cortex; noradrenaline release into the hippocampus is a marker of effective stimulation. Two industry RCTs (EO3, EO5) showed high-stimulation reductions of **24.5% vs 6.1%** and **27.9% vs 15.2%**. Efficacy grows with time — **16% at 3 months, 30% at year 1, 41% at years 2 and 3**; in another series 26% at 1 year, 30% at 5 years and **52% at 12 years**. Adverse effects are voice alteration/hoarseness, throat or neck pain, cough, dyspnoea, paraesthesia, headache; **fewer than 10% ever become seizure free** [YW pp. 646, 653-654, 667.e15].
- **DBS of the anterior nucleus of the thalamus (SANTE)** — 110 patients; 5 V, 90 µs, 145 Hz, 1 minute on / 5 minutes off; final blinded month **40.4% versus 14.5%** reduction (P = .0017); open-label **41% at 1 year, 56% at 2 years, 69% at 5 years**; responder rate 43% → 54% → 68%. Only **16% seizure free for ≥6 months** over 5 years. Adverse events: paraesthesia 18.2%, depression 14.8%, memory impairment 13.0%, implant-site infection 12.7%. FDA approval **2018**

[YW pp. 651, 659-661].

- **Responsive neurostimulation** — a cranially implanted generator with one or two depth or strip leads at the seizure onset zone, performing continuous electrocorticography with automated detection and stimulation; blinded reduction **41.5% vs 9.4%**; **44% at 1 year, 53% at 2 years, 66.5% at 6 years**; responder rate 64.6% at 6 years; **20.8% reported no seizures in the previous 3 months at 6 years**. FDA approval **2013**. Particular value in multifocal or bilateral onset and in eloquent cortex, and its chronic ECoG can re-lateralise a bitemporal patient and convert them into a resective candidate [YW pp. 661-663].

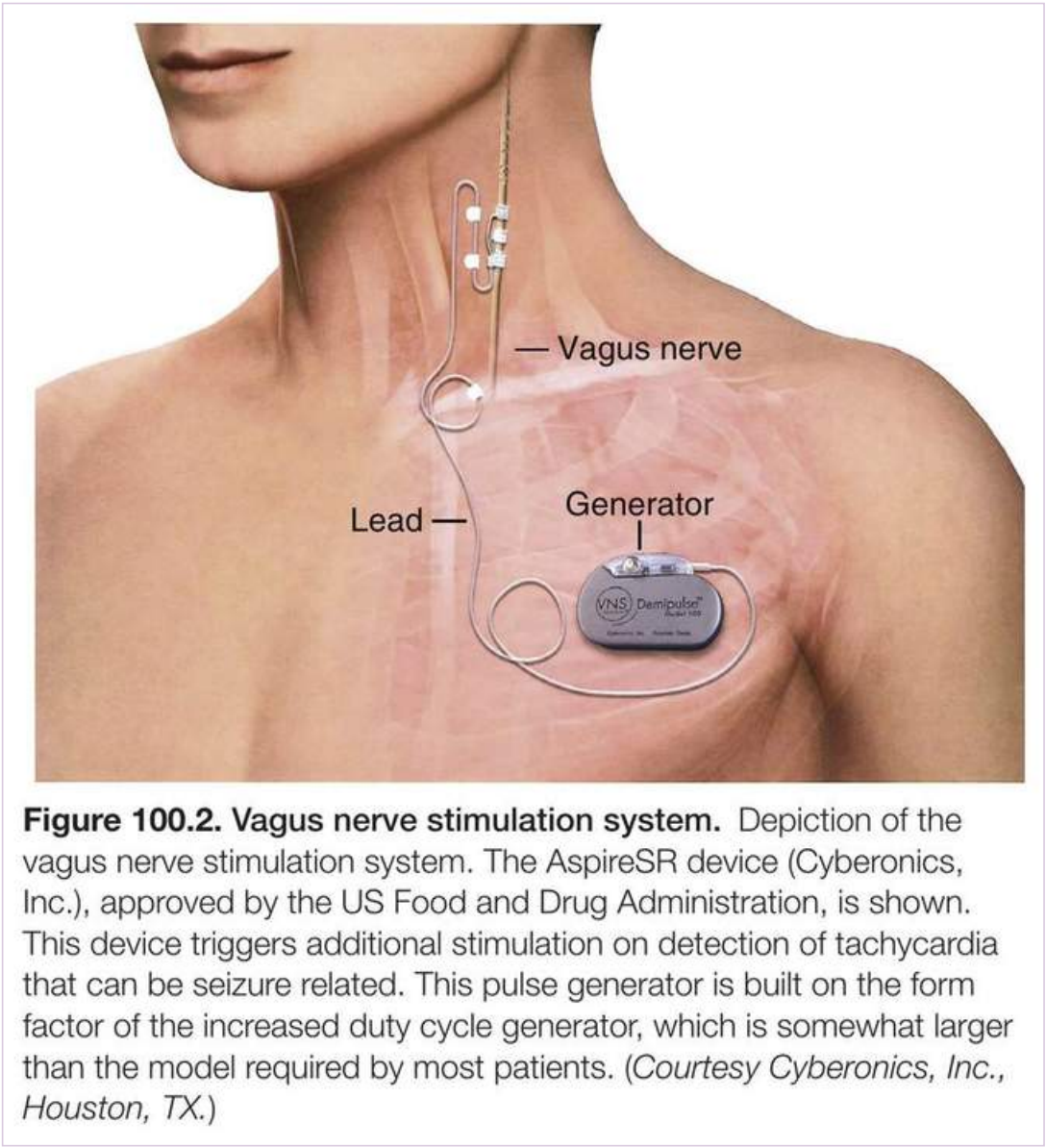


Figure 100.2. Vagus nerve stimulation system. Depiction of the vagus nerve stimulation system. The AspireSR device (Cyberonics, Inc.), approved by the US Food and Drug Administration, is shown. This device triggers additional stimulation on detection of tachycardia that can be seizure related. This pulse generator is built on the form factor of the increased duty cycle generator, which is somewhat larger than the model required by most patients. (*Courtesy Cyberonics, Inc., Houston, TX.*)

Reproduced from Youmans & Winn 8e, Fig. 100.2, p. 653 — Label when you reproduce it: the vagus nerve stimulation system — helical electrode coils around the left vagus nerve within the carotid sheath, lead tunnelled subcutaneously, and pulse generator in a subclavicular pocket. Note that the AspireSR version triggers additional stimulation when it detects seizure-related tachycardia.

16. Outcome reporting and the final word

- **Engel classification** — Class I free of disabling seizures (IA completely seizure free; IB non-disabling simple partial only; IC free of disabling seizures for ≥2 years; ID generalised convulsions only on AED withdrawal); Class II rare disabling seizures; Class III worthwhile improvement; Class IV no worthwhile improvement YW p.667.e2.
- **ILAE outcome scale** — 1 completely seizure free with no auras; 2 auras only; 3 one to three seizure days per year; 4 four seizure days per year up to 50% reduction; 5 <50% reduction to 100% increase; 6 >100% increase YW p.667.
- **Overall** — "resective epilepsy surgery is an effective treatment for drug-resistant focal epilepsy, with demonstrated

long-term rates of seizure freedom of at least 50% a decade after surgery," and "all prognostic factors converge into one central theme: **an epileptogenic zone that is well visualized and restricted in its extent (both electrically and semiologically) offers the best chances of cure when completely resected**" YW p.667.e1.

- **Cost-effectiveness** — by **8 years** after surgery the savings from seizure-free patients make surgical management cheaper than medical management; the marginal cost-effectiveness ratio is **$15,581 per QALY** (another study $27,200/QALY), against $324,537/QALY for lifetime tuberculosis screening of a 20-year-old YW p.667.e14.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Newer AEDs are better tolerated, not more effective** — this single sentence answers half the question YW p.498.
- **Three generations**: 1st = bromide → valproate; 2nd (1990s) = vigabatrin, lamotrigine, topiramate, zonisamide, levetiracetam, oxcarbazepine, gabapentin, pregabalin, felbamate, tiagabine; 3rd = lacosamide, perampanel, brivaracetam, eslicarbazepine, rufinamide, cannabidiol YW p.496.
- **Levetiracetam and brivaracetam act on SV2A with no direct ion-channel effect; perampanel is an AMPA blocker** — the two mechanisms unique to the newer drugs YW p.496.
- **Levetiracetam is the default in hepatic or renal failure**, is renally excreted unchanged, lacks drug interactions, has an IV form, and its key adverse effect is **agitation with mood lability and irritability** [YW pp. 498-499].
- **Lamotrigine needs slow titration because of Stevens-Johnson syndrome**, and hormonal contraception lowers its level [YW pp. 499-500].
- **Valproate is the most teratogenic AED and lowers offspring IQ; lamotrigine and levetiracetam are the pregnancy drugs of choice** YW p.499.
- **Valproate causes platelet dysfunction and bleeding** — avoid it around intracranial electrode implantation YW p.499.
- **Status epilepticus: lorazepam 4 mg IV (or midazolam 10 mg IM), then fosphenytoin 20 mg/kg, valproate 40 mg/kg or levetiracetam 60 mg/kg — all equivalent as second line** YW p.499.
- **Benzodiazepines lose efficacy after 24–48 hours of status because the GABA receptor internalises** YW p.496.
- **No AED is antiepileptogenic** — prophylaxis in a seizure-naïve tumour patient and beyond 7 days after head injury is not supported [YW pp. 496, 498].
- **Surgery, not a fourth drug, is the answer after two failures** — the chance of medical seizure freedom after that point is ≤1% YW p.497.
- **The best predictor of surgical cure is an epileptogenic zone that is well visualised, restricted electrically and semiologically, and completely resected** YW p.667.e1.

Pages read for this answer — Youmans & Winn 8e: 382, 496, 497, 498, 499, 500, 503, 539, 575, 596, 597, 598, 599, 601, 602, 604, 605, 606, 607, 608, 609, 610, 611, 615.e1, 615.e2, 615.e3, 615.e4, 615.e7, 622, 627, 630, 631, 636, 646, 651, 653, 654, 659, 661, 663, 667, 667.e1, 667.e2, 667.e14, 667.e15, 667.e16, 667.e17, 1107

a) Definition of intractable epilepsy. [2]
b) Symptomatic zone in epilepsy. [2]
c) Side effects of Levetiracetam. [2]
d) Types of hemispherectomy and indications. [4]

LONG | OCT 2023 · Paper III · Q3 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 99 *Hemispheric Disconnection Procedures* (J. Schramm), §Definition, §Development, §Indications, Patient Selection and Timing, §Presurgical Evaluation, §Goals of Surgery, §Side Effects and Complications, §Surgical Techniques, §Outcome and Factors of Influence, pp. 636-644 (Table 99.1, p. 637; Figs. 99.1-99.6, pp. 638-643). Supplementary: Ch. 81 *Antiseizure Medications: Principles of Clinical Use*, §Antiepileptic Drug Efficacy, §AED Selection, §Specific AED Concerns in Common Neurosurgical Practice, §Parenteral AEDs, pp. 496-501 (Fig. 81.1, p. 496; Tables 81.1-81.2, pp. 497-498); Ch. 83 *Evaluation of Patients for Epilepsy Surgery*, §Clinical Approach, pp. 503-506; Ch. 80 *Diagnosis and Classification of Seizures and Epilepsy*, §Seizure Classification, pp. 491-495 (Box 80.1, p. 492; Fig. 80.2, p. 493.e2); Ch. 95 *Resections for Extratemporal Epilepsy*, §Introduction, p. 605; Ch. 82 *Electroencephalography in Outpatient, EMU and ICU Settings*, §Interictal Recording, pp. 502.e5-502.e7; Ch. 84 *MRI for Epilepsy Surgery*, §Application to Epilepsy Surgery, p. 515; Ch. 86 *MEG/MSI*, §Role of MEG in Epilepsy Surgery, p. 527; Ch. 267 *Pediatric Epilepsy Surgery*, §Hemispherotomy and Disconnections, p. 2044; Ch. 79 *Malformations of Cortical Development*, §Surgery for MCD, p. 488.e7.

(a) Definition of intractable (drug-resistant) epilepsy [2]

1. The definition itself — say it in one sentence, then justify it

- **The operational definition** — intractable, refractory, pharmacoresistant or drug-resistant epilepsy is **"the failure of two adequately selected and dosed AEDs"** YW p.497. Ch. 83 gives the identical criterion: "pharmacoresistant epilepsy, defined as a failure to respond to two or more appropriately chosen and used antiepileptic medications" YW p.503. Ch. 267 confirms that **"the criterion defining which children are considered medically intractable is the same as that in adults"** YW p.2039.
- **Every word matters** — *two*, *adequately selected* (appropriate for the seizure and epilepsy type) and *adequately dosed* (titrated to efficacy or to the limit of tolerability). A drug stopped for a rash, or one that was the wrong drug for the syndrome, does not count as a failure.
- **The parent definition of epilepsy** it rests on — "classically defined as at least two unprovoked seizures occurring >24 hours apart," now amended to include "one unprovoked seizure with at least a **60% risk for recurrent seizure**" over the next 10 years [YW pp. 492, 497].

2. Why "two" — the evidence

- **The Kwan and Brodie Glasgow cohort of newly diagnosed epilepsy** showed that **47% became seizure free on the first AED, a further 13% on the second, and only 3.7% on the third. "Unfortunately, trials after a third AED showed a 1% or less likelihood of becoming seizure free."** These seizure-free rates "have proved durable over long-term follow-up" YW p.497.
- **Restated in the key-concepts box** — "after a continuation of seizures after three appropriately selected AEDs, a patient is considered to have a **less than 1% chance of being seizure free with medications alone**" YW p.496.
- **Ch. 101 puts it even more starkly** — "drug-resistant epilepsy has a **less than 5% chance** of being successfully treated with medications alone. Exploring candidacy for epilepsy surgery is thus a necessity in this patient population" YW p.667.
- **Prevalence** — "epilepsy affects 1% of the world's population, and **30% to 40% of cases are refractory to medical therapy**" YW p.646; another chapter gives "30% to 40% of all new cases of epilepsy ultimately become refractory to treatment" YW p.615.e1.

3. What the definition obliges you to do

- **It converts a medical problem into a surgical referral.** "From a neurosurgical perspective, it is then important to consider surgical therapy once the diagnosis of drug-resistant epilepsy is reached, as suggested by a practice parameter endorsed by multiple professional societies" YW p.497.

CHAPTER 17

Peripheral Nerve & Brachial Plexus

13
QUESTIONS SOLVED

Carpal Tunnel & Entrapment Neuropathies — 9 questions

Foot drop: different causes, diagnostic evaluation and management.

LONG | DEC 2020 · Paper II · Q3 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 284 *Nerve Injuries of the Lower Extremity* (A.G. Filler, M.A. Mahan), §Sciatic Nerve and Other Nerves of the Posterior Pelvis, §Peroneal Nerve, §Posterior Tibial Nerve, pp. 2195-2207 (Fig. 284.3, p. 2195; Figs. 284.11-284.14, pp. 2199-2200; Figs. 284.18-284.27, pp. 2202-2204; Table 284.1, p. 2195; Tables 284.3-284.5, pp. 2200-2201, 2205). Supplementary: Ch. 276 *Distal Entrapment Syndromes: Carpal Tunnel, Cubital Tunnel, Peroneal, and Tarsal Tunnel*, §Common Peroneal Nerve, pp. 2137-2139 (Box 276.5, p. 2138; Figs. 276.7-276.8, p. 2139); Ch. 272 *Peripheral Nerve Examination, Evaluation, and Biopsy*, §Motor Examination, §Peripheral Nerve Examination, pp. 2085-2090 (Fig. 272.1, p. 2086; Tables 272.1-272.2, pp. 2087, 2089); Ch. 271 *Pathophysiology of Surgical Nerve Disorders*, §Compartment Syndromes, §Entrapment Neuropathies, pp. 2076-2078 (Table 271.1, p. 2073); Ch. 273 *Peripheral Neuropathies*, §Clinical Evaluation, pp. 2093-2095 (Table 273.2, p. 2094); Ch. 274 *Monitoring of Neural Function*, pp. 2106-2109; Ch. 275 *Imaging for Peripheral Nerve Disorders*, pp. 2120-2123; Ch. 278 *Piriformis Syndrome...*, p. 2153; Ch. 286 *Avoiding Iatrogenic Injury Affecting Nerves*, pp. 2225-2227; Ch. 285 *Benign and Malignant Tumors of the Peripheral Nerve*, Table 285.5, p. 2217; Ch. 26 *Positioning for Peripheral Nerve Surgery*, p. 232.e4.

(a) Foot drop — definition and the single question that organises the whole answer [2]

1. What "foot drop" actually means

- **Foot drop is weakness of ankle dorsiflexion**, so that the forefoot cannot be lifted clear of the ground in the swing phase of gait. Youmans describes the clinical picture directly: patients "complain of footdrop or frequent tripping because of weakness in dorsiflexion and eversion of the foot. Patients will compensate for the footdrop by lifting the leg higher" — the high-stepping or steppage gait YW p.2138.
- **The dorsiflexor motor unit is a single long chain** — L4/L5 anterior horn cell → L5 ventral root → lumbosacral plexus → sciatic nerve (peroneal division) → common peroneal nerve (CPN) → deep peroneal nerve (DPN) → tibialis anterior, extensor hallucis longus and extensor digitorum longus. A lesion anywhere along that chain produces the same terminal sign, which is why **foot drop is a sign, never a diagnosis** [YW pp. 232.e4, 2137-2138].
- **The examiner's marks lie in localisation, not in naming the sign.** Youmans makes this the teaching case of the whole peripheral-nerve examination chapter: "Consider a unilateral footdrop. An upper motor neuron lesion affecting the pyramidal tract, a cord lesion affecting the L5 motor neuron pool, a spinal lesion interfering with L5 outflow, and peripheral lesions affecting the L5 nerve root, lumbosacral trunk, peroneal division of the sciatic nerve, and peroneal nerve itself all may result in footdrop" YW p.2087.

2. The anatomy you must be able to recite before you localise

- **Sciatic nerve** arises from the ventral rami of L4 to S3, lies anterior to piriformis in the lesser pelvis, enters the buttock through the greater sciatic foramen, and descends close to the midline of the thigh; **in the majority of individuals it divides into tibial and common peroneal branches at the middle to distal third of the thigh** YW p.232.e4. Youmans gives the surface rule: "The peroneal nerve separates from the sciatic nerve two-thirds of the way between the gluteal crease and the popliteal crease" YW p.2202.
- **Common peroneal nerve** travels on the lateral side of the popliteal fossa, **medial to the tendinous insertion of biceps femoris and lateral to the lateral head of gastrocnemius**, crosses plantaris, then curves round the lateral aspect of the

fibular neck **approximately 1 to 2 cm distal to the fibular head, where it is fixed to the bone by connective tissue** — the point of maximum vulnerability YW p.2137.

- **The peroneal tunnel** is the confined space the CPN enters after piercing the tendinous origin of peroneus longus, "bound medially by the periosteum of the fibula and laterally by the peroneus longus" — **this tunnel is the major site of entrapment of the CPN** YW p.2137.
- **Terminal trifurcation** — within peroneus longus the CPN divides into the **deep peroneal nerve** (tibialis anterior, extensor digitorum longus, extensor hallucis longus, peroneus longus; extensor digitorum brevis distally; sensation to first web space), the **superficial peroneal nerve** (peroneus longus and brevis; medial and intermediate dorsal cutaneous nerves to the dorsum of the foot) and an **articular branch to the tibiofibular joint and tibialis anterior** [YW pp. 2137-2138, 2203].
- **Two structural facts explain why this nerve fails so often**: the CPN "is the most frequently injured nerve in the lower extremity and is involved in nearly 25% of all traumatic peripheral nerve injuries"; and it "has a higher fascicle number and lower connective tissue content at the fibular neck than does the CPN within the popliteal fossa, which increases the nerve's susceptibility to stretch or compression injury" YW p.2137.
- **In any sciatic lesion the peroneal division suffers more than the tibial**: "As with other sciatic injuries resulting from stretch or compression, the peroneal or lateral division sustains a greater degree of injury than the tibial or medial division" YW p.2198.

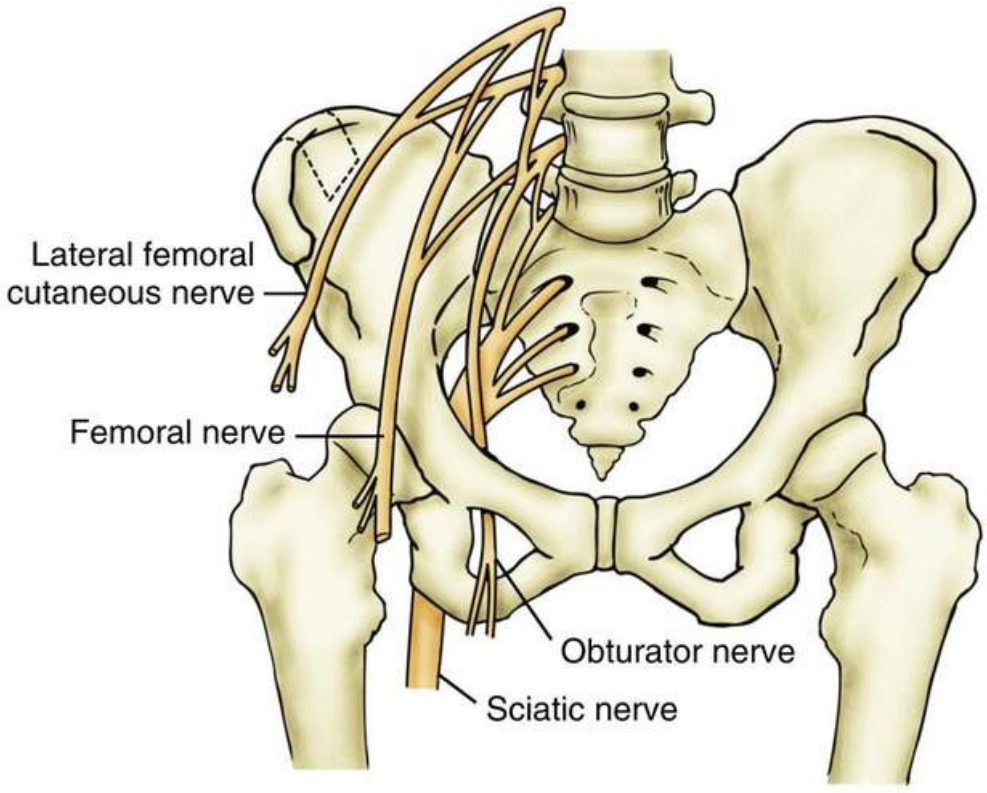


Figure 284.3. Schematic diagram of nerves of the lower extremities that can be injured at a pelvic level. Note that acetabular injury may involve the sciatic, femoral, and obturator nerves. *(Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of Mississippi Medical Center, Jackson, MS.)*

Reproduced from Youmans & Winn 8e, Fig. 284.3, p. 2195 — Label when you reproduce it: lateral femoral cutaneous nerve, femoral nerve, obturator nerve and sciatic nerve as they leave the pelvis — the four nerves that an acetabular or pelvic injury can take out together. Mark the greater sciatic notch and note that the sciatic nerve carries the whole dorsiflexor outflow (L4-S3).

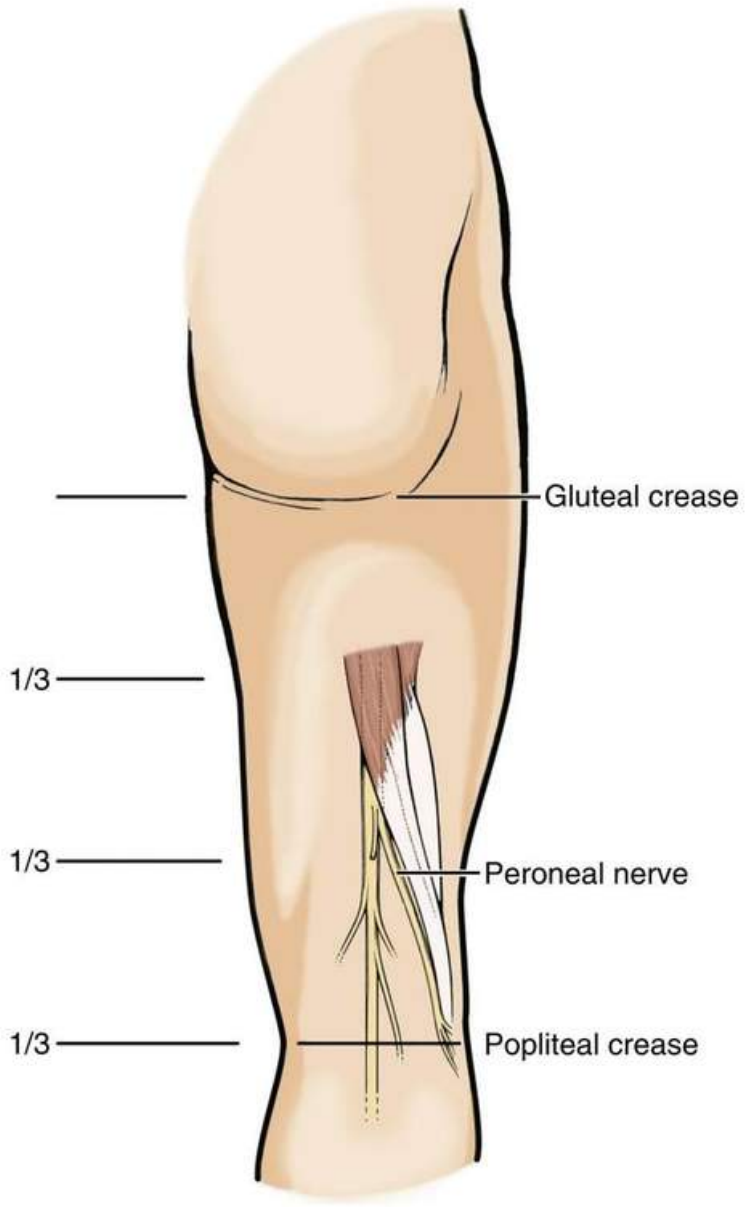


Figure 284.18. The peroneal nerve separates from the sciatic nerve two-thirds of the way between the gluteal crease and the popliteal crease. (*Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of Mississippi Medical Center, Jackson, MS.*)

Reproduced from Youmans & Winn 8e, Fig. 284.18, p. 2202 — Label when you reproduce it: gluteal crease, popliteal crease, the point two-thirds of the way down where the peroneal nerve separates from the sciatic nerve, the lateral sural branch, the tibial nerve, and the position of the stimulating and recording electrodes used for intraoperative nerve action potentials. This is the figure to draw when asked "where does the sciatic nerve divide?"

(b) Different causes of foot drop [4]

3. A level-by-level differential — work down the neuraxis

Table 1 · Causes of foot drop by anatomical level, with the examination finding that betrays each level — compiled from Youmans & Winn 8e, Ch. 272 p. 2087, Ch. 276 pp. 2137-2138 (Box 276.5), Ch. 284 pp. 2198-2205 and Ch. 271 pp. 2076-2078.

Level	Representative causes	Clue that gives the level away
Upper motor neuron (pyramidal tract)	Cerebral, brainstem or cord lesion	Increased reflexes and tone; "careful examination of the limb for increased reflexes and tone will help distinguish upper from lower motor neuron pathology" YW p.2087
Anterior horn / L5 motor neuron pool	Motor neuron disease, poliomyelitis-type syndromes, cord lesion at the L5 pool	Pure motor, no sensory loss, fasciculations; normal sensory NCS
L5 nerve root	Disc herniation, lateral recess or foraminal stenosis, extraforaminal osteophyte impingement of the descending L5 spinal nerve	**Sensory NCS normal** because the lesion is proximal to the dorsal root ganglion YW p.2106; weakness of other L5 muscles — gluteus medius, tibialis posterior (inversion) YW p.2087; SPN SNAP "should be spared in the case of L5 radiculopathy" YW p.2138
Lumbosacral plexus / lumbosacral trunk	Pelvic fracture, retroperitoneal haematoma, tumour, obstetric injury, gunshot injury (Fig. 284.2)	L5 territory weakness beyond the peroneal distribution plus femoral/obturator involvement; pseudomeningocele on imaging (Fig. 284.1) YW p.2195
Sciatic nerve — buttock level	Gluteal **injection injury** (the commonest single cause at this level), hip fracture-dislocation, total hip arthroplasty, contusion, compression, gunshot, laceration	Hamstring weakness; loss/diminution of the ankle reflex; peroneal division worse than tibial [YW pp. 2198-2200]
Sciatic nerve — thigh level	Femoral fracture, gunshot, laceration, contusion, compression, iatrogenic	Short head of biceps femoris abnormal on EMG — "it is the only peroneal-innervated muscle proximal to the peroneal tunnel; an electrical abnormality suggests a lesion proximal to the popliteal fossa" YW p.2138
Piriformis / deep gluteal	Piriformis syndrome, obturator internus syndrome, split sciatic nerve variants	Sciatic notch tenderness; electrodiagnosis "may show a delay in the peroneal H-reflex, or may be normal" YW p.2153
Common peroneal nerve at the fibular neck	Entrapment in the peroneal tunnel; habitual leg crossing; slimmer's palsy; squatting; knee dislocation; fibular neck fracture; intraneural ganglion; tumour; iatrogenic compression	Tinel sign at the fibular neck; sparing of inversion (tibialis posterior) and of the short head of biceps femoris
Deep peroneal nerve / anterior tarsal tunnel	Anterior tarsal tunnel syndrome, tight footwear/boots, anterior compartment syndrome	Weak toe extension with preserved eversion; first web space numbness only
Muscle / compartment	**Anterior compartment syndrome** — "a progressive peroneal palsy and associated footdrop" with tibial and fibular fractures and always soft-tissue swelling YW p.2077	Tense compartment, pain out of proportion, pressure measurement
Generalised neuropathy	Diabetes, CIDP, multifocal motor neuropathy, vasculitis, HNPP, Charcot-Marie-Tooth, leprosy, amyloid (Table 273.2) YW p.2094	Bilateral, stocking sensory loss, areflexia, abnormal contralateral studies

4. Causes acting on the common peroneal nerve itself — enumerate these, they carry the marks

- **Entrapment in the peroneal tunnel.** "In absence of a specific traumatic event, the most common cause of CPN entrapment is habitual leg crossing. Such patients usually cross the same leg, which causes repetitive injury to the CPN at the fibular neck; in these patients a skin dimple may even develop at the site of trauma" YW p.2138.
- **Slimmer's palsy** — "Patients who lose a significant amount of weight, as in the case of cancer or an eating disorder, may also be prone to injury to the CPN at the fibular neck (slimmer's palsy)" YW p.2138.

- **Occupational squatting** — "an increased incidence is seen in certain professions that require frequent squatting (e.g., roofers, carpet layers, strawberry pickers)"; also potato grubbing and do-it-yourself roofing; and "women may experience this condition after prolonged squatting during childbirth" [YW pp. 2138, 2202].
- **Positioning and iatrogenic compression** — "iatrogenic injury can occur as a result of improper cushioning or positioning of the leg, particularly in the dorsal lithotomy or lateral decubitus positions" YW p.2138; tight-fitting casts; anaesthetic positioning palsy; and importantly **antithrombosis and sequential pneumatic compression stockings** — "the use of pneumatic intermittent compression stockings can readily produce a severe peroneal palsy if the stockings are not carefully placed to avoid pressure on the peroneal nerve just below the fibular head", and bed-mounted retractors placed against the lateral leg after draping cause the same problem [YW pp. 2202, 2225].
- **Knee dislocation and posterolateral corner injury.** "The incidence of peroneal nerve injury in conjunction with knee dislocations has been reported to be between 14% and 40%; in most studies, the incidence reported is 25% to 35%" YW p.2202. A pull-off of the biceps femoris tendon with or without fibular head fracture is a classic mechanism, and because knee dislocation can also damage the popliteal artery or vein, **distal pulses must always be evaluated; nerve evaluation and repair remain secondary to viability of the limb** YW p.2202.
- **Knee and other joint surgery.** Peroneal palsy after total knee arthroplasty "was found to be 0.87% in a retrospective review of 2626 consecutive cases", attributed to direct traction, traction-induced vascular compromise, or over-tight bandages; after knee arthroscopy an incidence of 0.8% has been reported YW p.2202.
- **Intraneural ganglion cyst.** "The CPN is the peripheral nerve most often affected by intraneural ganglion cysts, and the diagnosis of a peroneal intraneural ganglia should be suspected in individuals with preferential involvement of the DPN and/or those with a mass lesion." Recent evidence implicates "an abnormal interaction between the articular branch of the CPN and the tibiofibular joint" YW p.2138. In the LSUHSC non-neural-sheath tumour series the peroneal nerve accounted for **15 of the intraneural ganglion cysts**, far more than any other nerve YW p.2217.
- **Missile and laceration injuries** — in the LSU experience missile injuries contributed only 4% of 278 peroneal-level injuries, most being low-velocity civilian wounds YW p.2202.
- **Deliberate tibial bone lengthening** has been associated with peroneal nerve injury YW p.2202.

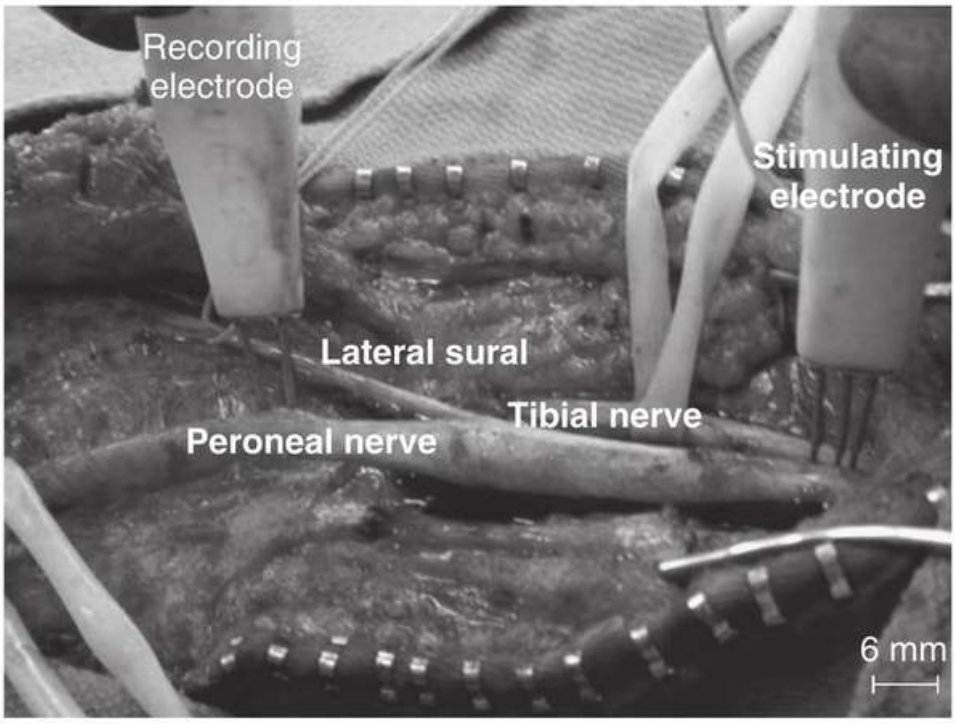


Figure 284.19. An anterior and posterior cruciate ligament disruption allowed this peroneal nerve to undergo significant stretch. Note the markedly thickened nerve. Nerve action potential (NAP) recording demonstrated no transmitted NAP across this segment.

Reproduced from Youmans & Winn 8e, Fig. 284.19, p. 2202 — Label when you reproduce it: the grossly thickened common peroneal nerve after an anterior and posterior cruciate ligament disruption allowed the nerve to stretch — the classic long neuroma-in-continuity in which no nerve action potential is transmitted. Describe what you would do next (resect and graft, because a flat iNAP means neurotmesis).



Figure 272.1. Some classical abnormalities on neuromuscular examination. (A) Left axillary palsy with deltoid atrophy *(arrowhead)*. (B) Right humeral level radial nerve palsy causing wrist and finger drops *(arrowhead)*. (C) Right sciatic palsy with atrophy of leg muscles and flail right foot *(arrowhead)*. Autonomic abnormalities including erythema, alopecia, and swelling are present in the right leg.

Reproduced from Youmans & Winn 8e, Fig. 272.1, p. 2086 — Label when you reproduce it: (A) left axillary palsy with deltoid atrophy; (B) right humeral-level radial nerve palsy with wrist and finger drop; (C) right sciatic palsy with atrophy of the leg muscles and a flail right foot, plus autonomic changes (erythema, alopecia, swelling). Panel C is the picture of a proximal cause of foot drop — note that the whole leg, not just the dorsiflexors, is wasted.

(c) Diagnostic evaluation [part of 4]

5. History — six questions that decide the level

1. **Onset and tempo** — instantaneous (laceration, fracture-dislocation, injection), over hours (compartment syndrome, haematoma), over days-weeks (compression from bedrest, weight loss), over months (tumour, entrapment). Acute neuropathies "manifest over days to weeks, whereas chronic neuropathies smolder over months to years" YW p.2093.
2. **Precipitant** — leg crossing, squatting, recent large weight loss, a cast or stocking, a knee injury, a gluteal injection, hip or knee surgery, childbirth.
3. **Pain** — pain over the fibular neck radiating into the DPN and SPN distributions favours peroneal tunnel entrapment YW p.2138; back and buttock pain radiating down the leg favours L5 root or piriformis.
4. **Sensory pattern** — first web space only (DPN), dorsum of foot (SPN), lateral calf plus dorsum (CPN), sole involvement as well (sciatic/plexus/polyneuropathy).
5. **Recovery so far** — ask specifically about "any dorsiflexion of the toes or foot while supine (i.e., with gravity eliminated), which may suggest recovery" YW p.2085.
6. **Systemic screen** — diabetes and impaired glucose tolerance, vitamin B12 deficiency, paraproteinaemia, vasculitis, HIV, drugs and toxins, family history (Charcot-Marie-Tooth, HNPP) YW p.2094.

6. Examination — a sequence that localises

- **Inspect** for atrophy, scars, skin dimple at the fibular neck, trophic and autonomic change; compare with the normal limb, using a tape measure from a fixed bony landmark for serial comparison [YW pp. 2086-2087].
- **Grade every muscle with the MRC scale** (Table 272.1: 5 normal; 4 against resistance with 4−/4/4+; 3 against gravity; 2 gravity eliminated; 1 flicker; 0 nothing) and test paretic muscles both with and without gravity YW p.2087.
- **The four discriminating muscles**:
  - **Tibialis posterior (inversion)** — L5 but tibial-innervated. "Coexistent foot inversion weakness may suggest either L5 radiculopathy or a sciatic nerve injury" YW p.2138.
  - **Gluteus medius (hip abduction)** — L5, superior gluteal nerve; weak in radiculopathy/plexopathy, normal in CPN lesions YW p.2087.
  - **Short head of biceps femoris** — peroneal division of sciatic above the knee; "weakness in this muscle may signify CPN injury above the knee" YW p.2138.
  - **Plantar flexion and the ankle jerk** — tibial; "it is not uncommon to find loss or diminution of the ankle reflex in patients with buttock- or midthigh-level sciatic nerve injuries who have complete peroneal division involvement clinically" YW p.2089.
- **Palpate and percuss the whole course** of the sciatic and common peroneal nerves "to feel for masses and tender areas", with close attention to the fibular neck for bony deformity and nerve enlargement; **the Tinel sign is frequently present at the site of compression** YW p.2138.
- **Ask the patient to heel-walk** — "which can identify subclinical dorsiflexion weakness" YW p.2138.
- **Serial Hoffmann-Tinel testing** is the single most useful bedside follow-up tool: an advancing sign at "about 1 mm/day or 1 inch/month … provides putative evidence of ongoing regeneration", while "lack of an advancing Hoffmann-Tinel sign may be a strong negative finding, suggesting complete neural interruption or poor regeneration" YW p.2089.
- **Autonomic and orthopaedic assessment** — the wrinkle test, skin temperature, and passive/active range of motion of the ankle to detect a fixed equinus contracture [YW pp. 2087, 2089].

7. Electrodiagnosis — what to ask the neurophysiologist for

- **Timing** — denervation potentials take about 2 weeks to appear because Wallerian degeneration must proceed, so an early study underestimates severity; a baseline study at 2-3 weeks with serial repeats is standard practice in nerve trauma [YW pp. 2175, 2184.e2].
- **Sensory NCS of the superficial peroneal nerve** — "SNAPs of the SPN may be reduced or absent but should be spared in the case of L5 radiculopathy" YW p.2138. This is the single most valuable discriminator, because "in radiculopathies the sensory NCVs are normal whereas the motor NCVs may be impaired" YW p.2106.
- **Motor NCS across the fibular neck** — "record from the extensor digitorum brevis or tibialis anterior while stimulating the CPN above and below the fibular neck to look for focal slowing, temporal dispersion, or conduction block" YW

p.2138.

- **Amplitude versus velocity** — "low-amplitude, slowed NCV suggests a demyelinating lesion, whereas low-amplitude NCV without slowing suggests axonal degeneration" YW p.2106.
- **Needle EMG** must sample "both peroneal-innervated muscles and nonperoneal L5-innervated muscles such as the tibialis posterior (TP) and flexor digitorum longus (FDL)", plus the short head of biceps femoris and the lumbar paraspinals YW p.2138. Radiculopathy shows "denervation (fibrillations, positive sharp waves) in two or more muscles in the same myotome supplied by different peripheral nerves" YW p.2109.
- **Late responses** — the F wave "measures the health of the entire length of the motor pathway including its proximal portion", and the peroneal **H-reflex** may be delayed in piriformis syndrome [YW pp. 2106, 2153].
- **Reinnervation markers** — nascent, unstable and polyphasic motor unit potentials with reduced recruitment appear weeks before clinical recovery [YW pp. 2095, 2184.e3].

8. Imaging

- **Plain radiographs of the knee** "must be performed to look for fracture or deformity"; of the hip/pelvis and femur where the mechanism suggests it YW p.2138.
- **MRI** "can identify swelling of the entrapped nerve with increased signal intensity, which can be easily appreciated on axial T2-weighted images", but is "most useful in demonstrating space-occupying lesions, such as intraneural ganglion cysts and unusually proximal or distal sites of entrapment" YW p.2138.
- **MR neurography** shows distortion of nerve course, calibre and image intensity, and can display the sciatic nerve through the piriformis and the peroneal division as a separate bundle [YW pp. 2120-2123]. It can also detect **denervation change in muscle as early as 4 days after an axonotmetic or neurotmetic injury**, with signal peaking about 4 months and fatty replacement supervening at 1-2 years YW p.2126.
- **Ultrasound** is inexpensive, dynamic, bedside-available and demonstrates nerve swelling, ganglia and mass lesions [YW pp. 2090, 2138].
- **Lumbar spine MRI** where an L5 radiculopathy is suspected — and remember extraforaminal impingement of the descending L5 spinal nerve by a lateral marginal osteophyte, which conventional spine MRI can miss YW p.2122.
- **Laboratory screen** where a generalised neuropathy is suspected: fasting glucose and 2-hour GTT, B12 with methylmalonic acid and homocysteine, serum protein immunofixation; further targeted tests per Table 273.2 [YW pp. 2094-2095].

(d) Management [4]

9. Principles

- **Treat the cause, protect the foot, and time the operation.** Youmans' management paradigm for peripheral nerve injury runs: complete sharp transection → microsurgical repair 0-3 days; complete blunt transection → repair at 2-4 weeks; neuroma-in-continuity with complete loss → monitor 2-3 months then explore; incomplete loss with significant distal sparing → most improve, monitor 2-3 months; avulsion/proximal injury → monitor up to 3-4 months YW p.2075, Box 271.1. The bedside shorthand is the **"rule of 3s": 3 days for sharp clean lacerations, 3 weeks for blunt lacerations, 3 months for injuries-in-continuity** YW p.2176, Table 281.2.
- **Expected spontaneous recovery** depends on Sunderland grade: grade I (neurapraxia) complete, grade II excellent to good, grade III variable, grade IV variable to poor, grade V none; regeneration with or without repair proceeds at **1 mm/day** YW p.2073, Table 271.1.

10. Non-operative management

- **Remove the cause** — "exacerbating factors such as habitual leg crossing should be strictly avoided"; reposition or remove compression stockings and bed-mounted retractors; pad the fibular neck in patients who have lost weight [YW pp. 2138-2139, 2225].
- **Ankle-foot orthosis** — "in patients with footdrop, treatment with an ankle-foot orthosis is important to prevent falls and ankle sprains" YW p.2139.

- **Physical therapy** — "physical therapy exercises are essential to prevent contractures"; maintain full passive range of motion at the ankle throughout the waiting period [YW pp. 2139, 2184.e4].
- **Neuropathic pain** — tricyclic antidepressants such as amitriptyline, or anticonvulsants such as gabapentin, "have demonstrated good benefit for neuropathic pain states" YW p.2181.
- **Timing of the decision** — "surgical decompression is often recommended for patients who show little or no improvement after 3 to 4 months" YW p.2139.

11. Emergency operations that must not wait

- **Compartment syndrome.** "A closed compartment syndrome with impending ischemic paralysis requires immediate decompression with properly placed, and usually extensive, longitudinal fasciotomies. Delay in treatment results in ischemic infarction of muscle, nerve, and other tissues, leading to contractures and other crippling deformities" YW p.2077. Measure tissue pressure with a needle, saline-filled tube and manometer; when the difference between cuff arterial pressure and tissue pressure falls below about 40 mm Hg, ischaemic infarction is likely YW p.2077.
- **Expanding haematoma or pseudoaneurysm** with progressive deficit — decompress YW p.2075.
- **Sharp laceration** of the nerve (glass, knife) — primary microsurgical repair within 72 hours [YW pp. 2075-2076].
- **Vascular injury with knee dislocation** — limb viability first; "nerve evaluation and repair remain secondary to viability of the affected limb" YW p.2202.

12. Operative decompression of the common peroneal nerve

- **Position and incision** — lateral position, affected leg uppermost and flexed at the knee; a curvilinear oblique incision over the fibular neck above the anticipated course of the CPN; general anaesthesia is usual, local with sedation is preferred by some, tourniquet optional YW p.2139. The alternative described in Ch. 284 starts "parallel and medial to the biceps femoris tendon and extends inferiorly to the popliteal crease, where it is directed more laterally to overlie the superior portion of the fibula" YW p.2202.
- **Steps** — preserve the lateral sural cutaneous and posterior femoral cutaneous branches; incise deep fascia over the palpable CPN; the nerve is surrounded by adipose tissue — identify and protect it; expose proximally and distally; follow the CPN round the fibular neck as it passes between the two heads of peroneus longus; **divide the fascia overlying peroneus longus and the constricting fascial band deep to the muscle, which is the main compression point**; visualise the origins of the DPN and SPN; probe the proximal and distal extents for occult compression [YW pp. 2139, 2203].
- **Intraoperative nerve action potentials** are then recorded across the lesion, and an external neuroplasty performed YW p.2139.
- **Closure** — "the skin is closed with either absorbable or nonabsorbable monofilament, usually in a mattress configuration because of the high rate of repetitive mechanical stress on the closure line during walking"; early mobilisation is encouraged YW p.2139.

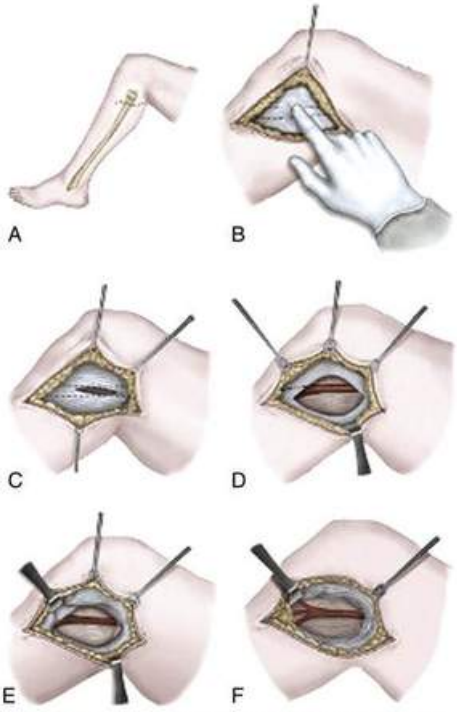


Figure 276.7. Schematic representation of decompression of the common peroneal nerve. (A) The incision is oriented obliquely along the course of the peroneal nerve just below the fibular head. (B) After the soft tissue is opened, the surgeon can palpate the peroneal nerve and roll it with a finger just below the fibular head. (C) The fascia overlying the peroneal nerve is opened. (D) The peroneal nerve is dissected, and the fascia above the peroneus musculature is opened. (E) The muscle is retracted to identify the fascial band directly below the muscle, which is the main compression point on the peroneal nerve. (F) The peroneal nerve and branches are completely decompressed. (*From Humphreys DB, Novak CB, Mackinnon SE. Patient outcome after common peroneal nerve decompression. J Neurosurg. 2007;107[2]:314–318.*)



Figure 276.8. Schematic representation of the medial aspect of the right ankle and foot to illustrate the site of entrapment of the tibial nerve. (1) Tendon of the posterior tibial muscle. (2) Tendon of the flexor digitorum longus muscle. (3) Tibial nerve. (4) Flexor retinaculum. (5) Medial plantar nerve. (6) Lateral plantar nerve. (*From Fernandez E, Pallini R, Lauretti L, et al. Neurosurgery of the peripheral nervous system: entrapment syndromes of the lower extremity. Surg Neurol. 1999;52:449–452.*)

repetitive mechanical stress on the closure line during walking. A soft compressive dressing is placed, and early mobilization is encouraged.[146]

In 2004, Kim and associates published a large series of patients who underwent surgery for CPN lesions at LSUHSC.[147] Over a 32-year period, 318 knee-level CPN lesions were managed surgically, 51% of which were stretch or contusion injuries, 12% were lacerations, 9% involved entrapment, 7% were caused by compression, and others included iatrogenic injuries, tumors, and gunshot wounds. Neuroplasty was performed in patients with recordable NAPs across the injured segment. Of the 121 patients in whom neuroplasty was performed, 107 (88%) recovered useful function. In patients in whom NAPs were absent, the injured segment was removed and grafted. Functional outcomes were more favorable in patients who required shorter grafts; 75% of patients who had grafts smaller than 6 cm achieved grade 3 or higher function compared with 38% in the 6- to 12-cm group and 16% in the 13- to 24-cm group. In the event of persistent footdrop after surgery, one may consider referral to an orthopedist

Reproduced from Youmans & Winn 8e, Fig. 276.7, p. 2139 — Label when you reproduce it: the six steps of common peroneal decompression — (A) oblique incision below the fibular head; (B) palpating and rolling the nerve; (C) opening the fascia over the nerve; (D) opening the fascia above the peroneus musculature; (E) retracting the muscle to find the fascial band that is the main compression point; (F) the fully decompressed nerve and its branches.

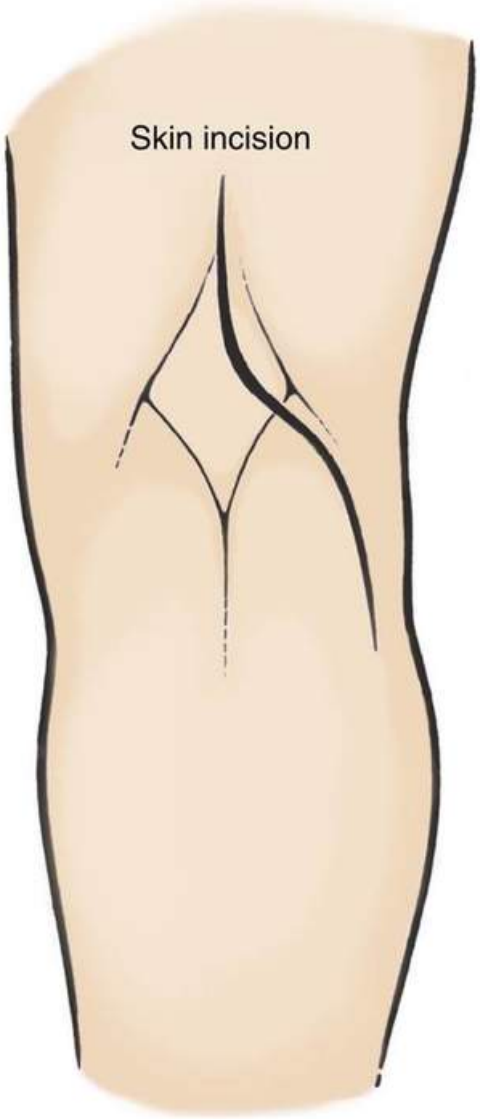


Figure 284.20. Skin incision for exposure of the common peroneal nerve. The incision runs superiorly just medial to the short head of the biceps femoris muscle and inferiorly between peroneus longus and gastrocnemius-soleus muscles. (*Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of Mississippi Medical Center, Jackson, MS.*)

Reproduced from Youmans & Winn 8e, Fig. 284.20, p. 2203 — Label when you reproduce it: the skin incision for exposure of the common peroneal nerve — superiorly just medial to the short head of biceps femoris, inferiorly between peroneus longus and the gastrocnemius-soleus. Mark the biceps femoris muscle, the common peroneal nerve and the peroneus longus.

13. Intraoperative decision-making — the nerve action potential rules the operation

- **A recordable NAP across the lesion means neurolysis alone.** In the LSUHSC series, "neuroplasty was performed in patients with recordable NAPs across the injured segment. Of the 121 patients in whom neuroplasty was performed, 107 (88%) recovered useful function" YW p.2139.
- **A flat NAP means resection and repair.** "In patients in whom NAPs were absent, the injured segment was removed and grafted" YW p.2139. iNAP reliably separates an axonotmetic lesion (positive trace) from a neurotmetic one (flat trace), and can be applied 2-3 months after focal injuries and 3-4 months after stretch/contusion or gunshot injuries; a minimum of about 5 cm of exposed nerve is needed for the two electrode sets YW p.2182.

14. Outcomes — quote these numbers

Table 2 · Louisiana State University results of surgery for 278 common peroneal nerve lesions, recovery to BMRC grade 4 or 5 — from Youmans & Winn 8e, Table 284.5, p. 2205.

Procedure	Result	Comment
Neurolysis (positive NAP)	**107/121 = 88%**	Best results in the series
End-to-end suture	**16/19 = 84%**	Short, clean gaps
Graft repair overall	**57/138 = 41%**	Length dominates the result
Graft < 6 cm	**27/36 = 75%**	
Graft 6-12 cm	**24/64 = 38%**	
Graft 13-24 cm	**6/38 = 16%**	Consider tendon transfer instead

- Across the 318 knee-level CPN lesions managed over 32 years the mechanisms were **51% stretch or contusion, 12% laceration, 9% entrapment, 7% compression**, the remainder iatrogenic injuries, tumours and gunshot wounds YW p.2139.
- For proximal (high) peroneal missile injuries the outlook is poor — "only 13.8% of patients with a high peroneal injury achieved a useful recovery with graft repair", whereas peroneal injuries in the lower third of the thigh recovered to BMRC grade 3 or better more than 60% of the time YW p.2203.
- Youmans is blunt about the two outcome measures patients actually care about: **"the ability to ambulate without a dorsiflexion orthosis, and the ability to run"** — and notes these benchmarks are rarely used in published studies YW p.2201.

