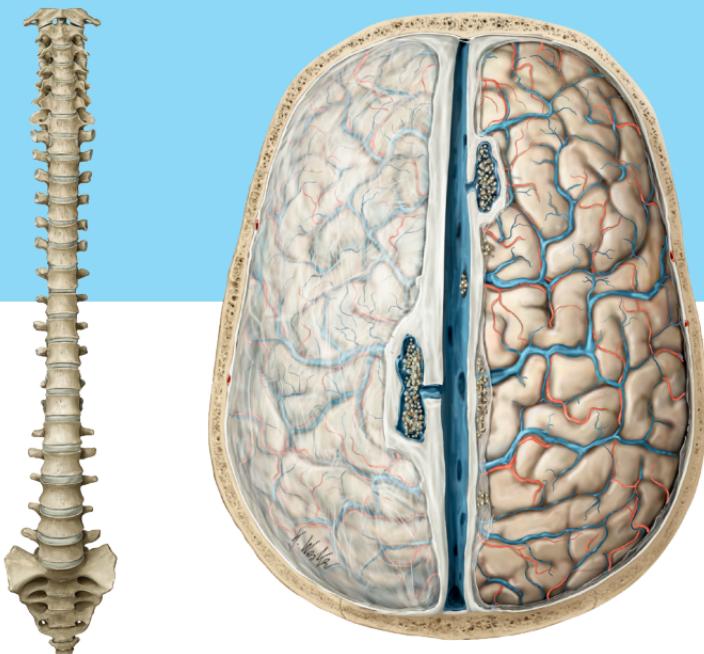


# Greenberg's Handbook of Neurosurgery

Mark S. Greenberg

Tenth Edition







Thieme



# **Greenberg's Handbook of Neurosurgery**

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## Dedication

*In recognition of the immeasureable positive influence my late mother, Mary Ann Greenberg née Arkes, had on our entire extended family, my late uncle Benjamin Arkes, her brother, sagely suggested that I dedicate my next edition to her. As my uncle Ben passed away just shy of his 100th birthday before the publication of this 10th edition, I am dedicating this book to both my mother, Mary Ann Greenberg, and my uncle Benjamin Arkes. And at his suggestion, I am using the honorific name Mark Arkes Greenberg for this edition.*

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## Preface

During the preparation of this, the 10<sup>th</sup> edition of the *Handbook of Neurosurgery*, it dawned on me that the origins and the perpetuation of this book are probably antithetical to that of the majority of medical books. Instead of creating a book in an effort to help take care of patients, this book arose as a result of taking care of patients. It began as a collection of notes that I kept as my needs emerged, first as a resident, and later as a practicing neurosurgeon. I added to it during my residency as we presented weekly grand rounds on patients whom we were treating in the OR, the wards, and the ICU. Later, in my practice, when I encountered a condition or a treatment that I had to research, I included the results of that research in the book for future reference. The book grew organically, instead of arising from a preplanned blueprint. I feel that this has probably been part of the book's success, as well as a source of some of the unevenness of coverage, for which I gradually make amends. While it may not have occurred to me that this was likely a different genesis than most books, I have always said that my patients appear on all the pages of this book. And it is to them that I am eternally grateful.

## Acknowledgments

I would like to take this opportunity to acknowledge the fantastic folks at Thieme Medical Publishers. Their support and willingness to take my opinions seriously has made it a pleasure to bring out this new edition. Special thanks go out to Thieme's amazing wizard of XML, Dr. Michael Wachinger, Senior Director International Business, Karen Edmonson, Senior Content Portfolio Manager, and Torsten Scheihagen, Senior Content Service Manager. Without their extraordinary help, this edition would not have been possible.

On the Neurosurgical side, I thank those who put up with me during my training (with special fondness for my chairman, Dr. John M. Tew, Jr.), and those who I am now happy to count among my friends and colleagues, especially my chairman and most trusted source for advice, Dr. Harry van Loveren.

## Abbreviations and Symbols

Abbreviations used only locally are defined in that section using boldface type. Numbers following entries below indicate the page number for the relevant section.

Abbreviations	
a.	artery (aa. = arteries)
ABC	aneurysmal bone cyst (p. 979) or airway, breathing, circulation
Abx.	antibiotics
AC	arachnoid cyst (p. 260)
ACA	anterior cerebral artery
ACAS	asymptomatic carotid artery stenosis (p. 1548) or Asymptomatic Carotid Atherosclerosis Study (p. 1549)
ACDF	anterior cervical discectomy & fusion (p. 1284)
ACE	angiotensin-converting enzyme
ACEP	American College of Emergency Physicians
ACh	acetylcholine (neurotransmitter)
AChA	anterior choroidal artery
ACoM A	anterior communicating artery
AC-PC line	anterior commissure-posterior commissure line (p. 58)
ACTH	adrenocorticotrophic hormone (corticotropin) (p. 151)
AD	autosomal dominant
ADH	antidiuretic hormone (p. 153)
ADI	atlantodental interval (p. 223)
ADPKD	autosomal dominant polycystic kidney disease (p. 1455)
ADQ	abductor digiti quinti (or minimi)
AED	antiepileptic drug (p. 485) (antiseizure medication (ASM))
AFO	ankle-foot-orthosis (p. 564)
AFP	alpha-fetoprotein (p. 635)
Ag	antigen
AHA	American Heart Association
AHCPR	Agency for Health Care Policy and Research (of the U. S. Public Health Service)
AICA	anterior inferior cerebellar artery (p. 81)
AIDP	acute inflammatory demyelinating polyradiculoneuropathy (p. 193)
AIDS	acquired immunodeficiency syndrome (p. 353)
AIM	astrocytoma, IDH-mutated (p. 658)
AIN	anterior interosseous neuropathy (p. 545)
AIS	acute ischemic stroke (p. 1536)
AKA	also known as
ALIF	anterior lumbar interbody fusion (p. 1795)
ALARA	As Low As Reasonably Achievable (p. 235) (radiation)
A-line	arterial line
ALL	anterior longitudinal ligament
ALS	amyotrophic lateral sclerosis (p. 1301)
AMS	acute mountain sickness (p. 1028)
AN	acoustic neuroma (p. 777)
ANA	antinearuclear antibodies
AOD	atlantooccipital dislocation (p. 1153)
AOI	atlantooccipital interval (p. 1154)
AP	antero-posterior

APAG	antipseudomonal aminoglycoside
APAP	acetaminophen (p.144)
APD	afferent pupillary defect (p.592)
APTT	(or PTT) activated partial thromboplastin time
ARDS	adult respiratory distress syndrome
ASA	American Society of Anesthesiologists or aspirin (acetylsalicylic acid)
aSAH	aneurysmal subarachnoid hemorrhage (p.1453)
ASAP	as soon as possible
ASM	antiseizure medication (p.485)
ASD	antisiphon device
ASHD	atherosclerotic heart disease
ASPECTS	Alberta stroke program early CT score (p.1559)
AT	anterior tibialis (tibialis anterior)
AT/RT	atypical teratoid/rhabdoid tumor (p.754)
ATT	antitubercular therapy (p.358)
AVM	arteriovenous malformation (p.1504)
AVP	arginine vasopressin (p.153)
β-hCG	beta-human chorionic gonadotropin (p.634)
BA	basilar artery
BBB	blood-brain barrier (p.90)
BC	basal cisterns (p.1109)
BCP	birth control pills (oral contraceptives)
BCVI	blunt cerebrovascular injury (p.1028)
BG	basal ganglia
BI	basilar impression/invagination (p.228)
BMD	bone mineral density (p.1209)
BMP	bone morphogenetic protein (p.1723)
BOB	benign osteoblastoma (p.990)
BP	blood pressure
BR	bed rest (activity restriction)
BSF	basal skull fracture (p.1064)
BSG	brainstem glioma (p.695)
Ca	cancer
CA	cavernous malformation (p.1525)
CAA	cerebral amyloid angiopathy (p.1612)
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAT	(or CT) computerized (axial) tomography
CBF	cerebral blood flow (p.1536)
CBV	cerebral blood volume
CBZ	carbamazepine (p.490)
CCAA	cavernous carotid aneurysms (p.1477)
CCB	calcium-channel blocker
CCF	carotid-cavernous (sinus) fistula (p.1519)
CCHD	congenital cyanotic heart disease
CCTHR	Canadian CT Head Rule (p.1007)
CCI	condyle-C1 interval (p.1154) (atlantooccipital interval)
ccO	continuous cardiac output
CD	Cushing's disease (p.867)
CEA	carotid endarterectomy (p.1565) or carcinoembryonic antigen (p.635)
CECT	contrast enhanced CT

cf	(Latin: confer) compare
cGy	centi-Gray (1cGy = 1 rad)
CHF	congestive heart failure
CI	confidence interval (statistics)
CIDP	chronic inflammatory demyelinating polyneuropathy (p. 195)
CIP	critical illness polyneuropathy (p. 569)
CJD	Creutzfeldt-Jakob disease (p. 399)
CM	cavernous malformation (p. 1525)
CMAP	compound motor action potential (EMG)
CMRO <sub>2</sub>	cerebral metabolic rate of oxygen consumption (p. 1537)
CMT	Charcot-Marie-Tooth (p. 568)
CMV	cytomegalovirus
CNL	chemonucleolysis
CNS	central nervous system
CO	cardiac output or carbon monoxide (p. 216)
CPA	cerebellopontine angle
CPM	central pontine myelinolysis (p. 119)
CPN	common peroneal nerve (p. 563)
CPP	cerebral perfusion pressure (p. 1036)
Cr. N.	cranial nerve(s)
CRH	corticotropin-releasing hormone (p. 151)
CRP	C-reactive protein
CRPS	complex regional pain syndrome (p. 525)
CSCS (CS <sup>2</sup> )	chronic subthreshold cortical stimulation (p. 1892)
CSF	cerebrospinal fluid (p. 414)
CSM	cervical spondylotic myelopathy (p. 1297)
CSO	craniosynostosis (p. 264)
CSVL	central sacral vertical line (p. 1314)
CSW	cerebral salt wasting (p. 122)
CTA	CT angiogram (p. 238)
CTP	CT perfusion (p. 239)
CTS	carpal tunnel syndrome (p. 546)
CTV	CT venogram
CVA	coronal vertical axis (p. 1314)
CVP	central venous pressure
CVR	cerebrovascular resistance (p. 1536)
CVS	cerebral vasospasm (p. 1439)
CVT	cerebral venous thrombosis (p. 1594)
CXR	chest X-ray
DACA	distal anterior cerebral artery (p. 1475)
DAI	diffuse axonal injury (p. 1026)
DBM	demineralized bone matrix (p. 1723)
DC	decompressive craniectomy
D/C	discontinue
DCI	delayed cerebral ischemia (p. 1432)
DDAVP	1-deamino-8-D-arginine vasopressin (desmopressin) (p. 129)
DDx	differential diagnosis (p. 1683)
DBS	deep brain stimulation (p. 1839)
DESH	disproportionately enlarged subarachnoid space hydrocephalus (p. 441)
DI	diabetes insipidus (p. 124)
DIG	desmoplastic infantile astrocytoma and ganglioglioma (p. 708)