15. Salvage when the nerve will not recover

- **Posterior tibial tendon transfer** — "In the event of persistent footdrop after surgery, one may consider referral to an orthopedist for TP tendon transfer. This procedure can be highly effective for footdrop caused by CPN injury, particularly in men younger than 30 years of age" YW p.2139. It requires "a strong posterior tibialis muscle with strong inversion", and "partial dorsiflexion recovery adds to the success of a tendon transfer procedure" YW p.2203.
- **Nerve transfer** — motor branches of the tibial nerve (including the soleus branch) have been transferred to the anterior compartment muscles, "with varying efficacy" and "conflicting results have been reported, although nerve transfer remains an intriguing alternative to standard repair of the peroneal nerve" [YW pp. 2202-2203]. Ch. 280 is more cautious still: "It seems that transfer of the posterior tibial tendon is a more reliable modality of reconstructing dorsiflexion in an intractable common peroneal nerve injury" YW p.2172.
- **Intraneural ganglion** — resect and address the source: "transection of this branch and/or resection of the superior tibiofibular joint significantly reduces recurrence rates and improves treatment outcomes" YW p.2138.
- **Permanent orthosis and gait retraining** where reconstruction fails.

16. Complication avoidance and prevention

- **Position every anaesthetised patient with the fibular neck free**; check the gaps in compression stockings; re-inspect after draping because bed-mounted retractors are applied when the legs are no longer visible YW p.2225.
- **Injection technique** — most gluteal injection injuries "result from needle insertion in the inferior medial section of the buttock instead of the superior lateral quadrant"; the sciatic nerve "is injured more than any other peripheral nerve in this manner", and animal work suggests "there is little to gain by immediate surgical maneuvers such as washing the nerve or internal neurolysis" YW p.2199.
- **Counsel weight-loss and postoperative patients** about leg crossing and prolonged squatting.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Foot drop is a sign, not a diagnosis** — the examiner wants a level, from pyramidal tract to deep peroneal nerve YW p.2087.
- **Three muscles crack the case**: tibialis posterior (inversion, L5 but tibial), gluteus medius (L5, superior gluteal) and the short head of biceps femoris (peroneal division above the knee) [YW pp. 2087, 2138].
- **Superficial peroneal SNAP is normal in L5 radiculopathy and abnormal in a CPN lesion** — the single most useful electrodiagnostic discriminator [YW pp. 2106, 2138].
- **The common peroneal nerve is the most frequently injured nerve in the lower limb — nearly 25% of all traumatic peripheral nerve injuries** YW p.2137.
- **Habitual leg crossing is the commonest non-traumatic cause; look for the skin dimple at the fibular neck** YW p.2138.
- **Knee dislocation carries a 25-35% risk of peroneal injury — and always check the distal pulses first** YW p.2202.
- **Suspect an intraneural ganglion when the deep peroneal division is preferentially involved** — the CPN is the nerve most often affected by them YW p.2138.
- **Rule of 3s** — 3 days for sharp lacerations, 3 weeks for blunt lacerations, 3 months for lesions-in-continuity YW p.2176.
- **Positive intraoperative NAP = neurolysis (88% useful recovery); flat NAP = resect and graft (41%)** [YW pp. 2139, 2205].
- **Graft length is destiny**: <6 cm 75%, 6-12 cm 38%, 13-24 cm 16% YW p.2205.
- **Anterior compartment syndrome causing foot drop is a surgical emergency — extensive longitudinal fasciotomy, not observation** YW p.2077.
- **When reconstruction fails, posterior tibial tendon transfer is the reliable answer, especially in men under 30** [YW pp. 2139, 2172].

Pages read for this answer — Youmans & Winn 8e: 232.e4, 2073, 2075, 2076, 2077, 2085, 2086, 2087, 2089, 2090, 2093, 2094, 2095, 2106, 2109, 2120, 2122, 2123, 2126, 2137, 2138, 2139, 2153, 2172, 2175, 2176, 2181, 2182, 2184.e2, 2184.e3, 2184.e4, 2195, 2198, 2199, 2200, 2201, 2202, 2203, 2205, 2217, 2225

a) Different categories of thoracic outlet syndrome.
b) Management of thoracic outlet syndrome.

LONG | DEC 2020 · Paper III · Q6 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 277 *Brachial Plexus Nerve Entrapments and Thoracic Outlet Syndromes* (A.G. Filler), §Subcategorization in the Definition of Thoracic Outlet Syndrome, §Neurogenic, Vascular, and Nonspecific Thoracic Outlet Syndrome, §Brachial Plexus Nerve Entrapment Syndromes, §Diagnostic Imaging in Thoracic Outlet Syndrome, §Image-Guided Injections of the Scalene Muscles and Distal Plexus, pp. 2142-2149 and the online operative sections §Neuroplasty Surgery for Thoracic Outlet Syndromes, §First Rib Resection, §Image Diagnosis and Surgical Outcomes, pp. 2149.e1-2149.e5 (Figs. 277.1-277.13, pp. 2144-2149; eFigs. 277.1-277.3, pp. 2149.e1, 2149.e4). Supplementary: Ch. 272 *Peripheral Nerve Examination, Evaluation, and Biopsy*, §Peripheral Nerve Examination, pp. 2085, 2089; Ch. 276 *Distal Entrapment Syndromes*, §Double Crush Syndrome, pp. 2135, 2141; Ch. 286 *Avoiding Iatrogenic Injury Affecting Nerves*, §Nerve Injuries Associated With Surgical Positioning, p. 2225; Ch. 275 *Imaging for Peripheral Nerve Disorders*, pp. 2119-2121 (Figs. 275.4, 275.8-275.9); Ch. 26 *Positioning for Peripheral Nerve Surgery*, pp. 232.e1-232.e2.

(a) Different categories of thoracic outlet syndrome [3]

1. Fix the terminology first — TOS is an umbrella term, not a disease

- **Youmans opens by warning that the term is deliberately loose:** "The term *thoracic outlet syndrome* (TOS) is used to refer to a wide variety of different neuropathy, neuritis, and entrapment syndromes that affect the brachial plexus as well as its contributory cervical and thoracic spinal nerves … In its most general sense the term covers any nerve in this body region, whereas in its most specific sense it refers only to those nonspinal anatomic elements emerging from the chest within the circle of the first rib" YW p.2142.

- **The umbrella also covers nerves that never enter the plexus** — "the accessory nerve to the extent that it affects the sternocleidomastoid and trapezius muscles, the long thoracic nerve as it affects the serratus anterior muscle, the dorsal scapular nerve as it affects the levator scapulae and rhomboid muscles, and the cervical plexus"; and "various vascular entrapments affecting the subclavian, brachial, and axillary arteries and veins, but also including the jugular vein in those contexts in which venous outflow is obstructed" YW p.2142.
- **What is excluded** — "From a nerve diagnosis point of view, only tumors or significant intrinsic nerve injuries and discontinuities of the brachial plexus are really excluded" YW p.2142.
- **Common aetiological theme** — "their origin is in degenerative or congenital problems, although the effects of moderately severe trauma, such as whiplash injury, are included as well" YW p.2142.

2. The broad division — and why it is no longer sufficient

- **Classically TOS is divided into two broad groupings: neurogenic and vascular** YW p.2142.
  - **Classical neurogenic TOS** — "a specific lower trunk entrapment causes fourth and fifth digit numbness with thenar and hypothenar weakness" YW p.2143.
  - **Vascular TOS** — "an angiographically demonstrable occlusion syndrome affecting the subclavian artery and/or vein is found" YW p.2143.
- **A third historical category — "nonspecific" or "disputed" TOS — is now obsolete.** It was defined by Wilbourn in an expansion of a 1985 lecture to the American Association of Electromyography and Electrodiagnosis; he objected to diagnostic methods "that relied purely on physical examination and in which the diagnosis could not be confirmed by radiography or computed tomographic scanning together with EMG". Youmans replies that "Wilbourn overlooked the limitations of EMG" and that "the use of MRN and confirmatory image-guided injections (neither of which were available prior to Wilbourn's 1985 presentation) have largely eliminated the 'wastebasket' classification of so-called disputed TOS" YW p.2143. The book's Key Concepts state flatly: **"Neurogenic TOS is no longer considered 'disputed,' 'nonspecific,' or 'purported'"** YW p.2142.
- **Why EMG fails here** — "EMG has never been extensively relied on in evaluating patients with possible TOS. This is because it is difficult to apply effectively in the brachial plexus, where the complexity of nerve elements and muscles defies simple needle placement paradigms" YW p.2143.

3. The ten subcategories — this is the classification the examiner wants

Table 1 · The ten subcategories of thoracic outlet syndrome recognised by Youmans & Winn 8e — reproduced in full from Ch. 277, p. 2142, with the defining imaging/clinical feature and the operation each subtype calls for (pp. 2144-2149, 2149.e1-2149.e4).

#	Subcategory	Defining feature	Treatment that fits it
1	**Vascular impingement at the thoracic outlet**	Angiographic subclavian artery/vein occlusion; positive Adson and Roos manoeuvres	Decompression, often first rib resection; vascular reconstruction
2	**Brachial plexus entrapment by proximal fibrous band**	Sharply defined, proximal, focal kink of the plexus on MRN (Fig. 277.2C2)	Supraclavicular neuroplasty and band division
3	**Interscalene brachial plexus entrapment (scalene syndrome)**	Smooth angulation/loss of space between elements at the scalene triangle	Anterior scalenectomy + neuroplasty; scalene block/botulinum/hyaluronidase first
4	**Middle scalene syndrome**	Mesial scapular border pain, long thoracic nerve impingement, winging	Partial middle scalene resection, long thoracic/dorsal scapular neuroplasty
5	**First rib neurological impingement syndrome**	Upward distortion of the plexus as it crosses the first rib (Fig. 277.3B)	First rib resection — "undoubtedly the best treatment for entrapment of the midplexus between the first rib and clavicle" YW p.2149.e1

6	**Cervical rib syndromes**	Bulbous pseudoarticulation on AP lordotic chest radiograph (Figs. 277.6, 277.7)	Resection of the cervical rib ± first rib
7	**Post-clavicle fracture syndromes**	Callus/malunion compressing the plexus	Neurolysis, callus resection, fracture fixation
8	**Gilliatt-Sumner hand**	Painless pure motor hand-intrinsic wasting, no sensory findings; hyperintense swollen lower trunk **without** mechanical deformation (Fig. 277.11)	**Non-surgical** — "surgical treatment is unlikely to be effective, and an inflammatory or vascular etiology is suspected" YW p.2148
9	**Distal plexus / axillary nerve entrapment**	Abnormal course, calibre or intensity of distal plexus; Tinel sign in the axilla; shoulder pain with deltoid weakness mistaken for rotator cuff tear	Transaxillary neuroplasty ± axillary neuroplasty
10	**Diffuse brachial plexus neuritis / neuropathy / fibrosis**	Hyperintensity without increase in calibre or distortion of course (Fig. 277.11D)	Medical — immunosuppression (montelukast, cyclosporine, etanercept) where autoimmune neuritis is proven YW p.2148

- **Each of the ten "has its own distinct presentation, physical examination findings, test results, treatment strategy, and outcomes, although some overlap may exist"** YW p.2142.
- **The practical value of the subclassification is operative**: "it permits the surgical treatment of TOS with more limited operations directed at different individual pathologies. Operations such as supraclavicular scalenectomy or transaxillary neuroplasty are less invasive and may have lower surgical risks than transaxillary first rib resection … MRN makes it possible to reserve the use of first rib resection for the small number of patients in whom the less invasive operations are not appropriate" YW p.2148.

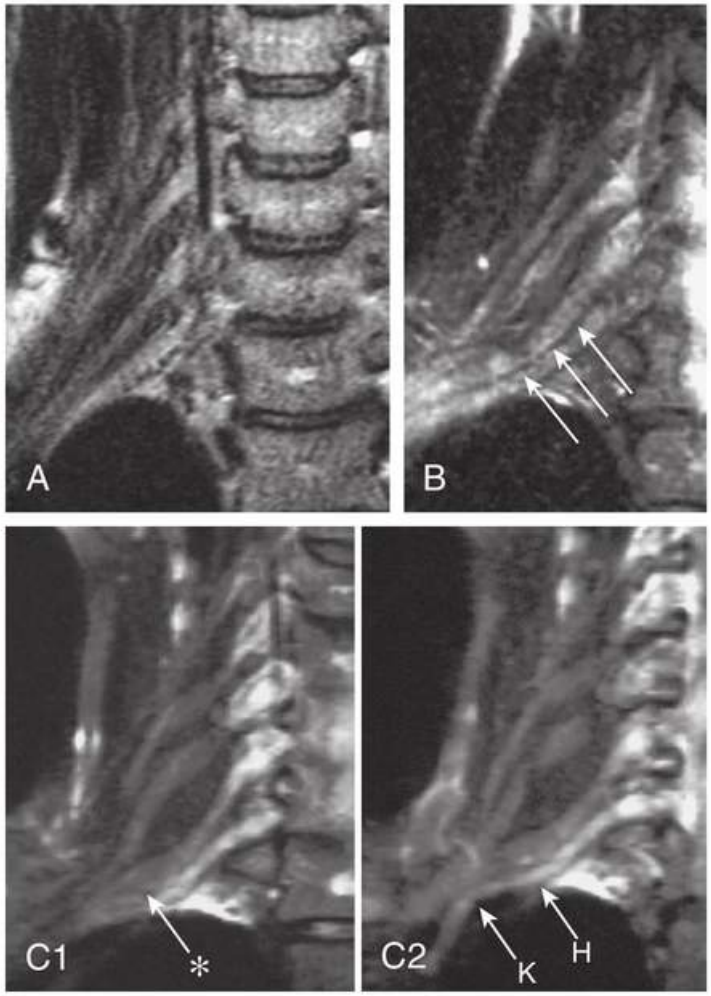


Figure 277.2. Differentiation of thoracic outlet syndrome (TOS) into categories is often well supported by imaging characteristics. (A) In the normal plexus, the cervical spinal nerves and trunks of the brachial plexus follow a straight trajectory with even spacing. (B) Scalene syndrome is demonstrated by a gentle deformation of the course of the nerve elements and loss of space between them *(arrows).* In patients with pain only, there is usually no nerve hyperintensity. (C1) Distortion of the shape of the C7 element (*) associated with a severe TOS case. (C2) A more anterior image plane in the same patient showing both a sharp kink *(K)* in the course of the lower trunk associated with a fibrous band and nerve hyperintensity *(H)* consistent with lower trunk motor symptoms. (*From Filler AG. Applications of MRI and other imaging techniques for studying peripheral nerve and muscle. In: Brown W, Bolton C, Aminoff M, eds. Neuromuscular Function and Disease: Basic, Clinical, and Electrodiagnostic Aspects. Vol. 2. WB Saunders; 2002.*)

Reproduced from Youmans & Winn 8e, Fig. 277.2, p. 2144 — Label when you reproduce it: (A) normal plexus — cervical spinal nerves and trunks in a straight trajectory with even spacing; (B) scalene syndrome — gentle deformation of the course and loss of space between elements (arrows), with no hyperintensity when pain is the only symptom; (C1) severe TOS with distortion of the shape of C7; (C2) a sharp kink (K) in the lower trunk from a fibrous band, plus nerve hyperintensity (H) matching lower-trunk motor symptoms. This single figure is the imaging classification of TOS.

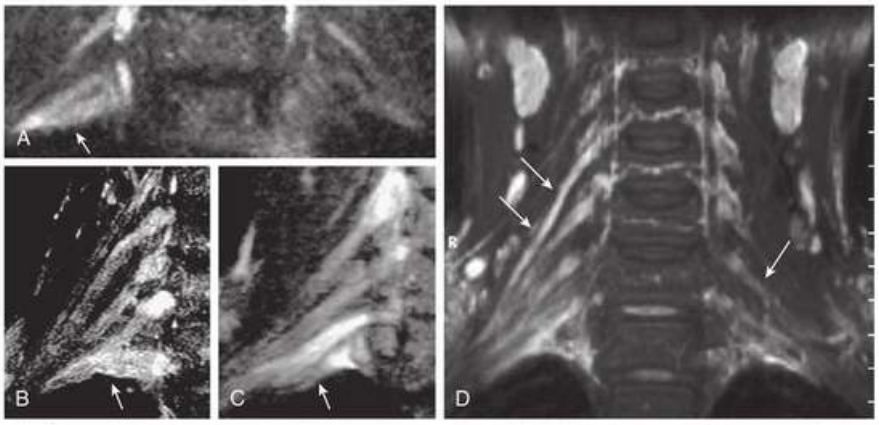


Figure 277.11. (A–C) Image findings in patients with painless pure motor weakness of hand intrinsic muscles with no sensory findings (Gilliatt-Sumner hand). There is hyperintensity and swelling in the elements of the lower trunk without mechanical deformation or other evidence of mechanical entrapment *(arrows)*. Surgical treatment is unlikely to be effective, and an inflammatory or vascular etiology is suspected. (D) Diffuse plexitis of unclear origin in the right brachial plexus. Note hyperintensity without any increase in caliber or any distortion in the course of the brachial plexus elements. *Arrows* at right plexus indicate hyperintense C5 spinal nerve. *Arrow* in left plexus indicates normal-appearing C7 spinal nerve. Management is generally nonsurgical, and physical therapy may not be helpful. *(From Filler AG. Applications of MRI and other imaging techniques for studying peripheral nerve and muscle. In: Brown W, Bolton C, Aminoff M, eds. Neuromuscular Function and Disease: Basic, Clinical, and Electrodiagnostic Aspects. Vol. 2. WB Saunders; 2002.)*

Reproduced from Youmans & Winn 8e, Fig. 277.1, p. 2144 — Label when you reproduce it: (A) the normal plexus on coronal MR neurography — smooth linear elements; (B) nerve-perpendicular cross-sectional views spatially correlated with the coronal image, with C5, C7, C8 and T1 identified by the small arrows and C6 marked by the cross. Explain that calibre and image intensity are followed element by element.

(b) Management of thoracic outlet syndrome [7]

4. Step 1 — a two-part clinical examination, because no single test covers all categories

- **"Aside from magnetic resonance neurography (MRN) of the brachial plexus, there is no single clinical test applicable to any and all categories of TOS"** YW p.2142.
- **The neurological examination** — sensory modalities (pinprick, light touch, temperature, vibration) mapped both dermatomally and by peripheral nerve; strength not only of biceps, triceps and grip but **"it is imperative to conduct a hand intrinsic muscle examination"** — lumbricals, digital interosseous abductors and adductors, first-to-fifth opposition, first-to-second pincer grip, and inspection for thenar or hypothenar atrophy YW p.2143.
- **Shoulder girdle testing in segments** — internal and external rotation with the elbow at the side, abduction tested separately through 0-30 degrees (supraspinatus) and 30-90 degrees (deltoid), then scapular rotators to 180 degrees, with protraction, retraction, abduction and adduction at each station; then biceps, triceps and brachioradialis reflexes compared immediately with patellar and Achilles reflexes YW p.2143.
- **The peripheral nerve examination** — systematic percussion of the ulnar nerve at Guyon canal and the cubital tunnel, the median nerve at the wrist with and without hyperextension, the recurrent median nerve at the thenar eminence, the radial, posterior interosseous, median and ulnar nerves at and above the elbow, the quadrangular space within the axilla, the deep surface of pectoralis from within the axilla, the distal plexus through pectoralis from an anterior infraclavicular contact point, the clavicle itself, and finally **distinct percussion of the anterior scalene, middle scalene and levator scapulae muscles** [YW pp. 2143-2144].
- **The diagnostic pattern to look for**: "In patients with fourth and fifth digit pain and intrinsic hand muscle weakness, if there is no sensitivity or Tinel sign elicited at the Guyon canal or the cubital tunnel but there is pain at the anterior scalene muscle with Tinel sign on percussion radiating to the fourth and fifth digits, then the diagnosis of TOS becomes likely" YW p.2144.
- **The logic that separates TOS from ulnar and median entrapment** — "the ulnar nerve … controls hand intrinsic muscles with C8 innervation but excludes the thenar eminence. However, the median nerve … conducts C6 sensory fibers to the first and second digits and C7 sensory fibers to the third digit along with T1 motor innervation to the thenar eminence. Therefore a patient with motor abnormalities affecting both thenar and hypothenar eminences but with sensory abnormality and pain into only the fourth and fifth digits is likely to have entrapment of the lower trunk of the

brachial plexus at the scalene triangle, which affects C8 and T1 only" YW p.2143.

- **Vascular manoeuvres** — "checking the patient's pulse with the arm in a resting position, then checking a second time with the patient looking away from the arm being tested and with that arm elevated overhead and retracted posteriorly. If the pulse drops out during this action, there is a positive **Adson maneuver**. For the **Roos test** the arm is positioned similarly, but the patient is instructed to rapidly and repetitively open and close the hand; rapid tiring signifies vascular compromise" YW p.2144. Ch. 272 adds that these tests "can reveal vascular compression when the arm is elevated, but may not reliably assess brachial plexus impingement" YW p.2089.
- **Winging is a localiser, and the type of winging names the nerve**:
  - **Long thoracic nerve (serratus anterior)** — with the patient facing a wall, hands on the wall, pushing back and then shrugging, "the scapula becomes displaced medially and superiorly and the mesial border moves posteriorly away from the body wall". **"This sign should be tested for in all patients being evaluated for TOS"** YW p.2144.
  - **Spinal accessory nerve (trapezius)** — "the superior angle of the scapula shifts laterally with arm abduction and external rotation against resistance" YW p.2144.
  - **Dorsal scapular nerve (rhomboids)** — "the inferior angle of the scapula shifting laterally on arm extension from a position of full flexion" YW p.2144.
- **The axillary nerve syndrome** — "pain and weakness affecting the deltoid muscle in a patient who does not have cervical spine findings of ipsilateral C4-C5 pathology affecting the C5 root"; the nerve "turns sharply in a posterior direction, passing through the quadrangular space (teres minor above, teres major below, humerus lateral, and long head of triceps medial) in the posterior wall of the axilla, where palpation should identify a painful nerve element" YW p.2144 . These patients "often present with failed 'rotator cuff' surgery undertaken for shoulder pain that has been misdiagnosed" YW p.2146.

5. Step 2 — imaging: MR neurography is the central investigation

- **"The advent of widespread use of MRN has revolutionized the imaging diagnosis of TOS"** YW p.2144. The normal plexus appears as "smoothly proceeding linear elements, appearing uniform in caliber and intensity in coronal and in nerve-perpendicular views" [YW pp. 2144-2145].
- **What counts as abnormal** — "any evidence of distortion of the course, caliber, or image intensity of the brachial plexus at the scalene triangle" YW p.2145.
- **Pattern recognition by subtype**:
  - Hypertrophied/spastic scalene with no band → smooth but unmistakable distortion of course YW p.2146.
  - Fibrous band → sharply defined focal kinking YW p.2145.
  - Circumferential post-traumatic fibrosis → decreased calibre with increased intensity (C8 in Fig. 277.8A), "more likely to respond to supraclavicular neuroplasty than to first rib resection" YW p.2146.
  - First rib impingement → upward distortion of the plexus as it crosses the rib — these patients "are often best managed with first rib resection when conservative management approaches fail" YW p.2146.
  - Post-operative midplexus fibrosis, or an incompletely resected proximal rib remnant, explains failure after first rib resection [YW pp. 2146-2147].
  - Gilliatt-Sumner hand and diffuse plexitis → bright, swollen elements with **no** mechanical deformation; surgery is unlikely to help YW p.2148.
- **Plain radiography still has one job** — "A cervical rib is often missed on MRI, so an anteroposterior lordotic chest radiograph is an important part of the diagnostic evaluation if there is any reason to suspect a cervical rib" YW p.2146.
- **A normal MRN is a positive finding** — "MRN is also helpful when it demonstrates a completely normal course and caliber for all nerve elements that are under suspicion. In the presence of these findings, it is possible to take a firm stance against surgical treatment" YW p.2148.

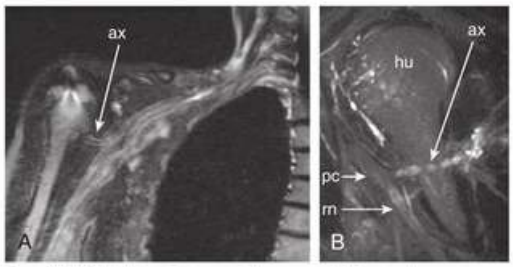


Figure 277.5. (A) Hyperintense axillary nerve *(ax)* in a performer who developed severe axillary and deltoid pain associated with choreographic work. Adhesion of the distal plexus may result in axillary nerve irritation because of differential motion at the quadrangular space through which it passes after a short distance of travel. Patients often present with failed "rotator cuff" surgery undertaken for shoulder pain that has been misdiagnosed. The axillary nerve syndrome presents with pain in the axillary nerve distribution over the shoulder joint and deltoid weakness. (B) Shoulder of a 17-year-old tennis instructor with shoulder pain and difficulty positioning his arm for his serve. The axillary nerve *(ax)* is seen arching out across the neck of the humerus *(hu)* after branching off the posterior cord *(pc)* of the brachial plexus at the origin of the radial nerve *(rn)*. The beaded appearance of the axillary nerve in this three-dimensional projection image is an artifact of the slice spacing. (*From Filler AG. Applications of MRI and other imaging techniques for studying peripheral nerve and muscle. In: Brown W, Bolton C, Aminoff M, eds. Neuromuscular Function and Disease: Basic, Clinical, and Electrodiagnostic Aspects. Vol. 2. WB Saunders; 2002.*)

Fig. 277.2C2). Another type of local fibrosis effect after traumatic injury to the scalene muscles is a circumferential fibrosis that causes constrictive compression of one of the nerve elements (Fig. 277.8A). This type of pathology is more likely to respond to supraclavicular neuroplasty than to first rib resection.

In the setting of a hypertrophied scalene muscle with no fibrous band, the distortion of the course of the plexus is

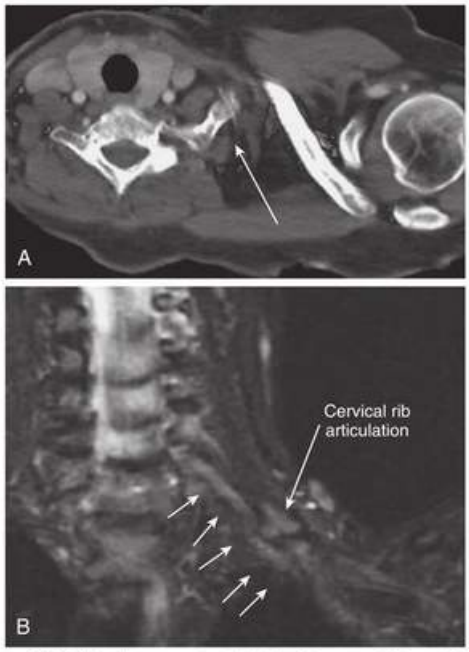


Figure 277.6. A bulbous pseudoarticulation between a C7 cervical rib and the first thoracic rib (A) caused a growing "mass" that impinged progressively on the plexus (B). This mass is similar to what was described in the first published account of a surgical treatment for a brachial plexus entrapment appearing in *The Lancet* in 1861.[10] *Arrow* in (A) points to proximal part of cervical rib. *Arrows* in (B) identify the course of the middle trunk of the brachial plexus as it is impinged on and distorted by the cervical rib articulation callus.

Reproduced from Youmans & Winn 8e, Fig. 277.6, p. 2146 — Label when you reproduce it: (A) the bulbous pseudoarticulation between a C7 cervical rib and the first thoracic rib, with the arrow on the proximal cervical rib; (B) the growing "mass" of articulation callus progressively impinging on and distorting the middle trunk (arrows). Note in your caption that this is the lesion described in the first published account of surgery for brachial plexus entrapment, in The Lancet in 1861.

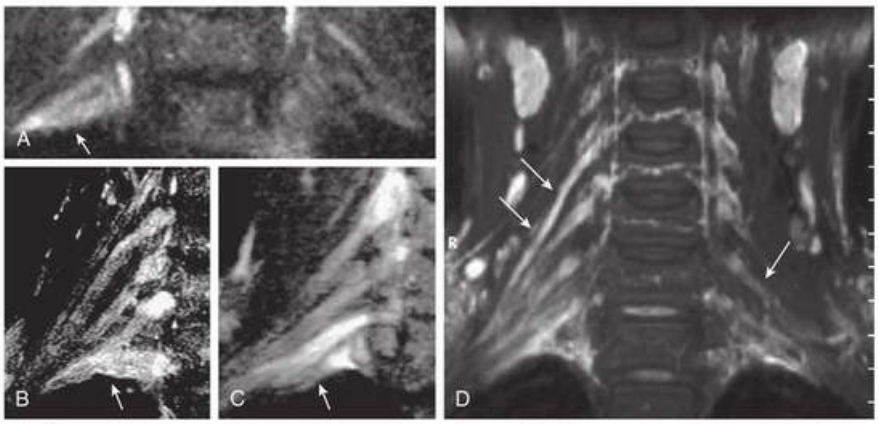


Figure 277.11. (A–C) Image findings in patients with painless pure motor weakness of hand intrinsic muscles with no sensory findings (Gilliatt-Sumner hand). There is hyperintensity and swelling in the elements of the lower trunk without mechanical deformation or other evidence of mechanical entrapment *(arrows)*. Surgical treatment is unlikely to be effective, and an inflammatory or vascular etiology is suspected. (D) Diffuse plexitis of unclear origin in the right brachial plexus. Note hyperintensity without any increase in caliber or any distortion in the course of the brachial plexus elements. *Arrows* at right plexus indicate hyperintense C5 spinal nerve. *Arrow* in left plexus indicates normal-appearing C7 spinal nerve. Management is generally nonsurgical, and physical therapy may not be helpful. (*From Filler AG. Applications of MRI and other imaging techniques for studying peripheral nerve and muscle. In: Brown W, Bolton C, Aminoff M, eds. Neuromuscular Function and Disease: Basic, Clinical, and Electrodiagnostic Aspects. Vol. 2. WB Saunders; 2002.*)

*Reproduced from Youmans & Winn 8e, Fig. 277.11, p. 2148 — Label when you reproduce it: (A-C) the Gilliatt-Sumner hand — hyperintensity and swelling of the lower trunk elements with **no** mechanical deformation (arrows), in patients with painless pure motor hand-intrinsic weakness and no sensory findings; (D) diffuse plexitis of the right brachial plexus with hyperintensity but normal calibre and course (compare the normal C7 on the left). Say in the caption that both of these are managed non-surgically.*

6. Step 3 — image-guided injection: diagnostic test and definitive treatment in one

- **"Among the most common tests performed to confirm a scalene syndrome is an image-guided anesthetic**

injection of the anterior scalene muscle"; "image-guided injections serve as critically important modern confirmatory tests and establish causality" [YW pp. 2143, 2148].

- **Why image guidance is mandatory** — "the anterior scalene muscle is a round structure, about 1 cm in diameter, progressing at a complex angle anteriorly and laterally along its length of about 7 cm. It is immediately posterior to the internal jugular vein and carotid artery, but also immediately anterior to the brachial plexus" YW p.2148.
- **The three leaks and what each causes**: "An inadvertent leak of anesthetic anteriorly blocks the phrenic nerve; medial leakage blocks the stellate and superior cervical ganglia, causing a temporary Horner syndrome; and posterior leakage causes a dense brachial plexus block" YW p.2148.
- **Interpretation** — "If the anesthetic injected is limited to the scalene muscle, then this will have no effect on cervical spinal pathology. However, it can completely relieve the pain symptoms of a scalene syndrome in the short term, often resulting in permanent relief without any requirement for surgery" YW p.2148.
- **Therapeutic agents and doses to quote**:
  - **Botulinum toxin 50-100 units in 2 mL saline** — "can lead to several months of muscle relaxation during which the muscle may heal any irritative lesions that are driving the spasm, so that persistent relief results" YW p.2148.
  - **Hyaluronidase, e.g. 150 units of Hylenex human recombinant hyaluronidase** — twofold role: "it is capable of dissolving hyaluronate polymer scarring that commonly entraps nerves, and it is also capable of improving the distribution of an injected medication beyond the immediate site of introduction" [YW pp. 2148-2149].
  - **Bupivacaine 5 mL at 0.5%** — "Bupivacaine has some mild myotoxicity, so there is an effect similar to that of botulinum toxin that can lead to muscle relaxation persisting beyond the duration of the usual anesthetic effect on nerves" YW p.2149.
  - **Depot steroid, e.g. betamethasone 0.5 mL at 6 mg/mL** YW p.2149.
- **Guidance modality** — anterior scalene injection can be done reliably with ultrasound or CT guidance; middle scalene, levator scapulae, distal plexus and axillary nerve injections "are only reported with open MRI guidance" YW p.2148.
- **The headline claim of the chapter — "Many cases of severe TOS can be resolved permanently by injections with hyaluronidase enzyme and botulinum toxin, so surgery is often unnecessary"** YW p.2142.

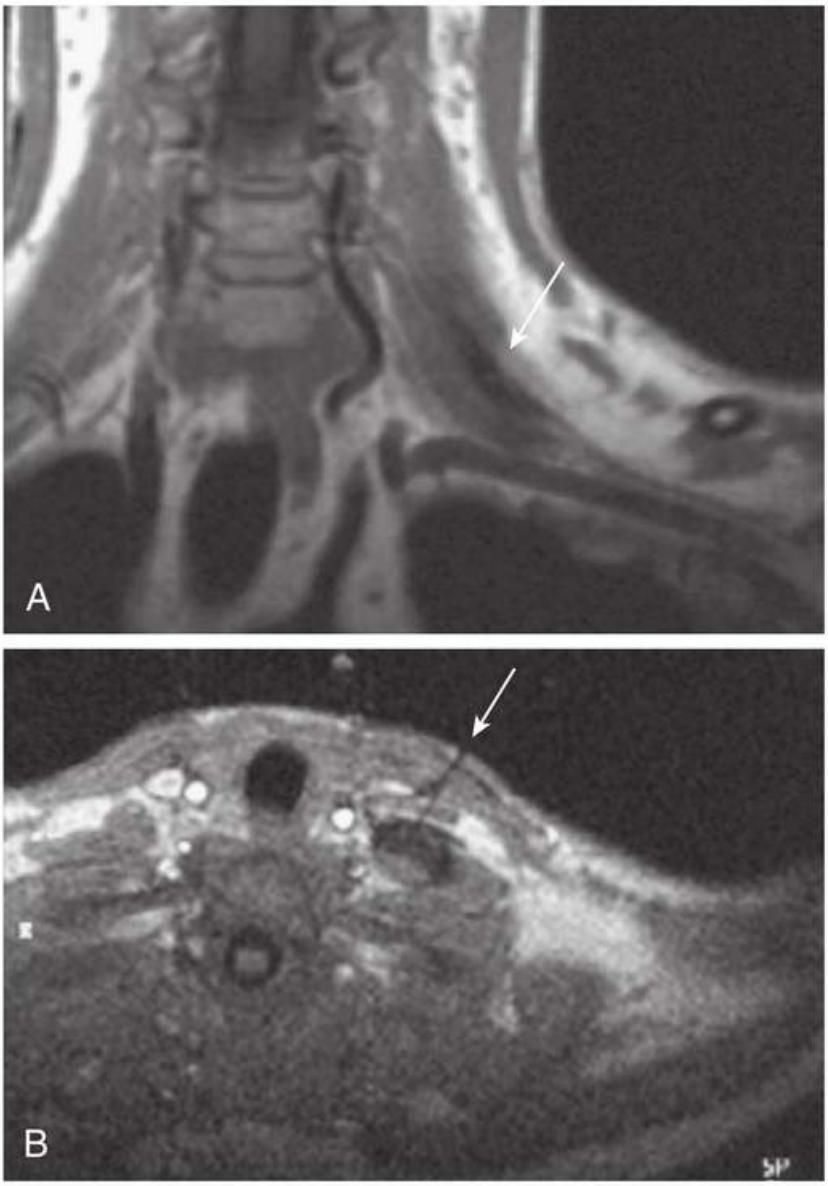


Figure 277.12. Open MRI–guided injection of the anterior scalene muscle. (A) In the coronal image, the *arrow* indicates a darkened area caused by the injectate within the anterior scalene muscle. (B) In the axial image, the titanium needle is seen passing into the anterior scalene muscle. The injectate has expanded the muscle; however, the failure of injectate to flow into the more posterior portions of the muscle suggests fibrosis within the muscle. (*From Filler AG. MR neurography and brachial plexus neurolysis in the management of thoracic outlet syndromes. In: Yao JST, Pearce WH, eds. Advances in Vascular Surgery. Precept Press; 2002:499–523*)

Reproduced from Youmans & Winn 8e, Fig. 277.12, p. 2149 — Label when you reproduce it: open MRI-guided injection of the anterior scalene muscle — (A) the coronal image with the darkened area of injectate within the anterior scalene (arrow); (B) the axial image with the titanium needle entering the muscle. Note in the caption that failure of the injectate to spread posteriorly indicates intramuscular fibrosis.

7. Step 4 — operative treatment: pick the operation from the subtype

- **Two neuroplasty approaches** — "The supraclavicular approach provides good access to all neurological components proximal to the clavicle, whereas the transaxillary approach is useful for entrapments occurring between the clavicle

and the point of entrance of the neurovascular bundle into the arm at the axilla" YW p.2149.e1.

- **What makes TOS surgery different** — "removal of muscle is often the key to resolution of the syndrome, as opposed to just neuroplasty (nerve release) or work on bone or vessels" YW p.2149.e1.
- **Monitoring** — intraoperative EMG electrodes in deltoid, triceps, biceps, serratus anterior (at the medial scapular border), thenar and hypothenar muscles, often also trapezius, levator scapulae, rhomboids, forearm flexors and extensors; **"An electrode for the diaphragm is mandatory because it is essential to be able to locate the phrenic nerve blindly during the approach"**; the arm is draped in a clear fluoroscopy drape so movement can be inspected YW p.2149.e1.

7.1 Supraclavicular scalenectomy and neuroplasty — operative steps in order

1. **Incision** parallel to and about 2 cm above the clavicle, starting 2 cm from the midline, extending laterally no more than 4-5 cm — going further laterally cuts supraclavicular cutaneous branches and causes chest numbness [YW pp. 2149.e1-2149.e2].
2. **Divide platysma**, develop the plane between the sternal and clavicular heads of sternocleidomastoid, sweep omohyoid upward, place blunt-tipped hinged Weitlaner or a Shadow-Line retractor YW p.2149.e2.
3. **Mobilise the scalene fat pad** off the jugular vein; the medial blade protects the internal jugular vein, the inferior blade the chylous and lymphatic structures, the superior blade the nerve to omohyoid YW p.2149.e2.
4. **Find the phrenic nerve by stimulation before you see it**, on the anterior surface of the anterior scalene. Chyle-carrying vessels (the thoracic duct on the left, the right lymphatic duct on the right) must be coagulated and packed with Surgicel and fibrin-soaked Gelfoam if breached — "The thoracic duct can carry more than 3 L of fluid per day", and an unrecognised leak may require re-exploration or chemical pleurodesis YW p.2149.e2.
5. **Identify the upper trunk** just superficial and lateral to the anterior scalene; if shoulder pain is prominent, also expose the suprascapular nerve and the distal accessory nerve YW p.2149.e2.
6. **Bring the subclavian artery into view** at both borders of the anterior scalene. Youmans is explicit about the disaster to prepare for: **"The most catastrophic event … would be a laceration of the subclavian artery with bleeding into the chest"** — mitigate with cross-matched blood in the bank, a large-bore intravenous line, and medium/small **Satinsky or Cooley vascular clamps on the instrument table during all thoracic outlet operations** YW p.2149.e2.
7. **Sling the anterior scalene** with a 0 silk tie passed between the phrenic nerve and the muscle; infiltrate bupivacaine **without epinephrine** (epinephrine constricts the small vessels feeding the nerve and "must be scrupulously avoided") YW p.2149.e2.
8. **Resect — do not simply cut — the anterior scalene.** "If the anterior scalene muscle is cut in a single straight line, the ends will retract … However, there is a significant risk of reconnection of the two cut ends over time … To minimize this particular recurrence risk, the surgeon should plan to completely remove a portion of the anterior scalene muscle that is nearly 2 cm in length" [YW pp. 2149.e2-2149.e3]. Each cut is made in small steps with bipolar coagulation and Metzenbaum scissors, guarding the phrenic nerve and, at the distal cut, the subclavian artery and a crossing transverse cervical artery.
9. **Expose the lower trunk, C8 and T1** deep and medial to the middle trunk: **"It is the lower trunk that is most frequently involved in the symptoms of TOS … A simple resection of the anterior scalene muscle should not be expected to improve symptoms of lower trunk involvement in TOS"** YW p.2149.e3.
10. **Partial middle scalene resection only** — "resection of both the anterior and middle scalene muscle will lead to some depression of the first rib and midshoulder region that will actually increase downward tension on the brachial plexus"; preserve the portion posterior and medial to the long thoracic and dorsal scapular contributions YW p.2149.e3.
11. **Neuroplasty** with DeBakey forceps on the adhesion and a Crile/tonsil clamp parallel to the nerve to pry adhesions open without pressure on the nerve; follow elements up to the spinal foramina and distally to the clavicle. Add accessory-nerve, long thoracic and dorsal scapular neuroplasty when the clinical picture demands YW p.2149.e3.
12. **Resect any enlarged cervical transverse process, cervical rib, or first rib remnant** at this point YW p.2149.e3.
13. **Close** — Valsalva to test for pneumothorax, restimulate all nerves including the phrenic, lay **Seprafilm adhesiolytic sheets** along all dissected nerve surfaces, reapproximate the scalene fat pad to the jugular vein fascia (the fat pad is a natural anti-adhesion barrier), then platysma and a subcuticular cosmetic closure. **Heavy lifting deferred 3 months**

YW p.2149.e3.

7.2 Transaxillary neuroplasty of the distal plexus and axillary nerve

- 3 cm incision at the **apex** of the axilla, higher than the incision used for first rib resection; supine or lateral decubitus; identify the neurovascular bundle by palpation and stimulation; an Omni-Flex renal-vein blade lifts the pectoral mass progressively; open the sheath and separate elements, freeing adhesions up to and just past the clavicle; identify the axillary nerve as it leaves the radial nerve into the quadrangular space and release it proximally; coagulate and divide the sharp fibrous bands that run anterior-to-posterior beneath the plexus; release pectoral adhesions; irrigate, lay adhesiolytic material, close [YW pp. 2149.e3-2149.e4].
- **Pectoralis minor resection** is advocated by some for distal plexus entrapment, but "axillary neuroplasty without the muscle resection appears to be effective in most of these patients", and no formal trial compares them YW p.2147.

7.3 First rib resection — reserve it, but know it

- **Best indication** — "First rib resection is undoubtedly the best treatment for entrapment of the midplexus between the first rib and clavicle" YW p.2149.e1.
- **Transaxillary technique** (most surgeons) with the arm abducted 90-180 degrees: incision below the axillary hairline; protect the brachial branches of the first intercostal nerve; subperiosteal rib stripping separates the rib from pleura, nerve and vessels; disconnect the anterior scalene, cut a small rib segment distally at that point, dissect posteriorly to release the middle scalene, resect the distal rib to the costochondral joint, then, after mobilising and protecting C8 and T1, remove the remaining rib back to the costovertebral joint so the rib is completely removed YW p.2149.e4.
- **Risks, verbatim** — "This operation is fraught with significant risks of major morbidities: pneumothorax is common, and injuries to brachial plexus components, major vessels, and sympathetic ganglia are additional concerns." Other reported complications of rib resection include "major nerve laceration, lung puncture, chyle duct leakage, and worsening of the condition from incomplete bone resection", as well as high rates of early recurrence [YW pp. 2149.e1, 2149.e4].
- **Alternatives** — supraclavicular first rib resection; endoscopic assistance ("not been widely adopted, but may play an important role in the future"); **transthoracic robotic-assisted first rib resection** as "a new methodology that may gain in importance going forward"; and **Kline's posterior subscapular approach** in the prone position through trapezius and rhomboids, which gives good access to C8 and T1 near their foramina but "should be reserved for individual complex reoperative cases in which severe fibrosis has been found to make the anterior approach ineffective" and cannot reach the anterior rib [YW pp. 2149.e4-2149.e5].
- **Does adding the rib help?** — "Particularly when a supraclavicular approach is used with scalenectomy, the incorporation of first rib resection into the operation does not seem to improve outcomes" YW p.2149.e1.

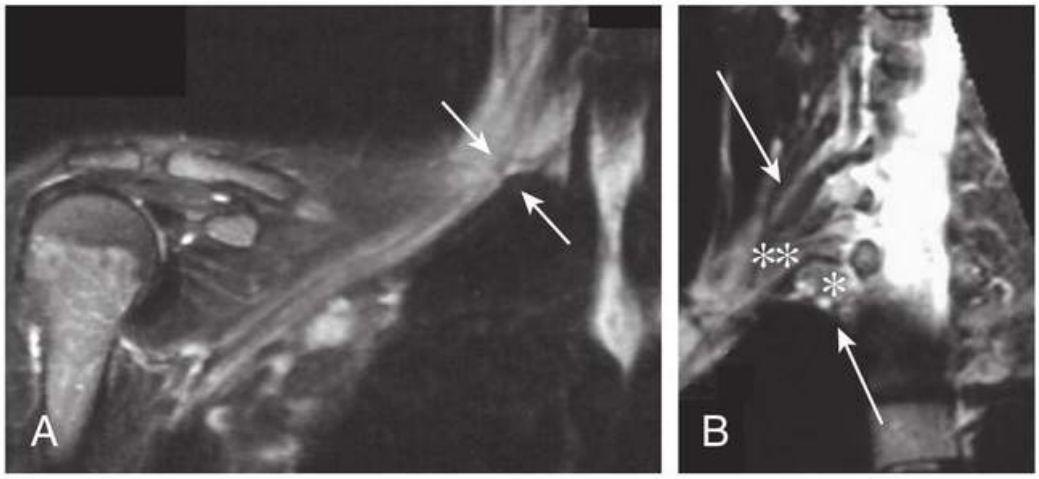


Figure 277.9. Impingement of brachial plexus by first rib remnant. This patient experienced a severe exacerbation of lower trunk symptoms after a first rib resection. (A) Coronal image demonstrates a sharp kink in the plexus over the elevated cupola of the right lung. (B) Oblique reformatted image demonstrates the proximal fragment of the rib in contact with the plexus element (*, the rib remnant; **, focal impingement in C8 root). The rib remnant was then resected via a supraclavicular approach, relieving the patient's symptoms.

Reproduced from Youmans & Winn 8e, Fig. 277.9, p. 2147 — Label when you reproduce it: impingement of the brachial plexus by a first rib remnant after previous first rib resection — (A) coronal image showing a sharp kink in the plexus over the elevated cupola of the right lung; (B) oblique reformat showing the proximal rib fragment (*) in contact with the plexus and focal impingement of the C8 root (**). Note that resecting the remnant via a supraclavicular approach relieved the symptoms.

8. Outcomes — the numbers to quote

- **Filler's imaging-directed series of 154 patients imaged**: 40% scalene syndrome, 23% distal plexus entrapment, 16% mild abnormalities insufficient to justify surgery, 5% no abnormality, 4% significant nerve trauma, 6% nerve tumours YW p.2149.e5.
- **77 patients went to surgery (97 primary operations, 9 bilateral, 11 with both proximal and distal pathology)**: supraclavicular recurrence **15%**, transaxillary recurrence **12%**; "Excellent or good outcomes occurred in 85% of cases for both operations at 3 months, but this dropped to 70% over a period of 6 months as recurrences developed. Only one recurrence took place at an interval greater than 6 months" YW p.2149.e5.
- **Seprafilm and RSD** — "for patients who underwent routine neuroplasty, who did not have RSD or other preoperative complicating conditions, and in whom Seprafilm was used, the recurrence rate was below 5%"; "the presence of RSD clearly increases the risk of recurrence". Reoperation for recurrence salvaged half, reducing the overall long-term recurrence rate to **7.5%** YW p.2149.e5.
- **Comparative trials** — a randomised comparison of first rib resection versus supraclavicular scalene surgery in 50 patients favoured first rib resection (75% versus 48% good to excellent), "however, that study has been criticized because the surgeons did not resect the anterior scalene muscle but merely cut it" — an approach long known to cause recurrence. Where scalenectomy was actually performed, prospective series achieved **70% good to excellent long-term outcome**, and Sanders' review found four reports of **63% to 80%** good to excellent with scalenectomy alone. Glynn found no difference between rib resection and scalenectomy YW p.2149.e5.
- **Cochrane and the nonspecific-TOS literature** — reviews emphasise "limitations arising from the nonuniformity of the diagnosis"; Landry found no difference between surgery and non-surgical treatment over 4 years in *nonspecific*

TOS, but Youmans notes that "if the outcomes are comparable but the surgical improvements happen more quickly, then an advantage of surgery can be found" YW p.2149.e5.

- **The chapter's own conclusion** — "The use of neuroplasty surgery to treat TOS subtypes is an effective alternative to first rib resection … Recurrence rates are low overall and should not be considered as a reason to avoid neuroplasty surgery" YW p.2149.

9. Traps, associations and complication avoidance

- **Double crush** — TOS coexisting with carpal tunnel syndrome is one of the classic double-crush combinations, along with cervical radiculopathy plus CTS and cubital tunnel plus Guyon canal syndrome; the proximal lesion "renders the nerve susceptible to distal or proximal compression" through impaired axonal flow, ischaemia and altered nerve elasticity YW p.2141.
- **Do not miss TOS before spine surgery.** "Shoulder traction applied during cervical spine surgery for radiographic optimization can lead to treatable postoperative arm weakness in patients with preexisting undiagnosed TOS" YW p.2142 . Youmans records a patient who woke with near-complete bilateral arm paralysis after lower cervical spine surgery with taped shoulders; foraminotomy failed, all imaging was normal, electrodiagnostics at 4 weeks confirmed extensive bilateral neuropathy, and **scalenectomy resolved the problem with rapid recovery despite a delay of more than 3 months**. In another patient, undiagnosed TOS plus park-bench positioning for suboccipital craniectomy produced permanent arm paralysis YW p.2225.
- **Coexistent hypothenar or first dorsal interosseous atrophy in a patient being worked up for carpal tunnel syndrome "may signify compression at the thoracic outlet or an ulnar entrapment neuropathy"** YW p.2129.
- **Thorough TOS and C8 assessment is mandatory before operating on a presumed cubital tunnel syndrome**, because both mimic ulnar neuropathy YW p.2135.
- **Autoimmune neuritis** — where diffuse plexitis is suspected "a full immunologic work-up should be carried out", and montelukast, cyclosporine or etanercept may be required YW p.2148.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **TOS is ten diagnoses, not one** — memorise the list: vascular; proximal fibrous band; interscalene; middle scalene; first rib; cervical rib; post-clavicle fracture; Gilliatt-Sumner hand; distal plexus/axillary; diffuse plexitis YW p.2142.
- **Classical neurogenic TOS = lower trunk = C8/T1 = fourth and fifth digit pain with BOTH thenar and hypothenar weakness.** Thenar involvement with only ulnar-side sensory loss is the giveaway YW p.2143.
- **"Disputed TOS" is dead** — MRN and image-guided scalene injection have replaced the wastebasket [YW pp. 2142-2143].
- **EMG is a poor tool in the plexus** — do not let a normal EMG exclude the diagnosis YW p.2143.
- **Always get an AP lordotic chest radiograph** — a cervical rib is often missed on MRI YW p.2146.
- **Test for scapular winging in every TOS patient**, and name the nerve by the type of winging YW p.2144.
- **Gilliatt-Sumner hand = bright swollen lower trunk with NO deformation = do not operate** YW p.2148.
- **The anterior scalene must be resected over ~2 cm, not simply divided**, or it re-forms as a hard fibrous band and the syndrome recurs YW p.2149.e3.
- **Resecting the anterior scalene alone does not treat lower-trunk symptoms** — the lower trunk must be separately exposed and released YW p.2149.e3.
- **A diaphragm EMG electrode is mandatory**, and epinephrine must never be added to the local anaesthetic near the plexus [YW pp. 2149.e1-2149.e2].
- **Have Satinsky or Cooley clamps on the table for every thoracic outlet operation** — subclavian artery laceration is the catastrophe to plan for YW p.2149.e2.
- **Botulinum toxin 50-100 units plus hyaluronidase 150 units can cure the syndrome without surgery** [YW pp. 2142, 2148-2149].
- **Never tape the shoulders down for a cervical radiograph in a patient who might have TOS** [YW pp. 2142, 2225].

Pages read for this answer — Youmans & Winn 8e: 232.e1, 232.e2, 2085, 2089, 2119, 2120, 2121, 2129, 2135, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2149.e1, 2149.e2, 2149.e3, 2149.e4, 2149.e5, 2225

a) Carpal tunnel syndrome. [5]
b) Management of hyperhidrosis. [5]

LONG | JUN 2021 · Paper II · Q6 | 10 marks

Also asked as: Carpal tunnel syndrome — also asked as JAN 2025 · Paper II · Q9 (a) Radial nerve injuries [5]; b] Carpal tunnel syndrome [5]) and APR 2026 · Paper II · Q3 (a) Carpal tunnel syndrome [4]; b] Management of a patient with pan-brachial plexus injury [6]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 276 *Distal Entrapment Syndromes: Carpal Tunnel, Cubital Tunnel, Peroneal, and Tarsal Tunnel* (C.P. Toussaint, S. Kvint, Z.S. Ali, E.L. Zager), §Median Nerve — Anatomy, Clinical Findings, Diagnostic Evaluation, Conservative Treatment, Surgical Techniques, §Double Crush Syndrome, pp. 2128-2133, 2141 (Boxes 276.1-276.2, pp. 2129-2130; Figs. 276.1-276.3, pp. 2129, 2131, 2133). Supplementary: Ch. 272 *Peripheral Nerve Examination, Evaluation, and Biopsy*, §Sensory Loss, §Peripheral Nerve Examination, pp. 2085, 2088-2090 (Fig. 272.2, p. 2088; Table 272.2, p. 2089); Ch. 271 *Pathophysiology of Surgical Nerve Disorders*, §Entrapment Neuropathies, pp. 2076-2077; Ch. 274 *Monitoring of Neural Function*, pp. 2106, 2109; Ch. 275 *Imaging for Peripheral Nerve Disorders*, pp. 2115-2116; Ch. 281 *Management of Acute Peripheral Nerve Injuries*, §The Role of Electrical Stimulation, p. 2183; Ch. 195 *Management of Pain by Percutaneous Anesthetic Injections and Neurolysis*, §Rationale for Sympathetic Blockade, §Stellate Ganglion Block, §Thoracic Sympathetic Block, pp. 1501-1502.

(a) Carpal tunnel syndrome [5]

1. Definition, burden and history

- **An entrapment neuropathy is "a pressure or pressure-induced injury to a segment of a peripheral nerve secondary to anatomic or pathologic structures"** YW p.2128. Carpal tunnel syndrome (CTS) is the archetype: compression of the median nerve within the carpal tunnel.
- **It is the commonest operation in peripheral nerve surgery.** "Carpal tunnel decompression is the most common operation for peripheral nerves, with more than 350,000 procedures performed annually" YW p.2128.
- **Prevalence** — "The prevalence of electrophysiologically confirmed symptomatic carpal tunnel syndrome (CTS) is approximately **3% in women and 2% in men**, with a peak prevalence in women older than 55 years of age. Studies have shown prevalence estimates as high as **16%** in the general population" YW p.2128.
- **Economic cost** — "CTS ranks as second among leading work time loss diagnoses, there is an estimated economic cost of up to **$2.8 billion** attributed to carpal tunnel release (CTR) annually" YW p.2128.
- **Historical milestones** — "The earliest description of CTS was by **Sir James Paget in 1854**, and in **1880, Putnam** published a series of 30 patients with pain and paresthesias in the median nerve distribution in the hand, as well as nocturnal numbness and pain that could be relieved with vigorous shaking of the affected hand. It was not until **1933** that the first report was published on the surgical treatment of CTS" YW p.2128.

2. Pathophysiology — the pressure thresholds are examiner-bait

- **"The underlying pathologic process of CTS is thought to be increased pressure within the carpal tunnel. Any condition that results in decreased space in the carpal tunnel or increased volume of structures contained within it may result in CTS. When the pressure within the tunnel exceeds perfusion pressure into the nerve, adequate circulation and nutrition to the nerve fibers are compromised"** YW p.2128.
- **Learn the four numbers**: at **30 mm Hg** axonal transport is impaired; between **30 and 40 mm Hg** paraesthesiae and neurophysiological changes appear; axonal block is seen at **50 mm Hg**; and at **60 mm Hg** "complete intraneural ischemia occurs, with resultant sensory and motor block" YW p.2128.
- **Tissue sequence** — "In the early stages of compression, morphometric changes may not be seen, but as the ischemia persists, **segmental demyelination** occurs. At this point, the injury is often **reversible** with treatment. Prolonged compression results in **edema**, which may result in **epineurial fibrosis** and further thickening of the nerve. **Damage to the myelin sheath and axonal disruption are end stages** of chronic compression that result in irreversible nerve damage" YW p.2128.
- **Fibre selectivity** — "Not all nerve fibers are equally susceptible to pressure; **large fibers are more susceptible than small fibers**, and fascicular location within the nerve may also affect vulnerability" YW p.2128. This explains why

two-point discrimination and vibration are lost before pinprick.

- **The longer view from the pathophysiology chapter** — chronic compression is now understood as "a primarily Schwann cell-mediated injury state" producing "alterations in paranodal myelination, axonal thinning, and segmental demyelination", with Wallerian degeneration only after more severe or sustained compression YW p.2077.
- **Nerves respond "with endoneurial edema, demyelination, distal axonal degeneration, and fibrosis, with intervening periods of regrowth of axons and remyelination"** YW p.2129.

3. Surgical anatomy of the carpal tunnel

- **The tunnel** is "a fibro-osseous passageway in the anterior aspect of the wrist that is formed by the carpal bones and flexor retinaculum, also known as the **transverse carpal ligament (TCL)**" YW p.2129.
- **Floor** — the volar radiocarpal ligament and bridging ligaments interconnecting the pisiform and hook of hamate medially with the tubercles of scaphoid and trapezium laterally YW p.2129.
- **Roof** — the TCL, "attaching medially to the pisiform and hook of the hamate and laterally to the scaphoid tuberosity and crest of the trapezium" YW p.2129.
- **Dimensions** — the tunnel is **4 to 6 cm long**; the TCL is **3 to 4 cm wide and 2.5 to 3.5 mm thick** YW p.2129.
- **Contents — ten structures**: the median nerve with its vascular bundle, four flexor digitorum superficialis (FDS) tendons, four flexor digitorum profundus (FDP) tendons and the flexor pollicis longus tendon. "A persistent median artery or anomalous muscles and tendons may also run in the carpal tunnel" YW p.2129.
- **Relations** — "The ulnar nerve (UN) and ulnar artery run superficially on the ulnar side of the TCL, and the tendon of the flexor carpi radialis is enveloped by two layers of the TCL on the radial side of the wrist" YW p.2129.
- **Course of the median nerve** — from the lateral and medial cords, travelling with the brachial artery and vein in the medial arm, through the cubital fossa, between the two heads of pronator teres, on the deep surface of FDS, superficial to FDS and deep to palmaris longus just proximal to the tunnel, and parallel to the second and third FDS tendons within it YW p.2129.
- **The palmar cutaneous branch** "arises from the radial side of the median nerve approximately **5 cm proximal to the TCL** and travels **superficial to the carpal tunnel** to provide sensory innervation to the thenar eminence" YW p.2129 — hence thenar sensory loss means the lesion is *above* the wrist.
- **The recurrent motor branch** usually arises distal to the TCL; **Lanz classified the variations into extraligamentous 50%, subligamentous 30% and transligamentous 20%**. It supplies **opponens pollicis, abductor pollicis brevis and flexor pollicis brevis** YW p.2129.
- **Riche-Cannieu anastomosis** — "an important anatomic variant … in which innervation of thenar muscles is provided by the UN" YW p.2129. It explains absent thenar wasting in severe CTS.
- **Distal median nerve** — palmar digital branches supply the **lateral two lumbricals** and sensation to "the palmar surfaces and the distal dorsal portions of the thumb, index finger, middle finger, and lateral half of the ring finger" YW p.2129.
- **Two compression points inside the tunnel** — "The first site is the **proximal edge of the TCL**, and the second is adjacent to the **hook of the hamate**" YW p.2129.

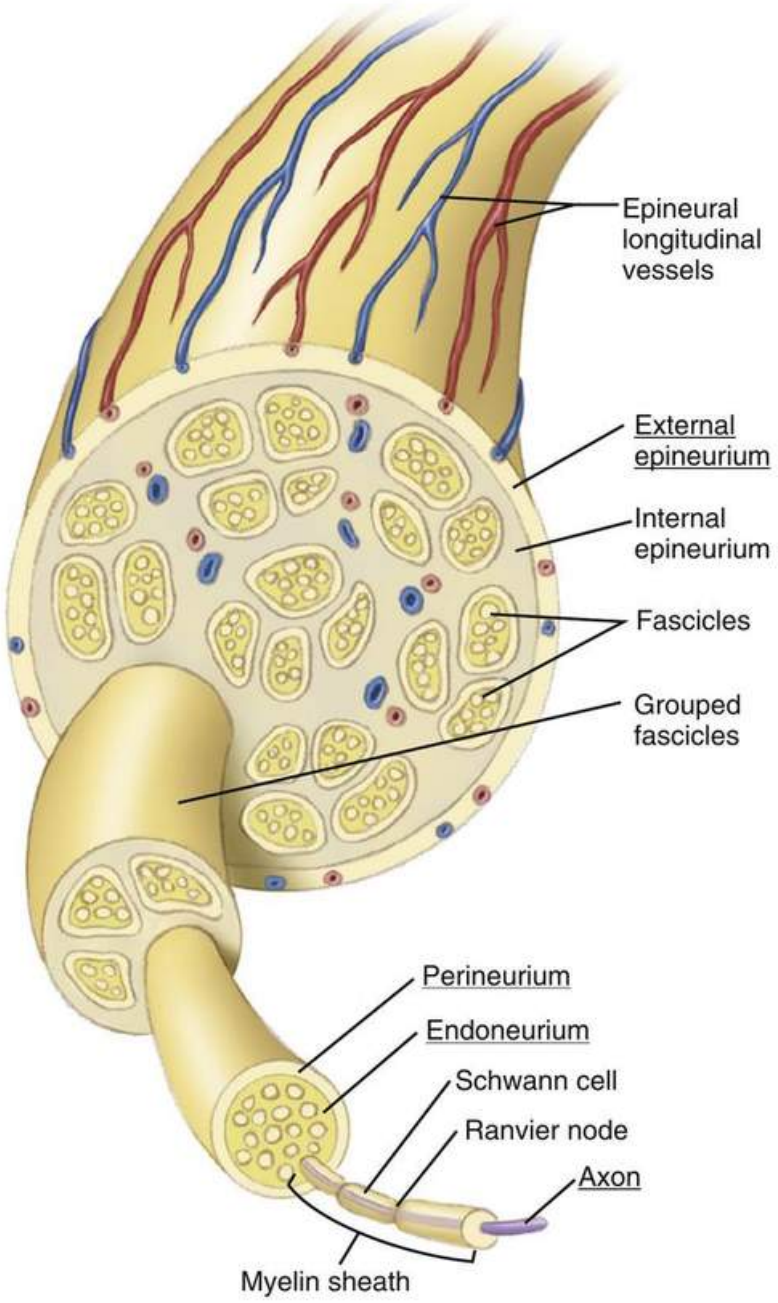


Figure 271.1. Microanatomy of peripheral nerve. Note the *underlined* specific neural elements that characterize Sunderland's grading for peripheral nerve injury and correlate with clinical outcome (epineurium, perineurium, endoneurium, myelin, and axon).

Reproduced from Youmans & Winn 8e, Fig. 271.1, p. 2072 — Label when you reproduce it: the microanatomy of a peripheral nerve — axon, myelin sheath, node of Ranvier, Schwann cell, endoneurium, perineurium, fascicle, grouped fascicles, internal epineurium, external epineurium and the epineural longitudinal vessels. These are precisely the layers that Sunderland's grades I-V destroy in sequence, and the layers whose fibrosis produces a chronic compression neuropathy.

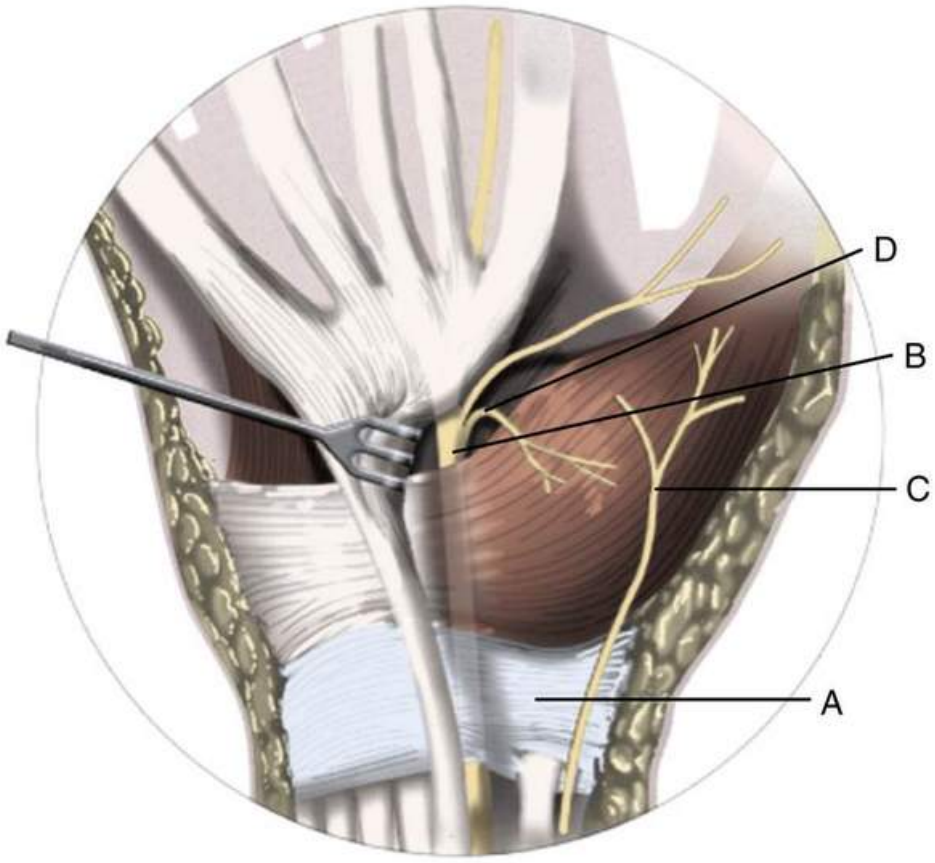


Figure 276.1. Surgical anatomy of the carpal tunnel. (A) Flexor retinaculum. (B) Median nerve. (C) Palmar cutaneous branch. (D) Recurrent motor branch. (*From Huang JH, Zager EL. Mini-open carpal tunnel decompression. Neurosurgery. 2004;54[2]:397–399.*)

Reproduced from Youmans & Winn 8e, Fig. 276.1, p. 2129 — Label when you reproduce it: (A) the carpal tunnel in cross-section; (B) the median nerve; (C) the palmar cutaneous branch running superficial to the ligament; (D) the recurrent motor branch. Add the flexor retinaculum (transverse carpal ligament), the pisiform and hook of hamate medially, the scaphoid tubercle and trapezial crest laterally, the nine flexor tendons and the ulnar neurovascular bundle lying superficial to the ligament on the ulnar side.

4. Aetiology — Box 276.1 reproduced in full

Table 1 · Common conditions associated with carpal tunnel syndrome — reproduced in full from Youmans & Winn 8e, Box 276.1, p. 2129, with the familial and hereditary associations added from p. 2130.

Category	Conditions
Metabolic / endocrine	Diabetes mellitus; pregnancy; hypothyroidism; acromegaly; renal failure; pyridoxine (vitamin B6) deficiency
Autoimmune / inflammatory	Rheumatoid arthritis; amyloidosis; sarcoidosis; tenosynovitis
Anatomic	Persistent median artery; anomalous tendons or muscles; congenital stenosis of the carpal tunnel; fracture and/or dislocation at the wrist
Infectious	Septic arthritis; Lyme disease; tuberculosis; histoplasmosis
Neoplasm	Nerve sheath tumour; ganglion cyst
Hereditary / familial	Familial CTS, often autosomal dominant; mucopolysaccharidoses; mucolipidoses; hereditary neuropathy with liability to pressure palsies YW p.2130

- **Occupation and sport** — "no conclusive evidence correlates repetitive stress with the development of CTS", but "certain sports are associated with the development of CTS. **Wheelchair athletes, archers, bicyclists, body builders, football players, golfers, and wrestlers** are prone to CTS" YW p.2130. Ch. 272 adds use of vibrating machinery YW p.2085.
- **Pregnancy** — third trimester especially; "symptoms often resolve on delivery" YW p.2131.
- **Alcoholism screening questions should also be asked** YW p.2130.

5. Clinical features

- **Cardinal symptom complex** — "Patients with CTS most often complain of **pain and paresthesias in the median nerve distribution** in the hand, particularly **after strenuous wrist movements or at nighttime**. The pain is often described as **burning and may radiate proximally**" YW p.2129.
- **The flick sign and the venous stasis theory** — "Sunderland postulated that the nocturnal occurrence of pain occurs because of **venous stasis** within the upper extremity related to hypotonia during sleep. Frequently, the patient will describe **improvement of symptoms by shaking the affected hand**, which may support the venous stasis theory" YW p.2129.
- **Ch. 272 calls the syndrome virtually pathognomonic from the history alone**: "descriptions of aching discomfort in the hand, wrist, and forearm along with nocturnal symptoms including paresthesias in the median nerve distribution are so characteristic as to be virtually diagnostic of carpal tunnel syndrome" YW p.2085.
- **Inspection** — examine the whole shoulder and limb for atrophy and asymmetry. "**Thenar atrophy** is important to identify because it is a clue to the severity of CTS, but it may be **absent in severe cases in patients with a Riche-Cannieu anastomosis**. Coexistent hypothenar or first dorsal interosseous muscle atrophy may signify compression at the thoracic outlet or an ulnar entrapment neuropathy" YW p.2130.
- **Palpation** of the entire median nerve from the plexus to the hand, hunting for masses, tenderness and bony abnormality; and consider the proximal entrapment sites (Box 276.2) — **arm**: Struthers ligament / supracondylar process of the humerus, lacertus fibrosus (bicipital aponeurosis); **forearm**: pronator teres (between the two heads); **hand**: FDS sublimis bridge, carpal tunnel [YW pp. 2130].
- **Motor testing** — in true CTS, strength should be **normal** in pronator teres, flexor carpi radialis, the whole of FDS, FDP to index and middle fingers, and flexor pollicis longus. Test index and middle lumbricals by PIP extension, and **thumb abduction with palpation of abductor pollicis brevis** YW p.2130.
- **Sensory testing** — full median sensory examination; "the presence of sensory abnormalities in the distribution of the palmar cutaneous branch of the median nerve implies that the median nerve lesion is above the wrist". **Semmes-Weinstein monofilament and vibratory testing** are "more sensitive and specific than two-point discrimination" YW p.2130. The median **autonomous zone** is "the volar aspect beyond the distal interphalangeal joint of the index finger" YW p.2088.
- **The hand postures to recognise** (Fig. 272.2) — the **benediction hand** of complete median palsy (index and middle finger fail to flex on making a fist); the **anterior interosseous palsy** with inability to make an "O" between thumb and index tips; the ulnar **claw hand**; and the **simian hand** of combined median and ulnar (lower trunk/medial cord) palsy [YW pp. 2087-2088].



Figure 272.2. Nerve palsies affecting the hand. (A) Anterior interosseous nerve palsy with an inability to oppose the tips of the thumb and index finger *(arrowheads)*. (B) This patient has a left-sided ulnar claw hand. Atrophy of the adductor pollicis is also evident *(arrow)*. (C) This patient has a complete median nerve palsy preventing him from fully flexing his thumb and index finger (i.e., benediction hand) when he attempts to make a tight fist. (D) A left-sided simian hand is present secondary to a lower trunk injury affecting both the median and the ulnar nerves.

Reproduced from Youmans & Winn 8e, Fig. 272.2, p. 2088 — Label when you reproduce it: the four diagnostic hand postures — (A) anterior interosseous nerve palsy, unable to oppose the tips of thumb and index to make an "O"; (B) left ulnar claw hand with adductor pollicis atrophy; (C) complete median nerve palsy — the benediction hand, index and middle finger failing to flex on making a tight fist; (D) left simian hand from a lower trunk injury affecting both median and ulnar nerves. Panel C is the end-stage picture of untreated median nerve compression.

6. Provocative tests — quote the sensitivity and specificity

Table 2 · Provocative tests in carpal tunnel syndrome, with sensitivity and specificity — from Youmans & Winn 8e, Ch. 276, p. 2130.

Test	How it is done	Sensitivity	Specificity
Tinel sign	Tapping over the carpal tunnel	45-75%	40-67%
Phalen test	Wrist flexed as far as possible, held 60 seconds	4-86%	48-54%
Durkan pressure provocation test	Examiner's thumb over the carpal tunnel, downward pressure for 30 seconds	**82-89%**	**90-99%**
Reverse Phalen test	Extension of wrist and fingers	—	—
Gilliat (tourniquet) test	Tourniquet-induced ischaemia	—	—
Ultrasonic stimulation test	—	—	—

- **"A positive finding occurs when the maneuver or position elicits symptoms in the distribution of the median nerve in the hand"** YW p.2130. The Durkan compression test has "a significantly better sensitivity and specificity" and is the one to perform if you can only do one.

7. Investigations

- **Electrodiagnosis** — "**Palmar sensory latency**, measured by stimulating sensory fibers in the palm and recording over the wrist, is the **most sensitive test for CTS**. Distal motor latency is usually prolonged but may be **normal in 25%** of patients with other signs and symptoms of CTS. Sensory nerve action potentials (SNAPs) are either unrecordable or of low amplitude at the wrist." Needle EMG of abductor pollicis brevis or opponens pollicis "may reveal spontaneous fibrillation potentials and positive sharp waves as well as an increased incidence of long-duration, polyphasic motor unit potentials." Always compare with the **ipsilateral ulnar and radial nerves**, because the contralateral median nerve may have subclinical CTS YW p.2130.
- **Electrodiagnostic grading of severity** YW p.2130:
  - **Mild** — SNAP or mixed nerve action potential (NAP) prolonged; SNAP amplitude may be below the lower limit of normal.
  - **Moderate** — the above **plus** prolongation of median motor distal latency.
  - **Severe** — median motor **and** sensory distal latencies prolonged, with absent SNAPs or mixed NAPs, or absent/reduced thenar compound motor action potentials, or both; fibrillations, reduced recruitment and motor-unit-potential change are often seen.
- **Inching studies** — NCV "performed with measurements made every centimeter along the median nerve pathway across the carpal tunnel … can precisely localize the site of impairment" YW p.2109.
- **Plain radiographs** of the wrist identify bony abnormality such as fracture YW p.2130.
- **Ultrasound** — "An entrapped peripheral nerve may appear hypoechoic, swollen, or flattened"; **a median nerve cross-sectional area of 10 mm² or larger at the level of the pisiform is the most commonly used parameter, with sensitivity reported as high as 97.9%**. Ultrasound is sensitive and specific both in patients with positive electrodiagnostics and "in patients with clinical signs of CTS but negative electrodiagnostic studies", and some authors now advocate it as an alternative to nerve conduction studies YW p.2130.
- **MRI and MR neurography** — increased signal on STIR or fat-suppressed T2 images, nerve thickening, and "MRI evidence of nerve enlargement can be demonstrated at the level of the pisiform bone, where its diameter is **1.6 to 3.5 times** that at the level of the distal radioulnar joint". **Diffusion tensor imaging** with reduced fractional anisotropy "can identify the precise location and severity of nerve compromise", and these techniques "may be useful in the diagnosis of CTS in patients with normal electrophysiologic studies or in those with an underlying systemic neuropathy altering the electrophysiologic results". MRI is "unlikely to be cost-effective in the diagnosis of routine CTS, but it may be useful in patients with complicated manifestations, unusually proximal entrapment, or recurrent symptoms after prior surgery" [YW pp. 2130-2131].

8. Conservative treatment — what actually works

- **"CTS is usually a progressive condition, but a course of conservative therapy should be completed before surgical intervention"** YW p.2131.
- **Piazzini's systematic review, reproduced as printed** YW p.2131:
  1. **Locally injected steroids produce a significant but temporary improvement.**
  2. **Wrist splints are effective, particularly if used full-time.**
  3. **Steroids are more effective than NSAIDs or diuretics.**
  4. **Ultrasound therapy may be effective; laser therapy shows variable results.**
  5. **Exercise therapy and pyridoxine (vitamin B6) are both ineffective.**
- **Why a splint works** — "a wrist splint places the wrist in the neutral position, which has been shown to create the least amount of pressure or friction, or both, within the carpal tunnel" YW p.2131.
- **Full-time versus night-time** — Walker and colleagues found "although full-time splinting provided better relief of symptoms and neurological improvement, splints limited the patient's ability to perform normal daily activities" YW p.2131.
- **Pregnancy** — expectant management, because symptoms usually resolve after delivery YW p.2131.
- **The trial evidence for surgery** — "Randomized controlled trials have also shown that **surgical decompression of the carpal tunnel is superior to both wrist splinting and steroids** in terms of relief of symptoms and neurophysiologic

outcome" YW p.2131.

9. Open carpal tunnel release — operative steps in order

- **Goal** — "complete division of the TCL and decompression of the median nerve, with preservation of the palmar cutaneous and recurrent motor branches" YW p.2131.
- **Anaesthesia and position** — outpatient, local anaesthesia ± mild sedation (alternatives: general, regional block, Bier block); supine with the arm abducted and forearm supinated on a hand table, wrist over a roll in extension; tourniquet optional; loupes and headlight YW p.2131.
- **Incision** — 3-4 cm (1.5-3 cm for mini-open), straight or slightly curvilinear, "starting at the distal wrist crease and ending at a point intercepting an imaginary line (the **Kaplan line**) drawn from the distal border of the extended thumb to the pisiform prominence, in line with the long axis of the radial side of the ring finger"; placed **ulnar to or in line with the palmaris longus tendon** and the major thenar crease YW p.2131.
- **Dissection** — No. 15 blade; protect the palmar cutaneous branch, "which is not consistently visualized"; small self-retaining (Alm or bur-hole) retractor; bipolar haemostasis YW p.2131.
- **Division of the TCL** — divide at its midpoint **in layers** with a No. 15 blade or small scissors, elevating each layer with a Jacobson, McCabe or flat dissector. **"The recurrent motor branch of the median nerve may be transligamentous or subligamentous and must be carefully avoided and protected."** Once the nerve is seen, extend the incision proximally and distally: proximally elevate the skin to see 2-3 cm into the forearm and incise the proximal TCL and distal antebrachial fascia; distally incise until the deep palmar fat pad is seen, avoiding the sensory and ulnar motor branches just beyond the ligament. Probe both ends with the surgeon's fifth finger or a Penfield No. 4 [YW pp. 2131-2132].
- **Explore the tunnel** for tumour, ganglion, anomalous muscle or other structural abnormality YW p.2132.
- **Do not do an internal neuroplasty** — "Internal neuroplasty (used here in place of the older term *neurolysis*, which can mean 'destruction of the nerve') of the median nerve is not generally recommended"; the Cochrane review "found no evidence supporting internal neuroplasty or neurolysis, epineurotomy, tenosynovectomy, or flexor retinaculum lengthening" [YW pp. 2132-2133].
- **Closure** — absorbable subcutaneous sutures, skin with absorbable or non-absorbable monofilament, bulky hand dressing, gentle range-of-motion exercises as early as possible. **"Postoperative splinting is not usually recommended because splinting has not been shown to improve wound healing, reduce postoperative pain, or diminish scar tenderness"** YW p.2132.



Figure 276.2. Mini-open carpal tunnel release. (A) Planned incision measuring 2 cm starting at the distal wrist crease and extending distally in line with the third interspace. (B) Intraoperative identification of the median palmar cutaneous nerve (identified with a No. 4 Penfield dissector). (C) After division of the transverse carpal ligament *(arrows)*, the median nerve *(MN)* is visualized. A Senn retractor is placed at the distal aspect of the incision to improve visualization.

Reproduced from Youmans & Winn 8e, Fig. 276.2, p. 2131 — Label when you reproduce it: mini-open carpal tunnel release — (A) the 2 cm planned incision starting at the distal wrist crease and running distally in line with the third interspace; (B) intraoperative identification of the median palmar cutaneous nerve with a No. 4 Penfield dissector; (C) the median nerve (MN) seen after the transverse carpal ligament has been divided (arrows), with a Senn retractor at the distal end of the incision.

10. Results and the alternatives to open release

- **Open CTR results (LSUHSC, 376 releases)** — "89% of the patients were satisfied with their results. Improvement in pain was seen in **87%**, improvement in paresthesias in **92%**, improvement in numbness in **56%**, and improvement in

weakness in **42%**. Major symptoms persisted in **6%**, and complications included wound infections, reflex sympathetic dystrophy, and hematoma" YW p.2132.

- **Endoscopic CTR (ECTR)** — performed since the late 1980s; **uniportal: Agee and Okutsu; biportal: Chow and Brown**. A tourniquet with local anaesthesia or a Bier block; antebrachial fascia divided bluntly; obturator and slotted cannula passed superficial to the median nerve and flexor tendons; the TCL divided proximal-to-distal or distal-to-proximal; "no attempt is usually made to visualize the median nerve" YW p.2132.
- **Claimed advantages and the actual evidence** — less postoperative pain, fewer wound complications, faster recovery, with **return to work averaging 54 days after open release versus 25 days after ECTR**; Hankins' series of **14,722** biportal procedures reported 82.6% complete resolution, 14.7% some resolution and 2.6% requiring open revision YW p.2132. However, **"open CTR remains the approach used by most peripheral nerve surgeons"**, the criticisms being "a steep learning curve; less visibility, which may result in incomplete sectioning of the TCL and increased nerve injury risk to both median recurrent and distal ulnar elements; increased cost … and the significant setup time and effort required" YW p.2132.
- **Cochrane verdict** — 33 studies; return to work favoured endoscopy by 0-25 days; ECTR had more transient nerve dysfunction (neurapraxia, numbness, paraesthesiae) while open release had more wound complications; **revision surgery was needed in 12 of 513 ECTR versus 5 of 370 OCTR (relative risk 1.2, 95% CI 0.5-3.1)**; "there is no strong evidence supporting replacement of the standard OCTR and … application of ECTR should be guided by patient and surgeon preference". Pain score, symptom severity and functional status initially favoured ECTR **but equilibrated by 8 to 12 weeks** [YW pp. 2132-2133].
- **Retractor-integrated endoscopy** was developed because the "bougie technique" of endoscope introduction has two pitfalls — "the already compressed carpal tunnel is dilated, compressing it further during manipulation", and dilators are introduced blind with "an increased risk for iatrogenic nerve injury". The retractor-endoscope enters a subcutaneous pocket above the plane of the nerve and gives direct vision. Krishnan's 47 patients at 24 months: **38 (81%) excellent or favourable, 9 (19%) fair or poor, with no nerve lesion and no thenar branch injury** YW p.2133.
- **Ultrasound-guided percutaneous release** — local anaesthetic fills and expands "the longitudinal safe zone, the area between the median nerve, the hook of the hamate, the TCL, and the flexor tendon"; a hook knife is advanced and the ligament transected retrograde. Chern's 91 consecutive patients had **100% resolution of sensory disturbance at 6 months with no intraoperative or postoperative complications** [YW pp. 2132-2133].
- **Thread carpal tunnel release (TCTR)** — Guo's 2015 series of 34 hands: ultrasound-guided hydrodissection of the TCL from the median nerve and of the interthenar fascia from the TCL, a thread looped around the ligament through these tracts with protective tubing, then pulled like a Gigli saw. **Average procedure time 7 minutes under local anaesthesia; 3-month outcomes comparable to literature controls; no postoperative complications** YW p.2133.
- **Bilateral disease — simultaneous or staged?** Simultaneous release reduces total disability time and surgical cost; the disadvantage is compromised self-care. Studies show "no significant difference in total disability time and return to work; however, **simultaneous procedures cost approximately 60% of staged procedures** and potentially require fewer follow-up visits". The chapter's own practice: **"stage CTRs and treat the more affected hand first, followed 2 to 6 weeks later by treatment of the other hand"** YW p.2133.

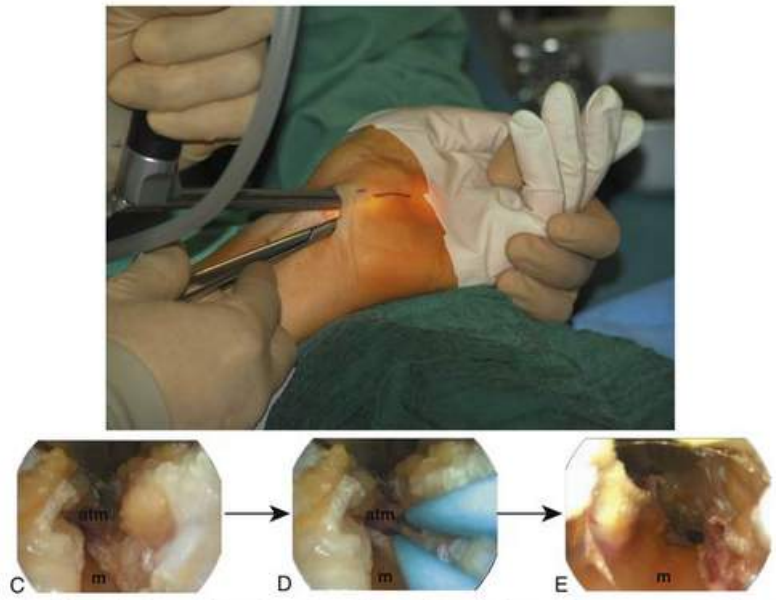


Figure 276.3. Surgical technique of retractor-integrated endoscopic carpal tunnel release. The narrow retractor-endoscope is used for carpal tunnel release. Macroscopic view in the middle of the image shows the mode of insertion of the endoscope. (A) The retractor is seen inserted above the plane of the transverse carpal ligament *(TCL)*. Both the TCL and the median nerve are clearly visualized. (B) Transection of the TCL is done with a pair of Jameson tendon scissors. (C) Transection of the TCL proceeds more distally. (C–D) Anomalous structures such as an accessory thenar muscle can be identified using this endoscopic technique because it offers an excellent aerial view of the surgical site with high magnification and resolution. All thin surgical instruments that are usually used can be brought into the operating field; here the use of bipolar cautery on the accessory thenar muscle is shown. (E) Complete decompression of the carpal tunnel is shown. The farthest dark circle in the middle of the picture is the entry point into the palm. *Arrows* indicate the steps of surgery. *m*, median nerve; *atm*, accessory thenar muscle. (*Modified from Quiñones-Hinojosa A, ed. Schmidek & Sweet: Operative Neurosurgical Techniques: Indications, Methods, and Results. 6th ed. Philadelphia: Saunders; 2012.*)

*Reproduced from Youmans & Winn 8e, Fig. 276.3, p. 2133 — Label when you reproduce it: retractor-integrated endoscopic carpal tunnel release — (A) the retractor inserted above the plane of the transverse carpal ligament (TCL) with both TCL and median nerve (m) clearly visible; (B) transection of the TCL with Jameson tendon scissors; (C-D) an accessory thenar muscle (atm) identified and coagulated; (E) complete decompression. Note that the endoscope enters *above* the nerve, which is the whole point of the design.*

11. Pitfalls and associated points

- **Double crush** — "common examples include cervical radiculopathy and CTS, thoracic outlet syndrome and CTS, and cubital tunnel syndrome and Guyon canal syndrome", explained by "impaired axonal flow, ischemia, and altered nerve elasticity, which lessen the nerve's resilience"; it remains "a controversial entity whose existence and prevalence have been subject to debate" YW p.2141.
- **Discrepant work-up** — "If there are discrepancies in the diagnostic work-up (e.g., carpal tunnel syndrome with completely normal nerve conduction parameters), operative intervention should usually be avoided, at least until the patient has been examined on multiple occasions and all other possible diagnoses are excluded" YW p.2090.
- **Bent wrists during long operations worsen CTS** — a positioning trap for the anaesthetised patient YW p.2225.
- **An emerging adjunct** — "Gordon demonstrated the efficacy of a 1-hour 20-Hz electrical stimulation regimen in patients with severe carpal tunnel syndrome from injured median nerves severed by constriction of the ligament at the wrist"; stimulation elevates neuronal cAMP and upregulates neurotrophic factors and growth-associated genes YW p.2183.

(b) Management of hyperhidrosis [5]

NOT COVERED IN YOUMANS — answered from the source named below

I searched Youmans & Winn 8e for "hyperhidrosis", "palmar hyperhidrosis", "sympathectomy", "thoracoscopic sympathectomy", "T2 ganglion" and "botulinum AND sweating". Hyperhidrosis appears in the 8th edition only as a *symptom* — of acromegaly YW p.1311, of continuous muscle activation YW p.689.e2, of autonomic dysfunction in peripheral neuropathy YW p.2093, of autonomic dysreflexia after spinal cord injury YW p.2038.e17, of syringomyelia YW p.2602, as a side effect of SNRIs and antidepressants [YW pp. 1485-1486], and as a reported complication of deep brain stimulation YW p.767. **There is no chapter, section, box or table in Youmans & Winn 8e on the diagnosis or surgical treatment of primary hyperhidrosis, and no account of thoracoscopic sympathectomy for it.** Sympathectomy in the 8th edition is discussed only as an ablative procedure for pain (Ch. 195, Ch. 201, Ch. 205) and as an occasional treatment for causalgia after injection injury [YW pp. 2078, 2181]. What follows is therefore built on the sympathetic anatomy and blockade technique that Youmans *does* give (Ch. 195, pp. 1501-1502), with the disease-specific management drawn from standard surgical practice and flagged as @@GUIDE@@.

12. The sympathetic anatomy Youmans does supply — learn this part from the book

- **Outflow** — "Efferent fibers of the sympathetic nervous system begin in the **intermediolateral column** of the spinal cord and exit along the **ventral roots from T1 to L2**. These fibers then leave the ventral root as **white rami communicantes** and enter the sympathetic chains, which lie on the **anterolateral aspect of the vertebral bodies**. These preganglionic fibers eventually synapse in one of the sympathetic ganglia. After synapsing, the postganglionic fibers then travel to their sites of action" YW p.1501.
- **Sympathetic functions listed by the book** include sweating, intestinal motility and piloerection YW p.1501.
- **Cervical ganglia** — "Three sympathetic ganglia reside in the neck in a narrow fascial space between the longus coli muscle and the scalene muscle group: the superior, middle, and inferior cervical ganglia. The inferior cervical ganglion is usually fused to the first thoracic ganglion in **80%** of the general population, and together they are called the **stellate ganglion** because of its 'star' shape. The stellate ganglion is **1 to 3 cm long** and lies **anterior to the transverse process of C7 and the first rib, immediately posterior to the vertebral artery, posterolateral to the carotid artery, and superior to the pleural dome**" YW p.1501.
- **What the stellate ganglion serves** — "The stellate ganglion supplies sympathetic fibers to the **ipsilateral head and upper extremity**. It is often used when vasodilation of the arm or face is desired" YW p.1501. This is precisely why interruption *above* it produces facial anhidrosis and Horner syndrome, and why hyperhidrosis surgery must stay below it.
- **Horner syndrome is the marker of stellate interruption** — "Horner syndrome's classic triad of **ptosis, miosis, and anhidrosis** is commonly seen and has often been erroneously taken as a sign of an effective block" YW p.1501.
- **The thoracic chain** — "The thoracic sympathetic chain, unlike the cervical sympathetic chain, is **close to the spinal (segmental) nerves, and there is no muscle or fascial layer separating the two**. This proximity limits the utility of the thoracic sympathetic block because of the higher probability of a somatic block. However, temporary or permanent sensory and motor blockade in the thoracic dermatomes is extremely well tolerated by most patients." The ganglia "can be temporarily blocked or ablated" under fluoroscopic or other image guidance YW p.1502.
- **Complications of cervical sympathetic intervention that Youmans names** — intra-arterial injection into the carotid or vertebral artery causing immediate seizure; high spinal or epidural anaesthesia from injection into a dural cuff or foramen; and the general morbidity of blockade. **Ultrasound guidance "has decreased the incidence of off-target effects compared with landmark-based techniques"**, allowing the carotid, internal jugular, vertebral artery, thyroid, trachea, longus colli, prevertebral fascia and C7 to be visualised, with colour Doppler before infiltration [YW pp. 1501-1502].
- **Lumbar chain** (for plantar hyperhidrosis) — "The lumbar sympathetic chains carry preganglionic fibers from the lower thoracic sympathetic nerves and enter the abdomen posterior to the medial arcuate ligament and anterior to the psoas muscle … the left sympathetic chain lies posterior and lateral to the aorta, and the right sympathetic chain lies posterior to the vena cava. **The separation of the spinal roots and the sympathetic ganglia allows the sympathetic nerves to be blocked or destroyed by neurolysis with less risk to the somatic nerves**" YW p.1502.
- **Sympathectomy for causalgia** — the one therapeutic use the peripheral nerve section endorses: "An occasional patient

may have a true causalgia after injection and may benefit from sympathectomy, especially if recurrent sympathetic blocks have provided temporary relief" [YW pp. 2078, 2181].

13. Management of hyperhidrosis — a staged plan

GUIDELINE UPDATE

Standard surgical practice (society guidance on the treatment of hyperhidrosis and thoracic sympathetic surgery), 2011 onwards — a stepped algorithm from topicals through iontophoresis, oral anticholinergics and botulinum toxin to endoscopic thoracic sympathectomy, with interruption placed at the rib level rather than the ganglion and the stellate ganglion preserved.

- **Define and classify first.**
  - **Primary (idiopathic, focal) hyperhidrosis** — bilateral, roughly symmetrical, focal (palmar, plantar, axillary, craniofacial), onset before about 25 years, at least weekly, ceasing in sleep, often with a family history, and causing social or occupational impairment.
  - **Secondary (generalised) hyperhidrosis** — a symptom of another disease. Youmans itself supplies most of that differential: **acromegaly** YW p.1311, **peripheral and autonomic neuropathy** YW p.2093, **syringomyelia** YW p.2602, **autonomic dysreflexia in spinal cord injury** YW p.2038.e17, **drug effect (SNRIs, tricyclics)** [YW pp. 1485-1486], and **post-DBS hyperhidrosis** YW p.767. Add thyrotoxicosis, phaeochromocytoma, lymphoma, tuberculosis, menopause, hypoglycaemia and anxiety. **Generalised, nocturnal or asymmetrical sweating is secondary until proved otherwise and is investigated, not operated on.**
- **Quantify** — Hyperhidrosis Disease Severity Scale (1-4), gravimetry, Minor's starch-iodine test to map the affected area and to plan botulinum injection.
- **Step 1 — topical antiperspirants**: 10-20% aluminium chloride hexahydrate in ethanol applied to dry skin at night; glycopyrronium tosylate cloth for the axilla. Cheap, first-line, limited by irritation.
- **Step 2 — tap-water iontophoresis** for palms and soles, 15-20 minutes, several times weekly, then maintenance; an anticholinergic may be added to the water. Contraindicated with a pacemaker, metal implants or pregnancy.
- **Step 3 — systemic anticholinergics**: oxybutynin (titrated from 2.5-5 mg daily) or glycopyrrolate 1-2 mg two to three times daily. Effective but limited by dry mouth, blurred vision, urinary retention and constipation. Clonidine and beta-blockers help selected patients.
- **Step 4 — botulinum toxin type A**, intradermal, mapped by the starch-iodine test: about 50 units per axilla and 100 units per palm in a grid of 1.5-2 cm. Onset 2-7 days, duration 4-9 months, repeatable. Palmar injection is painful and requires regional (median/ulnar) block, and carries a risk of transient intrinsic hand weakness — directly relevant to this chapter, since the toxin diffuses to the thenar muscles. This is the pivot point: a good response to botulinum predicts satisfaction with sympathetic interruption.
- **Step 5 — surgery: endoscopic thoracic sympathectomy (ETS).** Offered only for severe, disabling primary hyperhidrosis refractory to the above.
  - **Level selection by target** (name the rib, not the ganglion — the modern convention, because ganglia are variable and rib levels are reproducible):
    - **Craniofacial** — R3 (accepting the highest compensatory sweating risk); T2 interruption is now largely abandoned because of severe compensatory sweating and Horner risk.
    - **Palmar** — **R3** alone, or R3+R4.
    - **Palmar plus axillary** — **R4** or R4+R5.
    - **Axillary alone** — **R4+R5**.
    - **Plantar** — lumbar sympathectomy (L3-L4), separate operation, with a risk of retrograde ejaculation in men if L1-L2 is taken.
  - **Technique** — general anaesthesia with single- or double-lumen tube, semi-sitting or lateral position, one to three ports in the axilla, low-pressure CO_2 insufflation or lung deflation, identification of the chain over the rib heads, division or clipping of the chain **at the rib level** together with any **nerve of Kuntz** (accessory ramus bypassing the

chain, the usual cause of failure), lung re-expansion under vision, and a chest drain only if the pleura is breached. Bilateral single-stage surgery is standard.

- **Clipping versus cutting** — clipping is promoted as potentially reversible; reversal is unreliable, so the patient must be consented as for a permanent operation.

- **Counsel explicitly about the trade-off**: **compensatory (reflex) sweating of the trunk, back and thighs occurs in the majority of patients**, is the commonest cause of dissatisfaction, and is more frequent and more severe the higher the level of interruption. Other risks: Horner syndrome (from injury at or above the stellate ganglion — precisely the structure Youmans localises anterior to the C7 transverse process and first rib YW p.1501), pneumothorax, haemothorax, intercostal neuralgia, gustatory sweating, bradycardia and reduced exercise heart rate (especially with left-sided high interruption), and recurrence from an unrecognised nerve of Kuntz.
- **Follow-up** — assess at 6 weeks and 6 months with the severity scale; treat compensatory sweating medically (anticholinergics, topicals) rather than by attempting reversal.

14. How to answer this part in the examination

- **Say what you know from the book first** — the sympathetic outflow from T1-L2, the white rami, the paravertebral chain on the anterolateral vertebral body, the stellate ganglion's composition and position, the fact that the thoracic chain lies in direct contact with the segmental nerves, and Horner syndrome as the marker of stellate interruption. All of that is Youmans [YW pp. 1501-1502].
- **Then give the staged algorithm** — topical → iontophoresis → oral anticholinergics → botulinum toxin → endoscopic sympathectomy at the correct rib level — and finish on **compensatory sweating**, which is what the examiner is listening for.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Carpal tunnel release is the commonest peripheral nerve operation — >350,000 a year; prevalence 3% of women, 2% of men, up to 16% in some series** YW p.2128.
- **Learn the four pressures: 30 mm Hg impairs axonal transport, 30-40 gives paraesthesiae, 50 gives axonal block, 60 gives complete intraneural ischaemia** YW p.2128.
- **Large fibres fail first** — vibration and two-point discrimination go before pinprick YW p.2128.
- **Thenar sensory loss means the lesion is proximal to the wrist**, because the palmar cutaneous branch leaves 5 cm above the TCL and runs superficial to it YW p.2129.
- **Lanz: recurrent motor branch extraligamentous 50%, subligamentous 30%, transligamentous 20%** — the transligamentous 20% is the one you cut YW p.2129.
- **No thenar wasting in a severe case? Think Riche-Cannieu anastomosis** [YW pp. 2129-2130].
- **Durkan's compression test beats Tinel and Phalen** — sensitivity 82-89%, specificity 90-99% YW p.2130.
- **Palmar sensory latency is the most sensitive electrodiagnostic test; distal motor latency is normal in 25% of true CTS** YW p.2130.
- **Ultrasound cut-off: median nerve cross-sectional area ≥10 mm² at the pisiform, sensitivity up to 97.9%** YW p.2130.
- **Steroid injection helps but only temporarily; vitamin B6 and exercise therapy do not work at all** YW p.2131.
- **Never do an internal neurolysis or epineurotomy** — Cochrane found no evidence for it [YW pp. 2132-2133].
- **Endoscopic release returns patients to work sooner (25 vs 54 days) but needs more revisions; outcomes equalise by 8-12 weeks** [YW pp. 2132-2133].
- **Youmans has no chapter on hyperhidrosis** — answer from the sympathetic anatomy of Ch. 195 and say so.
- **In hyperhidrosis surgery, name the rib not the ganglion, spare the stellate ganglion, hunt for the nerve of Kuntz, and consent for compensatory sweating — the commonest cause of an unhappy patient.**

Pages read for this answer — Youmans & Winn 8e: 689.e2, 767, 1311, 1485, 1486, 1501, 1502, 2038.e17, 2076, 2077, 2078, 2085, 2087, 2088, 2090, 2093, 2109, 2128, 2129, 2130, 2131, 2132, 2133, 2141, 2181, 2183, 2225, 2602

Meralgia paresthetica:

a) Etiological factors. [2]
b) Clinical features. [3]
c) Investigations. [2]
d) Management. [3]

LONG | DEC 2021 · Paper II · Q7 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 278 *Piriformis Syndrome, Obturator Internus Syndrome, Pudendal Nerve Entrapment, and Other Pelvic Entrapments* (A.G. Filler), §Nerve Entrapments of the Anterior Pelvis: Ilioinguinal, Femoral, Obturator, and Lateral Femoral Cutaneous Nerves, pp. 2159-2160 (Fig. 278.9, p. 2159). Ch. 284 *Nerve Injuries of the Lower Extremity* , §Lateral Femoral Cutaneous Nerve, pp. 2197-2198 (Fig. 284.3, p. 2195; Figs. 284.9-284.10, p. 2198). Supplementary: Ch. 25 *Positioning for Spine Surgery*, §Reducing Position-Related Complications, pp. 231.e1, 231.e5-231.e6; Ch. 272 *Peripheral Nerve Examination, Evaluation, and Biopsy*, §Sensory Loss, §Peripheral Nerve Examination, pp. 2085, 2088-2090; Ch. 271 *Pathophysiology of Surgical Nerve Disorders*, §Entrapment Neuropathies, pp. 2076-2077; Ch. 276 *Distal Entrapment Syndromes*, §Double Crush Syndrome, pp. 2128, 2141; Ch. 275 *Imaging for Peripheral Nerve Disorders*, pp. 2115-2116, 2121-2123; Ch. 274 *Monitoring of Neural Function*, pp. 2106-2109; Ch. 279 *Techniques in Nerve Reconstruction and Repair*, §Nerve Graft Harvesting Techniques, p. 2167; Ch. 201 *Neurosurgical Management of Intractable Pain*, p. 1542.e5.

1. Definition and terminology — get these right in the first line

- **Meralgia paraesthetica is an entrapment neuropathy of the lateral femoral cutaneous nerve (LFCN).** Youmans states it plainly: "The lateral femoral cutaneous nerve travels obliquely over the psoas muscle, then lateral to the femoral nerve and medial to the anterior superior iliac spine. This nerve supplies sensation to the skin of the lateral thigh. **Meralgia paresthetica, or entrapment of the lateral femoral cutaneous nerve, may be idiopathic or may follow iatrogenic injury**" YW p.2159.
- **It is a pure sensory mononeuropathy.** The LFCN carries no motor fibres; therefore there is never weakness, never reflex loss and never wasting. Any motor sign forces you to a different diagnosis (L2/L3 radiculopathy, femoral neuropathy, lumbar plexopathy).
- **General definition to open with** — "An entrapment neuropathy is defined as a pressure or pressure-induced injury to a segment of a peripheral nerve secondary to anatomic or pathologic structures. Tension on a nerve associated with adhesion to an adjacent mobile or static anatomic structure may also be causative" YW p.2128.

2. Anatomy — the two facts that explain everything

- **Origin** — "The posterior branches of the roots of the **L2 and L3** spinal nerves unite to form the lateral femoral cutaneous nerve (LFCN)" YW p.2197.
- **Course** — obliquely across iliacus/psoas in the retroperitoneum, then **lateral to the femoral nerve and medial to the anterior superior iliac spine (ASIS)**, passing beneath or through the inguinal ligament to reach the thigh [YW pp. 2159, 2197].
- **Terminal division** — "the lateral femoral cutaneous nerve typically divides into at least two branches distal to the inguinal ligament" — an operative fact, because "care must be taken to resect or decompress **all** of the branches to avoid persistent symptoms" YW p.2160.
- **Territory** — "the skin of the lateral thigh" YW p.2159, the classic **"pants pocket" distribution** over the anterolateral thigh YW p.2159.
- **Why it is vulnerable** — it takes an acute angle beneath a tough, fixed ligament immediately medial to a bony prominence, and it lies directly under the pressure point of a prone patient on hip bolsters. Ch. 286 lists exactly that: nerves are injured "when the nerve is directly under a pressure point, such as the **lateral femoral cutaneous nerve on hip bolsters on a Jackson table**" YW p.2225.
- **Neighbours to keep in mind** — the femoral nerve lies between iliacus and psoas in the retroperitoneal space and is the nerve lateral to the femoral artery in the femoral triangle; the obturator nerve descends posterior to psoas, exits the obturator foramen and passes below the inguinal ligament just medial to the femoral vessels YW p.2159. An acetabular

or pelvic injury can involve sciatic, femoral and obturator nerves together YW p.2195.

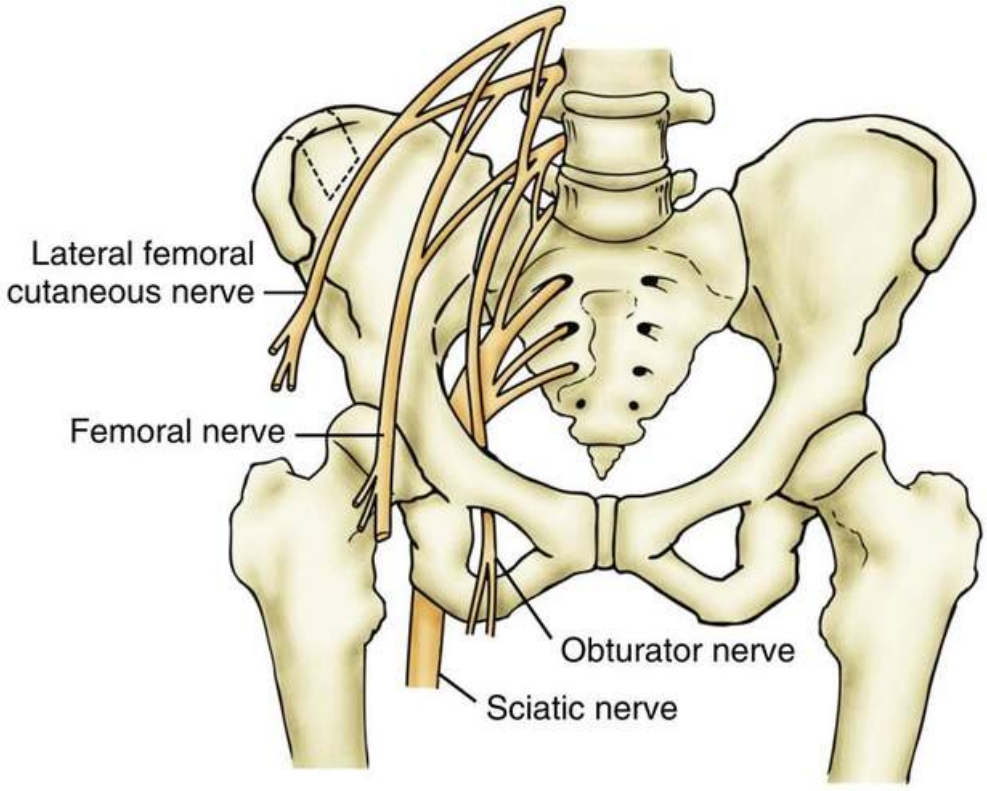


Figure 284.3. Schematic diagram of nerves of the lower extremities that can be injured at a pelvic level. Note that acetabular injury may involve the sciatic, femoral, and obturator nerves. *(Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of Mississippi Medical Center, Jackson, MS.)*

Reproduced from Youmans & Winn 8e, Fig. 284.3, p. 2195 — Label when you reproduce it: the four nerves that cross the pelvic brim — lateral femoral cutaneous nerve (lateral, running to the ASIS), femoral nerve, obturator nerve and sciatic nerve. Note in the caption that an acetabular fracture may injure sciatic, femoral and obturator nerves together, and that the LFCN is the most superficial and most lateral.

(a) Etiological factors [2]

3. Idiopathic / mechanical

- **Increased intra-abdominal pressure and "scissoring" of the nerve.** "Tightening of the abdominal fascia and **'scissoring' of the LFCN** may be a mechanism responsible for compression after abdominal or gynecologic operations" YW p.2197. The same mechanism explains the association with obesity, ascites, tight belts and corsets, and late pregnancy.
- **Direct external pressure medial to the ASIS.** "Direct external pressure on the LFCN medial to the ASIS is thought to be responsible for injury in **posterior spine operations, especially in the Relton-Hall Operating Frame**" YW p.2198; and the hip bolsters of a Jackson table YW p.2225.

4. Iatrogenic — the group that matters surgically

- **Abdominal and gynaecological surgery** — by fascial tightening/scissoring, or by "direct injury from retractor blades on the lateral abdominal wall" YW p.2197.