DIND	delayed ischemic neurologic deficit (p. 1440)
DIPG	diffuse infiltrating pontine glioma (see diffuse midline glioma (p. 683))
DISH	diffuse idiopathic skeletal hyperostosis (p. 1373)
DJK	distal junctional kyphosis
DKA	diabetic keto-acidosis
DLC	disco-ligamentous complex (p. 1181)
DLIF	direct lateral lumbar interbody fusion (p. 1802)
DOC	drug of choice
DM	diabetes mellitus
DMZ	dexamethasone
DNT or DNET	dysembryoplastic neuroepithelial tumors (p. 709)
DOE	dyspnea on exertion
DOMS	delayed onset muscle soreness (p. 1333)
DPL	diagnostic peritoneal lavage
DREZ	dorsal root entry zone lesion (p. 1886)
DSA	digital subtraction angiogram
DSD	degenerative spine disease (p. 1327)
DST	dural sinus thrombosis (p. 1594)
DTN	"door to needle"
DTs	delirium tremens (p. 214)
DTT	diffusion tensor tractography MRI (p. 245)
DVT	deep-vein thrombosis (p. 176)
DWI	diffusion-weighted imaging (p. 243) (MRI sequence)
EAC	external auditory canal
EAM	external auditory meatus
EAST	Eastern Association for the Surgery of Trauma
EBRT	external beam radiation therapy
EBV	Epstein-Barr Virus
ECM	erythema chronicum migrans (p. 364)
EDC	electrolytically detachable coils
EDH	epidural hematoma (p. 1072)
EHL	extensor hallucis longus
ELISA	enzyme-linked immunosorbent assay
ELST	endolymphatic sac tumors (p. 648)
EM	electron microscope (microscopy)
ENG	electronystagmography (p. 782)
ENT	ear, nose and throat (otolaryngology)
EOM	extra-ocular muscles (p. 596)
EOO	external oculomotor ophthalmoplegia
E/R	emergency room or department
ESR	erythrocyte sedimentation rate
EST	endodermal sinus tumor (p. 832)
EtOH	ethyl alcohol (ethanol)
ET tube	endotracheal tube
ETV	endoscopic third ventriculostomy (p. 453)
EVD	external ventricular drain (ventriculostomy)
EVT	endovascular therapy (p. 1913)
FCU	flexor carpi ulnaris
FDI	flexion-distraction injury (p. 1202)
FDP	flexor digitorum profundus
FIESTA	Fast Imaging Employing Steady-state Acquisition (p. 241) (MRI sequence)

FIM	Functional Independence Measure (p. 1643)
FLAIR	fluid-attenuated inversion recovery (p. 240) (MRI sequence)
FM	face mask
FMD	fibromuscular dysplasia (p. 209)
FSH	follicle stimulating hormone (p. 153)
F/U	follow-up
FUO	fever of unknown origin
GABA	gamma-aminobutyric acid
GBM	glioblastoma (p. 664) (obsolete: glioblastoma multiforme)
GBS	Guillain-Barré syndrome (p. 193)
GCA	giant cell arteritis (p. 203)
GCS	Glasgow coma scale (p. 318)
GCT	granular cell tumor (p. 853) or germ cell tumor (p. 831)
GD	Graves' disease
GFAP	glial fibrillary acidic protein (p. 631)
GGE	genetic generalized epilepsy (p. 481)
GGT	gamma glutamyl transpeptidase
GH	growth hormone (p. 153)
GH-RH	growth hormone releasing hormone (p. 153)
GMH	germinal matrix hemorrhage (p. 1630)
GNR	gram-negative rods
GnRH	gonadotropin-releasing hormone (p. 153)
GSW	gunshot wound
GTC	generalized tonic-clonic (seizure)
GTR	gross total resection
H/A	headache (p. 182)
H&H	Hunt and Hess (SAH grade) (p. 1424)
H&P	history and physical exam
HBsAg	hepatitis B surface antigen
HCD	herniated cervical disc (p. 1280)
hCG	human chorionic gonadotropin (p. 634)
HCP	hydrocephalus (p. 426)
HDT	hyperdynamic therapy (p. 1447)
HGB	hemangioblastoma (p. 822)
Hgb-A1C	hemoglobin A1C
hGH	human growth hormone
HH	hypothalamic hamartomas (p. 277) or homonymous hemianopsia
HHT	hereditary hemorrhagic telangiectasia (p. 1524)
HIV	human immunodeficiency virus
HLD	herniated lumbar disc (p. 1250)
HLA	human leukocyte antigen
H.O.	house officer
HN P	herniated nucleus pulposus (herniated disc) (p. 1250)
HNPP	hereditary neuropathy with liability to pressure palsies (p. 568)
HOB	head of bed
HPA	hypothalamic-pituitary-adrenal axis
HPF	high power field (used in histology, corresponds to 0.23 mm <sup>2</sup> )
HRQOL	health related quality of life
HSE	herpes simplex encephalitis (p. 397)
HTN	hypertension
IAC	internal auditory canal

IASDH	infantile acute subdural hematoma (p. 1081)
ICA	internal carotid artery
ICG	indocyanine green (p. 1466)
ICH	intracerebral hemorrhage (p. 1608)
IC-HTN	intracranial hypertension (increased ICP)
ICP	intracranial pressure (p. 1036)
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IDET	intradiscal endothermal therapy (p. 1258)
IDH	isocitrate dehydrogenase ► Table 37.2
IEP	immune electrophoresis
IG	image guidance (intraoperative)
IGF-1	insulin-like growth factor-1 (AKA somatomedin-C) (p. 153)
IIH	idiopathic intracranial hypertension (pseudotumor cerebri) (p. 955)
IJV	internal jugular vein
IMRT	intensity modulated radiation therapy
INO	internuclear ophthalmoplegia (p. 596)
iNPH	(idiopathic) normal pressure hydrocephalus (p. 438)
INR	international normalized ratio (p. 172)
IPS	inferior petrosal sinus
IPA	idiopathic paralysis agitans (Parkinson's disease) (p. 184)
ISAT	International Subarachnoid Hemorrhage Aneurysm Trial (p. 1458)
IT	intrathecal
ITB	intrathecal baclofen (p. 1847)
IVC	intraventricular catheter or inferior vena cava
IVH	intraventricular hemorrhage (p. 1671)
IVP	intravenous push (medication route) or intravenous pyelogram (X-ray study)
JPS	joint position sense
LBP	low back pain (p. 1226)
LDL	Lhermitte-Duclos disease (p. 716)
LE	lower extremity
LFTs	liver function tests
LGB	lateral geniculate body
LGG	low-grade glioma
LH	luteinizing hormone (p. 153)
LH-RH	luteinizing hormone releasing hormone (p. 153)
LMD	low-molecular-weight dextran
LMN	lower motor neuron (p. 531)
LMWH	low-molecular-weight heparin
LOC	loss of consciousness
LOH	loss of heterozygosity
LP	lumbar puncture (p. 1811)
LSO	lumbo-sacral orthosis
LOVA	longstanding overt ventriculomegaly in an adult (p. 437)
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MAST®	military anti-shock trousers
MB	medulloblastoma (p. 750)
MBEN	medulloblastoma with extensive nodularity (p. 746)
MBI	modified Barthel index ► Table 98.6
MCA	middle cerebral artery

mcg	(or $\mu$ g) microgram
MCP	mean carotid pressure or metacarpal phalangeal
MDCTA	multidetector CT angiography
MDB	medulloblastoma (p. 750)
MDMA	methylene dioxymethamphetamine (p. 185)
mg	milligram
MGMT	O <sup>6</sup> -methylguanine-DNA methyltransferase (p. 673)
MGUS	monoclonal gammopathy of undetermined significance (p. 575)
MHT	meningohypophyseal trunk (p. 77)
MI	myocardial infarction
MIB-1	monoclonal anti-Ki-67 antibody (p. 632)
MIC	minimum inhibitory concentration (for antibiotics)
MID	multi-infarct dementia
MISS	minimally invasive spine surgery
mJOA scale	modified Japanese Orthopedic Association (p. 1299) scale
MLF	medial longitudinal fasciculus
MLS	midline shift (p. 1110)
MM	myelomeningocele (p. 281) or multiple myeloma (p. 928)
MMD	moyamoya disease (p. 1581)
MMN	multifocal motor neuropathy (p. 1700)
MMPI	Minnesota Multiphasic Personality Inventory
mos	months
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (p. 185)
MRA	MRI angiogram (p. 243)
mRS	modified Rankin Scale ▶ Table 98.5
MRS	MRI spectroscopy (p. 244)
MRSA	methicillin resistant <i>Staphylococcus aureus</i>
MS	microsurgery or multiple sclerosis (p. 187)
MSO <sub>4</sub>	morphine sulfate
mtICI	modified treatment in cerebral ischemia (scale) ▶ Table 116.2
MTP	metatarsal phalangeal
MTS	mesial temporal sclerosis (p. 482)
MTT	mean transit time (p. 239) (on CT perfusion)
MUAP	motor unit action potential (p. 256)
MVA	motor vehicle accident
MVD	microvascular decompression (p. 1867)
MW	molecular weight
n.	nerve (nn. = nerves)
Na	(or Na <sup>+</sup> ) sodium
N <sub>2</sub> O	nitrous oxide (p. 109)
NAA	N-acetyl aspartate (p. 244)
NAP	nerve action potential (p. 535)
NASCET	North American Symptomatic Carotid Endarterectomy Trial (p. 1565)
NB	(Latin: <i>nota bene</i> ) note well
NC	nasal cannula
NCCN	National Comprehensive Cancer Network
NCD	neurocutaneous disorders (p. 637)
NCV	nerve conduction velocity
NEC	neurenteric cyst (p. 313) or necrotizing enterocolitis
NEXUS	National Emergency X-Radiography Utilization Study (p. 1142)
NF	(or NFT) neurofibromatosis (p. 637)

NF1	neurofibromatosis type 1 (p.638)
NF2	neurofibromatosis type 2 (p.640)
NG tube	nasogastric tube
NGGCT	non-germinomatous germ cell tumors (p.832)
NFPA	nonfunctioning pituitary adenoma (p.866)
NIHSS	NIH (National Institute of Health) Stroke Scale (p.1554)
NMBA	neuromuscular blocking agent (p.141)
NMO	neuromyelitis optica (Devic syndrome) (p.1698)
NOS	not otherwise specified (as used in WHO CNS5 (p.616))
NPH	normal pressure hydrocephalus (p.438)
NPS	neuropathic pain syndrome (p.518)
NS	normal saline
NSAID	non-steroidal anti-inflammatory drug (p.144)
NSCLC	non-small-cell cancer of the lung (p.911)
NSF	nephrogenic systemic fibrosis (p.243)
NSM	neurogenic stunned myocardium (p.1438)
N/V	nausea and vomiting
NVB	neurovascular bundle
OAD	occipital atlanto dislocation, see atlantooccipital dislocation (p.1153)
OALL	ossification of the anterior longitudinal ligament (p.1372)
OC	occipital condyle
OCB	oligoclonal bands (in CSF) (p.190)
OCF	occipital condyle fracture (p.1156)
ODG	oligodendroglioma (p.662)
OEF	oxygen extraction fraction
OFC	occipital-frontal (head) circumference (p.427)
OGST	oral glucose suppression test (for growth hormone) (p.882)
OMO	open-mouth odontoid (C-spine X-ray view)
OMP	oculomotor (third nerve) palsy
ONSF	optic nerve sheath fenestration (p.966)
OP	opening pressure (on LP) (p.1812)
OPG	optic pathway glioma (p.694)
OPLL	ossification of the posterior longitudinal ligament (p.1370)
OR or O.R.	operating room
ORIF	open reduction/internal fixation
OS	overall survival
OTC	over the counter (i.e., without prescription)
PACU	post-anesthesia care unit (AKA recovery room, PAR)
PADI	posterior atlantodental interval (p.223)
PAID	paroxysmal autonomic instability with dystonia (p.1048)
PAN	poly- (or peri-) arteritis nodosa (p.208)
PBPP	perinatal brachial plexus palsy (p.579)
PbtO <sub>2</sub>	brain tissue oxygen tension (p.1045)
PC	pineal cyst (p.948)
PCA	pilocytic astrocytoma (p.689) or posterior cerebral artery
PCB	pneumatic compression boot
PCC	prothrombin complex concentrate (p.174)
PCI	prophylactic cranial irradiation
PCN	penicillin
PCNSL	primary CNS lymphoma (p.840)
PComA	posterior communicating artery

PCV	procarbazine, CCNU, & vincristine (p. 628) (chemotherapy)
PCR	polymerase chain reaction
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PDN	painful diabetic neuropathy (p.518)
PDR	Physicians Desk Reference®
peds	pediatrics (infants & children)
PEEK	poly-ether-ether-ketone (graft material)
PET	positron emission tomography (scan)
p-fossa	posterior fossa
PFS	progression-free survival
PFT	pulmonary function test
PHN	postherpetic neuralgia (p. 522)
PHT	phenytoin (Dilantin®) (p.488)
PICA	posterior inferior cerebellar artery (p.81)
PIF	prolactin release inhibitory factor (p. 153)
PIN	posterior interosseous neuropathy (p. 559)
PION	posterior ischemic optic neuropathy (p.1261)
PitNET	pituitary neuroendocrine tumor (p.854) (formerly pituitary adenoma)
PIVH	periventricular-intraventricular hemorrhage (p.1630)
PJK	proximal junctional kyphosis
PLAP	placental alkaline phosphatase (p.832)
PLEDs	periodic lateralizing epileptiform discharges
PLIF	posterior lumbar interbody fusion
PM	pars marginalis (p. 57)
PMA	progressive muscular atrophy (p.191) or pilomyxoid astrocytoma (p.689)
PMD	perimetric mean deviation (p.589) (visual fields)
PMH	pure motor hemiparesis
PML	progressive multifocal leukoencephalopathy (p. 353)
PMMA	polymethylmethacrylate (methylmethacrylate)
PMR	polymyalgia rheumatica (p.206)
PMV	pontomesencephalic vein
PNEA	psychogenic non-epileptic attack (p.507)
POD	postoperative day
POVL	postoperative visual loss (p.1261)
PPV	positive predictive value: in unselected patients who test positive, PPV is the probability that the patient has the disease
PR	per rectum
PRES	posterior reversible encephalopathy syndrome (p.202)
PRF	prolactin releasing factor (p. 153)
PIF	prolactin (releasing) inhibitory factor (p. 153)
PRN	as needed
PRSP	penicillinase resistant synthetic penicillin
PSNP	progressive supra-nuclear palsy (p.186)
PSR	percutaneous stereotactic rhizotomy (for trigeminal neuralgia) (p.1861)
PSVL	posterior sacral vertical line (p.1355)
PSW	positive sharp waves (on EMG) (p.255)
pt	patient
PT	physical therapy or prothrombin time
PTC	pituicytoma (p.853)
PTCS	pseudotumor cerebri syndrome (p.955)

PTR	percutaneous trigeminal rhizotomy (p. 1861)
PTT	(or APTT) partial thromboplastin time
PUD	peptic ulcer disease
PVP	percutaneous vertebroplasty (p. 1212)
PWI	perfusion-weighted imaging (p. 244) (MRI sequence)
PXA	pleomorphic xanthoastrocytoma (p. 698)
q	(Latin: <i>quaque</i> ) every (medication dosing)
RA	rheumatoid arthritis
RAH	recurrent artery of Heubner (p. 74)
RAPD	relative afferent pupillary defect (p. 592)
RASS	Richmond agitation-sedation scale (p. 139)
RCVS	reversible cerebral vasoconstrictive syndrome (p. 1418)
rem	roentgen-equivalent man
REZ	root entry zone
RFR	radiofrequency rhizotomy (p. 1861)
rFVIIa	recombinant (activated) factor VII
rhBMP	recombinant human bone morphogenetic protein (p. 1723)
R/O	rule out
RNS®	responsive neurostimulation (p. 1892)
ROM	range of motion
ROP	retro-odontoid pseudotumor (p. 1678)
RPA	recursive partitioning analysis
RPDB	randomized prospective double-blind
RPLS	reversible posterior leukoencephalopathy syndrome; see posterior reversible encephalopathy syndrome (p. 202) (PRES)
RPNB	randomized prospective non-blinded
RTOG	Radiation Therapy Oncology Group
RTP	return to play (sports)
rt-PA or tPA	recombinant tissue-type plasminogen activator (AKA tissue plasminogen activator) e.g., alteplase
RT-QuiC	Real-Time Quaking-Induced Conversion assay (p. 403) (for CJD)
RTX	(or XRT) radiation therapy (p. 1898)
S/S	signs and symptoms
S2AI screws	S2-alar-iliac screws (p. 1807)
SAH	subarachnoid hemorrhage (p. 1453) or Selective amygdalo-hippocampectomy (p. 1893)
SBE	subacute bacterial endocarditis
SBO	spina bifida occulta (p. 280)
SBP	systolic blood pressure
SCA	superior cerebellar artery
SCD	sequential compression device
SCLC	small-cell lung cancer (p. 910)
SCI	spinal cord injury (p. 1132)
SCIWORA	spinal cord injury without radiographic abnormality (p. 1196)
SCM	sternocleidomastoid (muscle)
SD	standard deviation
SDE	subdural empyema (p. 350)
SDH	subdural hematoma (p. 1076)
SE	status epilepticus (for seizures) (p. 510)
SEA	spinal epidural abscess (p. 381)
SEGA	subependymal giant cell astrocytoma (p. 645)
SEP	(or SSEP) somatosensory evoked potential (p. 250)

SG	specific gravity
SHH	sonic hedgehog
SIAD	syndrome of inappropriate antidiuresis (p.117)
SIADH	syndrome of inappropriate antidiuretic hormone (ADH) secretion (p.118)
SIDS	sudden infant death syndrome
SIH	spontaneous intracranial hypotension (p.421)
sICH	spontaneous intracerebral hemorrhage (p.1608)
SIRS	septic inflammatory response syndrome
SjVO <sub>2</sub>	jugular venous oxygen saturation (p.1045)
SLE	systemic lupus erythematosus
SLIC	subaxial injury classification (p.1181)
SMC	spinal meningeal cyst (p.1400)
SMT	spinal manipulation therapy (p.1238)
SNAP	sensory nerve action potential (EMG) (p.255)
SNUC	sinonasal undifferentiated carcinoma (p.1674)
SOMI	sternal-occipital-mandibular immobilizer (p.1124)
SON	supraorbital neuralgia (p.521)
S/P	status-post
SPAM	subacute progressive ascending myelopathy (p.1221)
SPECT	single positron emission computed tomography (scan)
SPEP	serum protein electrophoresis
SQ	subcutaneous injection
SRS	stereotactic radiosurgery (p.1903)
SRT	stereotactic radiotherapy (p.1903)
SSEP	(or SEP) somatosensory evoked potential (p.250)
SSPE	subacute sclerosing panencephalitis (p.249)
SSRI	selective serotonin reuptake inhibitors
SSS	superior sagittal sinus
SSV	sagittal stable vertebra (p.1355)
STA	superficial temporal artery
STAT	immediately (abbreviation of Latin <i>statim</i> )
STICH	Surgical Trial in Intracerebral Haemorrhage (p.1624)
STIR	short tau inversion recovery (p.241) (MRI sequence)
STN	subthalamic nucleus
STSG	Spine Trauma Study Group
SUDEP	sudden unexplained death in epilepsy (p.480)
SUNCT	short-lasting unilateral neuralgiform H/A with conjunctival injection and tearing (p.520)
SVC	superior vena cava
SVM	spinal vascular malformations (p.1395)
SVR	systemic venous resistance
SVT	supraventricular tachycardia
SWN	schwannomatosis (p.642)
SWS	Sturge–Weber syndrome (p.652)
SXR	skull X-ray
Sz.	seizure (p.480)
T1WI	T1 weighted image (p.239) (MRI sequence)
T2WI	T2 weighted image (p.240) (MRI sequence)
TAL	transverse atlantal ligament (p.69)
TBA	total bilateral adrenalectomy (p.891)
TBI	traumatic brain injury (p.999)
TBM	tuberculous meningitis (p.360)