- **Iliac crest bone graft harvest.** This is the quotable dataset: "Harvesting of iliac crest as bone graft material in proximity to the anterior superior iliac spine (ASIS) has been known to damage this nerve. Damage was more common with a bone graft depth of more than 30 mm. **The incidence of nerve injury was 20% when graft length exceeded 45 mm, 16% when graft length was between 30 and 45 mm, and 8% when graft length was less than 30 mm.** It is recommended that the iliac crest graft be **no closer than 15 to 20 mm posterior from the ASIS**" YW p.2197.
- **Anterior hip arthroplasty** — "Anterior approaches for hip joint arthroplasty can also endanger the LFCN" YW p.2197.
- **Spine surgery positioning** — "Meralgia paresthetica is a common complication of spine surgery and usually has a benign course. Injury mechanisms to the LFCN likely include **external compression near the anterior superior iliac spine when prone, traction neuropraxia during retroperitoneal dissection, or direct surgical laceration when harvesting anterior iliac crest bone graft**" YW p.231.e5. It is listed among the common position-related complications of prone positioning YW p.231.e1.
- **Lateral transpsoas approaches** — "Breaking the table increases the surgical field between the ribs and the iliac crest and can facilitate access to the targeted disk spaces; however, an overzealous table break places the lumbar plexus in tension and increases the risk for plexopathy" YW p.231.e5.
- **Obstetric** — "Postpartum delivery injuries in mothers have also caused injury to the LFCN or exacerbated the symptoms of prior compression. **LFCN injury was the most common nerve injury associated with parturition in first-time mothers with prolonged second-stage labor**" YW p.2197.

5. Secondary and systemic contributors

- **Systemic disease lowering the threshold to compression** — "Systemic disorders such as **diabetes and amyloidosis** may cause nerve swelling and/or decreased tolerance to mild compression and should be considered in the evaluation of patients who present with entrapment symptoms" YW p.2128. Ch. 272 adds diabetes mellitus, pregnancy, renal failure and dialysis, amyloidosis, rheumatoid arthritis, hypothyroidism, acromegaly, **hereditary predisposition to pressure palsies**, vasculitides and lipid storage diseases as conditions that "predispose the patient to true nerve entrapments" YW p.2086.
- **Proximal (retroperitoneal) causes** — a pelvic or retroperitoneal mass, haematoma or tumour along the intrapelvic course; MR neurography is specifically credited with revealing "intra-abdominal and intrapelvic" nerve pathology that previously escaped detection YW p.2121.
- **Double crush** — an L2/L3 radiculopathy may render the LFCN more vulnerable distally, the mechanism being "impaired axonal flow, ischemia, and altered nerve elasticity, which lessen the nerve's resilience" YW p.2141.
- **Pathophysiology of the compression itself** — ischaemia and mechanical distortion together: mild rapidly reversible lesions are largely ischaemic, whereas "direct mechanical distortion is the major factor underlying more severe, long-lasting forms of pressure palsy"; chronic repetitive compression produces fibrosis, "which can exacerbate nerve ischemia, creating a vicious circle" YW p.2077.

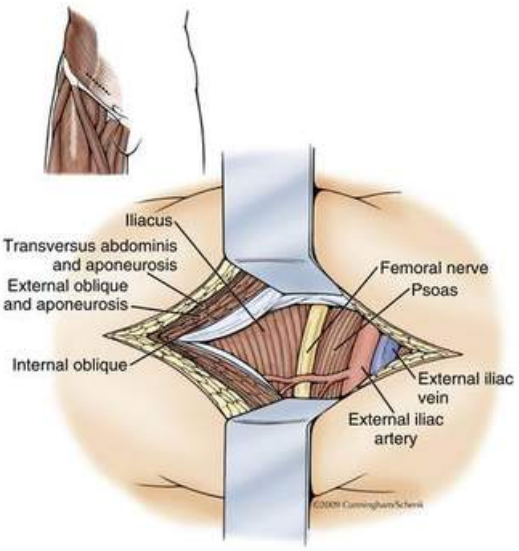


Figure 284.8. The retroperitoneal exposure of the femoral nerve. A transverse skin incision is made, and dissection is carried down to the level of the external and internal oblique muscles, which are separated in the respective directions of their fibers. A self-retaining retractor is used to keep the incision open while the transversalis fascia is opened, and fat must be mobilized. The femoral nerve is located lateral to the femoral artery. A self-retaining retractor system is then used to sweep and retract abdominal contents medially. The femoral nerve is identified lateral to the pulsatile femoral artery. It is dissected superiorly in the iliacus fascia toward the lateral edge of the psoas muscle. (*Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of*

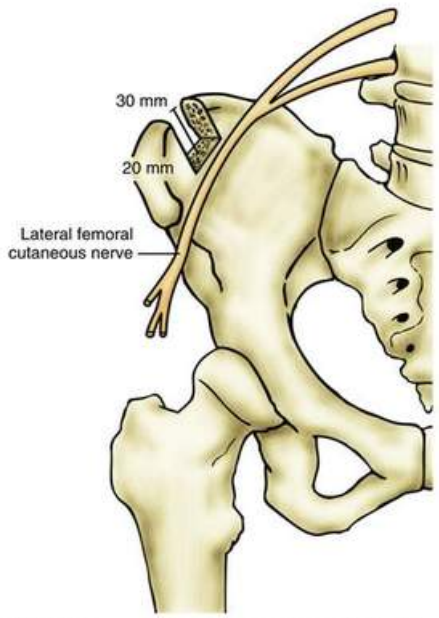


Figure 284.9. Diagram of danger zones for injury to the lateral femoral cutaneous nerve during iliac crest harvesting. Damage was more common in one study[59] with a graft depth of more than 30 mm and proximity to the anterior superior iliac spine of less than 1.5 to 2 cm. (*Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of Mississippi Medical Center, Jackson, MS.*)

Reproduced from Youmans & Winn 8e, Fig. 284.9, p. 2198 — Label when you reproduce it: the danger zones for the lateral femoral cutaneous nerve during iliac crest bone graft harvest — mark the anterior superior iliac spine, the 30 mm depth line and the 20 mm distance from the ASIS, and label iliacus, psoas, transversus abdominis and its aponeurosis, external and internal oblique, the external iliac artery and vein, the femoral nerve and the lateral femoral cutaneous nerve. This is the figure to draw when asked how to avoid meralgia paraesthetica.

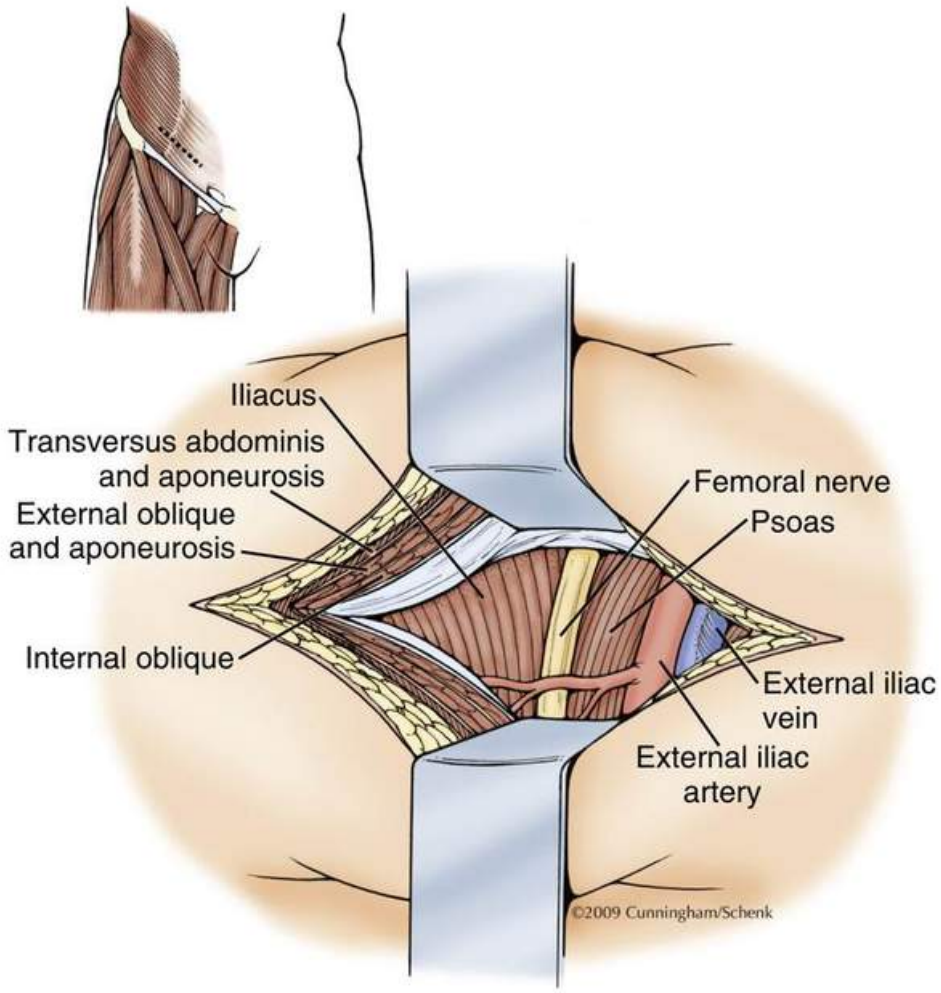


Figure 284.8. The retroperitoneal exposure of the femoral nerve. A transverse skin incision is made, and dissection is carried down to the level of the external and internal oblique muscles, which are separated in the respective directions of their fibers. A self-retaining retractor is used to keep the incision open while the transversalis fascia is opened, and fat must be mobilized. The femoral nerve is located lateral to the femoral artery. A self-retaining retractor system is then used to sweep and retract abdominal contents medially. The femoral nerve is identified lateral to the pulsatile femoral artery. It is dissected superiorly in the iliacus fascia toward the lateral edge of the psoas muscle. (*Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of Mississippi Medical Center, Jackson, MS.*)

Figu
fem
was
mm
to 2
Illus
MS.

Reproduced from Youmans & Winn 8e, Fig. 284.8, p. 2198 — Label when you reproduce it: the retroperitoneal exposure of the femoral nerve — label external oblique and its aponeurosis, internal oblique, transversus abdominis and aponeurosis, psoas, iliacus, the external iliac artery and vein, the femoral nerve lateral to the vessels, and the lateral femoral cutaneous nerve running laterally towards the anterior superior iliac spine. This is the plane in which retractor blades and "scissoring" of the abdominal fascia damage the LFCN.

(b) Clinical features [3]

6. Symptoms

- **The classic triad of sensory symptoms** — "The classic presenting symptoms are **numbness, hyperesthesia, and**

paresthesias in a **'pants pocket' distribution, over the anterolateral thigh**" YW p.2159.

- **Character of the dysaesthesia** — Ch. 272 describes the vocabulary patients use for sensory nerve disease: complete loss (anaesthesia), decrease (hypoaesthesia) or increase (hyperaesthesia) in sensation; "dysesthesias or paresthesias such as tingling, electric shock, or pins and needles sensations"; and **allodynia**, in which "light touch or other nonpainful stimuli may be perceived as painful" YW p.2085.
- **Aggravating and relieving factors** — standing and walking, hip extension, tight garments and belts typically aggravate; hip flexion and sitting relieve. Document these: "Any exacerbating or relieving maneuvers should be documented" YW p.2085.
- **Post-traumatic and postoperative cases behave differently** — "The symptoms after direct nerve injury may be **quite persistent and unremitting**, in contradistinction to injuries caused by simple compression" YW p.2198.
- **When the nerve has been irritated by entrapment, pain can be referred locally as well as distally**, because of the nervi nervorum — "the nerves innervating the epineurium and perineurium … that leads to perception of the local aspect rather than the referred distribution aspect of nerve impairment" YW p.2085. Hence tenderness at the ASIS itself.

7. Signs

- **A sharply demarcated sensory patch.** "Patterns of sensory loss may help discriminate between radiculopathies and focal peripheral neuropathies, with the latter characteristically having a **more demarcated pattern of sensory loss limited to a single peripheral nerve territory**" YW p.2088. Map it by having the patient close the eyes and point to the areas stimulated with a blunt object YW p.2088.
- **Grade the sensory loss** on the 5-to-0 sensibility scale (Table 272.2): 5 near-normal response to touch and pinprick; 4 localised, subnormal response without overresponse; 3 non-localised, subnormal response with some overresponse; 2 enough for slow protection, mislocalised with overresponse; 1 hypoesthesia and/or paraesthesia with deep pain; 0 no response. This gives a reproducible baseline for follow-up and for outcome comparison YW p.2089.
- **Tinel sign at the ASIS.** Systematic percussion along the nerve is part of the peripheral nerve examination: "An injured nerve often exhibits an overlying mechanical hypersensitivity. Evoking a shocklike electrical sensation or paresthesias along the nerve's distribution by percussing over the injured segment is called the **Hoffmann-Tinel sign**. This sign is often present over the nerve in an area of entrapment and can remain present for a long time, sometimes indefinitely" YW p.2089. Percuss just medial and inferior to the ASIS.
- **A pelvic compression manoeuvre and hip extension** reproduce the symptoms in most patients (the reverse of the relief obtained by sitting).
- **Normal motor examination, normal reflexes, no wasting** — confirm quadriceps power (femoral, L2-L4), hip adduction (obturator), knee jerk, and hip flexion. Youmans warns to test iliopsoas "by having the patient flex the hip … against resistance while lying flat" and quadriceps by knee extension, because femoral entrapment "typically results in iliopsoas and quadriceps weakness as well as anterior thigh pain" YW p.2159 — a picture which must **not** be present in pure meralgia.
- **Search for a mass along the nerve.** "It is good clinical practice to palpate the complete length of any peripheral nerve affected by entrapment or idiopathic palsy to **exclude a nerve sheath tumor**"; nerve sheath tumours "are usually mobile in a side-to-side manner but not along the nerve trajectory", and tapping them produces a positive Hoffmann-Tinel sign that identifies the parent nerve YW p.2089.
- **Autonomic assessment** — inspect for hair loss, sweating change and skin temperature difference in the patch; the wrinkle test (both limbs in water at about 40 °C for 20 minutes; absence of wrinkling indicates sympathetic denervation) is a simple bedside confirmation of autonomic involvement [YW pp. 2086, 2089].

8. Differential diagnosis

Table 1 · Differential diagnosis of anterolateral thigh numbness — compiled from Youmans & Winn 8e, Ch. 278 p. 2159, Ch. 284 pp. 2195-2198, Ch. 272 pp. 2086-2088 and Ch. 273 p. 2094.

Condition	Distinguishing feature

L2 or L3 radiculopathy	Back pain, dermatomal (not nerve-territory) loss, hip flexor/quadriceps weakness, reduced knee jerk; sensory NCS normal because the lesion is proximal to the dorsal root ganglion YW p.2106
Femoral neuropathy (pelvic or thigh level)	Iliopsoas and quadriceps weakness, anterior thigh pain, absent knee jerk, medial leg (saphenous) sensory loss YW p.2159
Lumbar plexopathy	Multiple nerve territories; often retroperitoneal haematoma, tumour, pelvic fracture or an overzealous table break [YW pp. 231.e5, 2195]
Iliacus or psoas haematoma	Femoral compression in a patient on anticoagulants or with haemophilia; acute painful hip flexion deformity [YW pp. 2159, 2197]
Ilioinguinal / iliohypogastric / genitofemoral neuralgia	The classic triad of burning pain in the region of the incision radiating into groin and medial thigh, decreased sensation in that nerve's distribution, and pain relief after nerve block; EMG may show denervation of pyramidalis YW p.2159
Hip joint pathology / trochanteric bursitis	Positive Patrick (FABER) test, mechanical pain, no true sensory deficit YW p.2087
Diabetic or other polyneuropathy; diabetic amyotrophy	Bilateral, stocking loss, other nerves abnormal, weakness and weight loss in amyotrophy YW p.2094
Retroperitoneal or pelvic mass along the intrapelvic course	Progressive, unremitting; shown by MR neurography YW p.2121

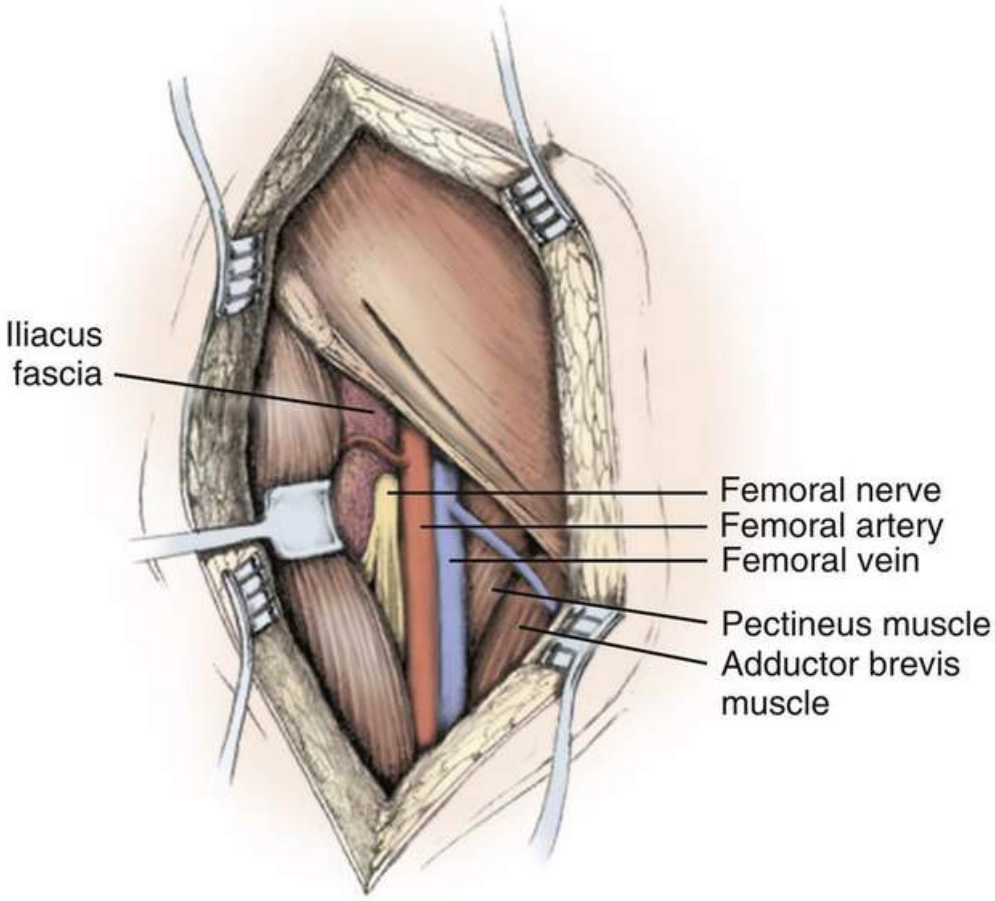


Figure 278.9. The right femoral nerve at the inguinal ligament is exposed in the femoral triangle. Note the lateral position of the nerve, followed in medial progression by the artery and the vein. The retractor draws the sartorius muscle medially. (*From Kline DG, Hudson AR, Kim DH. Atlas of Peripheral Nerve Surgery. Saunders; 2001.*)

Reproduced from Youmans & Winn 8e, Fig. 278.9, p. 2159 — Label when you reproduce it: the right femoral nerve exposed in the femoral triangle at the inguinal ligament — note the order from lateral to medial (nerve, artery, vein), the iliacus fascia, pectineus and adductor brevis, and the sartorius retracted medially. Use this to show where the femoral nerve lies relative to the lateral femoral cutaneous nerve, and to explain why femoral neuropathy gives weakness whereas meralgia paraesthetica never does.

(c) Investigations [2]

9. What to order, and why

- **The diagnosis is clinical; investigation is for confirmation, exclusion and surgical planning.** Youmans is explicit that imaging "does not replace, and should not be used as a substitute for, a careful clinical evaluation" YW p.2090.
- **Diagnostic LFCN block** — the decisive test. The ilioinguinal analogue makes the principle explicit: the classic diagnostic triad includes "**pain relief following nerve block**" YW p.2159. An anaesthetic block just medial and inferior to the ASIS that abolishes the symptoms confirms the level, predicts operative success and may itself be therapeutic.
- **Electrodiagnosis** — LFCN sensory nerve conduction (side-to-side amplitude and latency comparison) supports the diagnosis; it is technically difficult in the obese. Its greater value is exclusion: needle EMG of iliopsoas, quadriceps, adductors and the lumbar paraspinals excludes an L2/L3 radiculopathy, plexopathy and femoral neuropathy. Remember that "in radiculopathies the sensory NCVs are normal whereas the motor NCVs may be impaired" YW p.2106, and that

root lesions show "denervation (fibrillations, positive sharp waves) in two or more muscles in the same myotome supplied by different peripheral nerves" YW p.2109.

- **Ultrasound** — "Ultrasound has gained popularity because it offers the possibility of a **dynamic examination** and assessment of long nerve segments in a short time and offers rapid bedside availability, noninvasiveness, and low cost" YW p.2090. It shows the nerve at the ASIS, measures swelling, detects a mass, and guides the block.
- **MR neurography** — "**a technique based on enhancing signal differences between nerves and surrounding tissues, has increasingly been used for the diagnosis of entrapment neuropathies**" YW p.2130. It demonstrates focal distortion of the course, calibre or image intensity of the nerve, and — importantly for this nerve — it images the intrapelvic and intra-abdominal course, since "entrapment of the … intra-abdominal and intrapelvic course [of nerves] that previously were [inaccessible]" is now visualised YW p.2121. MRN achieves about 200 µm spatial resolution on the best scanners with a field of view of 10-20 cm per side YW p.2116.
- **Lumbar spine MRI** where the history or examination raises an L2/L3 root lesion, remembering that extraforaminal impingement by a lateral marginal osteophyte can be missed on routine sequences YW p.2122.
- **Pelvic/abdominal CT or MRI** if a retroperitoneal mass, haematoma or tumour is suspected; "computed tomography is excellent for evaluating retroperitoneal hematomas" YW p.2090.
- **Metabolic screen** where a predisposing systemic disease is likely — fasting glucose and 2-hour glucose tolerance test, HbA1c, thyroid function, and serum protein immunofixation for amyloidosis/paraproteinaemia [YW pp. 2094-2095, 2128].

(d) Management [3]

10. Step 1 — expectant management, because the natural history is good

- **"The natural history of meralgia paresthetica is usually one of resolution"** YW p.2198.
- **Postoperative meralgia after spine surgery "usually has a benign course"**, and may be missed early "when patients have surgical site pain and are under the influence of analgesics and narcotics" YW p.231.e5.
- **Remove the mechanical cause**: weight reduction, loosening or abandoning tight belts, corsets and low-waisted trousers; avoiding prolonged standing and hip extension; delivery of the pregnancy.
- **Reassure and explain** — the patch of numbness is permanent in some patients but functionally harmless, since the nerve is purely sensory.

11. Step 2 — medical and injection treatment

- **"Symptomatic treatment with tricyclic antidepressants or gabapentin may provide adequate relief for some"** YW p.2198. Ch. 281 agrees for neuropathic pain generally: "tricyclic antidepressants (such as amitriptyline) or anticonvulsants (such as gabapentin) … have demonstrated good benefit for neuropathic pain states" YW p.2181.
- **"In addition, local administration of topical steroids with or without anesthetic may prove efficacious"** YW p.2198 .
- **Image-guided perineural injection** — local anaesthetic plus depot steroid at the ASIS, under ultrasound or MRI guidance, is simultaneously diagnostic and therapeutic; the chapter's general position on entrapment injections is that image guidance "serves as critically important modern confirmatory tests and establish[es] causality" YW p.2143.

12. Step 3 — surgery, and the two operative strategies

- **Indication** — "Patients with postoperative injury may, however, need surgery" YW p.2198; in practice, persistent disabling dysaesthesia after an adequate trial of conservative treatment, with a positive diagnostic block.
- **"After the surgical approach has been selected, one of two operative strategies may be chosen"** YW p.2198 — **neuroplasty (decompression/neurolysis)** or **resection (neurectomy)**.
- **Where to operate** — "Treatment involves neuroplasty and/or resection of the nerve as it courses medial to the anterior superior iliac spine just below the inguinal ligament" [YW pp. 2159-2160].
- **Results** — this intervention "results in **amelioration of symptoms in more than 70% of cases**" YW p.2160.

- **The technical trap** — "Because the lateral femoral cutaneous nerve typically divides into at least two branches distal to the inguinal ligament, **care must be taken to resect or decompress all of the branches to avoid persistent symptoms** " YW p.2160.
- **How resection is done** — section of the LFCN with **removal of a segment so that the proximal end retracts into the abdomen**, away from the scar and away from weight-bearing pressure points (Fig. 284.10) YW p.2198.
- **The controversy** — "In some cases section of the LFCN may be helpful, but **this remains a controversial treatment in significant part because of the potential for the formation of a painful neuroma**" YW p.2198. The general principle for any sensory neurectomy applies: "Formation of a painful neuroma is always a risk when resection is chosen over neuroplasty" YW p.2159; and when the sural nerve is harvested, "the proximal end of the nerve should be implanted within muscles or beneath the fascia" precisely to avoid this YW p.2167. The same trick — burying the proximal stump in muscle or beneath fascia — should be used here.
- **Neurolysis versus transection** — Youmans cites both in the reference list ("Neurolysis for meralgia paresthetica: an operative series of 45 cases" and "meralgia paresthetica: transection versus neurolysis"), reflecting a genuinely unsettled question [YW pp. 2160.e1, 1542]. A reasonable practical policy: **neuroplasty first**, reserving neurectomy with proximal stump burial for failures.
- **Proximal (retroperitoneal/pelvic) LFCN injuries are different** — "For more proximal LFCN injuries, **there are no simple surgical treatments to be recommended, and most education is focused on prevention**" YW p.2198.

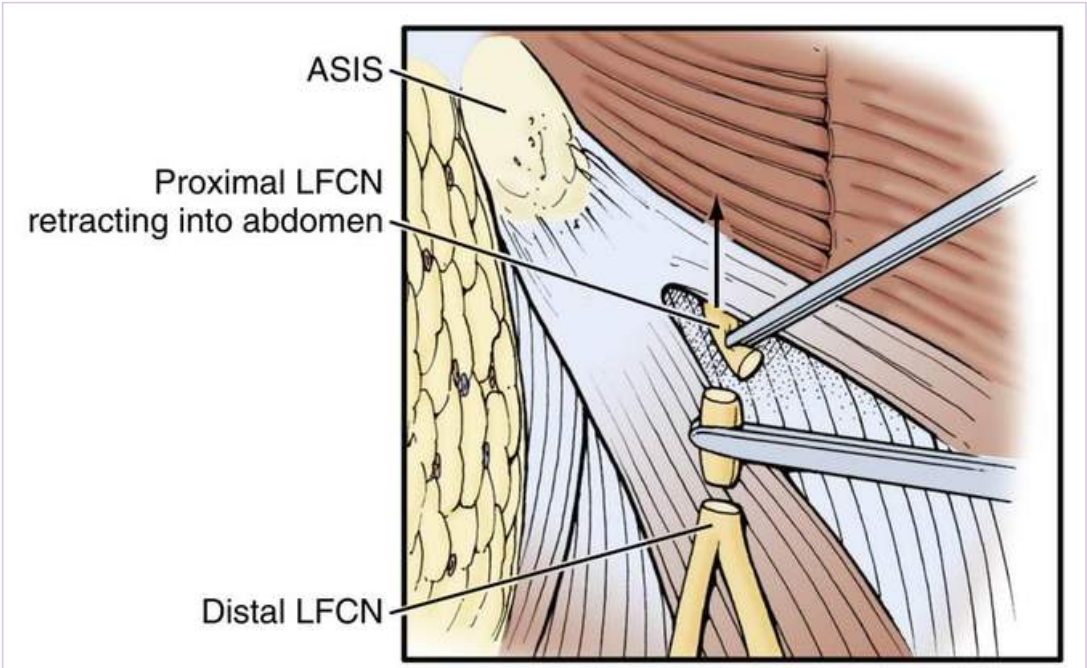


Figure 284.10. Removal of a section of the lateral femoral cutaneous nerve *(LFCN)*, which allows the proximal end to

Reproduced from Youmans & Winn 8e, Fig. 284.10, p. 2198 — Label when you reproduce it: removal of a section of the lateral femoral cutaneous nerve so that the proximal end retracts into the abdomen — mark the anterior superior iliac spine, the proximal LFCN retracting intra-abdominally and the distal LFCN stump. State in the caption why the proximal end is allowed to retract (to keep any neuroma away from the pressure point and the scar) and that neurectomy remains controversial because of neuroma pain.

13. Step 4 — salvage for intractable pain

- **Spinal cord stimulation** — "On occasion, spinal cord stimulation has been offered in the absence of any direct definitive treatment" YW p.2198; Youmans' pain chapters also list spinal cord stimulation for meralgia paraesthetica among the extremity pain indications YW p.1547.e1.
- **Intrathecal microdosing** — "long-lasting 'microdosing' in patients with chronic nonmalignant pain has been [reported for] relief of meralgia paresthetica" YW p.1542.e5.

- **Reassess the diagnosis before escalating** — "the working diagnosis should be constantly reconsidered over time … The physician should be skeptical when patients are referred for an exotic or rare entrapment syndrome because in many patients, further or redundant evaluation over time identifies another diagnosis. For these patients, the physician should always exclude radiculopathy, myelopathy, systemic neuropathy, inflammatory neuritis, and amyotrophic lateral sclerosis" YW p.2090.

14. Prevention — where most of the marks in a viva actually are

- **Iliac crest harvest** — stay **15-20 mm posterior to the ASIS**, keep the graft depth **under 30 mm**, and accept that injury rises from 8% (<30 mm) to 16% (30-45 mm) to **20% (>45 mm)** as the graft lengthens YW p.2197.
- **Prone positioning** — pad and position bolsters so the ASIS and the nerve medial to it are not compressed; the Relton-Hall frame and Jackson-table hip bolsters are named offenders [YW pp. 2198, 2225].
- **Keep the abdomen hanging free** in the prone patient — a principle Youmans re-emphasises for both venous pressure and nerve protection YW p.231.e5.
- **Avoid overzealous table break** in lateral transpsoas approaches, which tensions the lumbar plexus YW p.231.e5.
- **Retractor discipline** in abdominal and gynaecological operations — the blade on the lateral abdominal wall is the culprit YW p.2197.
- **Warn the patient beforehand** when anterior iliac crest graft or a lateral approach is planned; a documented preoperative discussion converts a complaint into an expected event.
- **Look for the sign postoperatively** — it is easily missed under analgesia YW p.231.e5.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Meralgia paraesthetica = entrapment of the lateral femoral cutaneous nerve (L2, L3 posterior branches); a purely sensory syndrome — any weakness means a different diagnosis** [YW pp. 2159, 2197].
- **"Pants pocket" numbness, hyperaesthesia and paraesthesiae over the anterolateral thigh is the whole clinical picture** YW p.2159.
- **Iliac crest graft: injury 8% if <30 mm deep, 16% at 30-45 mm, 20% if >45 mm — stay 15-20 mm behind the ASIS** YW p.2197.
- **It is the commonest nerve injury of parturition in first-time mothers with a prolonged second stage** YW p.2197.
- **The Relton-Hall frame and Jackson-table hip bolsters are the classic positioning causes** [YW pp. 2198, 2225].
- **Diagnostic LFCN block is the decisive test** — the same triad that defines ilioinguinal neuralgia YW p.2159.
- **Sensory NCS are normal in an L2/L3 radiculopathy but abnormal in LFCN entrapment** — the electrodiagnostic discriminator YW p.2106.
- **Natural history is resolution — treat expectantly first** YW p.2198.
- **Gabapentin, tricyclics and topical steroid ± anaesthetic are the medical options named in the book** YW p.2198.
- **Neuroplasty and/or resection medial to the ASIS just below the inguinal ligament relieves >70%** YW p.2160.
- **The nerve divides into at least two branches beyond the ligament — miss one and the operation fails** YW p.2160.
- **Neurectomy is controversial because of painful neuroma; bury the proximal stump in muscle or beneath fascia and let it retract intra-abdominally** [YW pp. 2159, 2167, 2198].
- **For proximal LFCN injury there is no good operation — prevention is the only real treatment** YW p.2198.

Pages read for this answer — Youmans & Winn 8e: 231.e1, 231.e5, 231.e6, 1542, 1542.e5, 1547.e1, 2077, 2085, 2086, 2087, 2088, 2089, 2090, 2094, 2095, 2106, 2109, 2116, 2121, 2122, 2128, 2130, 2141, 2143, 2159, 2160, 2160.e1, 2167, 2181, 2195, 2197, 2198, 2225

a) Halfman reflex and its significance. [5]
b) Meralgia paresthetica. [5]

LONG | DEC 2022 · Paper II · Q9 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 272 *Peripheral Nerve Examination, Evaluation, and Biopsy* (D. Umansky, R. Midha), §Reflex Tests, §Peripheral Nerve Examination, pp. 2085-2090 (Table 272.1, p. 2087; Table 272.2, p. 2089; Figs. 272.1-272.2, pp. 2086, 2088). Ch. 273 *Peripheral Neuropathies*, §Electrodiagnostic Evaluation, pp. 2093-2095 (Fig. 273.1, p. 2095; Table 273.2, p. 2094). Ch. 274 *Monitoring of Neural Function: Electromyography, Nerve Conduction, and Evoked Potentials*, §Other Peripheral Neurodiagnostics, §Common Clinical Disorders, §Surgical Applications, pp. 2106-2113 (Figs. 274.1-274.3, pp. 2106-2107; Fig. 274.6, p. 2109). Ch. 278 *Piriformis Syndrome...*, §Nerve Entrapments of the Anterior Pelvis, pp. 2153, 2159-2160 (Fig. 278.9, p. 2159). Ch. 284 *Nerve Injuries of the Lower Extremity*, §Lateral Femoral Cutaneous Nerve, pp. 2197-2198 (Figs. 284.9-284.10, p. 2198). Supplementary: Ch. 279 *Techniques in Nerve Reconstruction and Repair*, p. 2163; Ch. 282 *Early Management of Brachial Plexus Injuries*, p. 2184.e2; Ch. 315 *Evaluation and Treatment of Cervical Disk Herniation and Cervical Spondylotic Myelopathy*, §Myelopathy, p. 2467; Ch. 349 *Evaluation and Treatment of Adolescent Idiopathic Scoliosis*, p. 2731; Ch. 345 *Rehabilitation of Acute Spinal Cord Injury*, p. 2695; Ch. 127 *Management of Spasticity*, p. 855; Ch. 25 *Positioning for Spine Surgery*, p. 231.e5.

(a) "Halfman" reflex and its significance [5]

NOT COVERED IN YOUMANS — answered from the source named below

I searched Youmans & Winn 8e for "Halfman", "Halfman reflex" and "Halfmann" and nothing came back; there is no such eponym in the 8th edition, and none in standard neurological nomenclature. The question as printed is a transcription of **Hoffmann**, and in neurosurgery three distinct entities carry that name — the **Hoffmann reflex (H-reflex)**, the **Hoffmann sign** of upper motor neuron disease, and the **Hoffmann-Tinel sign** of nerve regeneration and entrapment. All three are described in Youmans & Winn 8e, and because the question sits in the peripheral nerve paper the H-reflex is almost certainly what is being asked; I have therefore answered the H-reflex in full and given the other two Hoffmann signs so that no version of the question is left uncovered.

1. The Hoffmann reflex (H-reflex) — what it is

- **Definition, verbatim from the book**: the H-reflex is "**a CMAP generated after antidromic conduction of a smaller stimulus triggering a monosynaptic reflex in the spinal cord anterior horn**", and together with the F wave it "may be used to evaluate for **proximal nerve conduction slowing**" YW p.2095.
- **It is the electrophysiological equivalent of the tendon jerk.** Ch. 127 makes the equivalence explicit when describing spasticity — treatment works by "[interrupting] the tendon jerk reflex and the H-reflex" through selective blockade YW p.855. The tendon jerk uses a mechanical tap to stretch the muscle spindle; the H-reflex bypasses the spindle by stimulating the Ia afferents electrically.
- **Where it sits among the "other" neurodiagnostic tests**: "The most common clinical tests additionally performed with EMG and NCV are the **F-wave, H-reflex, and repetitive nerve stimulation (RNS)** tests. These supplement the basic neurodiagnostic tests in certain circumstances" YW p.2106.

2. The reflex arc, step by step

1. **Sub-maximal electrical stimulus** is applied to a mixed nerve — classically the tibial nerve in the popliteal fossa, recording from soleus/gastrocnemius; the median nerve recording from flexor carpi radialis is the upper-limb equivalent.
2. Because **large-diameter fibres have the lowest electrical threshold**, a small stimulus preferentially excites the **Ia muscle-spindle afferents** rather than the alpha motor axons. Youmans provides the fibre physiology directly: the **Aα (Ia)** fibres are 13-20 μm in diameter and conduct at **70-120 m/s**, carrying muscle stretch information from the muscle spindle primary afferents YW p.2093.
3. The afferent volley travels orthodromically to the spinal cord and makes a **monosynaptic** connection onto the **alpha motor neurons of the anterior horn** YW p.2095.
4. The efferent volley travels back down the alpha motor axons to produce a late compound muscle action potential — the **H wave**.

5. **Graded recruitment curve** — at low stimulus intensity only the H wave is seen. As stimulus intensity rises, a direct **M wave** appears (orthodromic motor conduction) and grows, while the H wave is progressively extinguished, because the antidromic volley in the motor axons collides with and cancels the reflexly generated orthodromic volley. At supramaximal intensity the H wave disappears and only the **F wave** — "a much longer latency … [response that] occurs when the stimulation causes an antidromic volley that travels proximal to the anterior horn cell, where it may reflect off the cell and travel orthodromically back to the muscle" — remains YW p.2106.

3. H wave versus F wave — the comparison the examiner wants

Table 1 · H-reflex versus F wave versus M wave — built from Youmans & Winn 8e, Ch. 273 p. 2095 and Ch. 274 pp. 2106, 2109.

Feature	M wave	H-reflex (H wave)	F wave
Pathway	Direct orthodromic motor conduction	**Ia afferent → monosynaptic anterior horn cell → alpha motor axon** YW p.2095	Antidromic volley up the **motor** axon, "reflect[ed] off the cell" and back down YW p.2106
Is it a true reflex?	No	**Yes — monosynaptic, with a sensory limb**	No — it is a motor backfiring response, not a reflex
Stimulus intensity	Increases with intensity to supramaximal	**Sub-maximal (low) intensity**; abolished at supramaximal	**Supramaximal**
Amplitude	Large	Variable, submaximal	Small, variable from trial to trial
Which fibres	Alpha motor	**Largest, lowest-threshold Ia afferents**	Alpha motor
Principal clinical use	Distal motor conduction, conduction block	**S1 radiculopathy; proximal conduction; peroneal H-reflex in piriformis syndrome** [YW pp. 2109, 2153]	"Measures the health of the entire length of the motor pathway including its proximal portion … sensitive to impairment at the roots such as in radiculopathies and Guillain-Barré" YW p.2106
Behaviour in spinal shock	Present	**Lost**	"The F waves from the tibial nerve may also reflect changes in spinal motoneuron excitability … in contrast to H-reflexes, remaining retrievable during spinal shock" YW p.2695

4. Clinical significance — five uses, each with its citation

1. **The single most sensitive electrophysiological test for an S1 root lesion.** Youmans states it flatly: **"The H-reflex is a sensitive indicator for detecting S1 root lesions"** YW p.2109. This matters because ordinary nerve conduction studies are insensitive to radiculopathy: "Sensory NCVs are normal in radiculopathies because compression occurs proximal to the dorsal root ganglion. Motor NCV becomes abnormal in radiculopathy [only] when a sufficiently severe compression causes motor axon loss and sufficient time has passed for axonal degeneration" YW p.2109. The H-reflex interrogates the whole S1 arc — afferent and efferent, proximal and distal — and so detects the lesion when the distal studies are still normal. A side-to-side latency difference, or unilateral absence, is the abnormality sought.
2. **Deep gluteal / piriformis syndrome.** "Electrodiagnostic [testing] … may show a **delay in the peroneal H-reflex**, or may be normal" in piriformis syndrome YW p.2153. An abnormal peroneal H-reflex supports a proximal sciatic lesion at the sciatic notch where routine studies are normal.
3. **Proximal conduction in demyelinating polyneuropathy.** The H-reflex and F wave "may be used to evaluate for proximal nerve conduction slowing" YW p.2095, which is why they are abnormal early in Guillain-Barré syndrome and in CIDP. In multifocal motor neuropathy, Youmans notes that nerve conduction studies may reveal focal demyelination only "as loss of the H-reflex" YW p.2099.
4. **Intraoperative monitoring of proximal nerve and root function.** "At proximal levels, alternative techniques may be used … In some other peripheral cases, **F-wave and H-reflex testing may be used to assess possible nerve or root injury when convenient direct nerve hook placement is unavailable**" YW p.2112. Youmans' own suggested-reading list carries "Monitoring spinal nerve function with H-reflexes" YW p.2113.e1.

5. **Assessment of motor neuron excitability in spasticity and spinal cord injury.** Selective blockade in spasticity works by interrupting "the tendon jerk reflex and the H-reflex" YW p.855; and in acute spinal cord injury the H-reflex is lost during spinal shock while the F wave persists, which is why the F wave, not the H-reflex, is used to track motoneuron excitability over time YW p.2695. The H-reflex therefore returns, and becomes exaggerated, as spinal shock resolves and spasticity develops.
6. **A component of the central motor conduction time calculation.** The formula given in Youmans uses the F wave, not the H wave — **CCT = MEP − (F + M − 1)/2**, where MEP is the latency to muscle response, M the M-wave latency and F the F-wave latency, all from the same muscle YW p.2109 — but the H-reflex is the analogous late response with a true afferent limb, and is used in the same way to partition peripheral from central conduction.

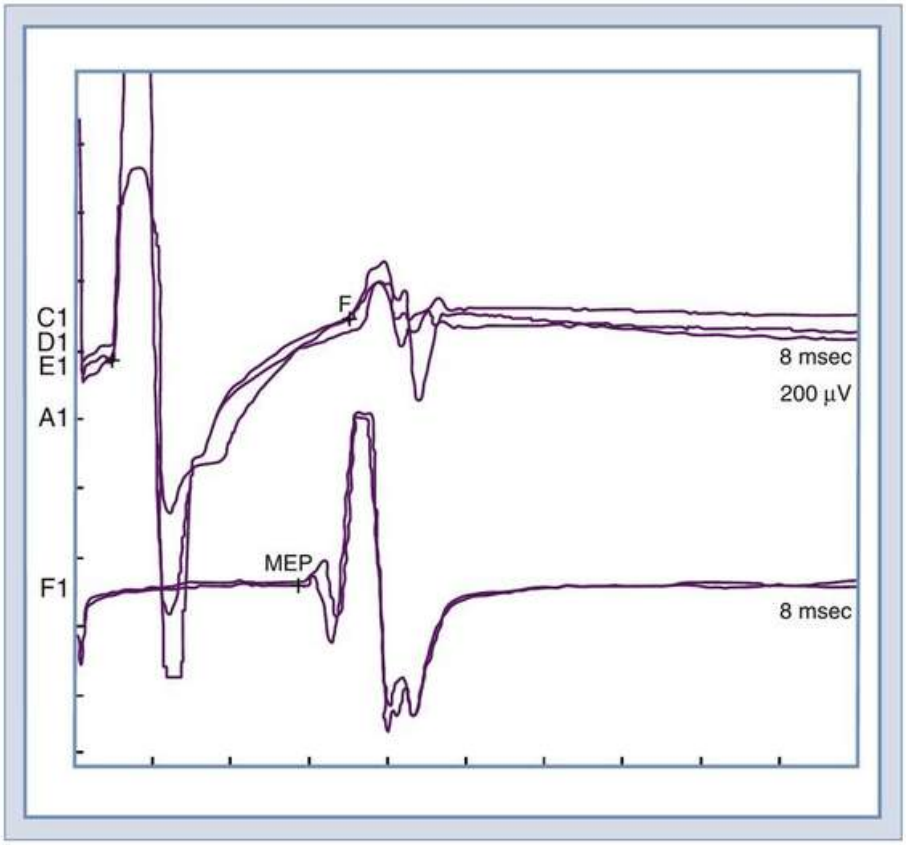


Figure 274.6. Central motor conduction test. *Top tracing,* M wave and F waves to median nerve stimulation. *Bottom tracing,* Motor evoked potential *(MEP)* from transcranial magnetic stimulation. All recordings are over the adductor pollicis brevis.

Reproduced from Youmans & Winn 8e, Fig. 274.6, p. 2109 — Label when you reproduce it: (top tracing) the M wave and the late F waves recorded over abductor pollicis brevis after median nerve stimulation; (bottom tracing) the motor evoked potential from transcranial magnetic stimulation. Write the central motor conduction time formula CCT = MEP − (F + M − 1)/2 under the figure and explain that the late responses (F wave, and by the same logic the H-reflex) are what allow the peripheral segment to be subtracted from the total conduction time.

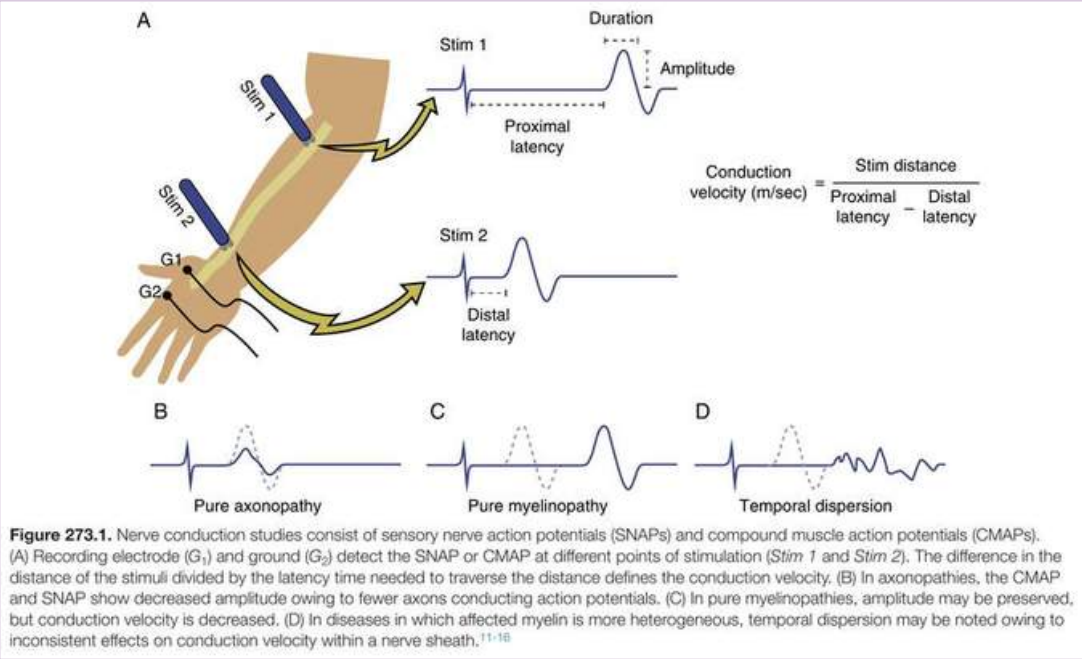


Figure 273.1. Nerve conduction studies consist of sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs). (A) Recording electrode (G_1) and ground (G_2) detect the SNAP or CMAP at different points of stimulation (*Stim 1* and *Stim 2*). The difference in the distance of the stimuli divided by the latency time needed to traverse the distance defines the conduction velocity. (B) In axonopathies, the CMAP and SNAP show decreased amplitude owing to fewer axons conducting action potentials. (C) In pure myelinopathies, amplitude may be preserved, but conduction velocity is decreased. (D) In diseases in which affected myelin is more heterogeneous, temporal dispersion may be noted owing to inconsistent effects on conduction velocity within a nerve sheath.[11-16]

Reproduced from Youmans & Winn 8e, Fig. 273.1, p. 2095 — Label when you reproduce it: nerve conduction studies — (A) stimulating electrodes (Stim 1, Stim 2), recording electrode G1 and ground G2, with amplitude, duration, distal latency, proximal latency and the conduction velocity calculation; (B) pure axonopathy with reduced amplitude and preserved velocity; (C) pure myelinopathy with preserved amplitude and slowed velocity; (D) temporal dispersion in acquired demyelination. Add the late responses (F wave and H-reflex) to the trace when you reproduce it.

5. How to record and interpret it in practice

- **Technique** — supine or prone patient, tibial nerve stimulated in the popliteal fossa with the cathode proximal, recording over soleus; long sweep (about 100 ms); start at a very low intensity and increase slowly, watching the H wave grow before the M wave appears.
- **Parameters reported** — H-wave latency (age- and height-dependent, typically about 30 ms in an adult), the **side-to-side latency difference** (the most reliable measure), the H/M amplitude ratio, and simple presence or absence.
- **Abnormal results and their meaning**:
  - Unilateral prolongation or absence with a normal contralateral response → **S1 radiculopathy**, proximal sciatic or tibial lesion.
  - Bilateral absence in an elderly patient → often non-specific; interpret with caution.
  - Delayed **peroneal** H-reflex → deep gluteal/piriformis syndrome YW p.2153.
  - Symmetrical prolongation with slowed conduction elsewhere → demyelinating polyneuropathy.
  - Exaggerated H/M ratio with a low threshold → increased motor neuron excitability (spasticity, upper motor neuron lesion).
- **Limitations** — the H-reflex localises to an arc, not a point; it does not distinguish a root lesion from a plexus or proximal nerve lesion; it is absent in many normal people in the upper limb; and Youmans' general rule applies: electrodiagnostic results "should always be considered in light of the presenting historical and examination findings" YW p.2091.

6. The other two Hoffmann eponyms — cover them so nothing is missed

- **Hoffmann sign (the finger flexor reflex).** An **upper motor neuron sign**. In cervical spondylotic myelopathy, "patients with upper motor neuron dysfunction may demonstrate increased leg rigidity and balance impairment. There may be **hyperreflexia below the level of compression with the possible presence of the Babinski reflex or Hoffmann phenomenon and pathologic clonus**. Close inspection of the hands may demonstrate visible hand intrinsic atrophy and flattening of the thenar eminence" YW p.2467. It is also part of the paediatric spinal screening examination: "Clonus, Babinski sign, **Hoffmann sign**, Wartenberg sign → consider neurological etiologies, brain/brainstem abnormalities,

intraspinal [pathology]" in adolescent idiopathic scoliosis YW p.2731. **Significance**: it points to a corticospinal tract lesion above C5-C6 and, in a patient presenting with hand clumsiness and wasting, separates cervical myelopathy from a peripheral nerve entrapment. The severity of the myelopathy is then quantified with the **modified Japanese Orthopaedic Association (mJOA) scale** YW p.2467.

- **Hoffmann-Tinel sign.** The peripheral nerve surgeon's most useful bedside instrument: "An injured nerve often exhibits an overlying mechanical hypersensitivity. Evoking a shocklike electrical sensation or paresthesias along the nerve's distribution by percussing over the injured segment is called the **Hoffmann-Tinel sign**. This sign is often present over the nerve in an area of entrapment and can remain present for a long time, sometimes indefinitely" YW p.2089. Its power is in serial testing: "If a Hoffmann-Tinel sign is found to be **advancing** along the anatomic distribution of the nerve, particularly if it does so at the expected rate of nerve regeneration (**about 1 mm/day or 1 inch/month**), this provides putative evidence of ongoing regeneration. Although an advancing Hoffmann-Tinel sign may be a positive indicator of regeneration, it is **associated with subsequent muscle reinnervation and functional recovery in only about half of patients. The lack of an advancing Hoffmann-Tinel sign may be a strong negative finding**, suggesting complete neural interruption or poor regeneration" YW p.2089. Ch. 282 adds the technique — "Starting distally and progressing toward the lesion site, tingling is perceived as soon as the frontal tip of the down-growing highly sensitive but not yet myelinated fibers is met" — and the caveat that "an advancing Tinel sign is not quantitative for the number of regenerating axons and does not guarantee functional outcome", while "lack of an advancing Tinel sign is a poor prognostic indicator" YW p.2184.e2. Ch. 279 uses it as one of the four criteria for exploring a closed injury at 3 months: no improvement in sensibility, muscle strength, neurophysiological tests, **and no progression of the Hoffmann-Tinel sign** YW p.2163. Tapping a nerve sheath tumour also "causes a positive Hoffmann-Tinel sign that helps confirm its parent nerve of origin" YW p.2089. Youmans even carries the historical citation: Turgut, Tubbs and Turgut, "**Paul Hoffmann (1884-1962 AD) and Jules Tinel (1879-1952 AD), and their legacy to neuroscience: the Hoffmann-Tinel sign**" YW p.2168.e1.

7. Putting the three together at the bedside

- A patient with hand wasting and numbness is examined for (i) a **Hoffmann sign** — positive means look up, at the cervical cord; (ii) a **Hoffmann-Tinel sign** at Guyon canal, the cubital tunnel, the carpal tunnel and the scalene triangle — positive means look at that point; and (iii) an **H-reflex** in the lower limb if an S1 root lesion or a proximal sciatic lesion is in question.
- All three are cheap, reproducible and quantifiable, and all three are graded and recorded serially — strength on the MRC scale (Table 272.1) and sensation on the 5-to-0 sensibility scale (Table 272.2) — so that change over time, not a single snapshot, drives the decision to operate [YW pp. 2087, 2089].

(b) Meralgia paraesthetica [5]

8. Definition and anatomy

- **"Meralgia paresthetica, or entrapment of the lateral femoral cutaneous nerve, may be idiopathic or may follow iatrogenic injury"** YW p.2159. It is a **pure sensory** mononeuropathy: there is never weakness, wasting or reflex loss.
- **Origin** — "The posterior branches of the roots of the **L2 and L3** spinal nerves unite to form the lateral femoral cutaneous nerve (LFCN)" YW p.2197.
- **Course** — "The lateral femoral cutaneous nerve travels obliquely over the psoas muscle, then **lateral to the femoral nerve and medial to the anterior superior iliac spine**. This nerve supplies sensation to the skin of the lateral thigh" YW p.2159.
- **Distal division** — "the lateral femoral cutaneous nerve typically divides into **at least two branches distal to the inguinal ligament**" YW p.2160.
- **Underlying mechanism** — an entrapment neuropathy is "a pressure or pressure-induced injury to a segment of a peripheral nerve secondary to anatomic or pathologic structures", in which ischaemia and mechanical distortion combine; mild lesions are largely ischaemic and reversible, whereas "direct mechanical distortion is the major factor underlying more severe, long-lasting forms of pressure palsy", and chronic compression produces fibrosis that worsens ischaemia in a vicious circle [YW pp. 2077, 2128].