TCA	tricyclic antidepressants
TCD	transcranial Doppler (p. 1443)
TDL	tumefactive demyelinating lesions (p. 190)
TE	time to echo (p. 239) (on MRI)
TEE	transesophageal echocardiogram
TEN	toxic epidermal necrolysis
TENS	transcutaneous electrical nerve stimulation
TGN	trigeminal neuralgia (p. 1857)
T-H lines	Taylor-Haughton lines (p. 61)
TIA	transient ischemic attack (p. 1536)
TICH	traumatic intracerebral hemorrhage (hemorrhagic contusion) (p. 1071)
TICI (mTICI)	treatment in cerebral ischemia (scale) (modified) ► Table 116.2
TIVA	total intravenous anesthesia
TLIF	transforaminal lumbar interbody fusion (p. 1801)
TLISS	thoracolumbar injury severity score (p. 1206)
TLJ	thoracolumbar junction
TLSO	thoracolumbar-sacral orthosis
TM	tympanic membrane
TP53	tumor protein 53
t-PA or tPA	tissue plasminogen activator
TR	time to repetition (p. 239) (on MRI)
TRH	thyrotropin releasing hormone; AKA TSH-RH (p. 153)
TS	transverse sinus
tSAH	traumatic subarachnoid hemorrhage (p. 1453)
TSC	tuberous sclerosis complex (p. 644)
TSE	transmissible spongiform encephalopathy (p. 399) (prion disease)
TSH	thyroid-stimulating hormone (thyrotropin) (p. 153)
TSV	thalamostriate vein
TTP	thrombotic thrombocytopenic purpura
TVO	transient visual obscurations (p. 961)
Tx.	treatment
UBOs	unidentified bright objects (on MRI)
UE	upper extremity
UMN	upper motor neuron (p. 531)
UTI	urinary tract infection
URI	upper respiratory tract infection
U/S	ultrasound
VA	vertebral artery or ventriculoatrial
VB	vertebral body
VBI	vertebrobasilar insufficiency (p. 1591)
VEMP	vestibular evoked myogenic potential (p. 782)
VHL	von Hippel-Lindau (disease) (p. 646)
VKA	vitamin K antagonist (e.g., warfarin)
VMA	vanillylmandelic acid
VP	ventriculoperitoneal
VS	vestibular schwannoma (p. 777)
VTE	venous thromboembolism
VZV	(herpes) varicella zoster virus
WBC	white blood cell (count)
WBXRT	whole brain radiation therapy (p. 919)
WFNS	World Federation of Neurosurgical Societies (grading SAH) (p. 1424)

WHO	World Health Organization
WHO CNS5	WHO Classification of Tumors of the Central Nervous System, 5th edition (p. 616)
wks	weeks
WNL	within normal limits
WNT	wingless/integrated (signal transduction pathway)
w/o	without
WRS	word recognition score (p. 780)
W/U	work-up (evaluation)
XLIF™	extreme lateral lumbar interbody fusion (p. 1802)
XRT	(or RTX) radiation therapy (p. 1898)

**Symbols**

R	prescribing information
→	causes or leads to
Δ	change
✓	check (e.g., lab or exam item to check)
↑	increased
↓	decreased
≈	approximately
↳	innervates (nerve distribution)
⇒	vascular supply
↳	a branch of the preceding nerve
★	crucial point
✗	caution; possible danger; negative factor...
Σ	summary
∴	therefore

**Instrumentation:** the following shorthand allows rapid identification of metrics for spinal instrumentation:

ENTRY	screw entry site
TRAJ	screw trajectory
TARGET	object to aim for
SCREWS	typical screw specifications

## Conventions

- **Box types.** The *Handbook of Neurosurgery* uses the following seven box types:

### Drug info

Drug description & dosage.

### Key concepts

Foundational knowledge in brief.

### Practice guideline

Evidence-based guidelines. See below (in this section) for definitions. For a listing of evidence-based guidelines contained in this book, see the index under "Practice guideline."

### Booking the case

These sections appear under certain specific operations to help when scheduling that surgery. Default information appears below (in this section); for example, a specific type of anesthesia will only be mentioned if something other than general anesthesia is typically used. A list of operations addressed by this means can be found in the index under "Booking the case."

### Σ

Summarizing or synthesizing information from the associated text.

### Side information

E.g., Greenberg IMHO.

### Signs / symptoms

A description of signs and symptoms.

► **Grading scales.** Many grading scales are presented in table format, and to assist the reader in using them, a table cell has been included where an entry is to be made that shows the possible values for that cell. In many cases, those values are summed with those in other similar cells to arrive at the "grade."

► **Cross references.** The terms "see below" and "see above" are normally used when the referenced item is on the same page, or at most on the following (or preceding) page. When further excursions are needed, the page number will usually be included.

► **Default values.** These details are not repeated in each section or "Booking the case" box.

1. position: (depends on the operation)
2. pre-op:
  - a) NPO after midnight the night before except meds with sips of water
  - b) antithrombotics: discontinue Coumadin® ≥ 3 days prior to surgery, Plavix® 5–7 d pre-op, aspirin 7–10 d pre-op, other NSAIDs 5 d pre-op
3. cardiology/medical clearance as needed
4. anesthesia: default = general anesthesia, unless otherwise specified
5. equipment: special devices such as ultrasonic aspirator, image guidance...
6. instrumentation: standard surgical instrument trays for a specific operation are assumed. Special instrumentation resident in the hospital will be listed
7. implants: this usually requires scheduling with a vendor (manufacturers representative/distributor) to provide
8. neuromonitoring will be listed if typically used
9. post-op: default care is on the ward (ICU is typically needed after craniotomy)
10. blood availability: specified if recommended
11. consent (these items use lay terms for the patient—not all-inclusive):

★ **Disclaimers:** *informed consent* for surgery requires disclosure of risks and benefits that would substantively affect a normal person's decision to have the operation. It cannot and should not attempt to include every possibility. The items listed in this section are included as memory joggers for some items for various procedures, but are not meant to be all-inclusive. The omission of information from this memory aid is not to be construed as implying that the omitted item is not important or should not be mentioned.

- a) procedure: the typical operation and some possible common contingencies
- b) alternatives: non-surgical (AKA "conservative") treatment is almost always an option
- c) complications:
  - risks of general anesthesia include: heart attack, stroke, pneumonia
  - infection: a risk with any invasive procedure
  - usual craniotomy complications include: bleeding intra-op and postop, seizure, stroke, coma, death, hydrocephalus, meningitis, and neurologic deficit related to the area of surgery including (for applicable locations): paralysis, language or sensory disturbances, coordination impairment...
  - usual spine surgery complications include: injury to nerve or spinal cord with possible numbness, weakness or paralysis, failure of the operation to achieve the desired result, dural opening which may cause a CSF leak, which occasionally needs surgical repair. Hardware complications (when used) include: breakage, pull-out, malposition. Although a rare complication, it is serious enough that it bears mentioning in cases positioned prone with possible significant blood loss (> 2 L): blindness (due to PION (p. 1261))

- **Evidence-Based Medicine: Definitions.** These definitions are referred to in the “Practice guideline” boxes.

Strength of recommendation		Description
Level I, II, III <sup>a</sup>	Level A, B, C, D <sup>b</sup>	
<b>Level I</b> High degree of clinical certainty	<b>Level A</b>	Based on consistent Class I evidence (well-designed, prospective randomized controlled studies)
	<b>Level B</b>	Single Class I study or consistent Class II evidence or strong Class II evidence especially when circumstances preclude randomized clinical trials
<b>Level II</b> Moderate degree of clinical certainty	<b>Level C</b>	Usually derived from Class II evidence (one or more well-designed comparative clinical studies or less well-designed randomized studies) or a preponderance of Class III evidence
<b>Level III</b> Unclear clinical certainty	<b>Level D</b>	Generally based on Class III evidence (case series, historical controls, case reports and expert opinion). Useful for educational purposes and to guide future research
	<b>Level U<sup>c</sup></b>	Lack of studies meeting Level A, B or C criteria

<sup>a</sup>as used in the Guidelines for the Management of Severe Traumatic Brain Injury, 3rd edition (Brain Trauma Foundation, et al.: Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. J Neurotrauma 2007;24 (Suppl 1): S59-64).

<sup>b</sup>as used in the Guidelines for the Surgical Management of Cervical Degenerative Disease (Matz PG, et al.: Introduction and methodology: guidelines for the surgical management of cervical degenerative disease. J Neurosurg Spine 2009;11 (2): 101-3).

<sup>c</sup> as used in the 2016 American Epilepsy Guidelines for treatment of Convulsive Status Epilepticus (Glauser T, et al.: Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16 (1): 48-61).

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# **Part I**

## **Anatomy and Physiology**

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I

# 1 Gross Anatomy, Cranial and Spine

## 1.1 Cortical surface anatomy

### 1.1.1 Lateral cortical surface

► Fig. 1.1. For abbreviations, see ► Table 1.1 and ► Table 1.2. The middle frontal gyrus (MFG) is usually more sinuous than the IFG or SFG, and it often connects to the pre-central gyrus via a thin isthmus.<sup>1</sup> The central sulcus joins the Sylvian fissure in only 2% of cases (i.e., in 98% of cases there is a "subcentral" gyrus). The intraparietal sulcus (ips) separates the superior and inferior parietal lobules. The IPL is composed primarily of the AG and SMG. The Sylvian fissure terminates in the SMG (Brodmann's area 40). The superior temporal sulcus terminates in the AG.

### 1.1.2 Brodmann's areas

► Fig. 1.1 also identifies the clinically significant areas of Brodmann's (Br.) map of the cytoarchitectonic fields of the human brain. Functional significance of these areas is as follows:

1. Br. areas 3, 1, 2: primary somatosensory cortex
2. Br. areas 41 & 42: primary auditory areas (transverse gyri of Heschl)
3. Br. area 4: precentral gyrus, primary motor cortex (AKA "motor strip"). Large concentration of giant pyramidal cells of Betz
4. Br. area 6: premotor area or supplemental motor area. Immediately anterior to motor strip, it plays a role in contralateral motor programming
5. Br. area 44: (dominant hemisphere) Broca's area (classically "motor speech area" see speech & language (p.90))

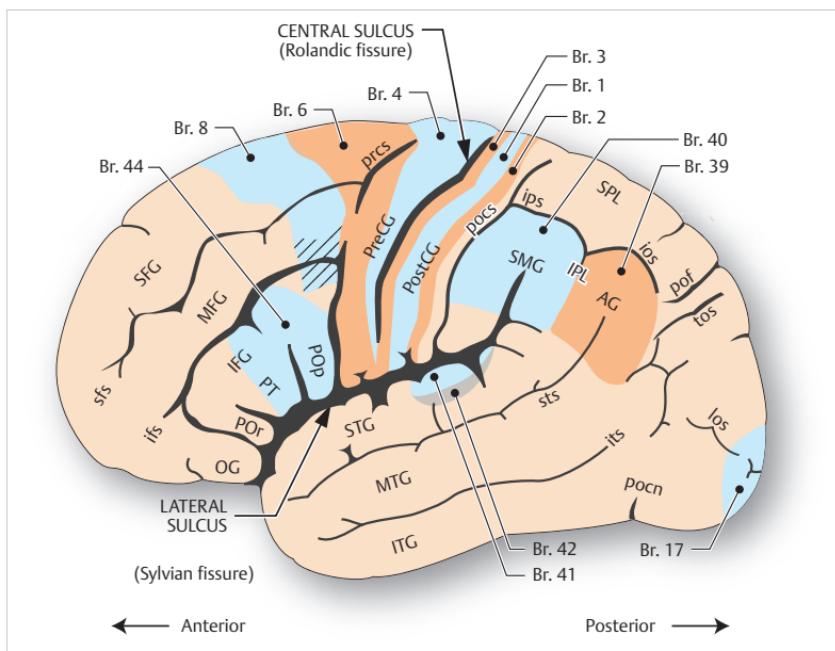


Fig. 1.1 Left lateral cerebral cortical surface anatomy.

Br. = Brodmann's area (shaded). See ► Table 1.1 and ► Table 1.2 for abbreviations (lowercase = sulci, uppercase = gyri).

**Table 1.1** Cerebral sulci (abbreviations)

Abbreviation	Sulcus
cins	cingulate sulcus
cs	central sulcus
ips-ios	intraparietal-intracippital sulcus
los	lateral occipital sulcus
pM	pars marginalis
pocn	pre-occipital notch
pocs	post-central sulcus
pof	parieto-occipital fissure
pos	parieto-occipital sulcus
prcs	pre-central sulcus
sfs, ifs	superior, inferior frontal sulcus
sps	superior parietal sulcus
sts, its	superior, inferior temporal sulcus
tos	trans occipital sulcus

**Table 1.2** Cerebral gyri and lobules (abbreviations)

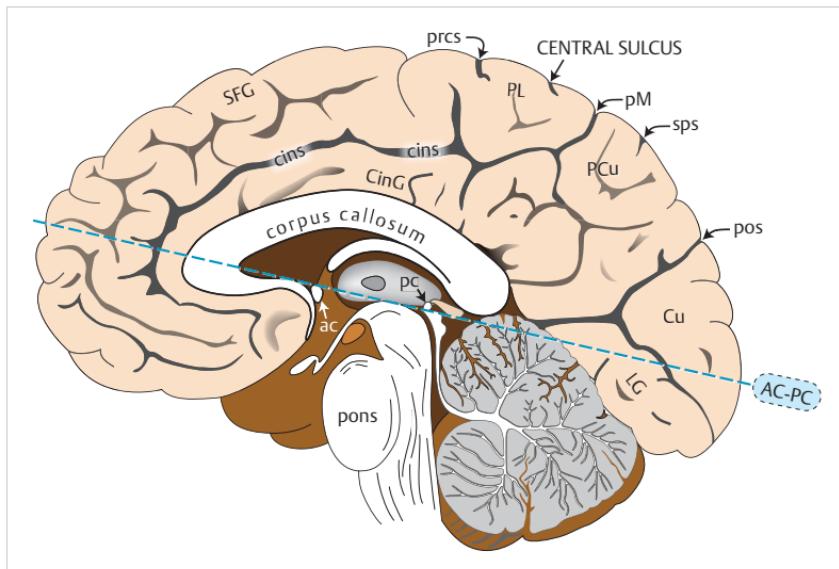
Abbreviation	Gyrus / lobule
AG	angular gyrus
CinG	cingulate gyrus
Cu	cuneus
LG	lingual gyrus
MFG, SFG	middle & superior frontal gyrus
OG	orbital gyrus
PCu	precuneous
PreCG, PostCG	pre- and post-central gyrus
PL	paracentral lobule (upper SFG and PreCG and PostCG)
IFG	inferior frontal gyrus
• POp	• pars opercularis
• PT	• pars triangularis
• POr	• pars orbitalis
STG, MTG, ITG	superior, middle & inferior temporal gyrus
SPL, IPL	superior & inferior parietal lobule
SMG	supramarginal gyrus

6. Br. area 17: primary visual cortex
7. Wernicke's area: (dominant hemisphere) most of Br. area 40 and a portion of Br. area 39 (may also include ≈ posterior third of STG). Significant in speech & language (p. 90)
8. the striped portion of Br. area 8 in ► Fig. 1.1 (frontal eye field) initiates voluntary eye movements to the opposite direction

### 1.1.3 Medial surface

#### Pars marginalis

► Fig. 1.2. The cingulate sulcus terminates posteriorly in the pars marginalis (pM) (plural: partes marginales). On axial imaging, the pMs are visible on 95% of CTs and 91% of MRIs,<sup>2</sup> they are usually the most prominent of the paired grooves straddling the midline, and they extend a greater distance into the hemispheres.<sup>2</sup> On axial CT or MRI, the pM is posterior to the widest biparietal diameter.<sup>2</sup> The pMs curve posteriorly in lower slices and anteriorly in higher slices (here, the paired pMs form the “pars bracket”—a characteristic “handlebar” configuration straddling the midline).



**Fig. 1.2** Medial aspect of the right hemisphere.

Abbreviations: see ► Table 1.1 for sulci and ► Table 1.2 for gyri; ac = anterior commissure, pc = posterior commissure, AC-PC = AC-PC line (see text) which is illustrated here according to the Talairach definition.

### AC-PC line

The “AC-PC line” connects the anterior commissure (AC) and the posterior commissure (PC) on a midline sagittal image (► Fig. 1.2). The AC is the horizontally oriented white matter tract connecting the left and right cerebral hemispheres that crosses in front of the fornix. The PC is the white-matter band at the level of the pineal that crosses at the posterior third ventricle. The AC-PC line is used in functional neurosurgery and is also used as the baseline for axial MRI scans (and for recent CT scanners). In the more entrenched Talairach definition,<sup>3</sup> it passes through the superior edge of the AC and the inferior edge of the PC (as illustrated in ► Fig. 1.2). Alternative Schaltenbrand definition<sup>4</sup>: the line passing through the midpoint of the AC & PC, allowing both AC & PC to be imaged on a single thin axial MRI slice. These definitions differ by  $5.81^\circ \pm 1.07^\circ$ .<sup>5</sup> The orbitomeatal line (p.238) (used in older CT scanners) is  $\approx 9^\circ$  steeper than the Talairach AC-PC line.<sup>5</sup>

### 1.1.4 Somatotopic organization of primary sensory and motor cortex

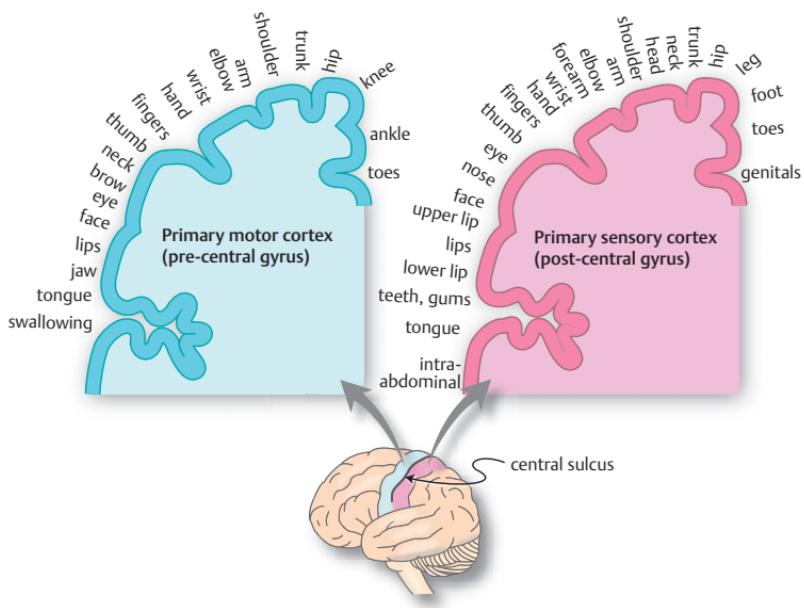
The primary motor cortex (AKA “motor strip”) and primary (somato)sensory cortex are organized somatotopically so that specific regions of the brain map correspond to specific areas of the body as shown in ► Fig. 1.3.