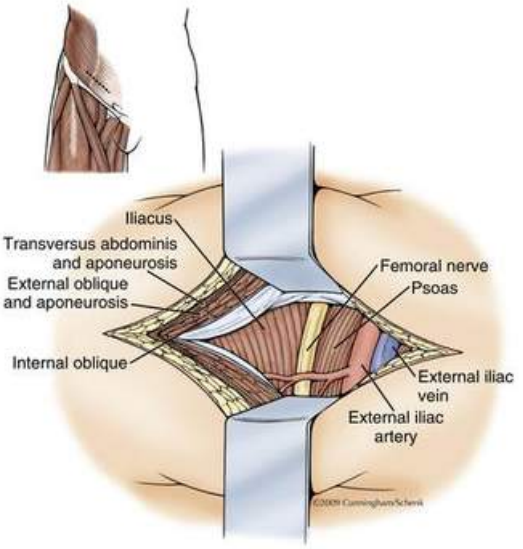


Figure 284.8. The retroperitoneal exposure of the femoral nerve. A transverse skin incision is made, and dissection is carried down to the level of the external and internal oblique muscles, which are separated in the respective directions of their fibers. A self-retaining retractor is used to keep the incision open while the transversalis fascia is opened, and fat must be mobilized. The femoral nerve is located lateral to the femoral artery. A self-retaining retractor system is then used to sweep and retract abdominal contents medially. The femoral nerve is identified lateral to the pulsatile femoral artery. It is dissected superiorly in the iliacus fascia toward the lateral edge of the psoas muscle. (*Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of*

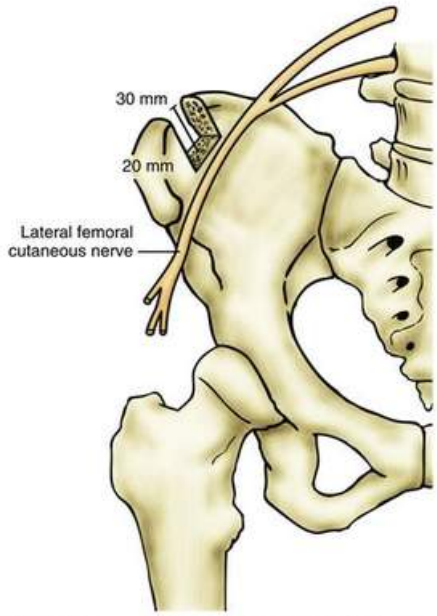


Figure 284.9. Diagram of danger zones for injury to the lateral femoral cutaneous nerve during iliac crest harvesting. Damage was more common in one study[59] with a graft depth of more than 30 mm and proximity to the anterior superior iliac spine of less than 1.5 to 2 cm. (*Copyright M. Schenk and W.K. Cunningham, Biomedical Illustration Services, University of Mississippi Medical Center, Jackson, MS.*)

Reproduced from Youmans & Winn 8e, Fig. 284.9, p. 2198 — Label when you reproduce it: the danger zones for the lateral femoral cutaneous nerve during iliac crest bone graft harvest — the anterior superior iliac spine, the 30 mm depth line and the 20 mm safety distance from the ASIS; plus iliacus, psoas, transversus abdominis and aponeurosis, external and internal oblique, external iliac artery and vein, the femoral nerve and the LFCN.

9. Causes

- **Mechanical / idiopathic** — "**Tightening of the abdominal fascia and 'scissoring' of the LFCN** may be a mechanism responsible for compression after abdominal or gynecologic operations" YW p.2197; obesity, ascites, tight belts and late pregnancy act the same way.
- **Iliac crest bone graft harvest** — "Damage was more common with a bone graft depth of more than 30 mm. The incidence of nerve injury was **20% when graft length exceeded 45 mm, 16% when graft length was between 30 and 45 mm, and 8% when graft length was less than 30 mm**. It is recommended that the iliac crest graft be **no closer than 15 to 20 mm posterior from the ASIS**" YW p.2197.
- **Retractor injury** — "direct injury from retractor blades on the lateral abdominal wall" YW p.2197.
- **Anterior hip arthroplasty** — "Anterior approaches for hip joint arthroplasty can also endanger the LFCN" YW p.2197.
- **Prone positioning** — "Direct external pressure on the LFCN medial to the ASIS is thought to be responsible for injury in posterior spine operations, especially in the **Relton-Hall Operating Frame**" YW p.2198; and nerves are injured "when the nerve is directly under a pressure point, such as the lateral femoral cutaneous nerve on **hip bolsters on a Jackson table**" YW p.2225.
- **Spine surgery generally** — "Meralgia paresthetica is a common complication of spine surgery and usually has a benign course. Injury mechanisms to the LFCN likely include external compression near the anterior superior iliac spine when prone, traction neuropraxia during retroperitoneal dissection, or direct surgical laceration when harvesting anterior iliac crest bone graft"; and it "may be missed during early convalescence when patients have surgical site pain and are under the influence of analgesics and narcotics" YW p.231.e5.
- **Childbirth** — "**LFCN injury was the most common nerve injury associated with parturition in first-time mothers with prolonged second-stage labor**" YW p.2197.
- **Systemic predisposition** — diabetes and amyloidosis "may cause nerve swelling and/or decreased tolerance to mild

CHAPTER 19

Radiosurgery & Radiation in Neurosurgery

7
QUESTIONS SOLVED

Stereotactic Radiosurgery, Gamma Knife & CyberKnife — 4 questions

a) Role of Cyberknife in neurosurgery. [3]
b) Cerebral hemispherectomy. [4]
c) Key-hole neurosurgery. [3]

LONG | JUN 2021 · Paper III · Q10 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 293 *Radiosurgery Technique* (Trifiletti, Lee, Schlesinger, Sheehan), §Radiation Sources for Radiosurgery, §Radiosurgical Devices — Gamma Knife/LINAC-Based Radiosurgery/Proton Radiosurgery, §The Gamma Knife Radiosurgical Procedure, §The Linear Accelerator–Based Radiosurgical Procedure, §Frameless Radiosurgery and the Spine, pp. 2274-2281 (Figs. 293.1-293.4, pp. 2275, 2276, 2281; Table 293.1, p. 2277). Supplementary: Ch. 290 *General and Historical Considerations of Radiotherapy and Radiosurgery*, §Robotic Positioning and Automated Collimation, pp. 2252-2254 (Figs. 290.3-290.4, pp. 2251-2252); Ch. 291 *Radiobiology of Radiotherapy and Radiosurgery*, §Basic Principles of Radiation Therapy, pp. 2257-2258 (Figs. 291.1-291.2, p. 2258); Ch. 28 *Robotics in Cranial Neurosurgery*, §Robotic Systems in Current Use — Stereotactic Radiosurgery, pp. 234, 234.e1-234.e2 (Fig. 28.1, p. 234.e2); Ch. 99 *Hemispheric Disconnection Procedures* (J. Schramm), §Etiology of Hemispheric Epilepsies, §Indications, §Presurgical Evaluation, §Surgical Techniques, §Outcome and Factors of Influence, §Complications, pp. 637-645 (Table 99.1, p. 637; Figs. 99.2-99.6, pp. 640-643); Ch. 437 *Intracranial Internal Carotid Artery Aneurysms*, §Surgical Approach — Lateral Supraorbital Approach, pp. 3548-3550 (Fig. 437.1, p. 3549); Ch. 33 *Brain Retraction*, §Tubular Retractor Systems and Endoscopy, pp. 262-264 (Figs. 33.5-33.6, pp. 263-264); Ch. 34 *Advantages and Limitations of Cranial Endoscopy*, pp. 266-268 (Fig. 34.1, p. 267).

(a) Role of CyberKnife in neurosurgery [3]

1. Definition — what the machine actually is

- **The CyberKnife (Accuray, Sunnyvale, CA) is a compact linear accelerator mounted on an industrial six-axis robotic arm, coupled to an orthogonal kV x-ray image-guidance system that tracks the target and the patient during treatment and re-aims the beam in real time** YW p.234.e1. Youmans defines it in exactly these terms: "The CyberKnife device comprises a linear accelerator (the radiation source) that is mounted on a robotic arm and an image-guidance system that tracks tumor and patient motion during treatment to realign the treatment beam in real time" YW p.234.e1.
- **It is a photon (x-ray) device, not a gamma-ray device.** Photons are produced electrically: the LINAC accelerates electrons to high velocity and directs them onto a high atomic-number (tungsten) target, generating primarily **bremsstrahlung** and secondarily **characteristic x-rays** YW p.2274. There is no radioisotope, so there is no source decay, no source replacement and no Nuclear Regulatory Commission licensing burden — the very reasons LINACs eclipsed ⁶⁰Co teletherapy [YW pp. 2251, 2269].
- **Classification within the radiosurgery family:** Youmans lists the CyberKnife among "specialized EBRT or radiosurgery x-ray devices … compact LINACs mounted on a robotic manipulator (i.e., CyberKnife unit)", alongside the rotational slip-ring TomoTherapy unit and the gyroscopic Zap-X system YW p.2257.
- **Historical marker for the viva:** the CyberKnife was **invented in 1987 by Adler**, combining a mobile LINAC on a robotic arm with an image-guided robotic system YW p.1381. **Clinical trials began in 1994 and US FDA approval for the treatment of intracranial tumors was granted in 1999** YW p.234.e1.

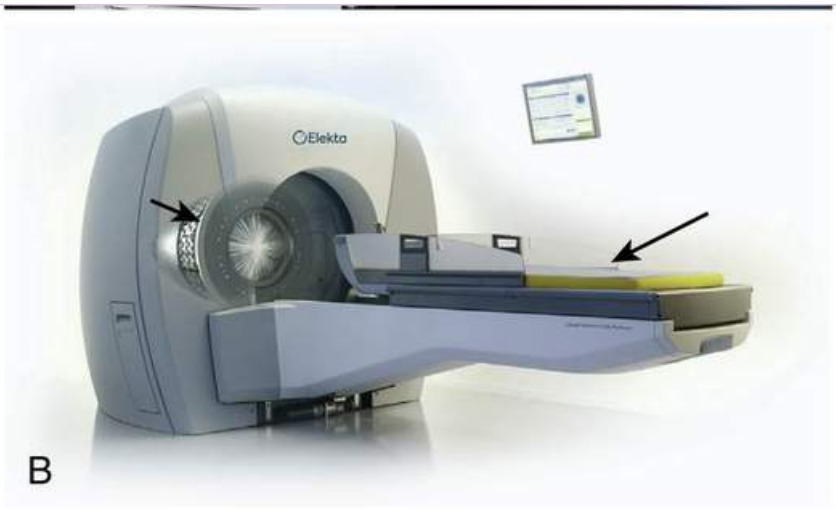




Figure 291.1. Radiotherapy machines and major components. (A) A typical linear accelerator (LINAC) and its components: gantry *(arrowhead)*, collimator *(short arrow)*, and treatment couch *(long arrow)*. (B) Leksell Gamma Knife Perfexion. Collimator body holding 192 cobalt 60 sources *(short arrow)* and treatment couch *(long arrow)*. (C) Leksell Gamma Knife Icon. Integrated cone beam CT *(short arrow)* and frame or mask adaptor *(long arrow)*, high-definition motion management system for tracking patient movement *(arrowhead)*. *(Courtesy Elekta AB, Stockholm, Sweden.)*

Reproduced from Youmans & Winn 8e, Fig. 291.1, p. 2258 — Label when you reproduce it: (A) a conventional C-arm LINAC — gantry, collimator head, treatment couch; (B) Leksell Gamma Knife Perfexion — collimator body holding 192 cobalt-60 sources and the treatment couch; (C) Gamma Knife Icon — integrated cone-beam CT, frame/mask adaptor and the high-definition motion-management camera. Use this to contrast an electrically generated x-ray source (which is what the CyberKnife is, but robot-mounted) with an isotope-based gamma source.

2. The robotic principle — why a robot at all

- **A conventional LINAC has one radiation source on a single-plane gantry**, so serially adding beams quickly extends treatment time beyond what is practical YW p.2252.

- **The strategy of the CyberKnife is to liberate the source from that single plane** by mounting it on an industrial robotic arm, which makes available a very large number of beam directions, called **"nodes" — up to 200 separate nodes treated serially per session to achieve one treatment** YW p.2252.
- **More, smaller, more finely controlled beams equal finer gradations of dose–target conformality**, which Youmans stresses is "particularly critical for SRS, in which lack of conformality has the greatest potential for toxicity given the high individual doses involved" YW p.2252.
- **Beam shaping** is by fixed or variable (iris) secondary collimators, or by micro-multileaf collimation on LINAC platforms generally; combinations of table, gantry and collimator rotations are what produce non-coplanar beam entry over the upper hemisphere of the skull in frame-based LINAC radiosurgery, and the robot achieves the same end by moving the whole accelerator [YW pp. 2252, 2276].
- **It sits within the general class of LINAC-based radiosurgical machines** that Youmans names: Edge (Varian), Versa HD (Elekta), TomoTherapy Hi-Art, **CyberKnife (Accuray)** and Novalis Radiosurgery (BrainLab) YW p.2276.
- **The robotic element is why the CyberKnife appears in the robotics chapter at all.** Youmans calls it "one of the earliest and most widely used robotic arm systems in cranial neurosurgery" and notes that "even though the system is completely noninvasive, it exemplifies the paradigm of programmable neurosurgical intervention involving real-time sensing and actuation and, to a limited extent, autonomous, on-the-fly control to compensate for small movements" YW p.234.e1.



Figure 28.1. The ROSA ONE. The ROSA ONE robotic arm developed by Zimmer Biomet Robotics *(Courtesy LucileBssg/CC BY-SA 4.0. https://en.wikipedia.org/wiki/File:ROSA_One%C2%AE_Robot_.jpg.)*

Reproduced from Youmans & Winn 8e, Fig. 28.1, p. 234.e2 — Label when you reproduce it: the articulated six-degree-of-freedom robotic arm, its base, the end-effector fixture and the stereotactic array. This is the ROSA ONE trajectory robot, but it illustrates the identical engineering idea — an industrial articulated arm repurposed for neurosurgery — that the CyberKnife applies to a miniature linear accelerator.

3. Image guidance and tracking — the defining feature

- **Frameless by design.** Table 293.1 of Youmans lists the CyberKnife as an x-ray (compact LINAC) source, **immobilised**

by mask, delivering **1–5 fractions** — in contrast to Gamma Knife surgery, which uses a stereotactic fixed frame *or* a mask YW p.2277.

- **Intrafraction imaging.** "Both the CyberKnife and Novalis systems use x-rays during treatment to confirm positioning continuously" YW p.2272. Youmans elaborates that the CyberKnife "utilizes multiple orthogonal skull x-rays obtained during the course of delivering a radiation treatment, which are rapidly integrated into a patient-specific algorithm, providing continuous feedback regarding interfractional motion" YW p.2294. This is called **intrafraction repetitive imaging**, and it is a genuine step above pre-treatment-only image guidance YW p.2294.
- **Consequence for accuracy:** the theoretical accuracy of frame-based radiosurgery is recognised to be **less than 1 mm**, and the accuracy of LINAC-based radiosurgery with a localising mask has **approached 1 mm** in later medical physics reports YW p.2279. Youmans concludes that with sophisticated frameless immobilisation devices, strict IGRT protocols and robotic positioning technology, "similar motion is being observed as compared with frame-based treatment", with **margins of 1.0 to 2.0 mm** achievable YW p.2267. Where a frameless approach is used for a single fraction, it is nonetheless "reasonable to consider use of a PTV margin of 1–2 mm to account for immobilisation error" YW p.2272.
- **Spinal tracking.** Image landmarking with radiopaque fiducials implanted in the vertebrae, or direct imaging of vertebral anatomy, is used to localise spinal targets YW p.2281. The data justify continuous tracking: respiration-induced vertebral motion is **less than 1 mm** supine (Yin), but other work shows spinal anatomy may move **more than 2 mm** during radiosurgery, and Agazaryan observed vertebral movement of **as much as 3 mm occurring in as little as 5 minutes** — hence the need for intra-fraction monitoring and correctional shifts even in short treatments YW p.2281.

4. Dosimetry — how a CyberKnife plan behaves

- **Prescription isodose line.** In LINAC-based radiosurgery the prescription isodose is typically **high, 70%–90%**, meaning the maximum dose is only 10%–30% greater than the dose at the lesion margin, so the plan is **more homogeneous** than a Gamma Knife plan, where the margin isodose is typically the **50% line** YW p.2280.
- **Dose falloff** in LINAC-based radiosurgery is also steep, but varies considerably with collimator size and with the planning method used (multiple isocentre, dynamic arcs, static beams) YW p.2280.
- **Penumbra.** The region of radiation falloff is the penumbra; dose within it may be high enough to cause radiation toxicity, so for lesions adjacent to brainstem, motor cortex or spinal cord, the dosimetric consequences of the penumbra must be explicitly considered YW p.2280.
- **Volume nomenclature.** LINAC-based radiosurgery uses conventional radiotherapy volumes more frequently than the Gamma Knife does — **GTV, CTV and PTV** — and the minimal dose thought to be clinically safe and effective is prescribed to the PTV YW p.2280.
- **Multi-fraction capability.** Because the mask is relocatable, the CyberKnife naturally supports **hypofractionated radiosurgery in two to five fractions** [YW pp. 2277, 2279], which is the route to treating larger lesions, lesions abutting the optic apparatus and re-treatments YW p.2272.

Table 1 · The radiosurgical and radiotherapy platforms compared — reproduced in full from Youmans & Winn 8e, Table 293.1, p. 2277.

#	Device	Radiation source	Immobilisation	Fractionation
1	Conventional radiotherapy	X-rays (LINAC)	Mask	Multiple fractions (25–30)
2	Intensity-modulated radiotherapy (IMRT)	X-rays (LINAC)	Mask	Multiple fractions (25–30)
3	Gamma Knife surgery	Gamma rays (cobalt-60)	Stereotactic fixed frame, or mask	1–5 fractions*
4	**CyberKnife**	**X-rays (compact LINAC)**	**Mask**	**1–5 fractions**
5	LINAC-based radiosurgery	X-rays (LINAC)	Stereotactic fixed frame, relocatable frame, or mask	1–5 fractions

6	Proton radiosurgery	Proton beam (cyclotron)	Stereotactic fixed frame, or mask	1–5 fractions
7	Proton radiotherapy	Proton beam (cyclotron)	Mask	Multiple fractions (25–30)

*Most Gamma Knife surgery was single fraction; hypofractionated Gamma Knife surgery (3–5 fractions) can be performed on the Icon and Perfexion models YW p.2277.

5. Clinical roles of the CyberKnife in neurosurgery — intracranial

- **Brain metastases** — single, oligometastatic and recurrent disease; the CyberKnife appears in Youmans' tabulated radiosurgical series for malignant intracranial tumours, including recurrent glioblastoma treated with **24 Gy in 1–3 fractions** YW p.2331.
- **Recurrent high-grade glioma** — CyberKnife series are among those Youmans tabulates for salvage radiosurgery of recurrent HGG, where a subset of patients derives benefit despite the infiltrative nature of the disease [YW pp. 2330-2331].
- **Brainstem glioma** — CyberKnife radiosurgery for adult brainstem glioma is specifically referenced in the chapter's literature YW p.2334.e5.
- **Benign skull base tumours** — head and neck paragangliomas, where control rates with Gamma Knife, LINAC and CyberKnife are **99%, 96% and 95%** respectively YW p.1393; jugulotympanic paraganglioma YW p.1394.
- **Trigeminal neuralgia** — CyberKnife robotic radiosurgery is included in the evidence base for destructive procedures for facial pain, with Barrow Neurological Institute pain-scale outcomes reported at 3, 7.75, 9 and 18 months [YW pp. 1531, 1557.e3].
- **Orbital lesions** — CyberKnife radiosurgery for orbital pathology is cited in the orbital tumour literature YW p.1562.e1.
- **Arteriovenous malformations** — the radiosurgery-based AVM grading scale (RBAS) has been shown to predict outcome after **LINAC-based, CyberKnife and proton beam radiosurgery**, not only after Gamma Knife YW p.2353.

6. Clinical roles — spinal and extracranial, where the machine earns its keep

- **Spinal radiosurgery is the CyberKnife's signature extracranial application.** Youmans notes that the CyberKnife "was developed by" a team addressing precisely the problem of spinal cord tolerance in spine radiosurgery YW p.2366.
- **Intramedullary spinal cord AVMs** — multisession CyberKnife radiosurgery has been used for intramedullary spinal cord arteriovenous malformations YW p.2371; Youmans records a series of patients (cervical, thoracic and conus medullaris) treated with CyberKnife where the mean marginal dose was **20.5 Gy** and mean volume **2.3 mL** [YW pp. 2367-2368].
- **Spinal hemangioblastoma** — Youmans reports the natural history and CyberKnife radiosurgical treatment of **87 patients with 103 CNS hemangioblastomas**, in von Hippel–Lindau and sporadic patients YW p.2369; CyberKnife ablation for intramedullary lesions has been reported with tumoral enhancement suggestive of necrosis YW p.2370.
- **Metastatic spine disease** — CyberKnife radiosurgery for metastatic spine tumours is described as safer and less expensive than open surgery in the referenced literature, and is used for radiosurgical decompression of metastatic epidural spinal cord compression [YW pp. 2383.e1-2383.e3].
- **Recurrent focal spinal metastases** after prior irradiation YW p.1803.e10.
- **General principle Youmans states explicitly:** "Exponential growth of the extracranial applications of radiosurgery is likely to be observed in the coming years, and it can be expected that radiosurgery will play an expanding role in the setting of spinal metastasis" YW p.2281.

7. Advantages, limitations and pitfalls

- **Advantages**
  - **No pins, no frame** — abolishes pin-site pain, bleeding and infection, and the need to remove a frame at the end of the day [YW pp. 2277, 2280].
  - **True multisession capability** — permits treatment of larger lesions and of lesions close to the optic apparatus,

where **fractionated radiosurgery will allow point doses of 25 Gy over five fractions to the optic apparatus**, well above the 8 Gy single-fraction constraint YW p.2279.

- **Extracranial reach** — the machine is not restricted to the head, unlike the Gamma Knife's fixed collimator helmet YW p.2277.
- **Continuous intrafraction verification**, so patient movement during a long session is corrected rather than merely detected [YW pp. 2272, 2294].
- **More homogeneous dose distribution** (prescription at 70%–90%) than the Gamma Knife YW p.2280.

- **Limitations**
  - **Treatment times are long** because up to 200 nodes are delivered serially YW p.2252; for LINAC-based techniques generally, multiple segments push treatment from ~10 minutes for a 3D conformal plan to **25–30 minutes** for an intensity-modulated plan, although flattening-filter-free beams have largely removed this problem [YW pp. 2266-2267].
  - **The accuracy debate.** Youmans states plainly that for frameless hypofractionated radiosurgery "the accuracy of such an approach has been the subject of some debate" YW p.2279.
  - **Loss of the physical guarantee of a frame.** Frame-based accuracy is <1 mm; frameless approaches approach but do not better it, and a 1–2 mm PTV margin may still be prudent for single-fraction work [YW pp. 2272, 2279].
  - **Imaging dose** — daily cone-beam CT or orthogonal kV imaging adds approximately **2 cGy per scan**, a consideration in children and in benign disease, though trivial relative to the therapeutic dose YW p.2267.
  - **Cost and access** compared with a conventional LINAC.

(b) Cerebral hemispherectomy [4]

8. Terminology — a ladder from resection to pure disconnection

- **The governing principle of modern surgery is stated by Youmans in a single line: "to forgo anatomic removal of brain tissue by instead disconnecting brain regions"** YW p.639. The evolution over the last two decades "was to replace resective steps with disconnective steps, which culminated in nearly exclusive disconnective surgery" YW p.645 .
- **Anatomic hemispherectomy** — a large hemicraniotomy, clipping of the anterior and middle cerebral arteries and the parasagittal veins, and stepwise or en-bloc removal of the hemisphere YW p.642.
- **Hemidecortication / hemicorticectomy** — rely on the principle that only the ictogenic cortex needs removal; the ventricle is not opened except at the temporal tip to remove the hippocampus; no callosotomy required, but extensive brain exposure is necessary, and in holohemispheric dysplasia or hemimegalencephaly the surgeon risks spatial disorientation YW p.642.
- **Functional hemispherectomy (Rasmussen)** — intermediate; partial resection with disconnection of the residual hemisphere.
- **Peri-insular hemispherotomy** — combines moderate-to-limited resection with disconnection; includes Schramm's peri-insular transcortical approach, Villemure's peri-insular hemispherotomy and the Japanese peri-insular modification YW p.642.
- **Transsylvian keyhole hemispheric deafferentation (Schramm)** and **vertical parasagittal hemispherotomy (Delalande)** — "two disconnection operations that involve little or no brain removal and extensive disconnections" YW p.639.
- **Endoscopic and interhemispheric transcallosal variants** and **extraventricular vertical hemispherotomy** have also been described YW p.639.

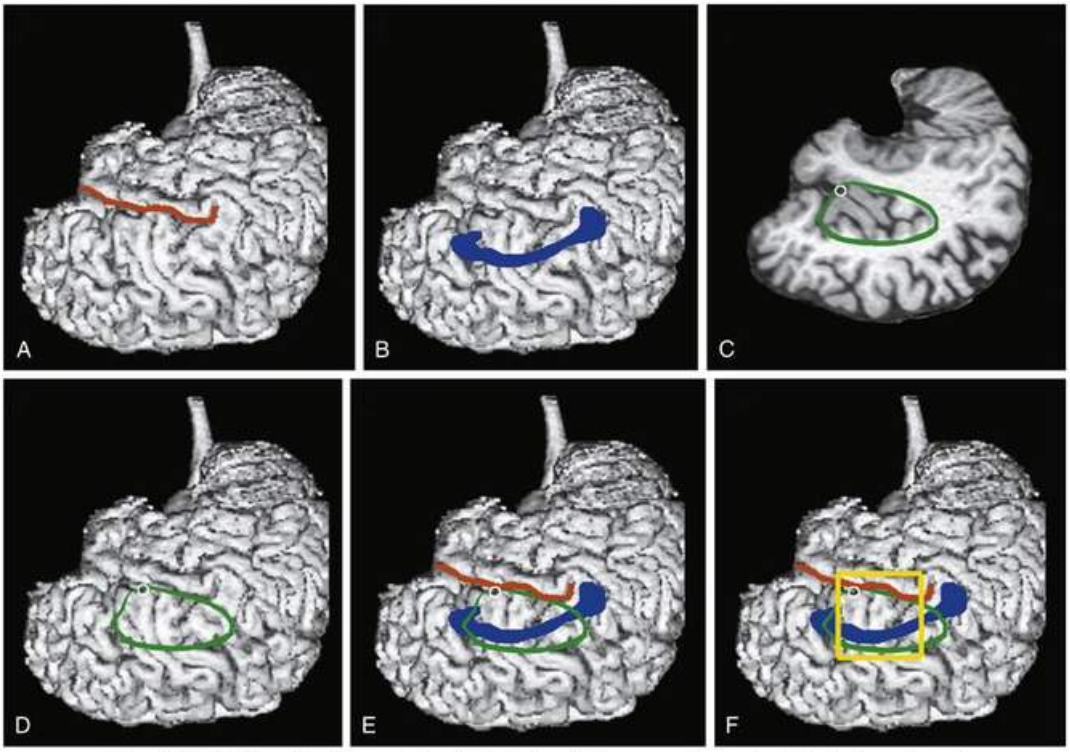


Figure 99.3. Relationship of important anatomic landmarks to one another projected onto the surface of a brain reconstructed from MR images. The images are arranged from the surgeon's perspective. The reformatted images are taken from an unaffected hemisphere. (A) The *red line* shows the sylvian fissure. (B) The shape and position of the corpus callosum are shown in *blue* as projected onto the surface. (C) The circular sulcus, which represents the border of the insular cistern, is portrayed in *green*. The *white ring* delineates the position of the ascending M1 just in front of the limen insulae. (D) Outline of the circular sulcus projected onto the lateral surface of the hemisphere. (E) Relationship of the position of the corpus callosum, circular sulcus, and sylvian fissure projected onto the surface. (F) Outline of a 4 × 4-cm craniotomy, shown in *yellow*, superimposed on the sylvian fissure, the outline of the circular sulcus, and the shape of the corpus callosum. *(Based in part on a figure from Schramm J, Kral T, Clusmann H. Transsylvian keyhole functional hemispherectomy. Neurosurgery. 2001;49:891.)*

Reproduced from Youmans & Winn 8e, Fig. 99.3, p. 640 — Label when you reproduce it: (A) the sylvian fissure in red; (B) the outline of the corpus callosum in blue, projected onto the surface; (C) the circular sulcus (border of the insular cistern) in green, with the white ring marking the ascending M1 just in front of the limen insulae; (D)–(E) the three landmarks superimposed; (F) the 4 × 4-cm craniotomy in yellow placed so that its upper border lies at the level of the corpus callosum and its lower border 0.5 cm below the sylvian fissure. This single figure is the whole geometry of the transsylvian keyhole hemispherotomy.

9. Aetiology — the diseases that lead to hemispheric surgery

- The diagnoses group into **inborn, perinatal and acquired** conditions YW p.637:
  - **Sturge-Weber syndrome (SWS)** — rare congenital disorder whose characteristic feature is **leptomeningeal angiomatosis**, in a proportion associated with a facial naevus (encephalotrigeminal angiomatosis); progressive epilepsy, cortical calcification, cerebral atrophy and, if the epilepsy is untreatable, mental retardation. Seizures usually develop by the end of the first year; occipital or parietal cortex is usually involved but changes remain restricted to one hemisphere YW p.637.
  - **Hemimegalencephaly (HME)** — enlarged hemisphere with abnormal architecture, pachygyria, polymicrogyria, grossly enlarged gyri and periventricular ectopic grey matter; commonly a neuronal migration disorder; frequent intractable seizures with variable hemiparesis and usually marked mental retardation YW p.637.
  - **Multilobar cortical dysplasia, polymicrogyria, lissencephaly** YW p.637.
  - **Cystic defects from intrauterine or perinatal infarction or haemorrhage (porencephaly)** YW p.637.
  - **Hemiplegia-hemiconvulsion-epilepsy syndrome (HHE)** YW p.637.
  - **Rasmussen encephalitis** — intractable epilepsy with progressive hemiparesis proceeding inexorably to hemiplegia, mental decline and hemispheric atrophy. **Median age at onset 4.2 years (range 2–11 years)** in a 16-patient multicentre study; **most brain damage occurs in the first 8 to 12 months**; focal seizures predominate and

epilepsia partialis continua develops in a large proportion; characteristic imaging is **perisylvian atrophy and encephalomalacia**; histology shows a **perivascular T-lymphocyte infiltrate** with neuronal destruction; progression is characterised by serial MRI YW p.637.

- **Hemiatrophy** of unclear, post-traumatic or post-encephalitic origin YW p.637.

Table 2 · Aetiology of seizures in a hemispheric disconnection series — reproduced in full from Youmans & Winn 8e, Table 99.1, p. 637.

#	Aetiology	n
1	Infarct, ischaemia, porencephaly	54
2	Cortical dysplasia, migration disorders	10
3	Hemimegalencephaly	12
4	Sturge-Weber syndrome	6
5	Rasmussen encephalitis	15
6	Hemiatrophy, unclear cause	7
7	Post-encephalitic, HHE, or other	6
—	**Total**	**110**

10. Indications and timing

- **The decision is straightforward for unihemispheric lesions that are inborn or occurred around birth** and manifested in infancy or early childhood as frequent intractable seizures YW p.637.
- **Also indicated for small infants with "catastrophic epilepsy"** manifesting early after birth, usually from severe hemispheric damage or an inborn malformation in which lengthy drug treatment is known to fail YW p.637.
- **Adults are candidates too** — "the procedure is also performed in adults with good seizure-freedom rates" YW p.637.
- **Why it works functionally:** the disconnection is performed on a mostly non-functional or partly destroyed hemisphere, where language and motor function have been, or will be, transferred to the other hemisphere — the rule when damage occurred in utero or perinatally. Patients typically already have spastic hemiparesis, and although the procedure nearly always results in loss of fine motor control of the hand and occasionally in deterioration of gait, **the majority of patients are able to walk and even to use the arm and hand to a certain degree** YW p.637.
- **Timing:**
  - Children with holohemispheric malformation or HME with unilateral severe continuous seizures may be operated **very early — in Schramm's group at 4 months** YW p.637.
  - **If hemiparesis is already well established or severe, little motor function will be lost** YW p.637.
  - **Rasmussen encephalitis is the hard timing decision** — the disease invariably leads to severe hemispheric atrophy with complete hemiplegia and loss of language; many institutions elect to proceed **before relentless seizures have damaged the unaffected hemisphere**, accepting earlier motor loss YW p.637. Earlier surgery also increases the chance that the healthy hemisphere compensates for loss of motor or speech function YW p.638.
  - **Problematic group:** children older than 7–8 years when the language-dominant hemisphere is affected by progressive disease; some language function may still develop after surgery even in children aged 4 to 7 years YW p.637.
  - **The epileptic encephalopathy argument** — the deleterious effect of frequent seizures on cognition, behaviour and other neurological function is itself a legitimate reason to operate, particularly where the cause is recognised as untreatable early in the clinical course YW p.638.

11. Contraindications

- **Absolute:** hemispheric deafferentation is contraindicated if the presurgical evaluation **cannot demonstrate that all typical ictal activity originates from the affected hemisphere** YW p.638.

- **Relative:** independently arising seizures from the "healthy" hemisphere. Occasional isolated contralateral seizure episodes may be acceptable because they do not automatically indicate an independent focus YW p.638.
- **Bilateral epileptogenic activity on EEG is seen in as many as 75% of patients** but may be secondary and propagated from the diseased hemisphere; it is associated with a somewhat reduced probability of seizure freedom, yet **77% of patients with suspected bilateral disease were either seizure free or had only "minor events"** in a large series [YW pp. 638-639].
- **Incomplete hemianopia** is occasionally considered a contraindication, especially in older children, but Schramm's experience is that patients who have grown up with incomplete hemianopia adjust well YW p.639.
- **Mental retardation is no longer a contraindication** in Schramm's institution and others YW p.639.

12. Presurgical evaluation

- **Mainstays: high-quality MRI and video-EEG monitoring of seizures** — in most patients this plus the clinical history is sufficient to establish the indication YW p.639.
- **Neuropsychological testing** wherever possible, to quantify post-operative change YW p.639.
- **Intracarotid amobarbital (Wada) test** — sometimes necessary to demonstrate the language-dominant hemisphere and exclude dissociated sensory and motor speech areas; particularly important in late-onset or progressive disease where hemispheric transfer of language is in doubt. **In patients with contralateral ictogenic activity, the Wada test differentiates conducted activity from an autonomous contralateral focus**: if contralateral ictal activity disappears when amobarbital is injected into the affected hemisphere, the contralateral activity is a conducted phenomenon and will not adversely affect prognosis YW p.639.
- **Brain biopsy** may be necessary to confirm Rasmussen encephalitis YW p.639.
- **Implanted electrodes are rarely necessary**; intradural recordings are used occasionally to identify the few patients in whom multilobar resection would suffice YW p.639.

13. Goals of surgery

- **(1) Cessation of seizures; (2) relief of the epileptic encephalopathy and neurological deterioration; (3) improvement of cognitive development and of behavioural disturbance** YW p.639. Achieving these leads to better psychosocial development and improved quality of life; Youmans concedes the second and third goals are "very ambitious and cannot be attained in all cases" YW p.639.

14. Operative technique — the transsylvian keyhole deafferentation in order

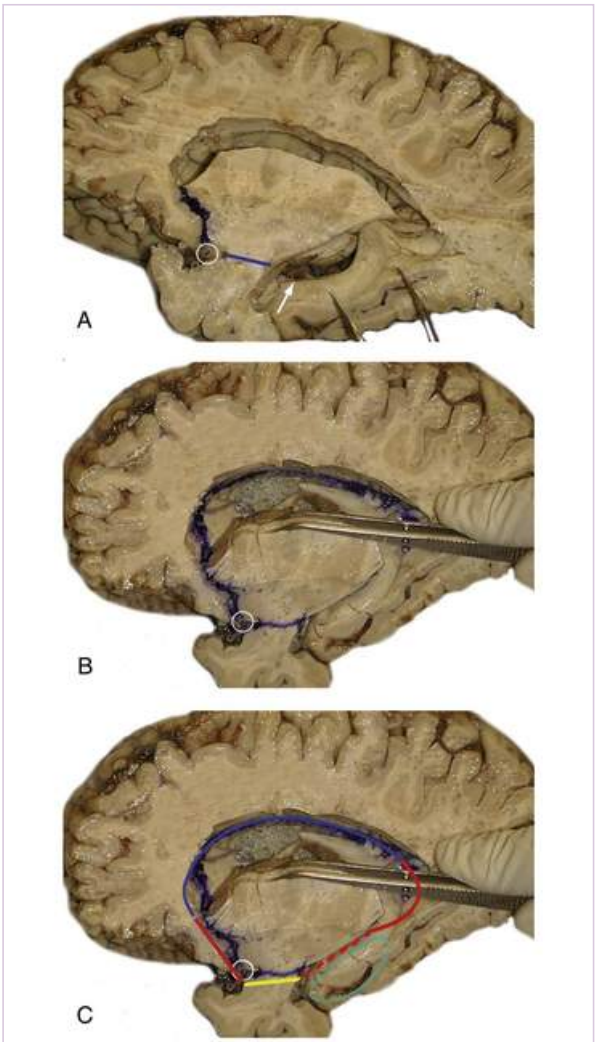


Figure 99.4. Demonstration of mesial disconnection lines for the technique of transsylvian/transventricular hemispheric deafferentation. (A) In a formalin-fixed brain, a parasagittal cut exposes the lateral ventricle and the temporal horn simultaneously. The *white circle* marks the position of the ascending M1 division of the middle cerebral artery. One *blue line* above M1 marks the frontobasal disconnection leading from the tip of the frontal horn to the base of the frontal lobe. The other *line* marks the transection of the temporal stem and disconnection of the amygdaloid body leading from the choroidal point to the arachnoid parallel to the ascending M1 down to the uncus. The *arrow* marks the choroidal point, which corresponds to the end of the choroidal fissure (i.e., the terminal end of the attachment of the choroid plexus). Anterior to this point, the entorhinal cortex is located between the head of the hippocampus and the amygdaloid body. (B) Paramesial transection of the callosal fibers within the lateral ventricle is shown by the *line* as a prolongation of the frontobasal disconnection. (C) The different types of disconnection lines shown in one picture: the *blue line* is the paramedian callosal transection, the *anterior red line* represents the frontobasal disconnection, the *yellow line* represents the temporomesial disconnection anterior to the choroidal point, the *posterior red line* shows the occipitotemporomesial disconnection through the trigonal area, and the *dotted red line* shows the temporomesial disconnection along the choroidal fissure, used if one chooses not to resect the hippocampus. The *green oval* shows resection of the hippocampus, which is frequently done to obtain a good specimen. (© Johannes Schramm.)

Reproduced from Youmans & Winn 8e, Fig. 99.4, p. 641 — Label when you reproduce it: (A) the parasagittal cut exposing lateral ventricle and temporal horn together, with the white circle on the ascending M1 division of the MCA, the blue line above M1 marking the frontobasal disconnection from the tip of the frontal horn to the frontal base, and the second line marking transection of the temporal stem and amygdala from the choroidal point to the uncus; the arrow on the choroidal point. (B) Paramesial transection of the callosal fibres within the lateral ventricle. (C) All disconnection lines in one picture — blue = paramedian callosal transection, anterior red = frontobasal disconnection, yellow = temporomesial disconnection anterior to the choroidal point, posterior red = occipitotemporomesial disconnection through the trigone, dotted red = temporomesial disconnection along the choroidal fissure when the hippocampus is left in place, and the green oval = hippocampal resection.

- **Craniotomy** — a **4 × 4-cm or 4 × 5-cm** craniotomy superior to the sylvian fissure, through a linear or curvilinear incision, to gain access to the insula and corpus callosum YW p.639. Neuronavigation is advisable so that the **upper border sits at the level of the corpus callosum and the lower border 0.5 cm below the sylvian fissure**, with the ascending M1 segment visualised at the anterior border YW p.641.
- **Step 1 — transsylvian exposure of the circular (limitans) sulcus of the insular cortex** via the small craniotomy. **Average length of the insula is 49 to 57 mm** YW p.639.
- **Step 2 — temporomesial disconnection** by a transventricular route through the temporal stem. A pure disconnection is possible from the **choroidal point** anteromesially through the lateral mass of the bulging amygdaloid body to the arachnoid covering the mesial uncus; alternatively uncus and amygdala are removed by suction. **The hippocampus may be left in place** provided the mesiotemporal disconnection is carried backwards along the choroidal fissure to the trigone, though some hippocampus may be harvested for histology YW p.639.
- **Step 3 — complete opening of the entire lateral ventricle** through a transcortical insular incision, from the insular cistern along the inferior, posterior and superior parts of the circular sulcus, from the temporal horn all the way posteriorly to the trigone and anteriorly to the tip of the frontal horn. **Care is taken to preserve the opercular branches of the MCA and the tributaries and anastomoses of the sylvian vein** [YW pp. 639-641].
- **Step 4 — mesial disconnection and callosotomy**, itself in two parts:
  - **Frontobasal and posteromediobasal lobar disconnection** — along a line from the ascending MCA through the bulk of the lateral frontal lobe to the tip of the frontal horn, then following the M1 segment and then the anterior cerebral artery, along A1 and later A2, around the anterior knee of the corpus callosum YW p.641.
  - **Paramesial callosotomy** — working from within the ventricle, the pericallosal artery is followed while callosal fibres are disconnected in a paramedian plane. Posteriorly, the **inferior rim of the falx and the anterior rim of the tentorium** are the markers of the medial extent, carried round to the trigone until the earlier temporomesial disconnection is met YW p.641.
- **Result:** reduced blood loss, reduced need for transfusion and decreased operative time compared with resective techniques YW p.641. Particularly quick and well suited to porencephalic cysts and marked atrophy of the insula–basal ganglia complex YW p.641.
- **Pitfalls of this technique:** limitations in HME unless combined with a suprasylvian window or opercular/temporal resection to gain space for post-operative swelling and better transinsular exposure YW p.641; a risk of **incomplete disconnection**, classically a frontobasal line placed too anteriorly (not in the coronal plane of M1/A1) leaving posterior orbitofrontal cortex connected — intraoperative MRI has been proposed to reduce this YW p.641; **hydrocephalus**, as with all transventricular disconnection procedures YW p.641.

15. The vertical parasagittal hemispherotomy (Delalande) — five steps

- Descriptively a **dorsal transcortical subinsular hemispherotomy**; a vertical approach with much less resection and more disconnection [YW pp. 641-642]:
  1. **Parasagittal frontal craniotomy approximately 3 × 5 cm**, one-third anterior and two-thirds posterior to the coronal suture.
  2. **Transcortical access to the lateral ventricle** via limited cortical resection, to reach the foramen of Monro and the posterior thalamic region.
  3. **Paramedian callosotomy including transection of the posterior column of the fornix.**
  4. **Lateral transection between the thalamus and the striatum**, starting in the lateral ventricle and reaching down to the temporal horn.
  5. **After completing the anterior callosotomy, resection of the posterior part of the gyrus rectus** and lateral extension of the transection line so that the head of the caudate meets the substriatal transection line lateral to the thalamus.
- **Results of the original series: 83 children, seizure-free outcome 74%, transfusion rate just 8%, shunt rate 16%** YW p.642. The insular cortex is automatically disconnected; shunting was most often required in the HME subgroup YW p.642. Advantage: low blood loss and preservation of superficially located large vessels including the MCA. Disadvantage: the long distance from cortical surface to the temporal horn and frontal base YW p.642.

Table 3 · Hemispheric procedures compared — compiled from Youmans & Winn 8e, Ch. 99, pp. 639-645.

#	Procedure	Craniotomy / exposure	Brain removed	Shunt rate	Comment
1	Anatomic hemispherectomy	Large hemicraniotomy	Whole hemisphere, en bloc or stepwise	Highest; independent risk factor for hydrocephalus (P < .0001)	Severe hypotension, blood loss, prolonged operative times YW p.642
2	Hemidecortication / hemicorticectomy	Extensive exposure	Cortex only; ventricle opened at temporal tip	20% and 32% reported	Risk of spatial disorientation in HME YW p.642
3	Peri-insular hemispherotomy (Villemure / Schramm / Japanese)	Peri-insular window	Frontoparietal and temporal opercula ± insular cortex, mesial temporal structures	8%–23%	Combined resection–deafferentation YW p.642
4	**Transsylvian keyhole deafferentation (Schramm)**	**4 × 4 or 4 × 5 cm above sylvian fissure**	**Little or none; insular cortex removed by subpial suction as routine policy**	**3% (keyhole group); 5.2% overall paediatric (6 of 95)**	Quickest; ideal for porencephaly and atrophy [YW pp. 639-641]
5	**Vertical parasagittal hemispherotomy (Delalande)**	**3 × 5 cm parasagittal**	**Limited cortical window only**	**16%**	74% seizure free in 83 children; transfusion 8% [YW pp. 641-642]

16. Outcome, complications and choice of procedure

- **Seizure freedom ranges from approximately 50% to 80%; more recent series report 75% to 90%, and for selected subgroups over 90%** YW p.644.
- **Cause dominates outcome** — congenital malformative disease does worse; **HME 40%–60% seizure freedom**, the poorest of all; SWS **80%–100%**; Rasmussen encephalitis **80% (20 patients) and 77% (83 patients)**; porencephalic defects the best at **95%** in Schramm's paediatric series YW p.644.
- **Technique matters less than cause, but Holthausen's 328 cases from 12 centres showed hemispherotomy 85.7% Engel class I versus the Rasmussen technique 66.1% and hemicorticectomy/hemidecortication 60.7%** YW p.644.
- **Acute post-operative seizures** occurred in **22.6% of 114 patients** and were associated with worse short-term outcome; **more than five acute post-operative seizures in the first 10 days** predicted worse control at 0.5 and 1 year YW p.644.
- **Long-term:** in one large cohort seizure freedom fell from **78% at 6 months to 70% at 2 years and 58% at 5 years**; in Schramm's paediatric series it was **84.6% at 1 year (n = 92), 80% at 10 years (n = 36) and 77% at 15 years (n = 25)** YW p.644.
- **Cognition and behaviour: 79%** of patients have below-average intelligence pre-operatively; hemispheric surgery does not reduce health-related quality of life and cognition frequently improves; **57% (33 of 55) had improved behaviour by parental report, IQ improved in 38% and declined in 9%, and schooling improved in 40%** YW p.644.
- **Unavoidable side effects to consent for: complete hemianopia and loss of some motor function** — fine pincer movement of thumb and index finger, and fine foot movement (inversion, eversion, fanning of toes); gait deterioration in a small percentage. **Adverse effects are more severe when the disease develops later in life and the hemiparesis is mild** YW p.639.
- **Complications:**
  - **Intraoperative** — marked blood loss, electrolyte disturbance, coagulation disorders; hypovolaemia with bradycardia, hypothermia and in extreme situations cardiac arrest YW p.644.
  - **Early post-operative** — electrolyte disturbance, diabetes insipidus or SIADH, swelling of the contralateral healthy hemisphere, transient temperature rises for up to 10 days that must be distinguished from bacterial meningitis;

subdural hygroma or acute haematoma; dysphagia; movement disorders YW p.644.

- **Incomplete disconnection — described as a cause of persisting seizures in 2% to 30% of patients, and it can occur with any technique** YW p.644.
- **Hydrocephalus** — in a multi-institutional review of **690 patients the rate was 23%, occurring as late as 8 years after surgery**; multivariate analysis identified **anatomic hemispherectomy (P < .0001) and previous brain surgery (P = .04)** as independent risk factors YW p.642. Shunt rates of 8% to 30% are described overall YW p.644.
- **Death** — historically 4%–6%, reduced to about 2% with functional hemispherectomy techniques, and in modern series about **1%, rarely 2%**; in a review of 153 cases plus Schramm's own series the rate was **0.7% (1 of 140)** YW p.644.

- **Choice of procedure:** "When seizure-free outcome rates are comparable for different procedures, safety considerations and differences in complication risk profiles play a dominant role" — and since seizure outcomes after hemispherotomy and functional hemispherectomy are similar, "it is hard to find arguments in favor of anatomic hemispherectomy." **The overriding rule is that the surgeon must be comfortable and knowledgeable about the technique chosen** YW p.643 . For **HME**, create a larger craniotomy — at least large enough to expose the entire insular cistern through an opercular resection, giving full visualisation of the opened ventricular system; pre-operative embolisation has been proposed in very young babies to reduce operative risk and gain time YW p.643.

(c) Key-hole neurosurgery [3]

NOT COVERED IN YOUMANS — answered from the source named below

Searched Youmans & Winn 8e for a dedicated chapter or section on "keyhole" neurosurgery (chaps "keyhole", chaps "minimally invasive", full-text search for "keyhole" AND "supraorbital", "minimally invasive" AND cranial). **There is no stand-alone chapter on keyhole neurosurgery, and the book nowhere gives Perneczky's formal definition or a taxonomy of keyhole craniotomies.** What the book does contain, and what is used below, is: an explicit description of the lateral supraorbital "keyhole" craniotomy with its own figure (Ch. 437, pp. 3548-3550, Fig. 437.1); the keyhole-concept hemispherotomy (Ch. 99, pp. 639-641); the enabling technologies — cranial endoscopy (Ch. 34, pp. 266-273), tubular retractors and the transcylinder approach (Ch. 33, pp. 262-264), and neuronavigation; and scattered application to meningiomas (Ch. 172, p. 1259; Ch. 178, p. 1338) and pituitary tumours (Ch. 175, p. 1303). The section below is built entirely from those Youmans passages; no outside source has been used, so no @@GUIDE@@ block is required.

17. The principle

- **A keyhole craniotomy is a deliberately small, precisely sited bone opening through which a deep target is reached by exploiting cisternal and sulcal corridors and the cone of vision of the microscope or endoscope, rather than by wide exposure and brain retraction.** Youmans' operative descriptions carry each of these elements even though it does not name the doctrine.
- **The bone window is defined by the target, not by the surface.** In the lateral supraorbital approach the craniotomy is **approximately 3 cm, extending from the "keyhole" bur hole behind the zygomaticofrontal junction to the supraorbital notch** YW p.3550. In the transsylvian keyhole hemispherotomy the window is **4 × 4 cm**, positioned by neuronavigation so that its upper border lies at the level of the corpus callosum and its lower border 0.5 cm below the sylvian fissure [YW pp. 639, 641].
- **Flattening bone rather than enlarging the flap buys angle.** The sphenoid wing is drilled flat; the orbital roof is exposed extradurally and drilled down; an orbitotomy or modified orbitozygomatic osteotomy may be added. Youmans states the purpose precisely: "Both of these maneuvers will allow greater degrees of freedom for microinstruments and allow for less brain retraction" [YW pp. 3549-3550].
- **Soft tissue is spared as much as bone.** The lateral supraorbital approach "involves less temporalis muscle dissection than a traditional pterional craniotomy" — the temporalis is dissected subperiosteally for only **1–1.5 cm** and retracted with fish hooks YW p.3550.
- **Brain relaxation replaces brain retraction.** In the lateral supraorbital route the exposure proceeds subfrontally until

the opticocarotid cistern is opened and CSF is drawn off to improve brain relaxation, and only then is proximal control obtained and the sylvian fissure split from lateral to medial YW p.3550. The keyhole hemispherotomy achieves the same by working within the ventricular system [YW pp. 639-641].

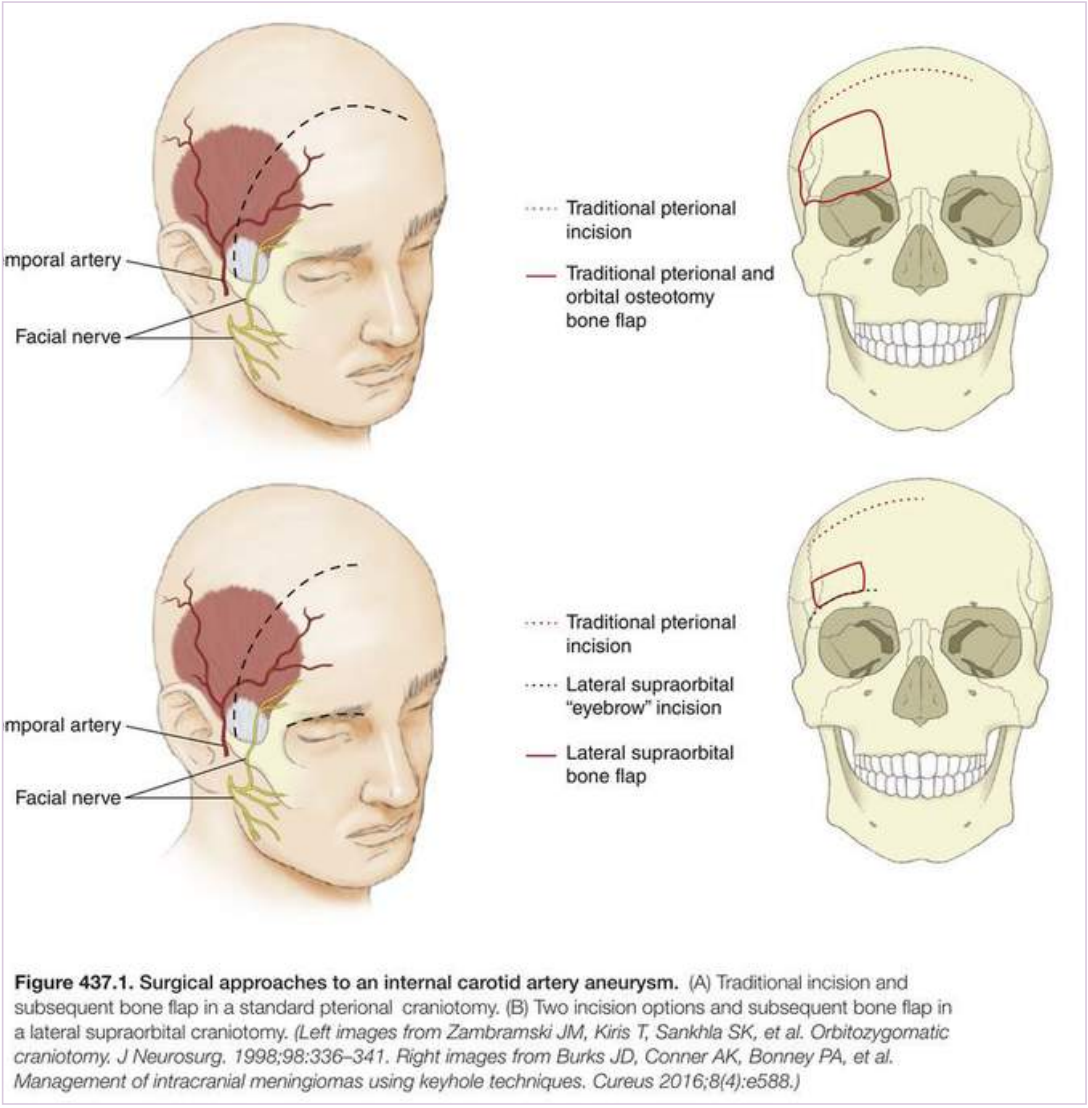


Figure 437.1. Surgical approaches to an internal carotid artery aneurysm. (A) Traditional incision and subsequent bone flap in a standard pterional craniotomy. (B) Two incision options and subsequent bone flap in a lateral supraorbital craniotomy. *(Left images from Zambramski JM, Kiris T, Sankhla SK, et al. Orbitozygomatic craniotomy. J Neurosurg. 1998;98:336–341. Right images from Burks JD, Conner AK, Bonney PA, et al. Management of intracranial meningiomas using keyhole techniques. Cureus 2016;8(4):e588.)*

Reproduced from Youmans & Winn 8e, Fig. 437.1, p. 3549 — Label when you reproduce it: (A) the traditional pterional incision, the pterional and orbital osteotomy bone flap, the superficial temporal artery and the frontalis branch of the facial nerve; (B) the two incision options for the lateral supraorbital craniotomy — behind the hairline, or the "eyebrow" incision — with the much smaller lateral supraorbital bone flap. This is the single best figure in Youmans for illustrating the keyhole concept: same target, a fraction of the exposure.