The regions are often drawn with a caricature of a human figure (the homunculus—Latin for “little man”) along with the labels shown here.

Some key points: the representation of the arm and face are draped over the convexity of the brain, while the foot and leg areas are located along the upper aspect of the medial surface. Areas with fine motor or sensory function (e.g., fingers, tongue) have a larger area of representation.

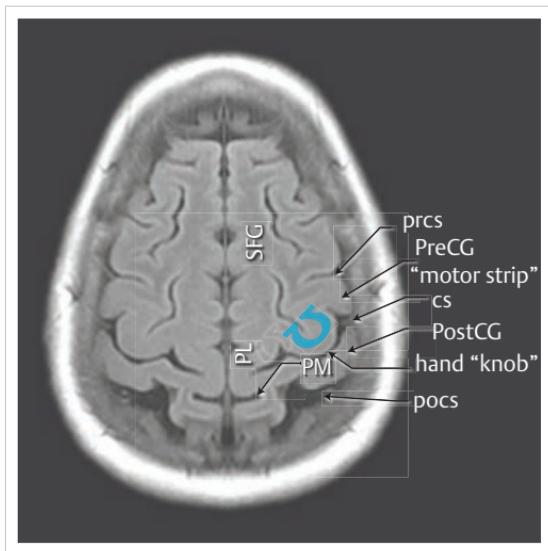
## 1.2 Central sulcus on axial imaging

See ► Fig. 1.4. Identification of the central sulcus is important to localize the motor strip (contained in the PreCG). The central sulcus (CS) is visible on 93% of CTs and 100% of MRIs.<sup>2</sup> It curves posteriorly as it approaches the interhemispheric fissure (IHF), and often terminates in the paracentral lobule, just anterior to the pars marginalis (pM) within the pars bracket (see above)<sup>2</sup> (i.e., the CS often does not reach the midline).



**Fig. 1.3** Somatotopic organization of primary sensory and motor cortex.

The labels are placed along a cross section of the brain taken through the motor (blue) and the sensory (pink) cortex indicated on the drawing of the brain shown below the slices.



**Fig. 1.4** Motor strip and hand knob.  
Retouched axial FLAIR MRI with labels for gyri/sulci shown in the left hemisphere, and an unlabeled mirror image shown as the right hemisphere for reference. The inverted blue  $\Omega$  (omega) illustrates the hand "knob" (see text).

See ▶ Table 1.1 and ▶ Table 1.2 for abbreviations.

## Pointers:

- parieto-occipital sulcus (pos) (or fissure): more prominent over the medial surface, and on axial imaging is longer, more complex, and more posterior than the pars marginalis<sup>6</sup>
- post-central sulcus (pocs): usually bifurcates and forms an arc or parenthesis ("lazy-Y") cupping the pM. The anterior limb does not enter the pM-bracket and the posterior limb curves behind the pM to enter the IHF

**Hand "knob":** The alpha motor neurons for hand function are located in the superior aspect of the pre-central gyrus<sup>7</sup> which appears as a knob-like protrusion (shaped like an inverted greek letter omega Ω) projecting posterolaterally into the central sulcus on axial imaging<sup>8</sup> (► Fig. 1.4). On sagittal imaging it has a posteriorly projecting hook-like appearance and is even with the posterior limit of the Sylvian fissure.<sup>8</sup>

## 1.3 Surface anatomy of the cranium

### 1.3.1 Craniometric points

See ► Fig. 1.5.

Pterion: region where the following bones are approximated: frontal, parietal, temporal and sphenoid (greater wing). Estimated location: 2 finger-breadths above the zygomatic arch, and a thumb's breadth behind the frontal process of the zygomatic bone (blue circle in ► Fig. 1.5).

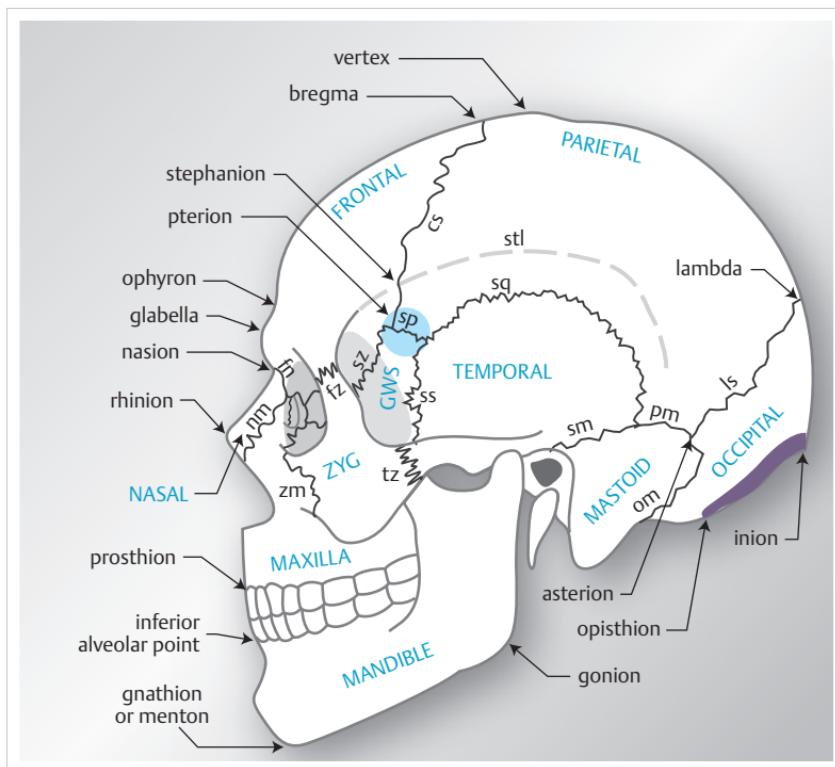


Fig. 1.5 Craniometric points & cranial sutures.

Named bones appear in all upper case letters. The blue circle is the pterion.

Abbreviations: GWS = greater wing of sphenoid bone; stl = superior temporal line; ZYG = zygomatic.

For basion, see ► Fig. 12.1.

Sutures: cs = coronal, fn = frontonasal, fz = frontozygomatic, ls = lambdoid, nm = nasomaxillary, om = occipitomastoid, pm = parietomastoid, sm = squamomastoid, sp = sphenoparietal, sq = squamosal, ss = sphenosquamous, sz = sphenozygomatic, tz = temporozygomatic, zm = zygomaticomaxillary.

Asterion: junction of lambdoid, occipitomastoid and parietomastoid sutures. Usually lies within a few millimeters of the posterior-inferior edge of the junction of the transverse and sigmoid sinuses (not always reliable<sup>9</sup>—may overlie either sinus).

Vertex: the topmost point of the skull.

Lambda: junction of the lambdoid and sagittal sutures.

Stephanion: junction of coronal suture and superior temporal line.

Glabella: the most forward projecting point of the forehead at the level of the supraorbital ridge in the midline.

Opisthion: the posterior margin of the foramen magnum in the midline.

Bregma: the junction of the coronal and sagittal sutures.

Sagittal suture: midline suture from coronal suture to lambdoid suture. Although often assumed to overlie the superior sagittal sinus (SSS), the SSS lies to the right of the sagittal suture in the majority of specimens<sup>10</sup> (but never by > 11 mm).

The most anterior mastoid point lies just in front of the sigmoid sinus.<sup>11</sup>

### 1.3.2 Relation of skull markings to cerebral anatomy

#### Taylor-Haughton lines

Taylor-Haughton (T-H) lines can be constructed on an angiogram, CT/MRI scout film, or skull X-ray. They can be constructed on the patient in the O.R. based on visible external landmarks.<sup>12</sup> T-H lines are shown as dashed lines in ► Fig. 1.6.

1. Frankfurt plane, AKA baseline: line from inferior margin of orbit through the *upper* margin of the external auditory meatus (EAM) (as distinguished from Reid's base line: from inferior orbital margin through the center of the EAM)<sup>13</sup>(p 313)
2. the distance from the nasion to the inion is measured across the top of the calvaria and is divided into quarters (can be done simply with a piece of tape which is then folded in half twice)
3. posterior ear line: perpendicular to the baseline through the mastoid process
4. condylar line: perpendicular to the baseline through the mandibular condyle
5. T-H lines (p.61) can then be used to approximate the Sylvian fissure (see below) and the motor cortex

#### Motor cortex

Numerous methods utilize external landmarks to locate the motor strip (precentral gyrus) or the *central sulcus* (Rolandic fissure) which separates motor strip anteriorly from primary sensory cortex posteriorly. These are just approximations since individual variability causes the motor strip to lie anywhere from 4 to 5.4 cm behind the coronal suture.<sup>14</sup> The central sulcus cannot even be reliably identified visually at surgery.<sup>15</sup>

1. method 1: the superior aspect of the motor cortex is almost straight up from the EAM near the midline
2. method 2<sup>16</sup>: the central sulcus is approximated by connecting:
  - a) the point 2 cm posterior to the midposition of the arc extending from nasion to inion (illustrated in ► Fig. 1.6), to
  - b) the point 5 cm straight up from the EAM
3. method 3: using T-H lines, the central sulcus is approximated by connecting
  - a) the point where the "posterior ear line" intersects the circumference of the skull (► Fig. 1.6; usually about 1 cm behind the vertex, and 3–4 cm behind the coronal suture), to
  - b) the point where the "condylar line" intersects the line representing the Sylvian fissure
4. method 4: a line drawn 45° to Reid's base line starting at the pterion points in the *direction* of the motor strip<sup>17</sup>(p 584-5)

#### Sylvian fissure AKA lateral fissure

On the skin surface: approximated by a line connecting the lateral canthus to the point 3/4 of the way posterior along the arc running over convexity from nasion to inion (T-H lines).