18. The lateral supraorbital keyhole craniotomy, step by step

- **Indication, as stated by Youmans:** "In some patients, a minimally invasive approach such as the lateral supraorbital (LSO) approach may be preferred. Considered a keyhole craniotomy, it involves less temporalis muscle dissection than a traditional pterional craniotomy." At the authors' institution **the LSO approach has become the mainstay for unruptured internal carotid artery aneurysms less than 1.5 cm in size** YW p.3550.
- **Contraindication:** "This approach is not typically favored in patients who present with a ruptured aneurysm, as the working corridor can be smaller and more technically challenging in the setting of a recent hemorrhage" YW p.3550. This is the single most important keyhole principle for the examination — **the keyhole gives away the margin for error, and a brain that is tight, swollen or bloody abolishes the corridor.**
- **Steps:**
  1. **Incision** planned either behind the hairline, as for a pterional craniotomy, or **within the eyebrow**, which offers a cosmetic advantage if the patient is bald YW p.3550.

2. **Head fixed in a Mayfield holder with 15–20 degrees of rotation to the side contralateral to the lesion** YW p.3550.
3. **Scalp dissected off the underlying muscle until the fat pad is visualised**, then interfascial or subfascial dissection to protect the frontalis branch of the facial nerve, which runs in the loose areolar tissue between the temporalis fascia and the galea [YW pp. 3549-3550].
4. **Temporalis dissected subperiosteally inferiorly for 1–1.5 cm** and retracted with fish hooks YW p.3550.
5. **A single bur hole at the keyhole**, and an **approximately 3-cm craniotomy from the keyhole to the supraorbital notch** YW p.3550.
6. **Orbital roof exposed extradurally and drilled down flat; orbitotomy added if more superior visualisation is needed** YW p.3550.
7. **Dura opened in a C-shaped fashion and reflected anteriorly toward the eye** YW p.3550.
8. **Lateral subfrontal exposure to the opticocarotid cistern; CSF release; proximal control; ICA dissected from the optic nerve; sylvian fissure then opened lateral to medial** YW p.3550.

- **Other keyhole corridors named in Youmans:** the **supraorbital keyhole craniotomy** appears in the list of transcranial approaches to pituitary tumours alongside frontotemporal, subfrontal, bifrontal and temporal craniotomies YW p.1303; the **supraorbital approach to tuberculum sellae meningiomas**, which allows preservation of the olfactory nerve and access to both optic canals YW p.1259; **modified minimally invasive supraorbital craniotomy, with or without endoscopic assistance**, for olfactory groove meningioma YW p.1338; **endoscopic endonasal supraorbital keyhole removal of craniopharyngiomas and tuberculum sellae meningiomas** [YW pp. 1081.e1, 1324.e1]; the **lateral supraorbital approach as a minimally invasive corridor for orbital lesions** YW p.1443.e1; and the **retrosigmoid approach**, which "affords an excellent view of the posterior cranial fossa contents" through a limited suboccipital window YW p.1285.

19. The enabling technologies — what makes a keyhole safe

- **Neuronavigation.** Youmans makes navigation mandatory for placing the hemispherotomy keyhole correctly YW p.641, and the evolution of frameless stereotaxy — the first FDA-approved proprioceptive arm system in **1993** and the first commercially available infrared optical tracking systems in **1996** — is what made small, target-defined craniotomies reliable YW p.2251.
- **The endoscope.** Cranial endoscopy is the classical keyhole magnifier: "Modern endoscopic cranial surgery developed from the growth in popularity of minimally invasive surgery through keyhole approaches" YW p.266.
  - **Rod-lens endoscopes dominate cranial endoscopy because of superior image quality**; they are heavier because the camera and fibreoptic light cable must be attached YW p.267.
  - **Viewing angles available are 0, 30, 45, 70 and 120 degrees; endoscopes range between 3 and 6 mm in diameter** YW p.267.
  - **The 0-degree scope minimises disorientation but leaves instruments passed through the working channel at the periphery of the field; the 30-degree scope gives better instrument control and, with simple rotation, an angle of view with a surface area twice as large as the 0-degree scope** YW p.267.
  - **Working channels in most endoscopes are limited to 2.4 mm** — the fundamental instrument constraint of purely endoscopic keyhole work YW p.268.
  - **Xenon light sources give the best illumination**; three-chip CCD cameras give better image quality than single-chip; **image quality is lost on screens exceeding 33 cm**, and monitor resolution should not exceed camera resolution YW p.267.
  - **Rigid holders** (for example the pneumatic Olympus EndoArm) improve comfort in long procedures but restrict freedom of movement; most need continuous manual adjustment at each joint, and a recent survey found most surgeons do not use one [YW pp. 267-268].

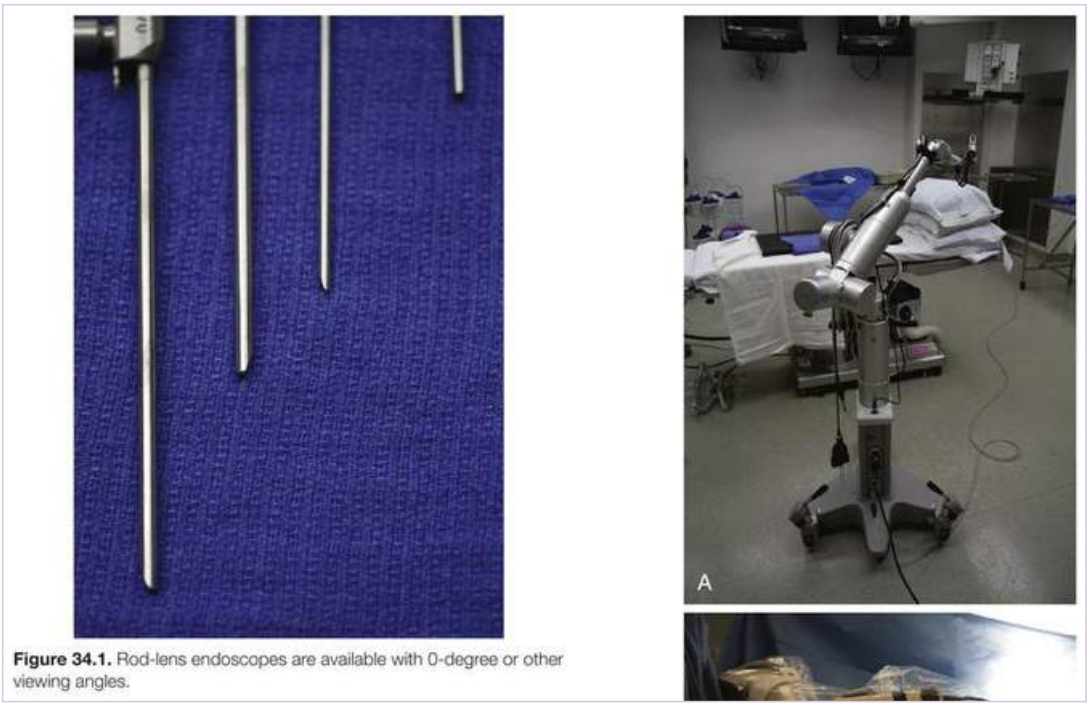


Figure 34.1. Rod-lens endoscopes are available with 0-degree or other viewing angles.

Reproduced from Youmans & Winn 8e, Fig. 34.1, p. 267 — Label when you reproduce it: rod-lens endoscopes with 0-degree and angled viewing optics — label the eyepiece, the light-post, the shaft and the angle of view. Say in the answer that 0-degree minimises disorientation while 30-degree doubles the surveyed surface area on rotation.

- **Tubular retractors — the "keyhole" taken down to the parenchyma.** Youmans explains that "tubular retractors have become popular throughout all surgical disciplines and are now being used in neurosurgery to access deep lesions of the brain", because they **disperse the force of retraction over a greater surface area than standard retractors**, minimising parenchymal damage [YW pp. 263-264].
  - **ViewSite Brain Access System (VBAS, Vycor Medical)** — collectively a **63% gross total resection rate** for tumours with complications in **only 2.8%** of cases, including transient memory loss and asymptomatic white-matter tract injury on DWI YW p.264.
  - **BrainPath (NICO Corporation)** — a meta-analysis of **20 papers and 289 procedures**: tumour resection 67%, haematoma evacuation 29%, colloid cyst 4%; **gross total resection 81%** for tumour and cystic lesions; for haematoma, **at least 75% of volume evacuated in 87% of cases and more than 90% of volume in 65%**; **complication rate 8.3%** (hemiparesis, new haemorrhage, aphasia). The system is designed so that a **neuronavigation probe can be fixed into the retractor's inner obturator** to guide placement YW p.264.
  - **The transcylinder approach** is illustrated in Youmans expressly as a way "to avoid retractor injury, limit surgical field, and protect surrounding brain during microsurgery", contrasted with handheld retractors and their associated parenchymal injury YW p.264.
- **Why retraction is the enemy the keyhole is designed to avoid:** cortical injury follows retractor pressures of **30 to 40 mm Hg sustained over 15 minutes**, whereas brief episodes under 7 minutes do not produce it; intermittent retraction preserves local CBF and histology better than continuous retraction; and a **reduction in evoked potentials of more than 50% is likely to produce permanent injury** YW p.262.

20. Advantages, limitations and the honest caveats

- **Advantages:** less soft-tissue dissection and muscle atrophy; better cosmesis with an eyebrow incision; less brain retraction because bone removal is traded for retraction; shorter opening and closing times; and, in the endoscopic domain, **significantly fewer neurological complications than open transcranial approaches for selected skull base tumours — 3.8% versus 35.3%** in the olfactory-groove/anterior skull base comparison Youmans quotes YW p.1338.
- **Limitations:**
  - **The corridor is unforgiving in the presence of swelling or haemorrhage** — hence the explicit advice against the

lateral supraorbital route in ruptured aneurysms YW p.3550.

- **Proximal control and manoeuvring room are reduced**; Youmans still recommends prepping the neck for all ICA aneurysms so that alternative avenues of proximal control exist YW p.3549.
- **Instrument calibre is constrained** — 2.4 mm working channels in most endoscopes YW p.268.
- **CSF leak rates are not reduced** by going endoscopic — "CSF leak rates are comparable between endoscopic and open approaches (16.0% versus 10.7%)" YW p.1338.
- **Some pathologies are better served by an open approach**: Youmans notes that olfactory groove meningiomas "can be more effectively resected via standard transcranial approaches or open modified minimally invasive supraorbital craniotomy" YW p.1338, and for colloid cysts the endoscopic route halves post-operative seizures (0.3% versus 4.3%) but the microsurgical route achieves higher reported gross total resection (96.8%) YW p.264.

- **The governing safety statement** applies equally to every keyhole corridor: the aim is "to improve visualization of the brain parenchyma during surgery while trying to minimize damage to vital structures" — the keyhole is a means to that end, never an end in itself YW p.262.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **CyberKnife in one line:** a compact LINAC on a six-axis industrial robot plus real-time orthogonal x-ray tracking — frameless, mask-immobilised, 1–5 fractions, up to **200 nodes** per session; invented by **Adler in 1987**, trials from **1994**, **FDA-approved for intracranial tumours in 1999** [YW pp. 234.e1, 1381, 2252, 2277].
- **The number that separates the two knives:** Gamma Knife prescribes at the **50% isodose** (inhomogeneous, very steep falloff); LINAC/CyberKnife prescribes at **70%–90%** (more homogeneous) [YW pp. 2275, 2280].
- **Frame beats frameless on paper but not in practice:** frame-based accuracy **<1 mm** and reproducibility **≈0.5 mm**; frameless with strict IGRT and robotic positioning achieves **1.0–2.0 mm** — and a **1–2 mm PTV margin** is reasonable for single-fraction frameless work [YW pp. 2267, 2272, 2279].
- **Hemispherotomy has three goals, not one:** stop the seizures, abolish the epileptic encephalopathy, and let cognition develop YW p.639.
- **Consent for hemispherotomy always includes two unavoidable deficits:** complete homonymous hemianopia and loss of fine pincer/fine foot movement — and the deficits hurt more the later in life the disease began YW p.639.
- **Cause beats technique in predicting seizure freedom:** porencephaly ~95%, Sturge-Weber 80%–100%, Rasmussen 77%–80%, **hemimegalencephaly only 40%–60%** YW p.644.
- **Hydrocephalus is the signature late complication: 23% in 690 patients, occurring up to 8 years after surgery**, with anatomic hemispherectomy and previous brain surgery the independent risk factors — the argument against big resections YW p.642.
- **Incomplete disconnection causes persisting seizures in 2%–30% and can occur with any technique** — early post-operative MRI using the blood in the disconnection slit as contrast is the way to prove completeness [YW pp. 643, 644].
- **The keyhole craniotomy that Youmans names by name** is the **lateral supraorbital**: eyebrow or behind-hairline incision, one bur hole at the keyhole, a **3-cm craniotomy to the supraorbital notch**, orbital roof drilled flat; the institutional mainstay for **unruptured ICA aneurysms <1.5 cm** and explicitly **not** favoured after rupture YW p.3550 .
- **Bone removal is traded for brain retraction:** flattening the sphenoid wing and unroofing the superior orbital fissure "allow greater degrees of freedom for microinstruments and allow for less brain retraction" — quote this line YW p.3550.
- **Retraction injury numbers worth carrying:** cortical injury at **30–40 mm Hg for 15 minutes**; **>50% drop in evoked potentials predicts permanent injury**; tubular retractors disperse force over a greater area (BrainPath GTR 81%, complications 8.3%) [YW pp. 262, 264].
- **Endoscope numbers:** 0/30/45/70/120-degree optics, **3–6 mm** shafts, **2.4 mm** working channel, and a 30-degree scope surveys **twice** the surface area of a 0-degree scope on rotation [YW pp. 267-268].

Pages read for this answer — Youmans & Winn 8e: 234.e1, 262, 263, 264, 266, 267, 268, 637, 638, 639, 640, 641, 642, 643, 644, 645, 1081.e1, 1259, 1285, 1303, 1324.e1, 1338, 1381, 1393, 1394, 1443.e1, 1531, 1557.e3, 1562.e1, 1803.e10, 2251, 2252, 2257, 2266, 2267, 2269, 2272, 2274, 2275, 2276, 2277, 2279, 2280, 2281, 2294, 2330, 2331, 2334.e5, 2353, 2366, 2367, 2368, 2369, 2370, 2371, 2383.e1, 2383.e2, 2383.e3, 3549, 3550

a) Gamma knife. [3]
b) Cyber knife. [3]
c) SRS. [4]

LONG | DEC 2022 · Paper III · Q1 | 10 marks

Also asked as: Radiosurgery platforms — also asked as JAN 2025 · Paper III · Q4 (a] Cyber knife [5]; b] Role of O-Arm in neurosurgery [5]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 293 *Radiosurgery Technique* (Trifiletti, Lee, Schlesinger, Sheehan), §History of Radiosurgery, §Radiation Sources for Radiosurgery, §Radiosurgical Devices, §The Gamma Knife Radiosurgical Procedure (all 11 steps), §Treatment Planning, §Dose Limitations to Critical Structures, §The Linear Accelerator–Based Radiosurgical Procedure, §Proton Beam Radiosurgery, pp. 2274-2281 (Figs. 293.1-293.4, pp. 2275, 2276, 2281; Table 293.1, p. 2277). Supplementary: Ch. 291 *Radiobiology of Radiotherapy and Radiosurgery*, §Basic Principles of Radiation Therapy, §Stereotactic Radiosurgery and Stereotactic Radiotherapy, §Radiobiologic Considerations for Different Radiation Techniques, pp. 2257-2267 (Figs. 291.1-291.2, p. 2258; Fig. 291.10, p. 2267); Ch. 290 *General and Historical Considerations of Radiotherapy and Radiosurgery*, §Robotic Positioning and Automated Collimation, pp. 2251-2255 (Figs. 290.3-290.4, pp. 2251-2252); Ch. 292 *Radiation Therapy Techniques*, §Stereotactic and Image-Guided Radiotherapy, §Hypofractionated Stereotactic Radiotherapy, pp. 2269-2273 (Tables 292.1, 292.3, 292.4, pp. 2270, 2272, 2273); Ch. 298 *Radiosurgery for Malignant Intracranial Tumors*, §Clinical Outcomes of Stereotactic Radiosurgery Alone, §Levels I and II Evidence, pp. 2326-2333 (Fig. 298.2, p. 2327; Table 298.1, p. 2328); Ch. 299 *Radiosurgery for Benign Intracranial Tumors*, §Topologic Differential Effect, §Vestibular Schwannomas, §Meningiomas, pp. 2336-2347 (Fig. 299.1, p. 2337; Tables 299.1-299.2, pp. 2339, 2342); Ch. 300 *Radiosurgery for Intracranial Vascular Malformations*, pp. 2349-2353; Ch. 301 *Radiosurgery for Functional Disorders*, pp. 2362-2365; Ch. 28 *Robotics in Cranial Neurosurgery*, p. 234.e1.

(a) Gamma Knife [3]

1. Definition and the single governing idea

- **The Gamma Knife (Elekta AB, Stockholm) "operates by precisely aligning the gamma-ray emissions from an array of ⁶⁰Co sources so they intersect at a point called the focus point"** YW p.2275. That sentence is the whole machine.
- **Each individual beam has a fairly low dose rate; the summation of the beams at the focus point creates a very concentrated dose.** Spreading the energy among 192 or 201 beams makes it possible to achieve a high dose within the target while largely sparing normal brain, because **"the dose quickly falls to a low level as the distance from the focus (or isocenter) increases"** YW p.2275.
- **This is the topologic differential effect** — Youmans' name for the basic principle of safety in radiosurgery: safety comes from the *geometry* of dose delivery in a single session, "as opposed to radiotherapy in which the attempt to spare the normal tissue is based on the search for a **biologic** differential effect related to fractionation" YW p.2336. Therefore **accuracy and precision, not fractionation, are what protect the patient**, and "an especially high spatial accuracy is required for both imaging and dose planning" YW p.2336.
- **Dosimetry is deliberately inhomogeneous.** "Dosimetry in Gamma Knife radiosurgery is quite different from that in traditional fractionated radiation therapy, the latter of which focuses on dose homogeneity within the target volume; the steep dose gradient and isocentric plane achieved by the Gamma Knife mean that the dose within the target is inhomogeneous" YW p.2275. The margin isodose is **typically the 50% line** YW p.2280.



Figure 293.2. Gamma Knife radiosurgery device.

Reproduced from Youmans & Winn 8e, Fig. 293.2, p. 2275 — Label when you reproduce it: the Gamma Knife radiosurgery device — the large spherical shield, the central body that holds the source array and primary collimation, the patient positioning system/treatment couch, and the docking of the frame adaptor. State beside it that the shield both collimates the beams to the focus point and protects patient and staff from the continuously emitting cobalt sources.

2. The physics of the source

- **⁶⁰Co is created in a reactor by neutron bombardment and activation of ⁵⁹Co** YW p.2274.
- **It decays by beta-minus (β) decay**: neutron-heavy ⁶⁰Co spontaneously converts a neutron into a proton, releasing an electron (β particle) and an antineutrino, and transmuting into **⁶⁰Ni** in an activated state. As the nickel drops to its ground state it **releases gamma photons at 1.17 and 1.33 MeV** — an average of **1.25 MeV** — and these photons are what are used for therapy [YW pp. 2274-2275, 2257].
- **Gamma rays and x-rays differ only in their manner of production, not in their subsequent behaviour when interacting with the environment** — gamma rays come from an atomic nucleus, x-rays from electron interactions [YW pp. 2274, 2269].
- **Both are indirectly ionising**: photons liberate charged particles (electrons), which then lose energy through a multitude of Coulomb interactions, each transferring a small part of the particle's kinetic energy to surrounding tissue and causing the biological effect YW p.2275.
- **Practical consequences of using an isotope:**
  - **⁶⁰Co has a half-life of 5.3 years; activity (dose rate) falls by approximately 1.1% per month, and sources are typically replaced every 5 years** to keep treatment times acceptable. **The activity of the sources must be measured and accounted for in the dose calculation before every treatment** YW p.2257.
  - **The sources emit continuously**, so the radiation source must sit in a shielded "off" position when not in use — unlike x-rays and electrons from LINACs and protons from cyclotrons, which are emitted only when switched on electronically YW p.2258. This is why Gamma Knife units are regulated by the **Nuclear Regulatory Commission** and require proper shielding YW p.2269.

3. Machine generations — know the models

- **1968 — the first Gamma Knife, containing 179 ⁶⁰Co sources in a hemispherical array, was born at Queen Sofia Hospital, Stockholm** YW p.2274.
- **Models U, B, C and 4C** use an **external, helmet-based system for final beam collimation**. Each helmet has removable collimators machined to particular field sizes — **4 mm, 8 mm, 14 mm and 18 mm**. Individual collimators can be replaced with solid **"plugs"** for beam shaping, mainly to protect critical structures proximal to the target. Any plan using more than one field size, or using plugs, obliges the operator to **change helmets or plugs during the procedure** [YW pp. 2275-2276].
- **Perfexion (2006)** — the external collimation system is replaced by a **single internal collimating structure** with machined collimators of **4, 8 and 16 mm**. The source array is **split into eight sectors of 24 sources each**, on carriages that slide on linear bearings driven by motors at the rear of the unit, so each sector can be aligned to any collimator size or to a **"blocked" position**. Each of the eight sectors may be configured independently, permitting a **"composite" isocentre made of multiple field sizes**; shielding with plugs (a highly manual process) is replaced by the fully automated setting of sectors to blocked YW p.2276. Youmans elsewhere describes the Perfexion as having "an integral tungsten collimator array divided into eight independently controllable collimator sectors and a fully robotic couch", whose "integral and fully automated collimating and positioning system results in a greater number of isocenter and collimator configurations with consequent improvements in plan quality and treatment delivery efficiency" YW p.2254.
- **Extend system** — a dental-impression-based **relocatable** frame available on the Perfexion, in place of the fixed stereotactic frame, for multisession treatment YW p.2276.
- **Icon (2015)** — introduces an **on-board cone-beam CT (CBCT)** and an **intrafraction motion tracking system**, making multisession Gamma Knife radiosurgery with **thermoplastic mask** immobilisation feasible [YW pp. 2254, 2276]. The CBCT is mounted to the front of the radiation unit and its isocentre has a known calibration relationship with the radiation isocentre, **so images acquired with the scanner are implicitly in stereotactic coordinate space** YW p.2276. The infrared system is the **Intra-Fraction Motion-Management System (IFMM)**, which tracks an IR-reflective nose marker against four fixed reference markers on the headrest, with a **default motion threshold of 1.5 mm**; exceeding it switches the beams to the blocked position, and persistent deviation pauses treatment for a fresh CBCT baseline [YW pp. 2276, 2278].
- **Frameless capability means hypofractionation:** up to **five fractions**, useful for tumours >2 cm, surgical cavities and eloquent-area tumours to reduce radiation necrosis, and allowing **20 metastases to be treated four or five targets per day over four days** rather than in one very long, more toxic session YW p.2258.

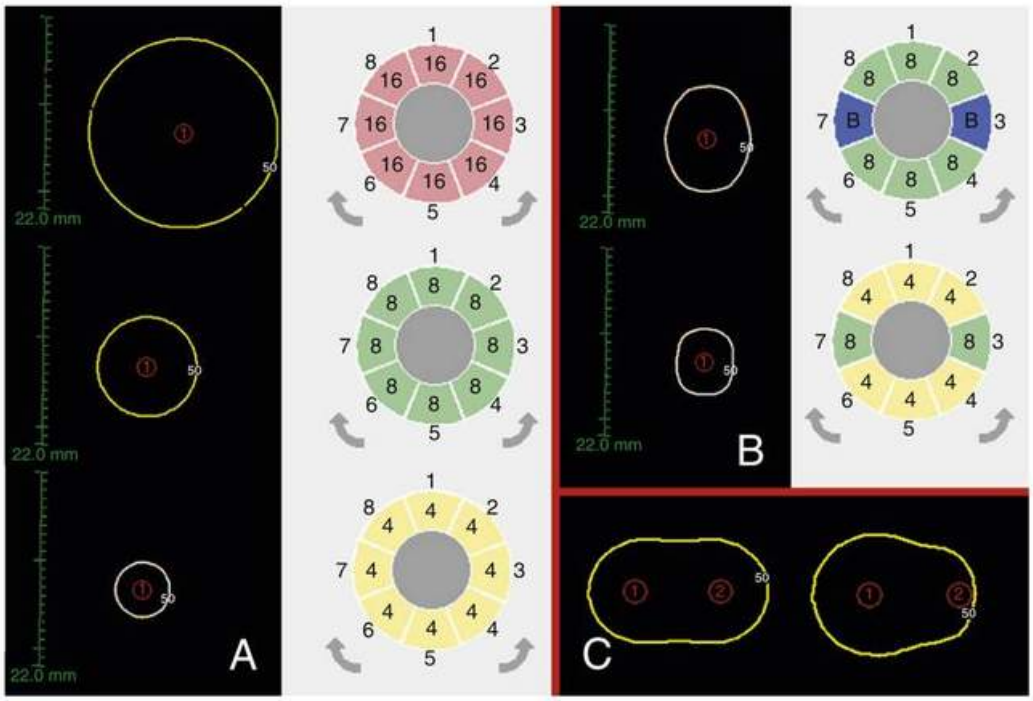


Figure 293.3. Customized Gamma Knife radiosurgery planning. Shot diameters vary based on collimator sizes (A). Composite collimators can create distinct dose clouds that can "shape" the prescription isodose lines to improve plan conformality (B). Combining shots in different positions in space, and weighting them differently, can also impact the dose cloud (C). Together, these techniques can serve to shape the prescription radiation isodose line to the tumor and avoid normal parenchyma.

Reproduced from Youmans & Winn 8e, Fig. 293.3, p. 2276 — Label when you reproduce it: (A) shot diameters determined by collimator size; (B) composite collimators producing distinct dose clouds that "shape" the prescription isodose line to improve conformality; (C) shots combined in different positions in space and weighted differently to reshape the dose cloud. Label the eight sectors, the 4/8/16 mm collimator positions and the "B" (blocked) sectors. This figure is the answer to "how do you make a Gamma Knife plan conformal?"

4. The Gamma Knife procedure — the eleven steps Youmans lists

1. **Daily quality assurance of the radiosurgical facility** YW p.2277.
2. **Stereotactic frame placement**, or custom mask creation plus a reference CBCT for stereotactic coordinates YW p.2277 .
3. **Frame adaptor and frame cap fitting check** YW p.2277.
4. **Stereotactic brain imaging with MRI, CT, angiography or a combination** YW p.2277.
5. **Coregistration of neurological images and importation into radiosurgical software** YW p.2277.
6. **Conformal radiosurgical dose planning by the radiosurgery team** YW p.2277.
7. **Dose and fractionation selection** YW p.2277.
8. **Dose limitations to critical structures: shielding and plugging technique** YW p.2277.
9. **Pretreatment CBCT and plan adjustment to current patient position** (if a custom mask is used, or for pretreatment QA of frame placement) YW p.2277.
10. **Stereotactic delivery of radiation** by positioning the head inside the collimator system; with mask-based treatment, CBCT and IR monitoring are used for registration and tracking YW p.2277.

11. **Removal of the stereotactic guiding device (or mask)** YW p.2277.

- **Frame placement craft — the marks are here.** Local anaesthesia with IV sedation; scalp prepared with alcohol and pin sites infiltrated with long-acting local anaesthetic; the team previews the pre-SRS MR images to plan frame position YW p.2277.
  - **The most important principle is to keep the lesion as close as possible to the centre of the frame**, to avoid collisions and optimise dosimetry. Collisions occur between the base ring, the post/pin assembly or the patient's head and the collimator helmet YW p.2277.
  - **Avoid placing a pin in a flexible or partially flexible bone flap** in patients with prior craniotomy YW p.2277.
  - **Caudal lesions** — place the ear bars in the **top holes** of the earpieces (frame sits lower); **higher lesions** — **bottom holes** (frame sits higher) YW p.2277.
  - **Anterior lesions** — shift the frame forward by placing the earpieces posteriorly; posterior edge of the earpiece at **75 to 90 mm** on the y dimension instead of 90–100 mm. **Posterior lesions** — earpieces forward, posterior edge at **110 to 125 mm**; anterior posts as low as possible on the supraorbital region [YW pp. 2277-2278].
  - **Sellar lesions** — use the angle of the optic apparatus as the frame axis; this approximates a line joining the lateral canthus to the top of the pinna, and demonstrates the entire optic apparatus in a single MRI slice YW p.2277.
  - **Lateral targets** — shift laterally toward the lesion, but ensure space remains contralaterally for the fiducial box; **try the fiducial box on the frame before sending the patient to MRI** YW p.2278.
  - **Frame stability** is evaluated by applying force to the base ring; on the Icon, CBCT can independently verify that the fixation pins have not shifted immediately before treatment YW p.2278.
- **Mask creation** — patient positioned on the patient positioning system; a soft pillow behind the head hardens on exposure to air to create a reproducible headrest; a **thermoplastic mask heated to approximately 165°F** is moulded to the bony facial structures and stiffens as it cools; an **IR-reflective nose marker** is applied YW p.2278.
- **Imaging protocol** — thin-slice stereotactic MRI with and without contrast. Pre-contrast: coronal and sagittal T1 (1-mm sections), fast spin-echo axial and coronal T2 (1 mm). Post-contrast: coronal T1 (1 mm), sagittal FSE T1 (1 mm), coronal spoiled gradient-recalled (SPGR) T1. **Dynamic MRI sequences have been used since 2010 for pituitary adenoma detection** YW p.2278. CT is the alternative if MRI is contraindicated, but target delineation is poorer, particularly after resection YW p.2278. **Stereotactic angiography is typically necessary for AVMs**, used with MRI or CT as a third modality; orthogonal images are better than oblique; up to **10 degrees of rotation in two dimensions** is acceptable; confirm all fiducials are visible before removing the catheter YW p.2278.
- **Planning** — target and surrounding structures contoured; **dose-volume histograms, conformality index, dose uniformity and gradient index** obtained and optimised YW p.2279. Youmans warns of two perceptual traps: **the Cornsweet effect**, which misleads the surgeon into prescribing high dose to an inappropriate contour, and **the "illusion of perfection"**, in which many different isodose lines all appear to fit the same tumour perfectly — which is why some experienced neurosurgeons create conformal plans **without outlining the target at all** YW p.2279.
- **Delivery and after-care** — the procedure is fully automated apart from positioning the head in the docking device at the selected gamma angle; a **clearance check** using a test tool that simulates the inner collimator is performed for shots in close contact with the collimator system, especially in multiple metastases; the patient is monitored by audio and video, and vital signs may be monitored [YW pp. 2279-2280]. After pin removal, oozing is controlled by compression or occasionally a suture; topical neomycin/bacitracin prevents pin-site infection; the patient is observed for a few hours and discharged if neurologically stable, with admission reserved for seizure, nausea, severe pain, anaesthetic complication or new deficit YW p.2280.

5. Dose constraints every candidate must know

- **Optic apparatus** — visual deterioration is rare and can be avoided if the single-fraction dose to the optic apparatus is restricted to **8 Gy or less**, although 10 to 12 Gy without ill effect has been described by some groups. Traditionally a distance of **3 mm or more** between tumour margin and optic apparatus is desirable; modern devices may allow as little as **1 to 2 mm**. **Fractionated radiosurgery allows point doses of 25 Gy over five fractions to the optic apparatus** YW p.2279.
- **Other cranial nerves** are more radioresistant than the optic nerve; effective doses of **19 to 30 Gy** have been delivered

with a low risk of appreciable side effects YW p.2279. In the benign-tumour chapter, cranial nerves within the cavernous sinus could tolerate more than **20 Gy**, whereas the **trigeminal nerve was potentially at risk beyond 19 Gy** YW p.2342.

- **Carotid artery** injury after SRS is rare — only one isolated case report YW p.2279.
- **Brainstem** — dose–volume effects dramatically affect dose selection for brainstem AVM, metastases and tumours; for trigeminal neuralgia the brainstem is limited to a **Dmax of 15 Gy**, which yields a **less than 5% risk of necrosis** [YW pp. 2261, 2279].
- **Pituitary** — margin doses of **20 Gy or more** for functioning adenomas, and **25 or 30 Gy** for improved hormonal normalisation rates; the trade-off against delayed hypopituitarism is unknown YW p.2279.
- **Trigeminal neuralgia** — maximum dose **70 to 90 Gy** (usually 80 Gy) through a **4-mm collimator** centred **2–4 mm anterior to the nerve's entry into the pons**, with the **20%–30% isodose line just encroaching on the brainstem surface** [YW pp. 2279, 2362].

(b) CyberKnife [3]

6. What it is, in the same terms as the Gamma Knife

- **A compact linear accelerator mounted on an industrial six-axis robotic arm, with an integrated orthogonal kV image-guidance system that tracks tumour and patient motion during treatment and realigns the beam in real time** YW p.234.e1.
- **Source:** x-rays generated electrically. The LINAC accelerates electrons to high energy and directs them onto a high atomic-number (tungsten) target; the electrons interact with target nuclei to generate primarily **bremsstrahlung** and secondarily **characteristic x-rays** YW p.2274. Therapeutic photons commonly range from **3 to 18 MV**, with **3 to 6 MV typically used for brain lesions** YW p.2257.
- **Classification:** Youmans groups it with the "specialized EBRT or radiosurgery x-ray devices … compact LINACs mounted on a robotic manipulator (i.e., CyberKnife unit)", alongside the rotational slip-ring TomoTherapy and the gyroscopic Zap-X YW p.2257, and lists it among LINACs designed specifically with radiosurgical applications in mind — Edge (Varian), Versa HD (Elekta), TomoTherapy Hi-Art, **CyberKnife (Accuray)** and Novalis Radiosurgery (BrainLab) YW p.2276.
- **History: invented in 1987 by Adler** YW p.1381; clinical trials from **1994**; **FDA approval for intracranial tumours in 1999** YW p.234.e1.
- **Geometry:** the robot liberates the source from the single-plane gantry of a conventional LINAC, giving a very large number of beam directions called **nodes** — **up to 200 nodes treated serially per session** YW p.2252. A higher number of smaller, more finely controlled beams gives finer gradations in dose–target conformality, which is "particularly critical for SRS, in which lack of conformality has the greatest potential for toxicity given the high individual doses involved" YW p.2252.
- **Immobilisation and fractionation, per Table 293.1:** mask immobilisation, **1–5 fractions** YW p.2277.
- **Tracking:** "Both the CyberKnife and Novalis systems use x-rays during treatment to confirm positioning continuously" YW p.2272; the system "utilizes multiple orthogonal skull x-rays obtained during the course of delivering a radiation treatment, which are rapidly integrated into a patient-specific algorithm, providing continuous feedback" — this is **intrafraction repetitive imaging**, a step above pre-treatment-only IGRT YW p.2294. For spinal targets, image landmarking uses implanted radiopaque vertebral fiducials or direct imaging of vertebral anatomy YW p.2281.

7. Dosimetric behaviour, and the contrast with the Gamma Knife

- **Prescription isodose 70%–90%**, so maximum dose is only 10%–30% above the margin dose and the plan is **more homogeneous** than a Gamma Knife plan prescribed at 50% YW p.2280.
- **Dose falloff is also steep** in LINAC-based radiosurgery, but varies with collimator size and with the planning technique (multiple isocentre, dynamic arcs, static beams) YW p.2280.
- **Multi-isocentre plans are more heterogeneous** than shaped-beam plans; the advantage of a heterogeneous plan is that **the hot spot can be moved to the area that needs it** — the most enhancing or most diffusion-restricted part of the target YW p.2280.

- **The clinical consequences of sparing normal tissue with multiple-isocentre prescriptions at the 50% isodose line rather than shaped-beam prescriptions at the 90% isodose line are not well defined**; the **gradient index is device dependent and not fixed to a particular isodose line**, and conformality and gradient indices should be optimised for every individual plan YW p.2280.
- **Volume nomenclature** — GTV, CTV, PTV are used more frequently in LINAC-based radiosurgery, and the prescription dose is delivered to the PTV YW p.2280.
- **Penumbra** — the region of dose falloff; dose within it may be high enough to cause toxicity, and although covering the lesion with an additional 1–2 mm expansile margin is attractive, "the risk of radiation-induced damage is not always justifiable"; intensity modulation can be used to optimise falloff near an eloquent area YW p.2280.

8. The LINAC-based radiosurgical procedure — the six steps

1. **Daily quality assurance of the radiosurgical facility** YW p.2279.
2. **Immobilising the target** — frame placement or mask creation YW p.2279.
3. **Imaging with MRI, CT, angiography or a combination** YW p.2279.
4. **Coregistration of images and importation into the radiosurgical software; intraprocedural imaging** YW p.2279.
5. **Dosimetry — prescribing to a target volume** YW p.2279.
6. **Methods of conformality in the LINAC machine** YW p.2279.

- **Conformality methods available on LINAC platforms** [YW pp. 2276, 2280-2281]:
  - **Shaped-beam radiosurgery** with an MLC that automatically changes beam shape according to the beam's-eye-view of the lesion, made possible by 3D reconstruction of the target in modern planning software. **Dynamic arcs and static beams** are the two contemporary approaches.
  - **Radiosurgery cones** — specialised tertiary collimators creating near-spherical spots of radiation at the isocentre, used instead of MLCs.
  - **Intensity-modulated radiosurgery (IMRS)** — first conceptualised by **Anders Brahme in 1988**, who proposed reversing the conventional trial-and-error planning paradigm so that optimum beam intensities are derived from the desired dose distribution. IMRS requires three components: **(1) inverse planning, (2) leaf sequencing, and (3) delivery with a tightly integrated accelerator and MLC**. The physical objective function used commercially is the **dynamically penalised maximum likelihood (DPL) algorithm**, whose advantage is the ability to compute a number of inverse plans simultaneously, allowing varying emphasis on target versus organs at risk YW p.2281.
  - **Volumetric modulated arc therapy (VMAT)** — dose rate, gantry, collimator and MLCs are simultaneously altered during beam delivery; **RapidArc (Varian)** changes three parameters at once: **(1) gantry rotation speed, (2) MLC aperture shape, and (3) dose rate**, delivering treatment several times faster than other dynamic techniques [YW pp. 2276, 2281].
  - **Single-isocentre, multiple-lesion VMAT** — a centrally located isocentre with MLC aperture patterns away from the central beam axis treats several targets simultaneously; **beam time stays roughly constant irrespective of the number of lesions**, at the cost of potentially increased low-dose spill to normal brain YW p.2276.

9. Where the CyberKnife is actually used, and where it is not

- **Intracranial:** brain metastases; recurrent high-grade glioma (Youmans tabulates CyberKnife series at **24 Gy in 1–3 fractions**) YW p.2331; adult brainstem glioma YW p.2334.e5; head and neck paragangliomas (control **95%** vs 99% Gamma Knife and 96% LINAC) YW p.1393; trigeminal neuralgia [YW pp. 1531, 1557.e3]; orbital lesions YW p.1562.e1; and AVMs, for which the radiosurgery-based AVM grading scale has been validated YW p.2353.
- **Spinal — the natural home of the platform:** intramedullary spinal cord AVMs treated by multisession CyberKnife radiosurgery YW p.2371, mean marginal dose **20.5 Gy** to a mean volume of **2.3 mL** in a mixed cervical/thoracic/conus series [YW pp. 2367-2368]; **87 patients with 103 CNS haemangioblastomas** in von Hippel–Lindau and sporadic disease YW p.2369; metastatic spine tumours and radiosurgical decompression of epidural spinal cord compression [YW pp. 2383.e1-2383.e3]; recurrent focal spinal metastases after prior radiation YW p.1803.e10.
- **Why the spine needs continuous tracking:** respiration-induced vertebral motion is **<1 mm** supine, but spinal anatomy may move **more than 2 mm** during radiosurgery, and vertebral movement of **up to 3 mm can occur in as little as 5**

minutes YW p.2281.

- **Limits:** long delivery times from serial node treatment YW p.2252; the accuracy of frameless hypofractionated approaches "has been the subject of some debate", with mask-based LINAC accuracy **approaching 1 mm** against frame-based **<1 mm** YW p.2279; a **1–2 mm PTV margin** may still be prudent in single-fraction frameless work YW p.2272; and imaging dose of approximately **2 cGy per cone-beam scan** YW p.2267.

(c) Stereotactic radiosurgery (SRS) [4]

10. Definitions — get the vocabulary exactly right

- **SRS** — "a therapy in which a single fraction of high-dose radiation is used to treat a target in the brain via three-dimensional stereotactic localization, and **the total dose is high enough to be considered ablative**" YW p.2263.
- **HSRT (hypofractionated stereotactic radiotherapy)** — the principle of SRS applied to hypofractionated delivery; **typically up to five high-dose-per-fraction treatments of more than 4 Gy per fraction** YW p.2263.
- **FSRT (fractionated stereotactic radiotherapy)** — fully fractionated radiation delivered with a stereotactic technique, aiming for **1.8 to 4.0 Gy per day**; typically used for benign large tumours such as an acoustic neuroma where SRS or HSRT would be contraindicated. The terms HSRT and FSRT are sometimes used interchangeably for up to five fractions YW p.2263.
- **SBRT / SABR / body radiosurgery** — SRS and HSRT practised in the body with sophisticated immobilisation and on-board image guidance YW p.2263.
- **What unites them:** "Surgical procedures in which these tools are used are all called radiosurgery because they share the idea of **using a high dose of focused ionizing beams through the intact skull**" YW p.2277.
- **Radiosurgery depends on the synthesis of stereotaxis and three-dimensional imaging** YW p.2276; stereotactic radiotherapy is defined by an immobilisation and delivery system "sufficiently precise to be able to deliver radiation therapy with a root mean square error of less than 2 mm" YW p.2271.

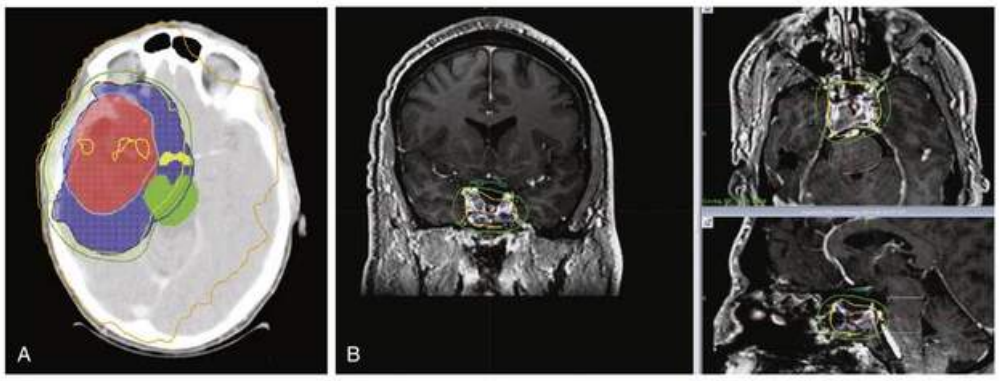


Figure 291.10. Intensity-modulated radiation therapy (IMRT) and Gamma Knife radiosurgery plan. (A) Axial section dose distribution from an IMRT plan for a patient with glioblastoma multiforme. The 51-Gy and 60-Gy planning target volumes are shaded in *blue* and *red*, respectively. Brainstem is shaded in *green* and optic chiasm is shaded in *yellow*. Isodose lines are indicated as follows: 63 Gy *(yellow)*, 60 Gy *(turquoise)*, 51 Gy *(green)*, and 20 Gy *(orange)*. Note that the 60-Gy isodose line conforms to the 60-Gy planning target volume and excludes the brainstem and optic chiasm. The 51-Gy isodose lines conform to the 51-Gy planning target volume, which encompasses the brainstem and chiasm. This lower dose is within tolerance of the brainstem and chiasm. In IMRT plans, the volume of low-dose irradiation (20 Gy) includes the majority of the brain. (B) Gamma Knife radiosurgery plan for a patient with a pituitary macroadenoma invading the cavernous sinus. Coronal *(left)*, axial *(top right)*, and sagittal *(bottom right)* sections of a pituitary adenoma plan showing a steep dose falloff. Isodose lines are indicated as follows: 15 Gy *(yellow)* and 8 Gy *(green)*. The tumor volume *(dark blue)*, optic chiasm *(light blue)*, and brainstem *(pink)* are outlined. *(Gamma Knife plan courtesy of Dr. Alireza Mohammadi and Dr. Gennady Neyman.)*

Reproduced from Youmans & Winn 8e, Fig. 291.10, p. 2267 — Label when you reproduce it: (A) an IMRT plan for glioblastoma — the 51-Gy and 60-Gy planning target volumes, brainstem in green, optic chiasm in yellow, and the 63/60/51/20-Gy isodose lines; note that the low-dose 20-Gy volume covers most of the brain. (B) A Gamma Knife plan for a pituitary macroadenoma invading the cavernous sinus in coronal, axial and sagittal planes, showing the steep dose falloff, with the 15-Gy and 8-Gy isodose lines and the outlined tumour, chiasm and brainstem. Put them side by side to make the single most examinable point: SRS trades dose homogeneity for a gradient.

11. Historical anchors

- **Radiosurgery was devised in 1951 by Lars Leksell**, who first used an **orthovoltage x-ray tube to focus radiation on**

the gasserian ganglion for facial pain YW p.2274.

- He investigated cross-fired protons, x-rays from an early-generation LINAC and ultrasound, and finally **Leksell and Larsson selected ⁶⁰Co** because of the cost of photon beams, the poor skull penetration of ultrasound and the imprecision of 1960s LINACs YW p.2274.
- **1954 — cyclotron implemented at Berkeley; 1957 — SRS with particle accelerators at Uppsala** YW p.2274. **Ernest Lawrence used helium ions and Jacob Fabrikant protons in California; Kjellberg in Boston treated pituitary tumours and AVMs with protons** YW p.2254.
- **Leksell's team were the first to use SRS to create functional lesions** (thalamotomy, capsulotomy, trigeminal neuralgia) and the first to apply it to benign tumours — craniopharyngiomas, schwannomas and meningiomas. **Application to malignant tumours occurred much later, in the late 1980s and early 1990s** YW p.2254.
- **1974 — Larsson proposed LINACs as radiosurgical sources; 1983 — first clinical LINAC radiosurgery reports by Betti and Derechinsky; 1985 — Colombo and Hartmann** YW p.2276. **1992 — first commercially available LINAC SRS unit (X-Knife, Radionics)** YW p.2254.
- **1987 — Lunsford acquired the first dedicated clinical Gamma Knife in the United States, in Pittsburgh; 1989 — the University of Virginia unit** YW p.2274.
- **Scale of practice: as of 2012 more than 300 Gamma Knife machines were in use worldwide and more than 700,000 patients had been treated — 44% with malignant tumours, 36% with benign tumours, 12% with vascular lesions and 7% with functional disorders**; thousands more had been treated with LINAC-based and charged-particle systems YW p.2274.

12. Radiobiology of SRS — why a single large dose works

- **A single ablative fraction abandons the 4 Rs that make fractionation work** (repair, redistribution, reoxygenation, repopulation) and substitutes geometric sparing [YW pp. 2264, 2336].
- **Three mechanisms are proposed** for the effect of radiosurgical doses YW p.2263:
  1. **Direct tumour cell kill** by DNA damage — clinical data in non-small cell lung cancer, melanoma and renal cell cancer correlating high biologically effective dose with improved control "suggest that the dominant effect of radiosurgery doses is death of the tumor cells themselves".
  2. **Shedding of tumour antigens stimulating antitumour immunity.**
  3. **Vascular collapse** contributing to ischaemia–reperfusion injury and diminished DNA damage repair. In mouse models, **radiosurgery doses of 10 to 15 Gy induced apoptosis of tumour-associated microvasculature mediated by ceramide**; endothelial cell death depended on **acid sphingomyelinase** but appeared independent of direct DNA damage, and recruitment of immune cells did not play a significant role in tumour regression in those models.
- **Whether SRS obeys linear-quadratic kinetics is controversial**, because SRS doses are inherently single fractions of **12 to 24 Gy**; nevertheless **BED calculations remain clinically meaningful even up to 20 Gy per fraction**, particularly for acute and late normal-tissue complications YW p.2263. The **universal survival curve** was developed to straighten the high-dose region while preserving the low-dose shoulder, but it "is not significantly better than the linear quadratic model" and its generalisability is unclear YW p.2263.
- **α/β values to quote:** late-responding normal tissue such as brain or spinal cord **2 to 3 Gy**; early-responding tissues and most cancers **about 10 Gy** YW p.2263. **BED = D (1 + d/[α/β])** YW p.2263.
- **Radiation-induced malignancy risk after SRS is very low — less than 0.05% at 15 years** — because normal tissues are exposed to very low doses YW p.2267. In the benign-tumour chapter the risk of a radiation-associated tumour is estimated at **less than 1 per 1000 patients treated with radiosurgery (range 0.01% to 2%), compared with 10% with external radiotherapy at 20 years** YW p.2336; Cahan's criteria for a radiation-induced tumour are quoted — the tumour must arise in a previously irradiated field, after a long interval, be pathologically different from the primary and absent at the time of irradiation, and the patient must have no genetic predisposition YW p.2336.

13. Indications — the whole menu

- **Malignant intracranial disease** [YW pp. 2326-2333]:

  - **Brain metastases** — definitive treatment of a limited number of metastases to avoid WBRT; boost after WBRT for larger or radioresistant lesions; salvage after WBRT failure; and adjuvant treatment of the resection cavity YW p.2272.
  - **Local control** with SRS alone for lesions ≤3 cm is **80% or higher**; in the prospective **JLGK0901** study of nearly 1200 Gamma Knife patients, the cumulative incidence of tumour progression at 1 year was **6.5% for volumes <1 mL, 13.3% for 1–4 mL and 21.0% for 4–10 mL** YW p.2326.
  - **Standard prescriptions: 20 Gy for tumours ≥2 cm and 22 Gy for those <2 cm**; when SRS is combined with WBRT the dose is reduced by approximately **30%** YW p.2326.
  - **RTOG 90-05 maximum tolerated doses after prior full-dose WBRT: 15 Gy for 31–40 mm, 18 Gy for 21–30 mm, 24 Gy for ≤20 mm maximum diameter** YW p.2326.
  - **Youmans' criteria for SRS alone:** tumour number **10 or fewer**, largest tumour **<3 cm**, cumulative intracranial tumour volume **<15 mL**, no leptomeningeal dissemination, **KPS ≥70%** [YW pp. 2326, 2330].
  - **Recurrent high-grade glioma** as salvage; **up-front SRS lacks evidence** in newly diagnosed HGG — RTOG 9305 showed median OS **13.5 vs 13.6 months** with and without SRS [YW pp. 2330-2331].
- **Benign intracranial tumours** [YW pp. 2336-2347]: vestibular schwannoma, meningioma, paraganglioma, pituitary adenoma (functioning and non-functioning), craniopharyngioma, jugular foramen schwannoma [YW pp. 2272, 2336, 2346].
- **Vascular malformations** — AVMs, dural AV fistulas, cavernous malformations [YW pp. 2349-2359].
- **Functional disorders** — trigeminal neuralgia, glossopharyngeal neuralgia, sphenopalatine neuralgia, cluster headache, essential and parkinsonian tremor (VIM thalamotomy), obsessive-compulsive disorder (anterior limb of internal capsule), depression (anterior cingulotomy) [YW pp. 2362-2365]; and epilepsy, including hypothalamic hamartoma and callosotomy [YW pp. 617-627].
- **Spine** — benign spine tumours, spinal vascular malformations, and malignant axial spine tumours [YW pp. 2367-2383].

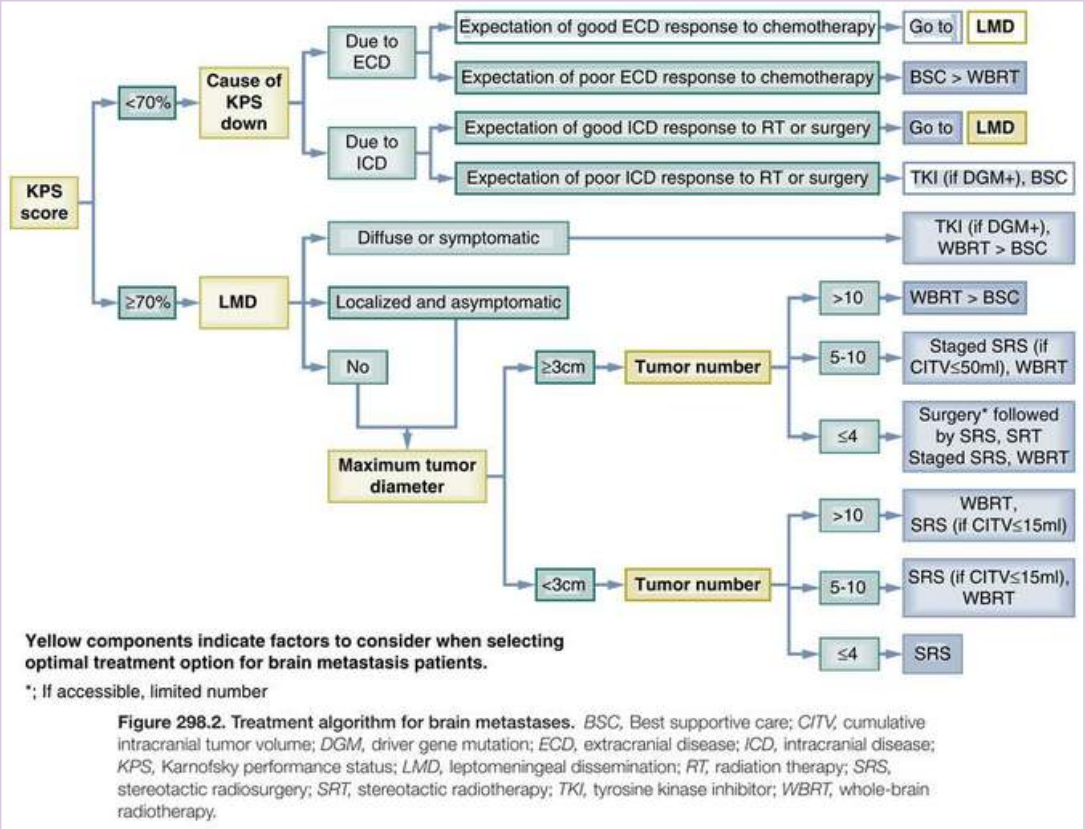


Figure 298.2. Treatment algorithm for brain metastases. *BSC,* Best supportive care; *CITV,* cumulative intracranial tumor volume; *DGM,* driver gene mutation; *ECD,* extracranial disease; *ICD,* intracranial disease; *KPS,* Karnofsky performance status; *LMD,* leptomeningeal dissemination; *RT,* radiation therapy; *SRS,* stereotactic radiosurgery; *SRT,* stereotactic radiotherapy; *TKI,* tyrosine kinase inhibitor; *WBRT,* whole-brain radiotherapy.

Reproduced from Youmans & Winn 8e, Fig. 298.2, p. 2327 — Label when you reproduce it: the brain-metastasis treatment algorithm — start at KPS score, branch at <70% (cause of decline: extracranial vs intracranial disease) versus ≥70%, then leptomeningeal disease, then maximum tumour diameter (≥3 cm vs <3 cm), then tumour number (≤4, 5–10, >10), ending in SRS, staged SRS, surgery followed by SRS/SRT, WBRT or best supportive care, with cumulative intracranial tumour volume thresholds of 15 mL and 50 mL. This is the single most quotable decision tree in the radiation section.