On the skull (once it is exposed in surgery): the anterior portion of the Sylvian fissure follows the squamosal suture (► Fig. 1.7)<sup>18</sup> and then deviates superiorly to terminate at *Chater's point*, which is located 6 cm above the EAM on a line perpendicular to the orbitomeatal line; it is also ≈ 1.5 cm above the squamosal suture along the same perpendicular line. A 4 cm craniotomy centered at Chater's point provides access to potential recipient vessels in the angular gyrus for EC/IC bypass surgery.<sup>19,20</sup>

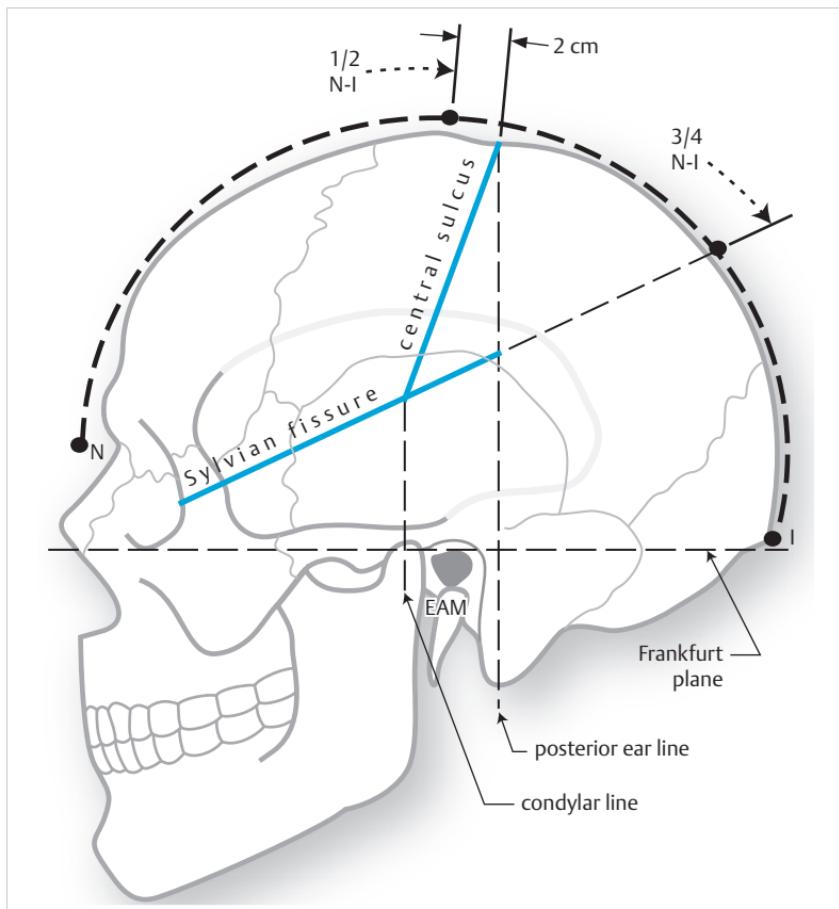


Fig. 1.6 Taylor-Haughton lines and other localizing methods.  
N = nasion. I = inion.

### Angular gyrus

Located just above the pinna, important on the dominant hemisphere as part of Wernicke's area (p.90). Note: there is significant individual variability in the location.<sup>21</sup>

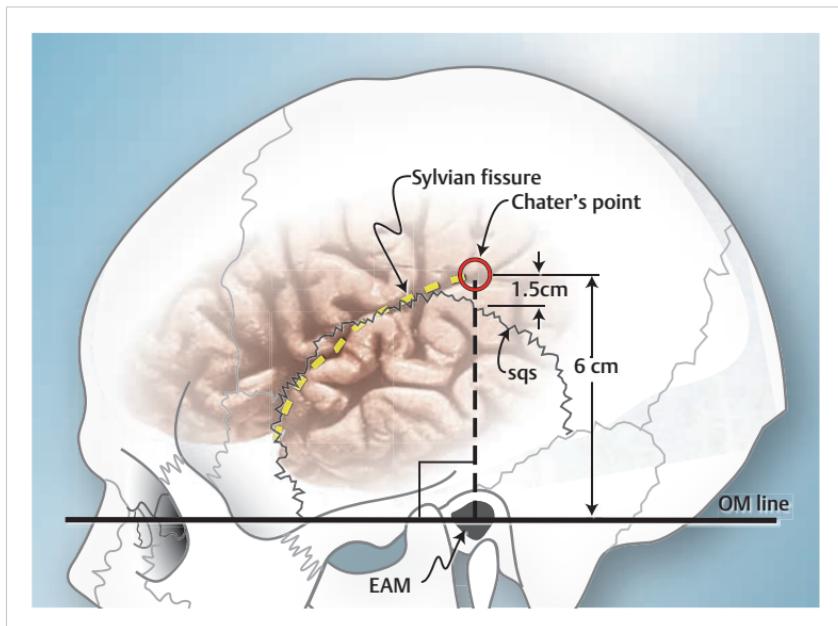
#### 1.3.3 Relationship of ventricles to skull

► Fig. 1.8 shows the relationship of non-hydrocephalic ventricles to the skull in the lateral view. Some dimensions of interest are shown in ► Table 1.3.<sup>22</sup>

In the non-hydrocephalic adult, the lateral ventricles lie 4–5 cm below the outer skull surface. The center of the body of the lateral ventricle sits in the midpupillary line, and the frontal horn is intersected by a line passing perpendicular to the calvaria along this line.<sup>23</sup> The anterior horns extend 1–2 cm anterior to the coronal suture.

Average length of third ventricle ≈ 2.8 cm.

The midpoint of Twining's line (• in ► Fig. 1.8) should lie within the 4th ventricle.



**Fig. 1.7 Chater's point.** Note the relationship of the Sylvian fissure to the squamosal suture.

Abbreviations: EAM = external auditory meatus; sqs = squamosal suture; OM line = orbitomeatal line (p. 238) (a line sometimes used in CT scanning that connects the lateral canthus to the midpoint of the EAM).

The dashed black line is perpendicular to the OM line. The red circle indicates Chater's point. The Sylvian fissure is highlighted by the broken yellow line and is situated under the anterior portion of the sqs.

## 1.4 Surface landmarks of spine levels

Estimates of cervical levels for anterior cervical spine surgery may be made using the landmarks shown in ► Table 1.4. Intraoperative C-spine X-rays are essential to verify these estimates.

The scapular spine is located at about T2–3.

The inferior scapular pole is  $\approx$  T6 posteriorly.

Intercristal line: a line drawn between the highest point of the iliac crests across the back will cross the midline either at the interspace between the L4 and L5 spinous processes, or at the L4 spinous process itself.

## 1.5 Cranial foramina and their contents

### 1.5.1 Summary

See ► Table 1.5.

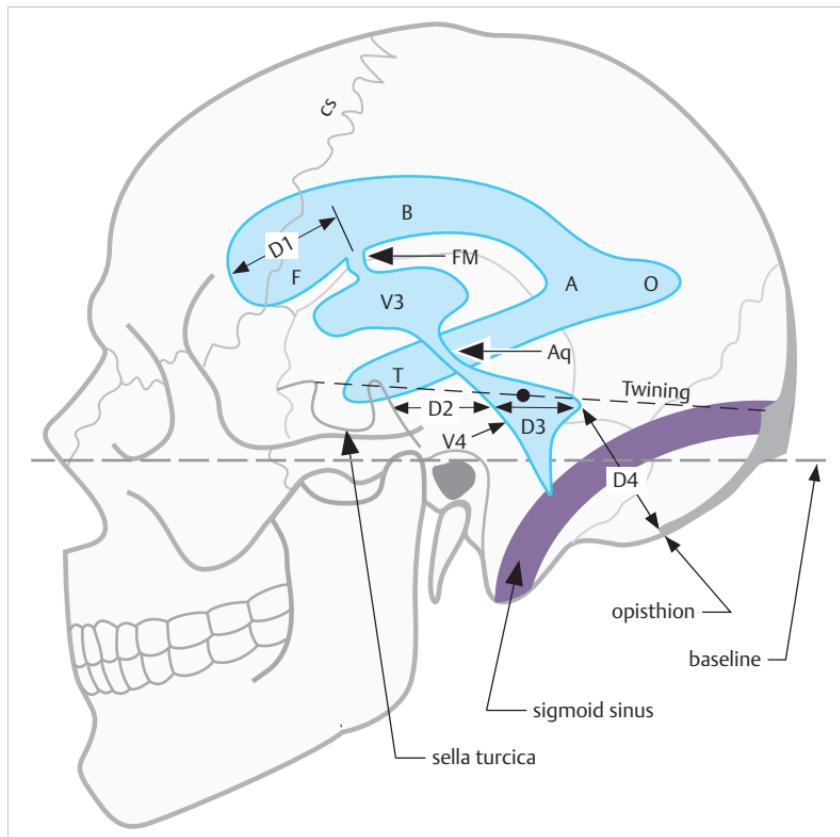
### 1.5.2 Porus acusticus

AKA internal auditory canal (► Fig. 1.9).

The filaments of the acoustic portion of VIII penetrate tiny openings of the lamina cribrosa of the cochlear area.<sup>25</sup>

Transverse crest: separates superior vestibular area and facial canal (above) from the inferior vestibular area and cochlear area (see below).<sup>25</sup>

Vertical crest (AKA Bill's bar—named after Dr. William House): separates the meatus to the facial canal anteriorly (containing VII and nervus intermedius) from the vestibular area posteriorly (containing the superior division of vestibular nerve). Bill's bar is deeper in the IAC than the transverse crest.



**Fig. 1.8 Relationship of ventricles to skull landmarks.**

Abbreviations: (F = frontal horn, B = body, A = atrium, O = occipital horn, T = temporal horn) of lateral ventricle. FM = foramen of Monro. Aq = Sylvian aqueduct. V3 = third ventricle. V4 = fourth ventricle. cs = coronal suture. Dimensions D1–4 see ▶ Table 1.3.