14. Dose selection and the volume limit

Table 1 · Dose guidelines for single-fraction radiosurgery of brain metastases — reproduced in full from Youmans & Winn 8e, Table 292.3, p. 2272.

#	Metastasis volume	Prescribed dose
1	<1 cm³	22–24 Gy
2	1–4 cm³	18–24 Gy
3	4–14 cm³	15–18 Gy
4	>14 cm³	12–15 Gy (consider a second-stage procedure or hypofractionation)

Table 2 · Common hypofractionated stereotactic radiotherapy schedules and their single-fraction equivalents — reproduced in full from Youmans & Winn 8e, Table 292.4, p. 2273.

#	Scheme	Single-fraction equivalent to tumour	Single-fraction equivalent to normal brain
	Malignant tumours		
1	9 Gy × 3	18 Gy	16.5 Gy
2	7 Gy × 5	20 Gy	17 Gy
3	6 Gy × 5	18 Gy	15 Gy
	Benign tumours		
4	6 Gy × 3	11.5 Gy	11.5 Gy

5	7 Gy × 3	13 Gy	13 Gy
6	5 Gy × 5	12.5 Gy	12.5 Gy

- **The 3-cm rule.** "As the PIV increases, the radiation exposure to the adjacent brain increases because the dose gradient is less steep when large volumes are covered. **It is this general concept that limits the size of intracranial radiosurgical targets to approximately 3 cm or less in average diameter**" YW p.2351.
- **Hypofractionation is the escape route** for larger lesions, lesions close to the optics and re-treatments; the most common benign scheme is **5 Gy × 5 fractions**, appropriate for vestibular schwannoma, meningioma and paraganglioma, and **benign tumours less than 30 cm³ appear to have low toxicity** with a hypofractionated approach [YW pp. 2272-2273].
- **Optic tolerance is life-expectancy dependent:** for benign tumours in patients with long life expectancy, **0.01 cm³ of the optics receiving 8 Gy carries a risk of optic neuropathy of about 1:1000**; for brain metastases, **maximum point doses of 10 Gy to the optics** are not unreasonable, giving roughly a **1%–2%** risk YW p.2272.

15. The randomised evidence for SRS in brain metastases

Table 3 · Randomised controlled trials of stereotactic radiosurgery for brain metastases — reproduced in full from Youmans & Winn 8e, Table 298.1, p. 2328.

#	Study (year)	Comparison	Primary endpoint	No. of tumours	Max size (cm)	Patients	Median survival (mo)	Significance
1	Kondziolka (1999)	WBRT vs WBRT + SRS	OS	2–4	2.5	14 / 13	7.5 / 11	P = .22
2	Andrews (2004), RTOG 9508	WBRT vs WBRT + SRS	OS	1–3	4	167 / 164	5.7 / 6.5	P = .014
3	Aoyama (2006), JROSG 99-1	WBRT + SRS vs SRS alone	OS	1–4	3	65 / 67	7.5 / 8.0	P = .42
4	Chang (2009)	WBRT + SRS vs SRS alone	Neurocognitive function	1–4	3	28 / 28	5.7 / 15.2	P = .003
5	Kocher (2011), EORTC 22952-26001	SRS/surgery alone vs SRS/surgery + WBRT	Performance-status deterioration	1–3	3.5 (SRS); no limit (surgery)	345 / 344	10.9 / 10.7	P = .89 (OS); P = .71 (PS)
6	Brown (2016)	WBRT + SRS vs SRS alone	Neurocognitive function	1–3	3	102 / 111	7.4 / 10.4	P < .001 (NCF); P = .92 (OS)
7	Brown (2017)	WBRT vs SRS alone (post-operative)	NCF and OS	1	5 (surgery)	96 / 98	11.6 / 12.2	P < .001 (NCF); P = .70 (OS)

8	Kayama (2018), JCOG0504	WBRT vs SRS alone (post-operative)	OS	1–4	>3 (one lesion only)	137 / 134	15.6 / 15.6	P = .027 (non-inferiority)

- **The message of the table:** adding WBRT to SRS improves **local and distant intracranial control** but **not survival**, and costs **neurocognitive function**. One-year local control exceeded **90%** in the SRS-plus-WBRT arm but was slightly under **70%** in the SRS-alone arm of JROSG 99-1 YW p.2327; the 1-year rate of new distant lesions was **41.5% with WBRT + SRS versus 63.7% with SRS alone** (P = .003) YW p.2327.
- **Brown 2016:** cognitive deterioration at 3 months in **63.5% after SRS alone versus 91.7% after SRS + WBRT** (P < .001), with better quality of life and no difference in functional independence YW p.2329.
- **Why survival does not improve:** "the majority of patients die due to extracranial disease progression" YW p.2327. In JLGK0901, **cumulative 1-year neurological death rates were 4.2% for a single metastasis, 1.7% for 2–4 and 4.3% for 5–10** YW p.2328.

16. Complications of SRS

- **Acute (within 3 days) and subacute (3 weeks) complications are relatively rare** — radiation-induced oedema or tumour bleeding; oedema rates are higher for large radioresistant tumours given relatively high prescription doses, and are usually controlled with steroids. **Tumour bleeding rates are high in hepatocellular carcinoma, malignant melanoma, choriocarcinoma and renal cell carcinoma** YW p.2328.
- **The most common complication is radiation necrosis**, seen as enlargement of an enhancing lesion with surrounding oedema, usually **6 to 12 months after SRS**. It consists of necrosis of the irradiated tumour and surrounding normal brain, usually combined with recurrent or remaining viable tumour cells. **The incidence of symptomatic radiation necrosis is usually less than 5%**, depending on target volume, prescription dose, pathology, interval, dose gradient, conformity and previous radiation history YW p.2328.
- **Distinguishing necrosis from recurrence** may be impossible on enhanced MRI alone because both components coexist and change over time; **T1/T2 mismatch, MR spectroscopy, SPECT and PET** are reportedly useful YW p.2328 . Management is steroids, sometimes surgery to reduce mass effect, and **bevacizumab**, whose effectiveness is now recognised [YW pp. 2328-2329].
- **In JLGK0901, treatment-related adverse events occurred in 145 of 1196 patients (12.1%)** over a median 12 months — CTCAE grades 1/2/3/4/5 in 46/54/29/11/5 patients, including 30 asymptomatic cases given steroids on the basis of MRI findings YW p.2328.
- **Frame-related:** pin-site discomfort, oozing, rarely infection; collision between frame hardware and the collimator helmet if the frame is badly placed [YW pp. 2277, 2280].

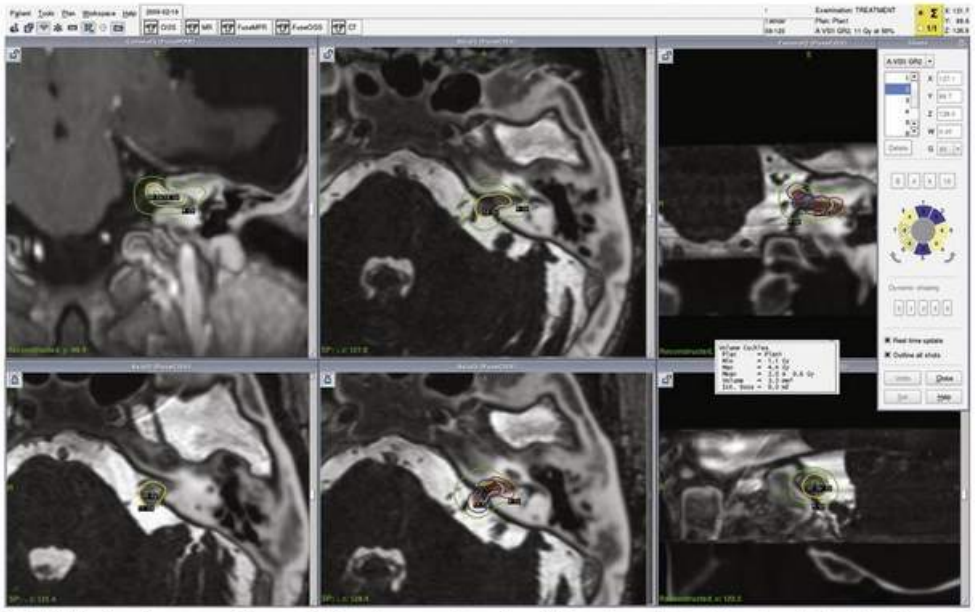


Figure 299.1. Vestibular schwannoma Gamma Knife radiosurgery in a stage II Koos tumor. Typical planning with Perfexion Gamma Knife device (Elekta Instruments, AB, Sweden). Note the avoidance of the cochlea in order to limit the risk of hearing loss.

Reproduced from Youmans & Winn 8e, Fig. 299.1, p. 2337 — Label when you reproduce it: a Koos stage II vestibular schwannoma planned on a Perfexion Gamma Knife — label the tumour contour, the shots filling the intracanalicular and cisternal components, the prescription isodose hugging the tumour margin, and above all the deliberate avoidance of the cochlea to limit the risk of hearing loss. This is what "conformal, selective, cochlea-sparing" actually looks like.

17. Outcome benchmarks worth quoting

- **Vestibular schwannoma with a 12–13 Gy margin dose:** 6-year actuarial resection-free tumour control **98.6%**; 6-year preserved facial nerve function **100%**, trigeminal function **95.6 ± 1.8%**, hearing **78.6 ± 5.1%** YW p.2336. In 871 primary cases, progression-free survival was **97% at 3 years, 95% at 5 years and 94% at 10 years**, with serviceable hearing **89.8% at 1 year, 76.9% at 3, 68.4% at 5 and 51.4% at 10 years** YW p.2336. The Marseille experience of 2000 patients reported long-term control **97%**, transient facial palsy **<1%** and hearing preservation between 50% and 95%, all treated with a **12-Gy marginal dose** YW p.2336. **Pseudoprogression — a significant transient increase in tumour size — occurs in 15%** and must not be mistaken for failure YW p.2337.
- **Meningioma:** Chin recommends **12–14 Gy for tumours >3 cm, 16 Gy for 1–3 cm and 18 Gy for <1 cm**; margin doses greater than 15 Gy do not provide better control (Kondziolka); **5-year control is uniformly above 90% for WHO grade I**, but falls to **50% for grade II and 17% for grade III** [YW pp. 2342, 2343].
- **Craniopharyngioma:** radiosensitive to radiosurgery even adjacent to the optic pathways — **efficient marginal doses reported as low as 9 Gy** YW p.2336.
- **AVM:** with complete nidus coverage, chance of obliteration is approximately **70%, 80% and 90% for 16, 18 and 20 Gy** respectively YW p.2350.
- **Trigeminal neuralgia:** significant pain reduction (Barrow Neurological Institute grade I–IIIB) in **75%–92% at 1 year**; pain relief begins on average **3 weeks** after treatment and may improve for up to 6 months; about half become completely pain free without medication; **one-third have significant recurrence at 2 years and one-half at 5 years**; sensory change in **20%** at 80 Gy, bothersome dysaesthesia in **10%** YW p.2362.
- **Essential tremor:** VIM target with a **4-mm collimator, central dose 130–140 Gy**, the 30% isodose kept medial to the internal capsule, producing a **4- to 5-mm circumscribed necrotic lesion**; systematic review reports mean tremor improvement of **88%** with rare recurrence YW p.2364.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Gamma Knife in one sentence:** 192 (Perfexion/Icon) or 201 (older) static ⁶⁰Co sources, each beam of low dose rate, converging on one focus point; margin prescribed at the **50% isodose**; dose deliberately **inhomogeneous** inside the target [YW pp. 2275, 2280].
- **⁶⁰Co numbers:** gammas at **1.17 and 1.33 MeV (mean 1.25 MeV)**; half-life **5.3 years**; activity falls **1.1% per month**; sources replaced every **5 years** [YW pp. 2257, 2275].
- **Collimator sizes:** older helmets **4, 8, 14, 18 mm**; Perfexion/Icon internal collimators **4, 8, 16 mm** plus "blocked", in **eight sectors of 24 sources** [YW pp. 2275-2276].
- **Icon = CBCT + IFMM infrared nose marker with a 1.5 mm default motion threshold** — that is what converts the Gamma Knife into a frameless, 1–5 fraction machine [YW pp. 2276, 2278].
- **CyberKnife = compact LINAC on a robot, up to 200 nodes, mask, 1–5 fractions, continuous orthogonal x-ray tracking**; Adler **1987**, FDA intracranial **1999** [YW pp. 234.e1, 1381, 2252, 2277].
- **The one-line distinction between the knives:** Gamma Knife prescribes at 50% (steep gradient, heterogeneous); LINAC/CyberKnife prescribes at **70%–90%** (homogeneous) — and the **gradient index is device dependent, not tied to any particular isodose line** YW p.2280.
- **Topologic differential effect** is the exam phrase for why SRS is safe: geometry substitutes for fractionation, so **accuracy and quality control are the safety mechanism** YW p.2336.
- **SRS is ablative single-fraction; HSRT ≤5 fractions at >4 Gy/fraction; FSRT 1.8–4.0 Gy/day** — do not use the terms loosely YW p.2263.
- **The 3-cm rule** exists because the dose gradient flattens as the prescription isodose volume grows YW p.2351.
- **Optic apparatus: 8 Gy single fraction (≈1:1000 risk in benign disease); 10 Gy point dose acceptable in metastatic disease (1%–2%); 25 Gy in 5 fractions if fractionated** [YW pp. 2272, 2279].
- **Brain metastasis doses: 22–24 Gy (<1 cm³), 18–24 (1–4), 15–18 (4–14), 12–15 (>14 cm³)**; RTOG 90-05 after prior WBRT: **24/18/15 Gy for ≤20/21–30/31–40 mm** [YW pp. 2272, 2326].
- **Adding WBRT to SRS buys control, not survival, and costs cognition** — Brown 2016: 3-month cognitive deterioration **63.5% vs 91.7%** YW p.2329.
- **Radiation necrosis peaks at 6–12 months, is symptomatic in <5%, and bevacizumab is now a recognised treatment** [YW pp. 2328-2329].
- **Secondary malignancy after SRS is <0.05% at 15 years** (≈<1 in 1000; range 0.01%–2%) versus **10% at 20 years after external beam radiotherapy** [YW pp. 2267, 2336].

Pages read for this answer — Youmans & Winn 8e: 234.e1, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 1381, 1393, 1531, 1557.e3, 1562.e1, 1803.e10, 2252, 2254, 2257, 2258, 2261, 2263, 2264, 2267, 2269, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2294, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334.e5, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2362, 2363, 2364, 2365, 2367, 2368, 2369, 2371, 2383, 2383.e1, 2383.e2, 2383.e3

a) Radiobiology and effects of radiation. [3]
b) Radiotherapy of gliomas. [4]
c) Priciples of Gamma knife. [3]

LONG | APR 2023 · Paper II · Q8 | 10 marks

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 291 *Radiobiology of Radiotherapy and Radiosurgery* (Yu, Suh, Ma, Sahgal), §Basic Principles of Radiation Therapy, §Direct and Indirect Effects of Radiation, §Effects of Ionizing Radiation, §Early and Late Effects of Radiation in Normal Tissue, §Functional Organization of Tissue, §Therapeutic Ratio, §Models of Cell Survival, §Stereotactic Radiosurgery and Stereotactic Radiotherapy, §Classic Descriptions of DNA Damage Repair, §Fractionation, §The Five Rs of Radiobiology, §Radiobiologic Considerations for Different Radiation Techniques, pp. 2257-2267 (Figs. 291.1-291.10, pp. 2258-2267). Supplementary: Ch. 296 *Fractionated Radiotherapy for Brain Tumors*, §Radiation Delivery: Technical Issues, §Clinical Applications — Gliomas, Glioblastomas, Anaplastic (WHO Grade III) Gliomas, Low-Grade Gliomas, pp. 2294-2305, 2301.e1, 2302.e1 (Figs. 296.1-296.4, pp. 2294-2296; eTable 296.1, p. 2302.e1); Ch. 292 *Radiation Therapy Techniques*, §Radiation Modalities, §Conventionally Fractionated Radiotherapy, §Whole-Brain versus Partial-Brain Radiotherapy, pp. 2269-2273 (Tables 292.1-292.4, pp. 2270-2273); Ch. 293 *Radiosurgery Technique*, §Radiation Sources for Radiosurgery, §Radiosurgical Devices — Gamma Knife, §The Gamma Knife Radiosurgical Procedure, §Treatment Planning, pp. 2274-2281 (Figs. 293.1-293.3, pp. 2275-2276; Table 293.1, p. 2277); Ch. 299 *Radiosurgery for Benign Intracranial Tumors*, §Topologic Differential Effect, §Long-Term Complications, p. 2336; Ch. 290 *General and Historical Considerations*, pp. 2251-2254; Ch. 298 *Radiosurgery for Malignant Intracranial Tumors*, §Gliomas, pp. 2330-2331.

(a) Radiobiology and effects of radiation [3]

1. Definitions and the types of therapeutic radiation

- **Ionizing radiation (IR)** is "radiation that has sufficiently high energy to dislodge electrons from the atoms or disrupt the bonds between the atoms and molecules" YW p.2274. It deposits energy in tissue, releasing secondary charged particles that cause further ionisation and thereby amplify the effect YW p.2257.
- **The radiations used clinically are x-rays, gamma rays, heavy-ion particles and electrons** YW p.2257.
  - **X-rays and gamma rays are both photons** — electromagnetic waves with no mass — and differ **only in origin**: x-rays from atom (electron) interactions, gamma rays from nucleus-based interactions YW p.2257. "The only difference between gamma rays and x-rays is the fact that gamma rays are emitted from a radioactive isotope, whereas therapeutic x-rays are generated by a linear accelerator" YW p.2269.
  - **Therapeutic x-rays are 3 to 18 MV**, orders of magnitude greater than the 50–150 kV of diagnostic x-rays; **3 to 6 MV is used for brain lesions and 6 to 18 MV for deeper body sites** YW p.2257.
  - **Gamma rays for CNS work come from ⁶⁰Co**, which decays to ⁶⁰Ni releasing photons of **1.17 and 1.33 MeV (average 1.25 MeV)** YW p.2257.
  - **Electrons** are light ions, generated by LINACs, useful only for superficial lesions; they technically have a Bragg peak but because they are light they scatter in all directions, so **the Bragg peak is obscured and not clinically relevant** YW p.2259.
  - **Protons** are positively charged, about **1000 times the mass of an electron**, generated at **200 to 250 MeV** by cyclotrons, and deposit the majority of their energy in a narrow predictable range — the **Bragg peak** — with minimal deposition beyond it YW p.2258.
  - **Carbon ions** possess the Bragg peak *and* produce considerably more double-stranded DNA breaks, because they are far more densely ionising — greater **linear energy transfer (LET)** per unit length — and therefore greater **relative biological effectiveness (RBE)**. Carbon ions "directly cause dense tracks of DNA damage that cannot be repaired efficiently" and may sensitise glioma stem-like cells while making the microenvironment less immunosuppressive [YW pp. 2259, 2296].
- **Brachytherapy** — implantation of radioactive sources directly into the target; it "delivers extremely high doses of radiation, often much greater than possible with EBRT", with rapid falloff millimetres beyond the source. **Low-dose-rate**: ¹²⁵I or ¹³¹Cs implanted in the tumour or cavity. **High-dose-rate**: a powerful isotope such as ¹⁹²Ir (e.g. 10 Ci) dwelling in position, then retracted. Brachytherapy "represents the most conformal radiation delivery that is presently possible, even as compared with particle therapy", but its

application is limited to sites amenable to direct source implantation, and as a glioblastoma boost over 50–60 Gy of EBRT **no survival benefit was observed**, so primary brain tumour brachytherapy "has largely been abandoned" [YW pp. 2259-2260].

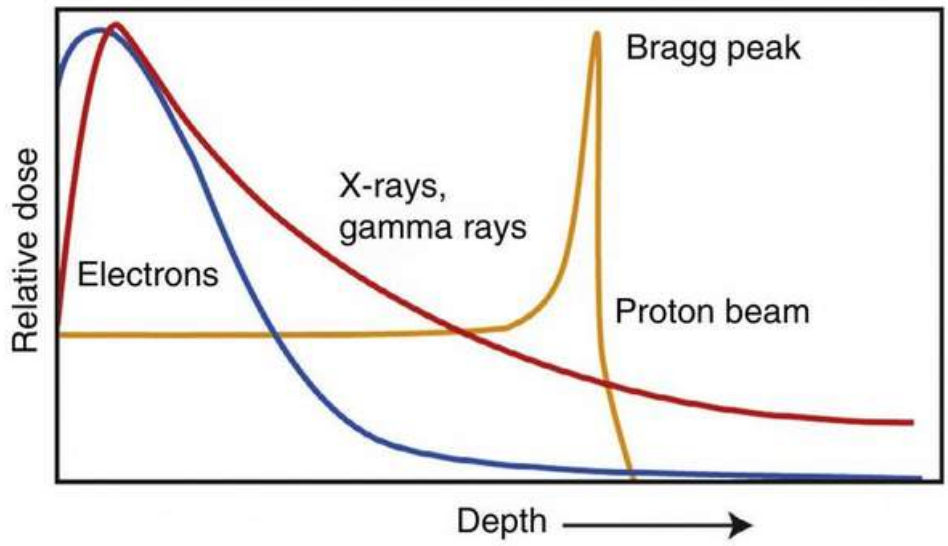


Figure 291.2. Depth dose curves of photons (x-rays and gamma rays), electrons, and protons. Photons *(red line)* are skin sparing and reach point of maximum dose (D_{max}) after a buildup region. Electrons *(blue line)* have a greater skin dose; after D_{max} is reached, the dose falloff is steep. Protons *(orange line)* have a sharp peak in dose distribution (Bragg peak), beyond which the dose quickly falls off.

*Reproduced from Youmans & Winn 8e, Fig. 291.2, p. 2258 — Label when you reproduce it: three depth-dose curves on one axis. Photons (x-rays/gamma rays) — skin-sparing, with a **buildup region** to a point of maximum dose (Dmax), then gradual attenuation with a significant exit dose. Electrons — greater skin dose, then steep falloff. Protons — low entrance dose, a sharp **Bragg peak**, then essentially no exit dose. Say beside it that the buildup region exists because liberated electrons are imparted a forward velocity and deposit their energy deeper than the surface.*

2. Direct and indirect action — the molecular starting point

- As photons or charged particles traverse tissue they deposit energy in their tracks, causing **ionisation of molecules**; these ionisations produce **free radicals** that damage biomolecules including DNA, and the ejected orbital electrons themselves produce further ionisation. The cascade continues until the photon or electron energy is insufficient to ionise YW p.2260.
- **Ionisation is random and affects all molecules** — lipids, proteins, nucleic acids and water. **Because water is the most prevalent molecule in cells it is most frequently ionised**, producing hydroxyl radicals (OH[−]) and other species that mediate DNA damage YW p.2260.
- **For therapeutic (low-LET) radiation, approximately two-thirds of DNA damage occurs via this indirect effect of hydroxyl radicals and only one-third by direct ionisation of DNA** YW p.2260. This single ratio is the most commonly asked number in the whole of radiobiology.
- **High-LET radiation reverses the emphasis** — ⁶⁰Co gamma rays and x-rays exhibit relatively sparse energy deposition within their tracks, whereas carbon-ion high-LET radiation is densely ionising and deposits significantly more energy within its track YW p.2260.

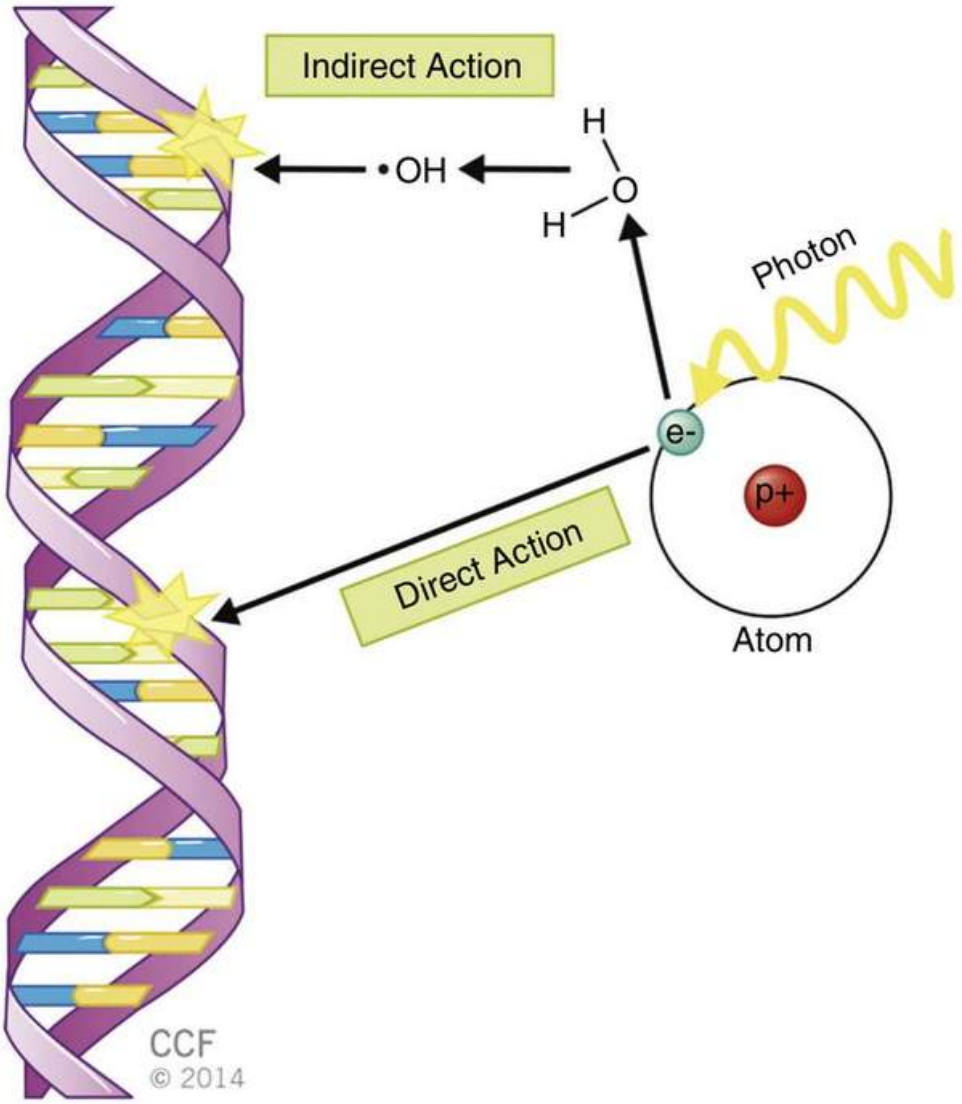


Figure 291.5. Indirect and direct mechanisms of DNA damage. Indirect action occurs when radiation causes ionization of a water molecule (or other intermediary) to form hydroxyl radicals, which then go on to cause DNA damage. Direct action occurs when DNA itself is damaged. With low–linear energy transfer radiation, two-thirds of DNA damage occurs through indirect action and one-third occurs through direct action. *e–*, Electron; *p+*, proton. (*Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.*)

Reproduced from Youmans & Winn 8e, Fig. 291.5, p. 2260 — Label when you reproduce it: the indirect pathway — a photon ionises a water molecule to generate a hydroxyl radical which then damages DNA; and the direct pathway — the photon or charged particle ionising DNA itself. Annotate "two-thirds indirect, one-third direct for low-LET radiation" and mark the electron (e) and proton (p) tracks.

3. Time scale and cellular fate

- **Ionisations occur in the picosecond range**, producing free radicals; **DNA damage occurs in less than 1 second**, and **DNA damage repair ensues over the next few hours to days** [YW pp. 2260-2261].
- **If sufficient damage occurs and cannot be repaired, cells may be eliminated through apoptosis, necrosis or other**

forms of cell death. If damaged cells do not die and the damage persists, cells may undergo **permanent growth arrest (senescence)**, or — if proliferative — exhibit **genomic instability that contributes to malignant transformation** YW p.2261.

- **Cellular and subcellular effects** include damage to DNA and cell membranes, producing changes in cell cycle, proliferation, cell death, growth arrest or senescence; DNA damage may result in **mutations, chromosomal breakage or translocations, and changes in DNA ploidy** YW p.2261.
- **Each step can be modulated:** shielding with multileaf collimators limits the volume of normal tissue exposed; **free radical scavengers** reduce DNA damage; and drugs altering DNA repair or the cell cycle may be used YW p.2261.

4. DNA repair — the pathways to name

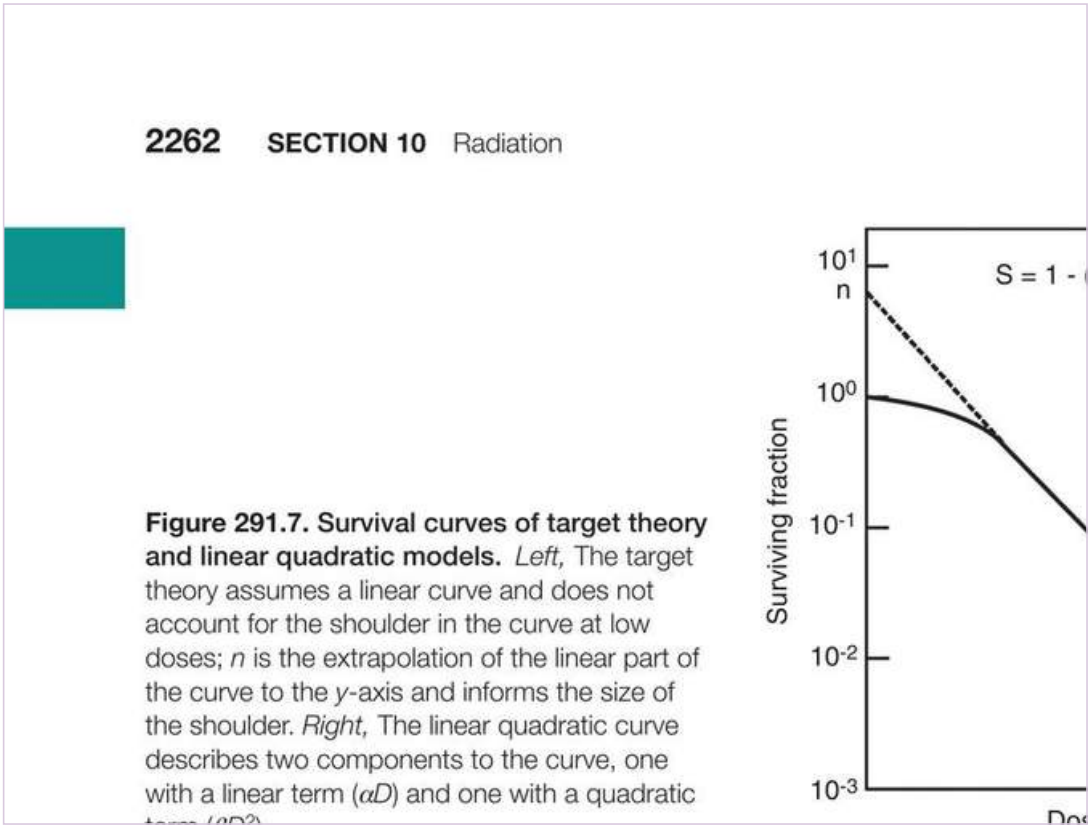
- **The most lethal lesion is the double-stranded break.** The cell may also recognise two single-stranded breaks in close proximity as a double-stranded break. **Clusters of DNA damage are termed multiply damaged sites**, are particularly difficult to repair, and often result in cell death YW p.2264.
- **Non-homologous end joining (NHEJ)** — directly ligates the broken ends; **error prone**, with small nucleotide deletions; **occurs in all phases of the cell cycle**. Broken ends are coated with the **Ku70/Ku80 heterodimer**, the catalytic subunit **DNA-PKcs** is recruited, and **XRCC4/LIG4** ligates the ends YW p.2264.
- **Homologous recombination (HR)** — uses the **sister chromatid** as template, so repair is faithful; therefore it occurs **only during late S and G2 phases**, after DNA synthesis. The **MRE11-RAD50-NBS1 (MRN) complex** assists; **BRCA1 and BRCA2** participate; **BRCA1 and 53BP1 regulate the choice between HR and NHEJ** [YW pp. 2264-2265].
- **Checkpoints:** G2-M and G1-S are the most important checkpoints for the DNA damage response; when damage is detected cells arrest to permit repair before proceeding YW p.2264.
- **Classic radiobiological damage classification, which predates molecular biology** [YW pp. 2263-2264]:
  - **Lethal damage** — results in cell death, typically from double-stranded breaks.
  - **Sublethal damage** — insufficient to cause death alone; more pronounced in the low-dose region of the survival curve; triggers death only after enough accumulates (several single-strand breaks yielding a lethal double-strand break). **Fractionated radiation revealed its existence**: two 3-Gy fractions leave a greater surviving fraction than a single 6-Gy fraction.
  - **Potentially lethal damage** — repair dependent on contextual cues such as cellular quiescence or adverse microenvironment (low pH, reduced temperature); assessed by delayed plating; **quiescent contact-inhibited cells repair DNA more efficiently than actively cycling cells**.
- **Chromosomal consequences:** unrepaired double-strand breaks produce **translocations, DNA rings, double minutes and loss of parts or whole chromosomes**; acentric chromosomes may be lost in subsequent replications. Aberrations that do not involve lethal exchange or DNA loss — **inversions and balanced/Robertsonian translocations** — are generally tolerated, but translocations can place genes under a foreign promoter or create fusion genes, as in **t(9;22) producing BCR-ABL** YW p.2265.

5. Models of cell survival — the equations

- **The functional readout is clonogenic survival** — survival of cells with replicative potential; their elimination is necessary for durable tumour control, and clonogenic survival "remains the 'gold standard' for evaluating cell kill by irradiation" YW p.2262.
- **Poisson model of tumour control: P = e^{−n}**, where P is the probability of tumour control and n the average number of surviving clonogens. **Reduction of a population of 10⁹ cells by at least 9 logarithms gives a 37% probability of control; reduction by 10 logarithms gives about 90%** YW p.2262.
- **Target theory: S = 1 − (1 − e^{−D/D_0})ⁿ**, where S is surviving fraction, D the dose, **D_0 the dose that reduces survival to 37% of the starting number**, and n the extrapolation of the curve to 0 Gy. **n relates to the size of the shoulder** — the higher n, the greater the shoulder, implying that multiple hits must accumulate before survival falls YW p.2262.
- **Linear-quadratic theory:** target theory wrongly predicts zero cell kill at low dose, so the LQ model was developed. **S**

= exp − (αD + βD²), where **α is the rate of cell kill by a single hit and β the rate by a two-hit mechanism**; the αD term governs the probability that a single event produces two lesions and the βD² term that two independent events cause the two lesions. The LQ model "is now more widely accepted than the target theory and is frequently used in clinical practice" [YW pp. 2262-2263].

- **The α/β ratio is the dose at which the linear and quadratic terms contribute equally to cell kill** YW p.2263:
  - **Late-responding normal tissues (brain, spinal cord): α/β = 2 to 3 Gy.**
  - **Early-responding normal tissues (skin, GI tract) and most cancers: α/β ≈ 10 Gy.**
- **Biologically effective dose: BED = D (1 + d / [α/β])**, where D is total dose and d dose per fraction. Youmans' worked example: for 30 Gy in 10 fractions with α/β = 10 Gy, **BED = 30 (1 + 3/10) = 39**; solving 39 = D (1 + 2/10) gives **D = 32.5 Gy**, so 30 Gy at 3 Gy per fraction ≈ 32.5 Gy at 2 Gy per fraction for tumour control YW p.2263.
- **The universal survival curve** was developed for single-fraction radiosurgery because some authors argue the LQ model overestimates cell kill at high dose; it preserves the low-dose shoulder but "straightens" the high-dose region. It fits lung SBRT data but "is not significantly better than the linear quadratic model", and its generalisability is unclear YW p.2263.



Reproduced from Youmans & Winn 8e, Fig. 291.7, p. 2262 — Label when you reproduce it: two survival curves side by side, dose on the x-axis and log surviving fraction on the y-axis. Left — target theory, $S = 1 - (1 - e^{-D/D_0})^n$, with n as the extrapolation number that sets the size of the shoulder. Right — the linear-quadratic curve, $S = e^{-(\alpha D + \beta D^2)}$, with the α (single-hit, linear) and β (two-hit, quadratic) components of cell kill labelled separately and the continuously bending shoulder marked.

6. The five Rs of radiobiology — the rationale for fractionation

- **(1) Repair.** Fractionation allows repair of sublethal damage in normal tissue between fractions; essentially each fraction reproduces the shoulder of the survival curve. **The time needed between fractions is set by the half-life of DNA repair** — the spinal cord has slow repair kinetics with a **half-life of about 4 hours**, so at least **6 hours** must separate fractions YW p.2264.
- **(2) Redistribution. Cells in S phase are relatively radioresistant; cells in late G2 and M are most sensitive.** The difference relates to which repair pathway is operating — in S phase cells can use both HR and NHEJ, while in G2/M they mainly use NHEJ. Graphically, S-phase cells have a broader shoulder and M-phase cells minimal or no shoulder.

Over a 5- to 6-week course, "the majority of cells should have been redistributed to a more sensitive phase for at least some of the dose fractions"; radiation also **synchronises** cells at checkpoints [YW pp. 2265-2266].

- **(3) Reoxygenation. Cancers contain regions of hypoxia (pO_2 < 10 mm Hg)**, because proliferation outruns perfusion or the oxygen diffusion range of **70–100 microns** from vessels, or because of vascular collapse, occlusion and leakiness. **Oxygen is arguably the most important radiosensitiser** — it generates free radicals and helps form peroxides that "fix" DNA damage. **The oxygen enhancement ratio for most cells is 2.5 to 3 using x-rays**, meaning three times the dose is needed under hypoxia. Between fractions, transiently collapsed vessels reopen and tumour shrinkage lets previously hypoxic cells move into oxic areas — "a situation that does not occur with single doses" YW p.2266. Youmans is emphatic that **the superiority of fractionated irradiation is because it exploits tumour hypoxia via reoxygenation**, not because the normal-tissue shoulder is broader; in fact "the shoulder on the normal cell survival curve is less than that of many cancer cells" YW p.2264.
- **(4) Repopulation.** After irradiation, cells divide to repopulate tissue. **Early-responding normal tissues — skin, haematopoietic cells, intestinal cells — begin to repopulate at about 4 weeks**; repopulation of late-responding tissue such as brain and spinal cord is less clinically significant. **Cancer cells may undergo accelerated repopulation with shorter doubling times**, notably in head and neck cancer, which is why prolonged treatment breaks are discouraged and accelerated fractionation protocols were developed YW p.2266.
- **(5) Radiosensitivity.** Inherent differences between cell types, determined by efficiency of DNA repair and thresholds for apoptosis. **Bone marrow cells, gametes, germ cells and normal stem cells are typically very radiosensitive**; **melanoma, sarcoma and renal cell cancer are traditionally radioresistant**. Within any tumour, **cancer stem cells preferentially repair DNA compared with their non-stem counterparts** YW p.2266.

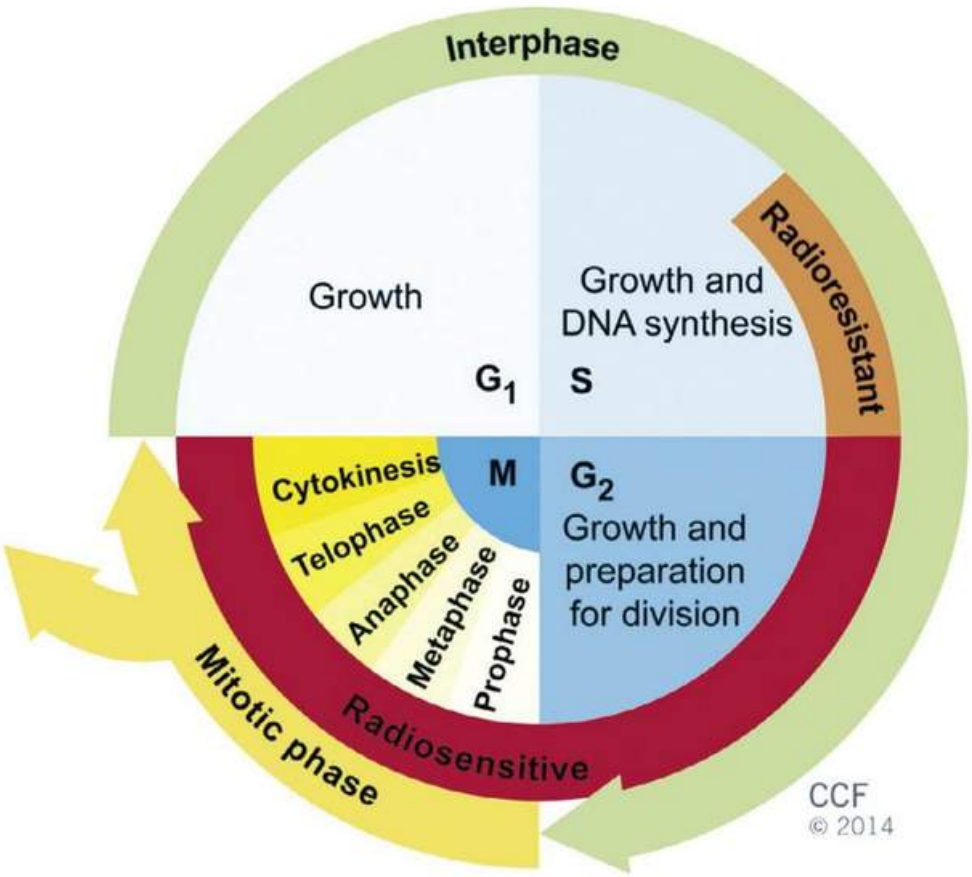


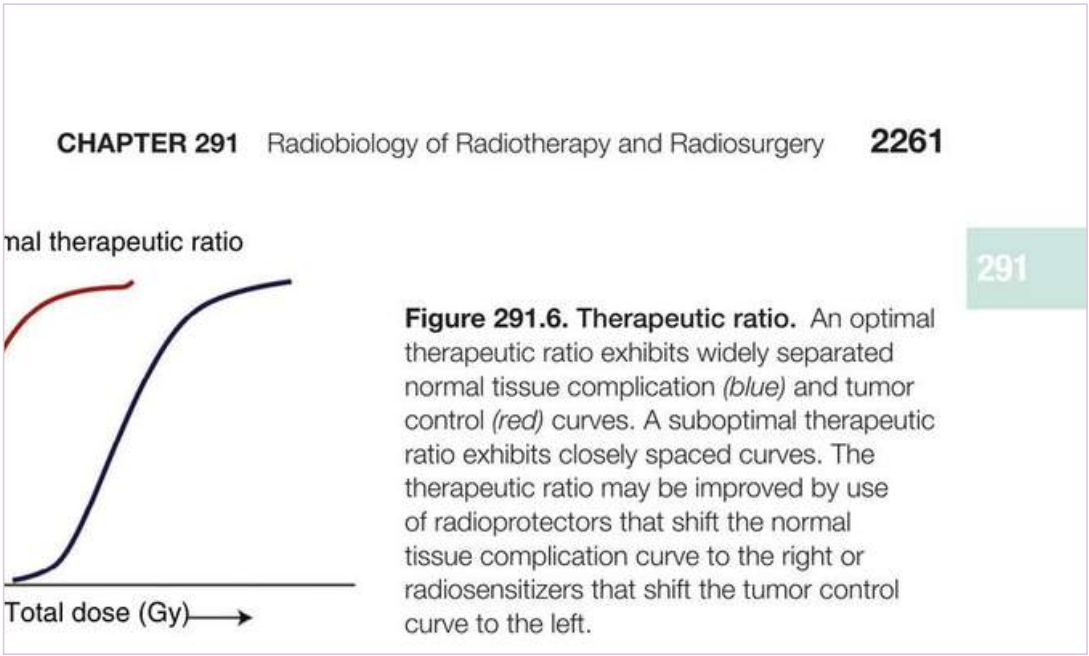
Figure 291.9. Radiation sensitivity varies in the cell cycle. The cell cycle includes interphase (G_1, *S*, and G_2) and mitotic (*M*) phases. Cells are most sensitive to radiation in the G_2 to M phases and least sensitive in late S phase. (*Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.*)

*Reproduced from Youmans & Winn 8e, Fig. 291.9, p. 2265 — Label when you reproduce it: the cell cycle drawn as a circle with G1, S, G2 and M. Shade **G2–M as the most radiosensitive** and **late S as the most radioresistant**. Add the checkpoints at G1-S and G2-M and note that M-phase cells have essentially no shoulder on the survival curve, S-phase cells the broadest.*

7. Normal-tissue effects, the therapeutic ratio and tissue architecture

- **Early effects** predominate in rapidly dividing tissue: erythema, desquamation, local inflammation. **In the brain, local inflammation manifests as raised intracranial pressure** — headache, nausea, vomiting or focal deficit depending on tumour location. **In the spine, weakness or sensory loss from oedema, and transient demyelination producing Lhermitte sign at 1–3 months** YW p.2261.
- **Late effects** occur in slowly dividing or quiescent cells, which reveal damage only when they attempt to replicate — hence the delay. **Late effects relate to total dose and dose per fraction** YW p.2261:
  - **CNS**: neurocognitive deficits, neuroendocrine deficiency, neuropathy, myelopathy.
  - **Skin/subcutaneous**: tanning, fibrosis, atrophy, alopecia.
  - **Vascular**: telangiectasia, vasculopathy, cavernomas, atherosclerosis — contributing to stroke, dementia or vessel rupture.
  - **Bone**: growth-plate damage and stunted growth in children; osteoradionecrosis and spontaneous fracture in adults. **Vertebral compression fracture after high dose-per-fraction spine radiosurgery ranges from 11% to as high as 40%.**

  - **Joints** — stiffness or arthritis; **muscle** — atrophy.
  - **Others**: cataract, infertility, teratogenesis, malignant transformation and radiation-induced malignancy.
- **Functional organisation of tissue determines the dose constraint** YW p.2261:
  - **Serial organs** — the **spinal cord** is the archetype, because injury upstream causes loss of function distally. Radiation myelopathy after spine radiosurgery was predicted by irradiation of **small volumes (e.g. <0.1 mL) of cord to a high Dmax**, which is why recommendations are based on **cord Dmax** and not on larger volumes.
  - **Parallel organs** — kidney, lung, liver: damage to a few subunits does not compromise the organ, so a high Dmax is permissible provided volume-based limits (mean dose, dose to a third of the organ) are respected.
  - **Illustrative clinical example:** in trigeminal neuralgia "we aim to deliver **80 to 90 Gy to the root entry zone** of the trigeminal nerve while limiting the **brainstem to a Dmax of 15 Gy**, because we know this dose is safe and yields a **less than 5% risk of necrosis**. We would not limit 1 mL, or one-third of the brainstem, to 15 Gy and allow a very high Dmax because this would not be safe" YW p.2261.
  - **Skin and brain functional subunits are not well defined**; migration of stem cells from unirradiated areas may repair injury YW p.2261.
- **The therapeutic ratio** is the relationship between the dose–response curve for tumour control and that for normal-tissue complication. "For a given probability of tumour cure, there is always a probability of complications", and the ratio differs for each normal tissue considered. **An optimal therapeutic ratio shows widely separated curves; a suboptimal one shows closely spaced curves.** It is improved by shifting the tumour control curve left (**radiosensitisers**) or the normal-tissue complication curve right (**radioprotectors**). Radioprotectors such as free-radical scavengers "have fallen out of favor because of increased side effects", and **radioprotection is more commonly achieved with treatment planning techniques that limit the amount of normal tissue receiving high dose**. Crucially, "**drugs or techniques that uniformly shift the curves do not improve the therapeutic ratio**" — the key is to widen the separation [YW pp. 2261-2262].



Reproduced from Youmans & Winn 8e, Fig. 291.6, p. 2261 — Label when you reproduce it: two panels of probability-of-effect against total dose. Left — a suboptimal therapeutic ratio with the tumour control (red) and normal tissue complication (blue) curves close together. Right — an optimal ratio with the curves widely separated. Mark the arrow labelled "radiosensitisers" shifting the tumour curve to the left and "radioprotectors" shifting the normal-tissue curve to the right.

8. Radiobiology of the different delivery techniques

- **3D conformal radiotherapy** — CT-based planning, generally **three to seven beam angles** converging on the target; each angle may be segmented or use field-within-field to improve homogeneity YW p.2266.

- **IMRT and arc therapy (VMAT)** — hundreds to thousands of beamlets; particularly useful when the target abuts brainstem, chiasm or optic nerves. **Three drawbacks**: (1) more radiation from the treatment head increases **scatter**; (2) the **low-dose volume is larger** than with 3D conformal therapy, theoretically increasing secondary malignancy risk; (3) **treatment time rises from about 10 minutes to 25–30 minutes**, raising concerns about intra-treatment repair and reduced effective dose rate — though **flattening-filter-free (FFF) beams now allow IMRT and arc therapy in 10 minutes or less** with no apparent increase in adverse radiation effects [YW pp. 2266-2267].
- **IGRT** — setup margins typically **3 to 5 mm**; even with a frame there is some motion, and with modern frameless immobilisation, strict IGRT protocols and robotic positioning, **margins of 1.0 to 2.0 mm** are achievable. Daily cone-beam CT costs about **2 cGy per scan**. **MR-LINAC** now permits continuous MRI while the beam is on, for intrafraction monitoring without ionising radiation YW p.2267.
- **SRS and SRT** — deliver highly conformal radiation to smaller targets at greater doses than achievable with IMRT or arc therapy; **the dose gradient is maximised by the stereotaxy technology**, normal tissues are exposed to very low doses, and this "may contribute to the very low risk of radiation-induced malignancies associated with SRS (**<0.05% at 15 years**)" YW p.2267.
- **Mechanisms specific to radiosurgical doses** YW p.2263:
  - **Direct tumour cell kill** — supported by clinical data in NSCLC, melanoma and renal cell cancer showing that high BED correlates with improved control, suggesting "the dominant effect of radiosurgery doses is death of the tumor cells themselves".
  - **Immunogenic effect** — shedding of tumour antigens stimulating antitumour immunity.
  - **Vascular collapse** — contributing to ischaemia–reperfusion injury and diminished DNA repair. In mouse models, **10 to 15 Gy induced ceramide-mediated apoptosis of tumour-associated microvasculature**, dependent on **acid sphingomyelinase** and independent of direct DNA damage; recruitment of immune cells did not play a significant role in tumour regression in those models.

(b) Radiotherapy of gliomas [4]

9. Why radiotherapy at all — the biological case

- **Gliomas account for only about 31% of CNS tumours but represent 80% of malignant CNS tumours**, and their clinical impact far outweighs their incidence because of an extremely high fatality rate YW p.2301.
- **Glioblastomas (grade IV astrocytoma) account for about 54.4% of all gliomas; 1- and 5-year survival rates are only 35% and 5%** YW p.2301.
- **Malignant gliomas rarely metastasise; mortality is primarily attributed to nearly universal local failure, which leads to early institution of RT as an adjunct to surgery in an attempt to improve local control** YW p.2301.
- **Even near-gross-total resection (>98%) improves overall survival, but the infiltrative nature of GBM prohibits complete surgical eradication in most patients** — hence adjuvant radiotherapy as a cornerstone of treatment YW p.2301.
- **Classification has moved to an integrated molecular framework** — histology combined with **IDH status and other genetic parameters (1p/19q, ATRX, TP53)** — "with the understanding that the key molecular signatures outweigh histologic characteristics" YW p.2301.
- **Fractionation is what makes radical dose possible**: it exploits inherent repair differences between normal and neoplastic tissue, permits reoxygenation of hypoxic tumour regions between treatments, and prevents malignant cells being treated only during the radioresistant portion of the cell cycle — "as can happen with single-fraction treatments such as SRS" YW p.2294. **Typical daily fraction sizes for malignant CNS disease are 1.8 to 3 Gy** YW p.2294.

10. Target volumes — the vocabulary the examiner wants

- **Gross tumour volume (GTV)** — the volume assigned to gross disease visible on planning imaging (CT or MRI) YW p.2269.
- **Clinical target volume (CTV)** — GTV plus a margin of normal tissue to account for microscopic extent. **The CTV depends on histology and on suspicion of residual disease: a glioblastoma plan may use a 5- to 20-mm CTV,**

whereas a benign meningioma may use 0 to 5 mm, because the meningioma is thought to have little invasion whereas glioblastoma infiltrates YW p.2269.

- **Planning target volume (PTV)** — an extra margin around the CTV for setup uncertainty; **0 mm with rigid frame fixation in radiosurgery up to 5 mm with an Aquaplast mask** YW p.2270.
- **RTOG practice for glioblastoma, stated exactly** YW p.2301.e1:
  - **CTV1 = the contrast-enhancing lesion + the resection cavity + surrounding oedema/non-enhancing tumour (best seen on T2/FLAIR), expanded by 2 cm**, treated to **46 Gy**.
  - **After 46 Gy, a coned-down CTV2 = the contrast-enhancing lesion + a 2-cm expansion**, treated to **60 Gy**. **CTV2 must not exceed the boundaries of CTV1 at any point.**
  - Clinical judgement is used to avoid full dose to high-toxicity structures such as the chiasm, and to exclude regions behind natural anatomic barriers — **cerebellum (tentorium), contralateral hemisphere (falx), ventricles**.
  - Some groups omit peritumoral oedema and T2 abnormality from the CTV and simply place a 2-cm margin around contrast enhancement; this mildly decreases the percentage brain volume receiving 30, 46 and 50 Gy "while leaving the central pattern of failure unaltered".
- **Why partial-brain rather than whole-brain irradiation:** CT showed the tumour margin within **2 cm** of the autopsy-determined extent in 29 of 35 patients; on serial CT, **90% of patients had an element of local recurrence within 2 cm of the primary site**; and **true multifocality was found in only 3% of untreated and 6% of treated gliomas** YW p.2301.e1. A trial comparing whole-brain 60.2 Gy with whole-brain 43 Gy plus a 17.2-Gy boost found no survival difference, and **involved-field radiotherapy (IFRT) became the standard of care for GBM** YW p.2301.e1.
- **The T2/FLAIR problem remains unresolved:** conventional MRI cannot distinguish peritumoral oedema from tumour infiltration; MR spectroscopy shows tumour involving approximately **50% of the T2 changes** while also identifying frequent extension beyond them YW p.2301.e1.

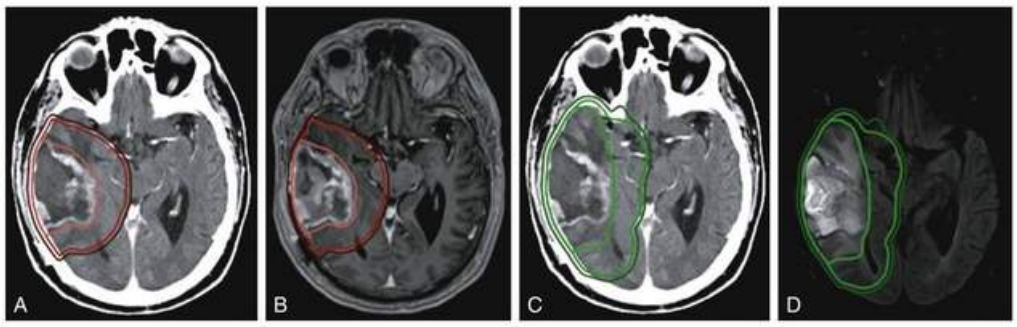


Figure 296.2. Target volume delineation for a patient with a right temporal glioblastoma to be treated with fractionated external beam radiotherapy is performed with fusion of the axial postcontrast magnetic resonance imaging (MRI) and fluid-attenuated inversion recovery (FLAIR) sequences with the treatment planning computed tomography (CT) scan. (A and B) The high-dose region is delineated on the treatment planning CT scan (A) by outlining the contrast-enhanced volume on MRI (B) and adding a 1.5- to 2.0-cm anatomically constrained margin to account for the clinical target volume (CTV) and a 0.3-mm margin for the planning target volume (PTV; *light red, red,* and *dark red*). (C and D) The low-dose region is delineated on the treatment planning CT scan (C) by outlining the FLAIR volume on MRI (D) and adding a 1.5- to 2.0-cm anatomically constrained margin to account for the CTV and a 0.3-mm margin for the PTV (*light green, green,* and *dark green*).

Reproduced from Youmans & Winn 8e, Fig. 296.2, p. 2295 — Label when you reproduce it: (A) the high-dose region drawn on the planning CT by (B) outlining the contrast-enhancing volume on MRI and adding a 1.5- to 2.0-cm anatomically constrained margin for the CTV plus 0.3 mm for the PTV (three nested red contours); (C) the low-dose region drawn on the planning CT by (D) outlining the FLAIR volume on MRI and adding the same margins (three nested green contours). This one figure teaches GTV → CTV → PTV and the two-phase glioblastoma plan simultaneously.

11. Dose — where 60 Gy came from, and why it has never moved

- **The historical dose-response is from the Brain Tumor Study Group serial trials, which showed a dose-response relationship from 45 to 62 Gy: median survival rose from 14 weeks with less than 45 Gy to 42 weeks with 60 Gy** YW p.2302.e1.
- **A randomised Medical Research Council trial confirmed it: median survival 12 months with 60 Gy versus 9 months with 45 Gy (P = .007). "These data established the standard postoperative radiation dose at 60 Gy"** YW p.2302.e1.

Table 1 · Local control of glioblastoma as a function of dose — reproduced in full from Youmans & Winn 8e, eTable 296.1, p. 2302.e1.

#	Dose (Gy)	Median survival (weeks)	25th-percentile survival	P
1	0	18	N/A	N/A
2	<45	14	N/A	Not significant
3	50	28	52	<.001
4	55	36	57	<.001
5	60	42	68	<.001

- **Every attempt at dose escalation above 60 Gy has failed** YW p.2302.e1:
  - **70 Gy versus 60 Gy** in >600 patients in an intergroup RTOG/ECOG study — no survival gain.
  - **RTOG 83-02**, a phase 1 dose-escalation trial of twice-daily RT in >700 patients from 64.8 to 81 Gy — the 72-Gy arm had the best survival, but toxicity beyond that worsened survival. A quality-adjusted survival analysis of 786 patients gave an average of 18.5 months overall with the **72-Gy arm best at 20.8 months**.
  - **RTOG 94-11** (64 Gy or 70.4 Gy by tumour size ≤20 cm² or >20 cm²) — no statistically significant survival advantage.
  - **66 Gy (1.1 Gy twice daily), 70 Gy (2 Gy daily) and 70.4 Gy (1.6 Gy twice daily)** — all failed against standard 59.8–60 Gy.
  - **University of Michigan 90 Gy by 3D conformal technique in 34 patients** — feasible with no significant toxicity but **median survival only 11.7 months**, and "the pattern of failure was not significantly altered, with all patients having central, in-field, or marginal recurrences".
  - **A later Michigan phase 1/2 IMRT study with concurrent radiosensitising chemotherapy in 38 patients (66–81 Gy over 6 weeks) found a maximum tolerated dose of 75 Gy in 30 fractions**, with in-field failure probability falling as dose rose and **median OS 20.1 months**; escalation with IMRT or protons plus radiosensitisers is being tested in **NRG BN001**.
  - **Marks showed the risk of brain necrosis rises substantially above 60 to 70 Gy**, which is the physical ceiling YW p.2302.e1.

12. Chemoradiotherapy and the modern standard

- **The Stupp regimen** — "the utility of adjuvant chemotherapy in conjunction with RT was revolutionized by Stupp and colleagues, who reported an improvement in median survival from **12.1 to 14.6 months** with concurrent and adjuvant administration of **temozolomide (TMZ)** with RT" YW p.2302.
- **Nothing since has beaten it.** Research on dose, timing, dose intensification and number of TMZ cycles, TMZ-sensitising agents such as O⁶-benzylguanine, antiangiogenic agents and immune checkpoint inhibitors — **"none of these approaches … has improved survival."** A German trial of RT with TMZ and lomustine gave a possible signal but remains unvalidated YW p.2302.
- **Radiosensitiser trials have all been negative** YW p.2302: **hyperbaric oxygen** consistently disappointing; nitroimidazoles (**metronidazole, misonidazole**) failed confirmatory RTOG study; **efaproxiral (RSR13)**, which shifts the oxygen-haemoglobin dissociation curve, gave no categorical survival benefit; halogenated pyrimidines including **BUdR** showed an apparent favourable effect in retrospective RTOG/NCOG analysis but subsequent trials "failed to demonstrate any survival benefit"; **motexafin gadolinium (MGd)**, a redox modulator with in-vitro uptake in glioblastoma nuclei, was tolerated but not effective.
- **Molecular subtype predicts the pattern of failure** — "tumors with an **unmethylated MGMT promoter** are more likely to recur within the radiation field" YW p.2302.
- **A new recursive partitioning analysis incorporating MGMT protein, c-Met protein and age** stratifies patients better than prior clinical models, even with MGMT promoter methylation included YW p.2303.

13. Anaplastic (WHO grade III) glioma

- **Median survival of anaplastic astrocytoma is in the 2- to 3-year range** YW p.2303.

- **Volumes and dose:** partial-brain fields. **Initial GTV = the hypodense oedema or T2/FLAIR abnormality; boost GTV = the contrast-enhancing volume; CTV = a 2- to 3-cm margin around GTV. The initial volume is treated to 46 to 50.4 Gy and the boost volume to 59.4 to 60 Gy** YW p.2303.
- **More aggressive is worse in this histology.** In 149 patients, median survival was **3 years with RT alone, 2.3 years with chemoradiotherapy and 1.2 years with chemotherapy plus misonidazole**; Laramore's analysis of 163 patients showed the same phenomenon, and neutron boost and misonidazole sensitisation both decreased survival YW p.2303.
- **Trial evidence: RTOG 9813** (RT plus BCNU vs RT plus TMZ) — TMZ did not significantly improve time to progression or OS but was better tolerated. **NOA-04** — time to treatment failure did not differ whether RT or chemotherapy (TMZ or PCV) was given first. **CATNON** (1p/19q non-co-deleted tumours, four arms) — interim results showed improved survival with RT plus adjuvant TMZ, **HR for OS 0.65, 5-year OS 55.9% with adjuvant TMZ versus 44.1% without** YW p.2303.
- **Anaplastic oligodendroglioma:** in the updated dose-intense pre-RT TMZ followed by RT plus TMZ experience, median PFS was **5.9 years** with median OS not reached; in co-deleted patients neither was reached, with **6-year PFS 77% and OS 82%** versus **49% and 60%** for co-deleted patients receiving RT only in RTOG 9402 (P = .0042 and P = .012) YW p.2304.
- **Practical point:** "Most centers in the United States treat anaplastic astrocytoma like GBM with concurrent and adjuvant TMZ" YW p.2303.

14. Low-grade (WHO grade II) glioma

- **WHO grade II diffuse astrocytoma, oligodendroglioma and mixed tumours have a more prolonged natural history**, but **in the molecular era patients with histologically low-grade tumours lacking the IDH mutation have extremely poor outcomes, akin to higher-grade tumours** YW p.2304.
- **The role of RT was defined by three randomised studies of radiation dose and timing** YW p.2304. **EORTC 22845** randomised **314 patients** to immediate post-operative RT or delayed treatment at progression. RT was **54 Gy in 1.8-Gy fractions**, targeted to the tumour on preoperative CT plus 2 cm for the first 45 Gy, with a cone-down to GTV + 1 cm for a 9-Gy boost. Immediate RT gave **longer PFS (median 5.3 versus 3.4 years)** and **better seizure control at 1 year (25% versus 41% incidence)** but **no difference in overall survival (7.4 versus 7.2 years)**.
- **An important negative finding:** most recurrences were higher grade regardless of whether the patient had RT, "dispelling the notion that radiation contributes to the malignant degeneration of these tumors" YW p.2304.
- **Current standard:** "the current standard for most patients with WHO grade II glioma (except for gross totally resected tumors in patients younger than 40) is combination chemoradiotherapy"; the TMZ-versus-PCV debate continues. **Patients with IDH wild-type tumours might not derive any benefit from chemotherapy**, and de-intensification or toxicity reduction (including a proton trial through NRG) is warranted for the most favourable subgroups YW p.2304.
- **Dose choice in practice:** radiation oncologists frequently use **54 Gy in 1.8-Gy fractions**, based on the radiation arm of EORTC 22845, or on the argument that the increase in toxicity between **45 Gy** (the lowest dose supported by randomised evidence) and 54 Gy is likely limited YW p.2304.
- **Fraction size matters for cognition:** a seminal EORTC series showed that in patients with low-grade gliomas receiving radiotherapy, **fraction sizes greater than 2 Gy led to worsened cognition**; recent multi-institutional series use **1.8 Gy per fraction** YW p.2270.

15. Elderly and frail patients

- **60 Gy over 6 weeks in 30 fractions may not be necessary.** Roa's randomised trial comparing **40.05 Gy over 3 weeks** with standard 60 Gy over 6 weeks found **no significant difference in survival, but less steroid requirement and more patients completing treatment** on the 3-week arm YW p.2302.e1.
- **The Nordic trial** randomised to standard RT, TMZ alone, or **34 Gy in 10 fractions**; for patients older than 70 years a survival benefit (**HR 0.59; P = .02**) was reported for the hypofractionated regimen YW p.2302.e1.
- **The IAEA phase 3 study** compared **40.05 Gy in 15 fractions over 3 weeks** with **25 Gy in 5 fractions over 1 week** in elderly/frail GBM patients and found **no differences in PFS, OS or quality of life** YW p.2302.e1.
- **TMZ continues to benefit elderly patients even with hypofractionated regimens** YW p.2302.e1. For elderly

glioblastoma patients and those with poor performance status, **40 Gy in 15 fractions should be considered** YW p.2264.

16. Technique — how the plan is actually made and delivered

- **Immobilisation** with a molded Aquaplast face mask decreases the margin for daily setup variability and constrains intrafraction motion YW p.2294.
- **Planning is on the fused product of diagnostic high-resolution MRI and a planning CT performed in the treatment position** YW p.2294.
- **Image guidance** — daily biplanar orthogonal x-ray, cone-beam CT, optical imaging or megavoltage CT improves positional reproducibility and permits smaller error margins; **intrafraction repetitive imaging as with the CyberKnife** is a further step; on-board MRI will allow **adaptive radiotherapy** YW p.2294.
- **IMRT** is a subset of 3D conformal RT that improves conformality by non-uniform delivery, modulating photon flux; it matters most for **concave or convex targets near the optic apparatus, vestibulocochlear structures, hypothalamic-pituitary axis, hippocampus or brainstem**, and "we now have level I evidence that such conformal techniques produce superior outcomes in terms of cognitive, intellectual, and endocrine functional preservation" [YW pp. 2294-2295].
- **FSRT** — a hybrid incorporating the spatial advantages of radiosurgery with the biological advantages of fractionation, using multiple non-coplanar fixed or arced fields, robotic devices and mini-multileaf collimators, with **reported precision between 1 and 3 mm**; used for lesions needing high precision that cannot be treated by SRS because of size or proximity to critical structures YW p.2295.
- **Charged particles** — most dose deposited at a specific depth with no exit dose, dramatically decreasing integral dose; **pencil beam scanning** further reduces unnecessary dose in the entry path and laterally. Applied most commonly to skull base chordoma and chondrosarcoma, which need high doses and sit among radiosensitive structures, and advocated for childhood and benign tumours and for patients with long expected survival [YW pp. 2295-2296].
- **An immunological argument for reducing integral dose:** "recent data suggest that in glioblastoma multiforme patients treated with combination chemoradiotherapy, development of **posttreatment lymphopenia (<500 cells/mm³) is highly predictive of tumor-related early mortality**; furthermore, reduction in the volume of brain exposed to low doses decreases the rate of acute severe lymphopenia" YW p.2296.

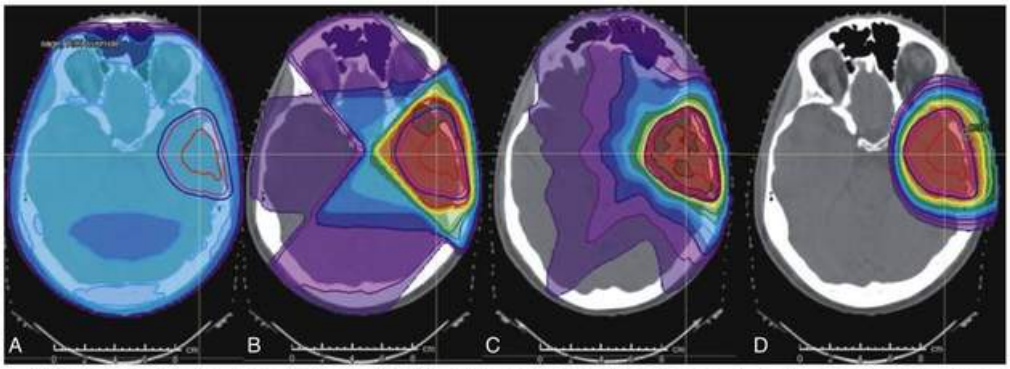


Figure 296.1. Examples of isodose distribution for a patient with a left temporal primary brain tumor treated with (A) opposed lateral two-dimensional radiotherapy, (B) three-dimensional conformal radiotherapy, (C) intensity-modulated radiotherapy, and (D) pencil beam scanning proton therapy. Each stepwise transition in advanced radiotherapy results in a reduction in extraneous or unnecessary dose to the normal tissues of the brain.

Reproduced from Youmans & Winn 8e, Fig. 296.1, p. 2294 — Label when you reproduce it: four isodose distributions for the same left temporal primary brain tumour — (A) opposed lateral two-dimensional radiotherapy, (B) three-dimensional conformal radiotherapy, (C) intensity-modulated radiotherapy, (D) pencil-beam scanning proton therapy. Point out in the answer that each stepwise transition reduces extraneous dose to normal brain, and that this is the whole technical history of glioma radiotherapy in one picture.

17. The place of radiosurgery in glioma

- **Up-front SRS lacks evidence in newly diagnosed high-grade glioma.** The only multicentre randomised phase 3 trial, **RTOG 9305**, evaluated SRS added to fractionated radiotherapy; with median follow-up of 61 months, **median OS was 13.5 months with SRS and 13.6 months without** [YW pp. 2330-2331].
- **The reasons are biological:** infiltration into adjacent brain and propensity for dissemination mean the sharp dose falloff

of SRS "plays a limited role" in a tumour that is never a discrete target YW p.2330.

- **Salvage SRS for recurrent HGG may benefit a carefully selected subset**, and the chapter tabulates numerous series; a three-fraction hypofractionated SRT regimen for recurrent HGG had a **maximum tolerated dose of 11 Gy per fraction**; combination with **bevacizumab** may permit reirradiation by reducing radiation necrosis risk YW p.2331.

(c) Principles of the Gamma Knife [3]

18. The five founding principles

1. **Cross-firing.** The Gamma Knife "operates by precisely aligning the gamma-ray emissions from an array of ⁶⁰Co sources so they intersect at a point called the focus point. **Each beam individually has a fairly low dose rate. However, the summation of the beams at the focus point creates a very concentrated dose**" YW p.2275. Spreading the energy among **192 or 201 beams** achieves a high target dose while sparing normal brain, because dose falls quickly away from the isocentre YW p.2275.
2. **Stereotaxis.** "Radiosurgery depends on the synthesis of stereotaxis and three-dimensional imaging." The **Leksell frame has known dimensions and implicitly defines a reference stereotactic coordinate system once placed on the patient** YW p.2276. On the Icon, the CBCT isocentre has a known calibration relationship to the radiation isocentre, so its images are **implicitly in stereotactic coordinate space** YW p.2276.
3. **Steep dose gradient in preference to dose homogeneity.** Unlike fractionated radiotherapy, Gamma Knife dosimetry deliberately accepts an **inhomogeneous** dose within the target in exchange for a very steep gradient outside it, with the margin prescribed typically at the **50% isodose line** [YW pp. 2275, 2280].
4. **Topologic differential effect.** This is "the basic principle for safety in radiosurgery due to the delivery of a high dose in a single session, as opposed to radiotherapy in which the attempt to spare the normal tissue is based on the search for a biologic differential effect related to fractionation." It follows that **accuracy and precision are paramount**, that an especially high spatial accuracy is required for both imaging and dose planning, and that **quality control plays a major role in ascertaining safety** — radiosurgery is "a purely image-guided operation, with no immediate possible control of the effect of the procedure" YW p.2336.
5. **Conformality and selectivity by shot planning.** The neurosurgeon plans by defining one or more **isocentres, commonly called "shots"**, and "by carefully manipulating the location of the isocentres and the **dwell time** at each location, the neurosurgeon can create a highly conformal treatment plan, sparing normal adjacent brain structures" YW p.2276.

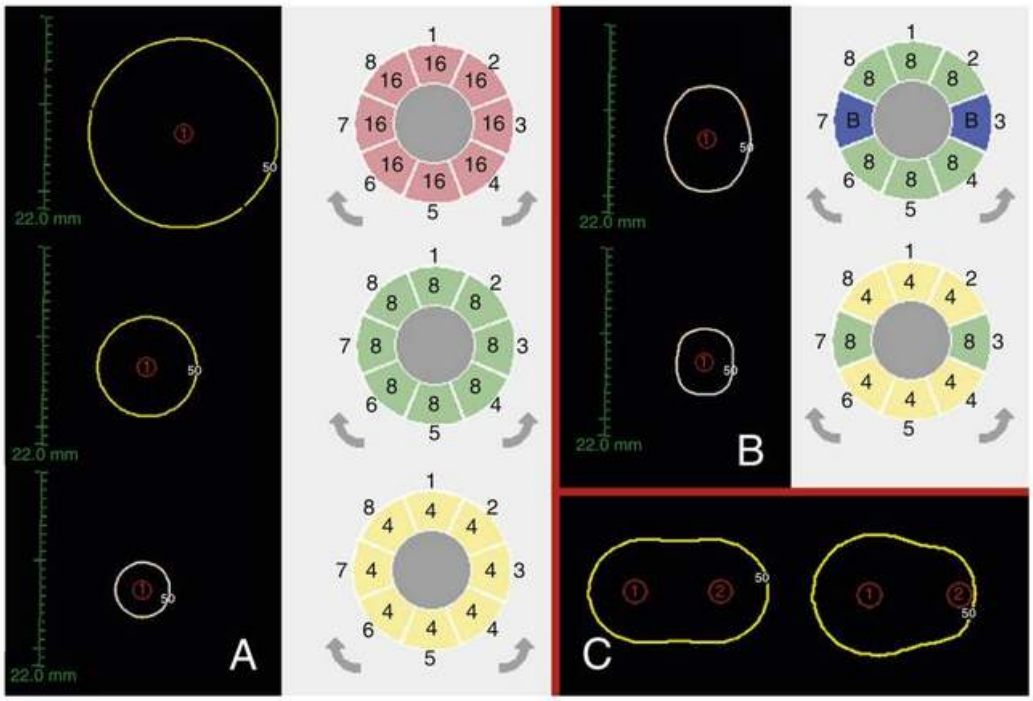


Figure 293.3. Customized Gamma Knife radiosurgery planning. Shot diameters vary based on collimator sizes (A). Composite collimators can create distinct dose clouds that can "shape" the prescription isodose lines to improve plan conformality (B). Combining shots in different positions in space, and weighting them differently, can also impact the dose cloud (C). Together, these techniques can serve to shape the prescription radiation isodose line to the tumor and avoid normal parenchyma.

Reproduced from Youmans & Winn 8e, Fig. 293.3, p. 2276 — Label when you reproduce it: (A) shot diameters varying with collimator size (4, 8, 16 mm); (B) composite collimators — the eight sectors set to different collimator sizes or to "B" (blocked) — creating distinct dose clouds that shape the prescription isodose line; (C) shots placed at different points in space and differently weighted, reshaping the dose cloud. Annotate that these three manoeuvres — size, composite sector configuration and weighting/dwell time — are the only three degrees of freedom the planner has, and together they produce conformality.

19. Source physics, machine architecture and the practical consequences

- **⁶⁰Co is created in a reactor by neutron bombardment and activation of ⁵⁹Co, decays by β emission to activated ⁶⁰Ni, which on dropping to ground state releases gamma photons at 1.17 and 1.33 MeV** [YW pp. 2274-2275].
- **Half-life 5.3 years; dose rate falls approximately 1.1% per month; sources typically replaced every 5 years; source activity must be measured and entered into the dose calculation** YW p.2257.
- **The sources emit continuously**, hence a shielded "off" position, heavy shielding requirements and **Nuclear Regulatory Commission** regulation [YW pp. 2258, 2269].
- **Machine components** YW p.2275: a **large spherical shield** containing the source array, protecting patient and staff; a **central body** holding the source array and the **primary collimation system** that directs the rays to the focus; a **treatment table** that moves and precisely positions the head; a **control suite**; and a **treatment planning system** used by the neurosurgeon together with a radiation oncologist and medical physicist.
- **Collimation generations:** older models (U, B, C, 4C) with external helmets of **4, 8, 14 and 18 mm** plus manual **plugs**; Perfexion and Icon with a single internal collimator of **4, 8 and 16 mm**, the source array **split into eight sectors of 24 sources**, each independently set to any collimator size or to **blocked**, allowing a **composite isocentre** [YW pp.

2275-2276].

- **Multisession capability:** the **Extend** relocatable dental-impression frame on Perfexion; the **Icon's CBCT plus IFMM infrared nose-marker tracking with a default 1.5 mm motion threshold**, enabling mask-based hypofractionated treatment of up to five fractions [YW pp. 2276, 2278].
- **Team requirement:** Youmans states as a key concept that "the success of radiosurgery is dependent on a team-based approach, including integration between a neurosurgeon, radiation oncologist, and radiation physicist, at a minimum" YW p.2274.

20. Planning principles and dose constraints

- **Imaging must be of high quality and stereotactically accurate.** Youmans requires quality control of the MRI unit, a special frame holder to avoid movement, and checking of image accuracy for **each sequence** by comparing known frame measurements with image measurements and the distance from the posterior to the middle fiducials; measurements are checked again after network transfer to confirm no distortion [YW pp. 2278-2279].
- **MRI's weakness is distortion** from field inhomogeneity and non-linearity, gradient non-linearity and magnetic susceptibility, which is why Youmans "recommends the systematic use of a second modality" — CT is less informative but has high resolution and much lower distortion risk YW p.2336.
- **Planning metrics:** dose-volume histograms for target and critical structures, **conformality index, dose uniformity and gradient index** YW p.2279.
- **Perceptual traps in contouring:** a lesion boundary "is not always a distinct, sharp line but is rather a smudge of transition between enhancement and nonenhancement"; **the Cornsweet effect** can mislead into prescribing high dose to an inappropriate contour, and the **"illusion of perfection"** makes many different isodose lines appear to fit the same tumour — reasons why some experienced neurosurgeons plan without outlining the target at all YW p.2279.
- **Critical structure limits** YW p.2279: **optic apparatus ≤8 Gy in a single fraction** (10–12 Gy without ill effect described by some), with **3 mm** classically desirable between tumour margin and optic apparatus (modern devices 1–2 mm), and **25 Gy over five fractions** if fractionated; other **cranial nerves 19–30 Gy** with low risk; **brainstem Dmax 15 Gy** in trigeminal neuralgia work, giving <5% necrosis risk YW p.2261; **carotid injury after SRS is rare** (one isolated case report).
- **Shielding and plugging** are used where a tumour extends into an eloquent area, to lower dose to critical structures YW p.2279.
- **Pituitary dose principles:** there is a direct correlation between effect on tumour volume and endocrine remission rate; because most sellar lesions are small, dose-volume considerations are not usually limiting; **a margin dose of 20 Gy or more** is delivered to allow rapid hormonal normalisation and growth control, and **25 or 30 Gy** may be chosen for better hormonal normalisation in functioning adenomas, accepting an unknown increment in delayed hypopituitarism YW p.2279.

21. Safety, quality assurance and complications

- **Daily quality assurance of the facility is step 1 of the procedure** YW p.2277.
- **Frame integrity is critical** — "as the frame defines the stereotactic coordinate system, the integrity of the frame system is critical to the overall accuracy and precision of the radiosurgical procedure"; the manufacturer recommends evaluating frame stability by applying force to the base ring, and the Icon's CBCT can independently verify that fixation pins have not shifted immediately before treatment YW p.2278.
- **Collision avoidance** — the frame adaptor and frame cap fitting check provides the geometry of all frame parts and of the patient's head in relation to the planning system, needed to predict collisions with the collimator system; if the frame cap does not fit, exact post and screw geometry must be entered into the planning system YW p.2278. A **clearance check** with a test tool simulating the inner collimator is rotated around the head for shots in close contact with the collimator, especially in multiple metastases [YW pp. 2279-2280].
- **Accuracy:** the theoretical accuracy of frame-based radiosurgery such as the Gamma Knife "is usually recognized to be less than 1 mm" YW p.2279; frame fixation reproduces position to an accuracy of approximately **0.5 mm** YW p.2272.
- **Complication profile:** pin-site oozing managed by compression or suture, topical antibiotics for pin-site infection,

observation for a few hours then discharge; admission for seizure, nausea, severe pain, anaesthetic complication or new deficit YW p.2280.

- **Late risk:** the risk of a radiation-associated tumour after radiosurgery is estimated at **less than 1 per 1000 patients (range 0.01% to 2%), compared with 10% with external radiotherapy at 20 years**, and must be disclosed to every patient before the procedure; Cahan's criteria define a radiation-induced tumour YW p.2336. Youmans separately gives **<0.05% at 15 years** YW p.2267. **Malignant transformation of vestibular schwannoma has been reported but its frequency is turning out not to be increased by SRS** YW p.2336.

Table 2 · Radiation modalities and their common clinical indications in CNS oncology — reproduced in full from Youmans & Winn 8e, Table 292.1, p. 2270.

#	Radiation modality	Common clinical indications
1	Three-dimensional conformal radiotherapy (3DCRT)	Glioblastoma, low-grade glioma, whole-brain radiotherapy
2	Intensity-modulated radiotherapy (IMRT)	Cases in which 3DCRT is indicated but cannot meet threshold dose constraints
3	Stereotactic radiosurgery (SRS)	Single or oligometastatic brain metastases, meningiomas, trigeminal neuralgia, schwannoma, pituitary adenomas
4	Hypofractionated stereotactic radiotherapy (IGRT)	Meningiomas larger than can be safely treated with single-fraction SRS
5	Conventionally fractionated stereotactic radiotherapy (IGRT)	Meningiomas or pituitary adenomas in close proximity to or encasing the optic structures
6	Proton beam therapy	Craniospinal irradiation
7	Brachytherapy	Patients with recurrent brain tumours or metastases who have previously received full-dose radiotherapy

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Two-thirds of DNA damage from therapeutic (low-LET) radiation is indirect, via hydroxyl radicals; one-third is direct.** Quote this figure first in any radiobiology answer YW p.2260.
- **The five Rs: repair, redistribution, reoxygenation, repopulation, radiosensitivity** — and the reason fractionation works is **reoxygenation**, not a broader normal-tissue shoulder [YW pp. 2264, 2266].
- **α/β = 2–3 Gy for brain and spinal cord (late-responding); ≈10 Gy for most tumours and early-responding tissue.** BED = D(1 + d/[α/β]) YW p.2263.
- **Radiosensitivity by cell-cycle phase: G2–M most sensitive, late S most resistant** — and the shoulder width mirrors it [YW pp. 2265-2266].
- **Oxygen enhancement ratio 2.5–3; hypoxia is pO_2 <10 mm Hg; oxygen diffusion range 70–100 microns** YW p.2266.
- **Spinal cord repair half-time ≈4 hours → at least 6 hours between fractions** YW p.2264.
- **Serial organ = cord (constrain Dmax in <0.1 mL); parallel organ = lung/liver/kidney (constrain mean or one-third volume).** The trigeminal example — 80–90 Gy to the root entry zone with brainstem Dmax 15 Gy — is the cleanest illustration YW p.2261.
- **The therapeutic ratio is improved only by widening the separation of the curves; a uniform shift of both curves changes nothing** YW p.2262.
- **60 Gy is the glioblastoma dose because median survival rose from 14 weeks (<45 Gy) to 42 weeks (60 Gy), and MRC randomised data gave 12 versus 9 months** — and every escalation above it, up to 90 Gy, has failed YW p.2302.e1.
- **RTOG glioblastoma volumes: CTV1 = enhancement + cavity + FLAIR + 2 cm to 46 Gy; coned-down CTV2 = enhancement + 2 cm to 60 Gy, never exceeding CTV1** YW p.2301.e1.
- **Partial-brain is justified because 90% of recurrences are within 2 cm of the primary site and true multicentricity is only 3%–6%** YW p.2301.e1.
- **Anaplastic glioma: 46–50.4 Gy initial, 59.4–60 Gy boost, 2–3 cm CTV; CATNON gave HR 0.65 for adjuvant TMZ (5-year OS 55.9% vs 44.1%)** YW p.2303.

- **Low-grade glioma: EORTC 22845 — immediate 54 Gy improves PFS (5.3 vs 3.4 years) and 1-year seizure control (25% vs 41%) but not OS (7.4 vs 7.2 years); and RT does not cause malignant degeneration** YW p.2304 .
- **Fraction size >2 Gy worsens cognition in low-grade glioma; use 1.8 Gy** YW p.2270.
- **Gamma Knife principles in five words: cross-firing, stereotaxis, gradient, topologic differential effect, shot planning.** The margin isodose is 50%; frame accuracy <1 mm with ≈0.5 mm reproducibility [YW pp. 2272, 2275-2276, 2279, 2336].
- **Two planning illusions to name: the Cornsweet effect and the illusion of perfection** — which is why some surgeons plan without contouring YW p.2279.

Pages read for this answer — Youmans & Winn 8e: 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2269, 2270, 2272, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2294, 2295, 2296, 2301, 2301.e1, 2302, 2302.e1, 2303, 2304, 2330, 2331, 2336

a) Cyber knife. [5]
b) Role of O-Arm in neurosurgery. [5]

LONG | JAN 2025 · Paper III · Q4 | 10 marks

Also asked as: Radiosurgery platforms and intraoperative imaging — also asked as DEC 2022 · Paper III · Q1 (a] Gamma knife [3]; b] Cyber knife [3]; c] SRS [4]).

Source: Youmans & Winn Neurological Surgery, 8th ed. — Ch. 28 *Robotics in Cranial Neurosurgery* (Rapoport, Morgan, Baker, Bruhat, Grady), §Robotic Systems in Current Use in Cranial Neurosurgery — Stereotactic Radiosurgery, §Trajectory-Finding Robotic Systems, pp. 234, 234.e1-234.e2 (Fig. 28.1, p. 234.e2). Ch. 293 *Radiosurgery Technique*, §Radiation Sources for Radiosurgery, §Radiosurgical Devices — Linear Accelerator–Based Radiosurgery, §The Linear Accelerator–Based Radiosurgical Procedure, §Methods of Conformality, §Frameless Radiosurgery and the Spine, pp. 2274-2281 (Figs. 293.1, 293.3, pp. 2275-2276; Table 293.1, p. 2277). Ch. 364 *Image-Guided Spinal Navigation: Principles and Clinical Applications*, §Registration, §Spinal Navigation Techniques, §Clinical Applications and Results, pp. 2837-2841 (Figs. 364.1-364.5, pp. 2838-2841). Ch. 29 *Spinal Robotic Surgery*, §Evolution of Intraoperative Navigation, §First-Generation Spinal Robots, pp. 235, 235.e1-235.e2 (Figs. 29.1-29.3, pp. 235.e2-235.e3). Supplementary: Ch. 290 *General and Historical Considerations of Radiotherapy and Radiosurgery*, §Robotic Positioning and Automated Collimation, pp. 2251-2255; Ch. 291 *Radiobiology of Radiotherapy and Radiosurgery*, §Basic Principles of Radiation Therapy, pp. 2257-2258 (Figs. 291.1-291.2, p. 2258); Ch. 292 *Radiation Therapy Techniques*, §Stereotactic and Image-Guided Radiotherapy, pp. 2271-2273 (Tables 292.3-292.4, pp. 2272-2273); Ch. 296 *Fractionated Radiotherapy for Brain Tumors*, §Treatment Setup, p. 2294; Ch. 302 *Radiosurgery for Benign Spine Tumors and Spinal Vascular Malformations*, pp. 2367-2371; Ch. 150 *Frame and Frameless Stereotactic Brain Biopsy*, p. 1045; Ch. 339 *Evaluation and Treatment of C2 (Axis) Fractures*, pp. 2648-2650; Ch. 344 *Evaluation and Treatment of Osteoporotic Fractures*, p. 2687; Ch. 370 *Minimally Invasive Transforaminal Lumbar Interbody Fusion*, p. 2871; Ch. 112 *Deep Brain Stimulation for Dystonia*, p. 743; Ch. 209 *Percutaneous Cordotomy and Trigeminal Tractotomy*, pp. 1581, 1583.

(a) CyberKnife [5]

1. Definition — the one sentence to open with

- **The CyberKnife (Accuray, Sunnyvale, CA) is a compact linear accelerator mounted on an industrial articulated robotic arm, integrated with an orthogonal kilovoltage x-ray image-guidance system that tracks the tumour and the patient throughout treatment and realigns the treatment beam in real time.** Youmans' own words: "The CyberKnife device comprises a linear accelerator (the radiation source) that is mounted on a robotic arm and an image-guidance system that tracks tumor and patient motion during treatment to realign the treatment beam in real time" YW p.234.e1.
- **It is therefore a *photon* radiosurgical device of the LINAC family, not an isotope device.** Youmans classes it among the "specialized EBRT or radiosurgery x-ray devices … compact LINACs mounted on a robotic manipulator (i.e., CyberKnife unit)", alongside the rotational slip-ring TomoTherapy unit and the gyroscopic Zap-X system YW p.2257, and lists it among LINACs purpose-designed for radiosurgery: **Edge (Varian Medical Systems), Versa HD (Elekta AB), TomoTherapy Hi-Art, CyberKnife (Accuray) and Novalis Radiosurgery (BrainLab)** YW p.2276.
- **Its place in the robotics chapter is not incidental.** Youmans calls the CyberKnife "one of the earliest and most widely used robotic arm systems in cranial neurosurgery" and says that "even though the system is completely noninvasive, it exemplifies the paradigm of programmable neurosurgical intervention involving **real-time sensing and actuation** and,

to a limited extent, **autonomous, on-the-fly control** to compensate for small movements" YW p.234.e1. It is the only radiation device in the book discussed as a robot.

2. Historical anchors

- **1987 — invented by Adler**, combining a mobile LINAC on a robotic arm with an image-guided robotic system YW p.1381.
- **1994 — clinical trials begin.**
- **1999 — US FDA approval for the treatment of intracranial tumours** YW p.234.e1.
- **Context:** LINACs were first proposed as radiation sources for radiosurgery by **Larsson and colleagues in 1974**; the earliest clinical reports of LINAC-based radiosurgery came from **Betti and Derechinsky in 1983** and **Colombo, Hartmann and coworkers in 1985**; the **first commercially available LINAC SRS unit was the X-Knife (Radionics) in 1992** [YW pp. 2254, 2276]. The CyberKnife belongs to the generation after those, whose developments Youmans lists as "more sophisticated software packages, the development of **iterative robotic LINAC source positioning**, MLCs for IMRT and VMAT, and robotic couches capable of position correction during treatment delivery, such as offered by the **CyberKnife, Novalis, and Varian TrueBeam** systems" YW p.2254.

3. The physics of the source

- **X-ray generation:** "linear accelerators (LINACs) generate x-rays by accelerating electrons and directing them to strike a high atomic-number target. The electrons interact with the target nuclei and generate primarily **Bremsstrahlung** and secondarily **characteristic x-rays**" YW p.2274.
- **Machine architecture behind that:** microwaves produced by a **klystron** accelerate electrons to high velocity within the accelerator tube; a **bending magnet** directs the energetic electrons onto the target, producing the treatment beam YW p.2251.
- **Energies:** therapeutic x-rays commonly range from **3 to 18 MV**, orders of magnitude above diagnostic photons of 50–150 kV; **3 to 6 MV** is typical for brain lesions YW p.2257.
- **Indirect ionisation:** photons liberate charged particles (electrons), which lose energy through Coulomb interactions, each transferring a small part of the particle's kinetic energy to tissue, causing ionisation and the biologic effect YW p.2275.
- **Skin sparing:** high-energy photons exhibit a **buildup region** on entering tissue, because liberated electrons are imparted a forward initial velocity and deposit their energy deeper — the skin-sparing effect YW p.2275.
- **Advantages of an electrically generated source over an isotope:** no decay (no 1.1% per month loss, no five-yearly source change), no continuous emission requiring a shielded "off" position, and regulation under state rather than Nuclear Regulatory Commission jurisdiction — the very factors that led to the eclipse of ⁶⁰Co teletherapy [YW pp. 2251, 2257-2258, 2269].

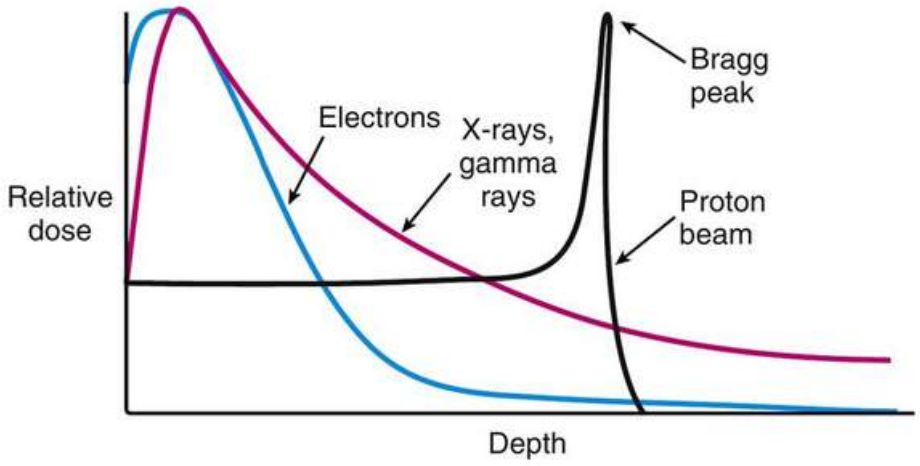


Figure 293.1. Comparison of dose deposition for photon beams (x-rays and gamma rays), electron beams, and proton beams. Note that photon beams have a "buildup region," which provides a measure of skin-sparing at the surface of the part of the patient being irradiated. Electron beams exhibit less skin sparing and a sharper dose falloff. Proton beams deposit most of the dose at the end of their range, a phenomenon called the Bragg peak. Photons also have a maximum dose range in tissue.

Reproduced from Youmans & Winn 8e, Fig. 293.1, p. 2275 — Label when you reproduce it: relative dose against depth for three beam types — photons (x-rays and gamma rays) with a buildup region giving skin sparing, then gradual attenuation and an exit dose; electrons with less skin sparing and a sharper falloff; and protons with the Bragg peak at the end of range and essentially no exit dose. Use it to state that the CyberKnife is a photon machine and therefore has an exit dose, which is exactly why it needs many beam directions.

4. The robotic principle — why the beam is put on an arm

- **The problem being solved:** "a conventional LINAC has only a single radiation source mounted on a single-plane gantry so that serially adding beams can extend treatment times beyond the practical" YW p.2252.
- **The solution:** "One strategy is to liberate the source from the LINAC's traditional single-plane design, for example, by mounting it on a robotic arm making available a large number of beam directions or '**nodes**.' With the CyberKnife (Accuray, Sunnyvale, CA), a small variably collimated LINAC mounted on an industrial robotic arm uses **up to 200 separate nodes treated serially per session** to achieve one treatment" YW p.2252.
- **Why this matters dosimetrically:** "A higher number of smaller and more finely controlled beams makes possible finer gradations in dose-target conformality. This is particularly critical for SRS, in which lack of conformality has the greatest potential for toxicity given the high individual doses involved" YW p.2252.
- **The engineering context** is the same one that produced trajectory robots in neurosurgery: "A ubiquitous feature of industrial robots is the articulated robotic arm. This type of robot has emerged as a dominant design in contemporary robotic surgery, which is perhaps not surprising given that these robots are in many cases intended to function like the arms and hands of a surgeon" YW p.234.e1.
- **Beam shaping** on LINAC platforms is by **multileaf collimators (MLCs)** that shape the field at each position and may be modulated, or by **specialised tertiary collimators often called radiosurgery cones**, which create near-spherical spots of radiation at the isocentre YW p.2276.

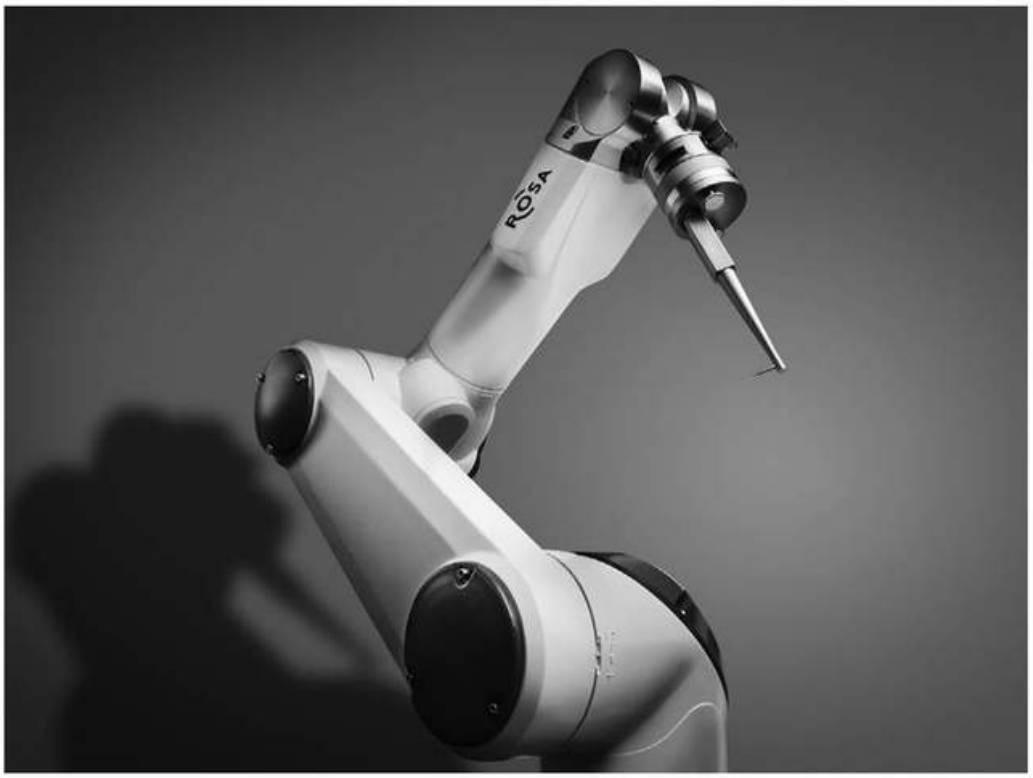


Figure 28.1. The ROSA ONE. The ROSA ONE robotic arm developed by Zimmer Biomet Robotics *(Courtesy LucileBssg/CC BY-SA 4.0. https://en.wikipedia.org/wiki/File:ROSA_One%C2%AE_Robot_.jpg.)*

Reproduced from Youmans & Winn 8e, Fig. 28.1, p. 234.e2 — Label when you reproduce it: the six-degree-of-freedom articulated robotic arm — base, shoulder, elbow and wrist joints, the end-arm fixture and the stereotactic array. This is the ROSA ONE, but the point to make is that the CyberKnife uses the identical industrial articulated-arm architecture, with a miniature linear accelerator in place of an instrument holder.

5. Image guidance and motion management — the defining feature

- **Frameless by design.** Table 293.1 lists the CyberKnife as: source **x-rays (compact LINAC)**, immobilisation **mask**, fractionation **1–5 fractions** YW p.2277.
- **Continuous intrafraction verification.** "Both the CyberKnife and Novalis systems use x-rays during treatment to confirm positioning continuously" YW p.2272. In the fractionated-radiotherapy chapter Youmans is more specific: "A step above pretreatment image guidance is the availability of **intrafraction repetitive imaging**, as with the CyberKnife system. This system utilizes multiple orthogonal skull x-rays obtained during the course of delivering a radiation treatment, which are rapidly integrated into a patient-specific algorithm, providing continuous feedback regarding interfractional motion" YW p.2294.
- **Complementary tracking technologies in frameless SRS generally:** a radiocamera system triangulates on **infrared fiducials** placed on the patient throughout treatment YW p.2272; intraprocedural orthogonal radiographs or cone-beam CT during delivery confirm localisation and correct errors, which "helps physicians perform hypofractionated (i.e., two- to five-fraction) radiosurgery" YW p.2279.
- **Spinal targets** are localised by **radiopaque fiducials implanted in the vertebrae** or by **direct imaging of vertebral anatomy**; immobilisation uses moldable cushions with the patient supine to reduce respiratory target movement YW p.2281.
- **The justification for continuous tracking, in numbers:** respiration-induced vertebral body motion is **less than 1 mm** supine on fluoroscopic study (Yin); another report shows spinal anatomy may move **more than 2 mm** during radiosurgery; and Agazaryan observed vertebral movement varying by **as much as 3 mm, occurring in as little as 5**

minutes — "these results suggest a need for intra–dose fraction patient monitoring and imaging and correctional shifts, even for patients whose overall treatment times are expected to be relatively short" YW p.2281.

- **Accuracy achieved:** "In later medical physics reports, the accuracy of LINAC-based radiosurgery with a localizing mask has **approached 1 mm**" YW p.2279, against a theoretical frame-based accuracy of **less than 1 mm** YW p.2279 and frame reproducibility of approximately **0.5 mm** YW p.2272. Youmans concludes that "with modern technology extreme precision is possible with the use of sophisticated frameless immobilization devices, strict IGRT protocols, and **robotic positioning technology** such that similar motion is being observed as compared with frame-based treatment. Ultimately margins of **1.0 to 2.0 mm** are achievable" YW p.2267.

6. Planning and dosimetry on a robotic LINAC

- **Six procedural steps of LINAC-based radiosurgery** YW p.2279: (1) daily quality assurance of the radiosurgical facility; (2) immobilising the target — frame placement or mask creation; (3) imaging with MRI, CT, angiography or a combination; (4) coregistration of images and importation into the radiosurgical software, plus intraprocedural imaging; (5) dosimetry, prescribing to a target volume; (6) methods of conformality in the LINAC machine.
- **Prescription isodose is high — typically 70% to 90%** — so the maximum dose is only **10% to 30%** greater than the margin dose, and the dose distribution is **more homogeneous** than in Gamma Knife radiosurgery, where the margin isodose is typically the **50% line** YW p.2280.
- **Dose falloff is steep but device- and technique-dependent**, varying with collimator size and with the type of planning — multiple isocentre, dynamic arcs or static beams YW p.2280.
- **Volume nomenclature:** although the concepts of conventional radiation therapy are used in Gamma Knife procedures, **LINAC-based radiosurgery applies GTV, CTV and PTV more frequently**; the minimal dose thought to be clinically safe and effective is prescribed to the PTV, and the dose that adequately covers the target is the **prescription radiation dose** YW p.2280.
- **Penumbra** — the area of radiation falloff; dose within it may be high enough to cause toxicity. For lesions adjacent to brainstem, motor area or spinal cord the dosimetric consequences must be considered; adding a 1–2 mm expansile margin is attractive but "the risk of radiation-induced damage is not always justifiable", and **intensity modulation can be used to optimise dose falloff in the vicinity of an eloquent area** YW p.2280.
- **Heterogeneity can be used deliberately:** different weighting and arc lengths give asymmetrical falloff at the cost of heterogeneity, and **a multiple-isocentre technique yields a more heterogeneous plan than a shaped-beam technique — the advantage being that the hot spot can be moved to where it is wanted**, for example the most enhancing or most diffusion-restricted part of the target. "The gradient index is device dependent and not fixed to a particular isodose line" YW p.2280.
- **Conformality methods available** [YW pp. 2276, 2280-2281]:
  - **Shaped-beam radiosurgery** with an MLC that automatically changes beam shape from the **beam's-eye-view (BEV)** reconstruction of the lesion; **dynamic arcs and static beams** are the two contemporary approaches.
  - **Radiosurgery cones** for near-spherical isocentric spots.
  - **Intensity-modulated radiosurgery (IMRS)** — the concept was first described by **Anders Brahme**, who in **1988** proposed reversing the conventional trial-and-error planning paradigm so that optimum beam intensities are derived from the desired dose distribution by deterministic technique. IMRS requires **(1) inverse planning, (2) leaf sequencing, and (3) delivery with a tightly integrated accelerator and MLC**. The commercial physical objective function is the **dynamically penalised maximum likelihood (DPL) algorithm**, whose advantage is computing several inverse plans simultaneously so that varying emphasis can be placed on target versus organs at risk, with the surgeon selecting the plan on the basis of the DVH and dose distribution YW p.2281.
  - **Volumetric arc therapy — RapidArc (Varian)** delivers dose in a single or few gantry rotations by simultaneously changing **(1) gantry rotation speed, (2) MLC aperture shape and (3) dose rate**, several times faster than other dynamic techniques YW p.2281.
  - **Single-isocentre, multiple-lesion VMAT** — a central isocentre with off-axis MLC apertures treats several targets at once, keeping beam time roughly constant regardless of lesion number, at the cost of increased low-dose spill YW p.2276.

7. Clinical roles of the CyberKnife in neurosurgery

- **Intracranial malignant disease**
  - **Brain metastases** — single, oligometastatic, post-operative cavity and recurrent disease; the general indications for radiosurgery in metastases are (1) definitive treatment of non-numerous metastases to avoid WBRT, (2) boost after WBRT for larger or radioresistant lesions, (3) salvage after WBRT failure, and (4) adjuvant therapy to the resection cavity YW p.2272.
  - **Recurrent high-grade glioma** — Youmans tabulates CyberKnife series for recurrent glioblastoma, including a regimen of **24 Gy in 1 to 3 fractions** YW p.2331.
  - **Brainstem glioma** — survival and efficacy of CyberKnife radiosurgery for adult brainstem glioma over a 10-year experience is cited YW p.2334.e5.
- **Benign skull base and cranial nerve disease**
  - **Head and neck paragangliomas** — long-term control **99% with Gamma Knife, 96% with LINAC and 95% with CyberKnife**, "remain as good as" one another YW p.1393; jugulotympanic paraganglioma YW p.1394.
  - **Trigeminal neuralgia** — CyberKnife robotic radiosurgery appears in the tabulated evidence base for destructive procedures, with Barrow Neurological Institute pain scores at 3, 7.75, 9 and 18 months [YW pp. 1531, 1557.e3].
  - **Orbital lesions** YW p.1562.e1.
- **Vascular** — the radiosurgery-based AVM grading scale "has predicted outcomes after LINAC-based, **CyberKnife**, and proton beam radiosurgery" as well as Gamma Knife YW p.2353.
- **Spine — the CyberKnife's distinctive territory**
  - **Intramedullary spinal cord AVMs** by **multisession CyberKnife radiosurgery** YW p.2371; in one of the largest series of intramedullary spinal cord AVMs (cervical, thoracic and conus medullaris) treated with CyberKnife, **mean volume was 2.3 mL and mean marginal dose 20.5 Gy**, with a history of haemorrhage in **50%** and prior treatment in about **50%** [YW pp. 2367-2368]. A separate five-patient series received **20 Gy**, with nidus obliteration at 5.5 and 3 years in two and no change in three; **radiosurgery with a 20-Gy dose was thought to be a safe treatment** YW p.2367.
  - **Spinal haemangioblastoma** — natural history and CyberKnife radiosurgical treatment of **87 patients with 103 CNS haemangioblastomas** in von Hippel–Lindau and sporadic disease YW p.2369; **CyberKnife ablation for intramedullary lesions** with tumoral enhancement suggestive of necrosis on follow-up YW p.2370.
  - **Metastatic spine tumours** — described as "safer and less expensive … than open surgery", and used for **radiosurgical decompression of metastatic epidural spinal cord compression** [YW pp. 2383.e1-2383.e3].
  - **Recurrent focal spinal metastases** after prior radiation YW p.1803.e10.
- **Radiobiological point specific to a multi-node, mask-based, fractionated machine:** the fractionated approach "allows intrafraction repetitive imaging, as with the CyberKnife system" *and* **reoxygenation of hypoxic tumour regions between treatments**, providing improved efficacy through oxygen fixation of radiation damage — an advantage single-fraction Gamma Knife treatment cannot offer YW p.2294.

8. Advantages, limitations and the honest caveats

Table 1 · The CyberKnife against the Gamma Knife and a conventional LINAC — compiled from Youmans & Winn 8e, Table 293.1, p. 2277 and Ch. 293 pp. 2274-2281, Ch. 291 pp. 2257-2258.

#	Feature	Gamma Knife (Perfexion / Icon)	CyberKnife	Conventional / dedicated LINAC
1	Radiation source	Gamma rays from 192 static ⁶⁰Co sources (1.17 and 1.33 MeV)	X-rays from a compact LINAC (3–18 MV)	X-rays from a LINAC
2	Source behaviour	Continuous emission; decays 1.1%/month; replaced ~5-yearly	Electrically generated; no decay	Electrically generated; no decay

CLINICA PUBLICATION



350 QUESTIONS. 350 ANSWERS.

Every one sourced and cited.

Every DrNB / DNB Neurosurgery exit examination question from June 2020 to April 2026, answered in full from Youmans and Winn Neurological Surgery, 8th Edition (2022), with 2,830 textbook pages cited line by line.

350 Questions answered	**35** Papers · 2020–2026	**21** Topic chapters
1,147 Textbook figures	**953** Tables built	**2,830** Pages cited

THIS SAMPLE

500 pages from all 9 volumes

Chapter openers, worked answers, figures and tables

THE COMPLETE SET · 9 VOLUMES

1 2 3 4 5 6 7 8 9

Visit www.clinicapublication.com to order

Reviewed by Dr Sumit Mehra · Clinica Publication

Questions are reproduced from National Board of Examinations papers for academic revision only.
This compilation is independent of, and not endorsed by, the National Board of Examinations or the publisher of the cited textbook.