**Table 1.3 Dimensions from ▶ Fig. 1.8**

Dimension (▶ Fig. 1.8)	Description	Lower limit (mm)	Average (mm)	Upper limit (mm)
D1	length of frontal horn anterior to FM		25	
D2	distance from clivus to floor of 4th ventricle at level of fastigium <sup>a</sup>	33.3	36.1	40.0
D3	length of 4th ventricle at level of fastigium <sup>a</sup>	10.0	14.6	19.0
D4	distance from fastigium <sup>a</sup> to opisthion	30.0	32.6	40.0

<sup>a</sup> fastigium: the apex of the 4th ventricle within the cerebellum

**Table 1.4** Cervical levels<sup>24</sup>

Level	Landmark
C1–2	angle of mandible
C3–4	1 cm above thyroid cartilage ( $\approx$ hyoid bone)
C4–5	level of thyroid cartilage
C5–6	crico-thyroid membrane
C6	carotid tubercle
C6–7	cricoid cartilage

**Table 1.5** Cranial foramina and their contents<sup>3</sup>

Foramen	Contents
nasal slits	anterior ethmoidal nn., a. & v.
superior orbital fissure	Cr. Nn. III, IV, VI, all 3 branches of V1 (ophthalmic division divides into nasociliary, frontal, and lacrimal nerves); superior ophthalmic vv.; recurrent meningeal br. from lacrimal a.; orbital branch of middle meningeal a.; sympathetic filaments from ICA plexus
inferior orbital fissure	Cr. N. V-2 (maxillary div.), zygomatic n.; filaments from pterygopalatine branch of maxillary n.; infraorbital a. & v.; v. between inferior ophthalmic v. & pterygoid venous plexus
foramen lacerum	usually nothing (ICA traverses the upper portion but doesn't enter, 30% have vidian a.)
carotid canal	internal carotid a., ascending sympathetic nerves
incisive foramen	descending septal a.; nasopalatine nn.
greater palatine foramen	greater palatine n., a., & v.
lesser palatine foramen	lesser palatine nn.
internal acoustic meatus	Cr. N. VII (facial); Cr. N. VIII (stato-acoustic)—see text & ▶ Fig. 1.9
hypoglossal canal	Cr. N. XII (hypoglossal); a meningeal branch of the ascending pharyngeal a.
foramen magnum	spinal cord (medulla oblongata); Cr. N. XI (spinal accessory nn.) entering the skull; vertebral aa.; anterior & posterior spinal arteries
foramen cecum	occasional small vein
cribriform plate	olfactory nn.
optic canal	Cr. N. II (optic); ophthalmic a.
foramen rotundum	Cr. N. V2 (maxillary div.), a. of foramen rotundum
foramen ovale	Cr. N. V3 (mandibular div.) + portio minor (motor for Cr. N. V)
foramen spinosum	middle meningeal a. & v.
jugular foramen	internal jugular v. (beginning); Cr. Nn. IX, X, XI
stylomastoid foramen	Cr. N. VII (facial); stylomastoid a.
condyloid foramen	v. from transverse sinus
mastoid foramen	v. to mastoid sinus; branch of occipital a. to dura mater

<sup>3</sup>Abbreviations: a. = artery, aa. = arteries, v. = vein, vv. = veins, n. = nerve, nn. = nerves, br. = branch, Cr. N. = cranial nerve, fmnn. = foramen, div. = division

The “5 nerves” of the IAC:

1. facial nerve (VII) (mnemonic: “7-up” as VII is in superior portion)
2. nervus intermedius: the somatic sensory branch of the facial nerve primarily innervating mechanoreceptors of the hair follicles on the inner surface of the pinna and deep mechanoreceptors of nasal and buccal cavities and chemoreceptors in the taste buds on the anterior 2/3 of the tongue
3. acoustic portion of the VIII nerve (mnemonic: “Coke down” for cochlear portion)
4. superior branch of vestibular nerve: passes through the superior vestibular area to terminate in the utricle and in the ampullæ of the superior and lateral semicircular canals (mnemonic superior = LSU (Lateral & Superior semicircular canals and the Utricle))
5. inferior branch of vestibular nerve: passes through inferior vestibular area to terminate in the saccule

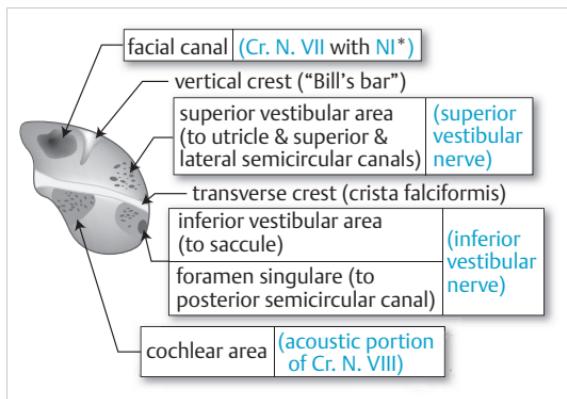


Fig. 1.9 Right internal auditory canal (porus acusticus) & nerves.  
Abbreviations: Cr. N. = cranial nerve; NI = nervus intermedius.

## 1.6 Internal capsule

### 1.6.1 Architectural anatomy

For a schematic diagram, see ► Fig. 1.10; ► Table 1.6 delineates the thalamic subradiations. Most IC lesions are caused by vascular accidents (thrombosis or hemorrhage).

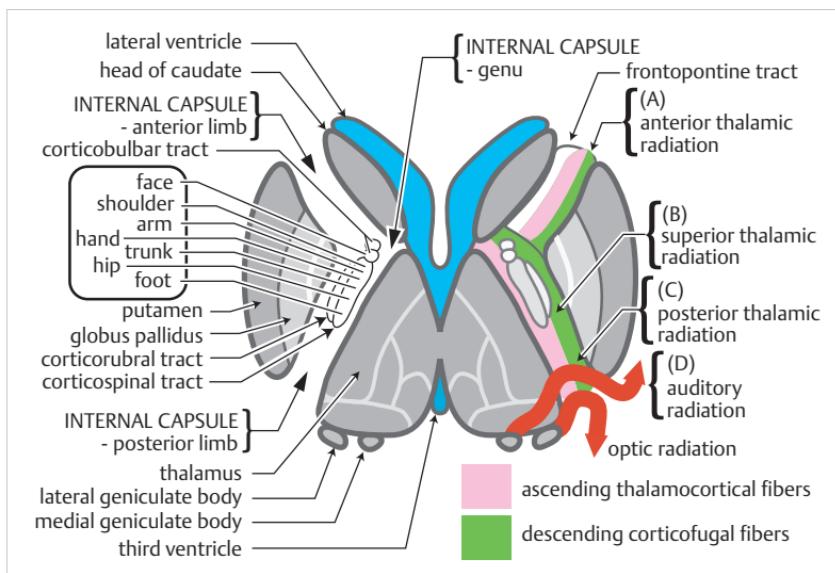


Fig. 1.10 Internal capsule schematic diagram.  
Axial cut. The left side of the diagram shows tracts; the right side shows radiations.

### 1.6.2 Vascular supply of the internal capsule (IC)

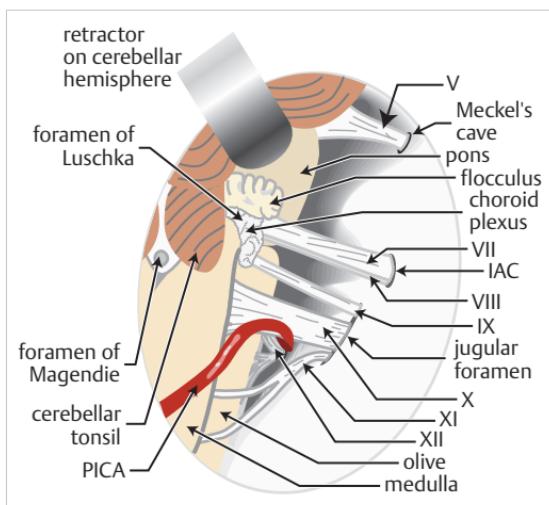
1. anterior choroidal: ⇒ all of retro Lenticular part (includes optic radiation) and ventral part of posterior limb of IC
2. lateral striate branches (AKA capsular branches) of middle cerebral artery: ⇒ most of anterior AND posterior limbs of IC
3. genu usually receives some direct branches of the internal carotid artery

**Table 1.6** Four thalamic "subradiations" (AKA thalamic peduncles), labeled A-D in ► Fig. 1.10

Radiation	Connection	Comments
anterior (A)	medial & anterior thalamic nucleus	↔ frontal lobe
superior (B)	rolandic areas	↔ ventral thalamic nuclei general sensory fibers from body & head to terminate in postcentral gyrus (areas 3,1,2)
posterior (C)	occipital & posterior parietal	↔ caudal thalamus
inferior (D)	transverse temporal gyrus of Heschl	↔ MGB (small) includes auditory radiation

## 1.7 Cerebellopontine angle anatomy

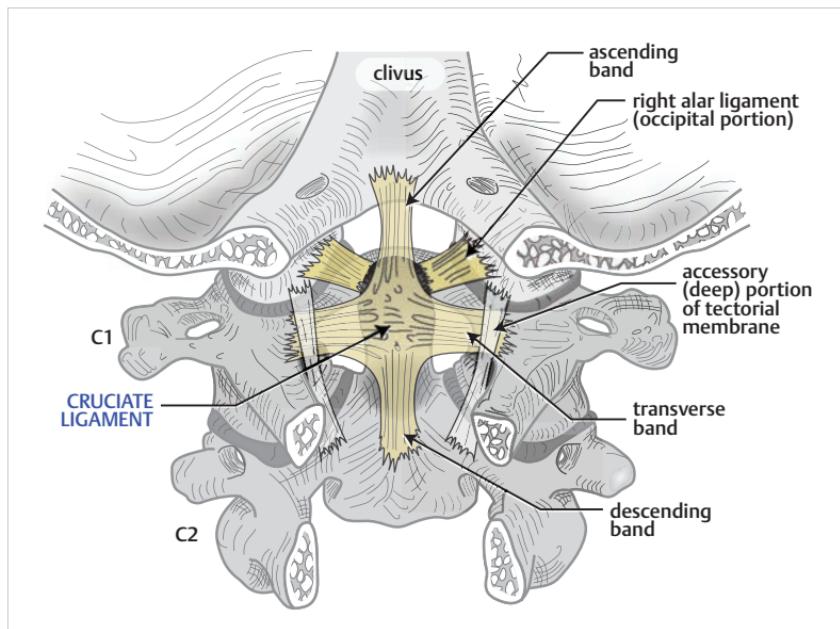
For normal anatomy of right cerebellopontine angle, see ► Fig. 1.11.



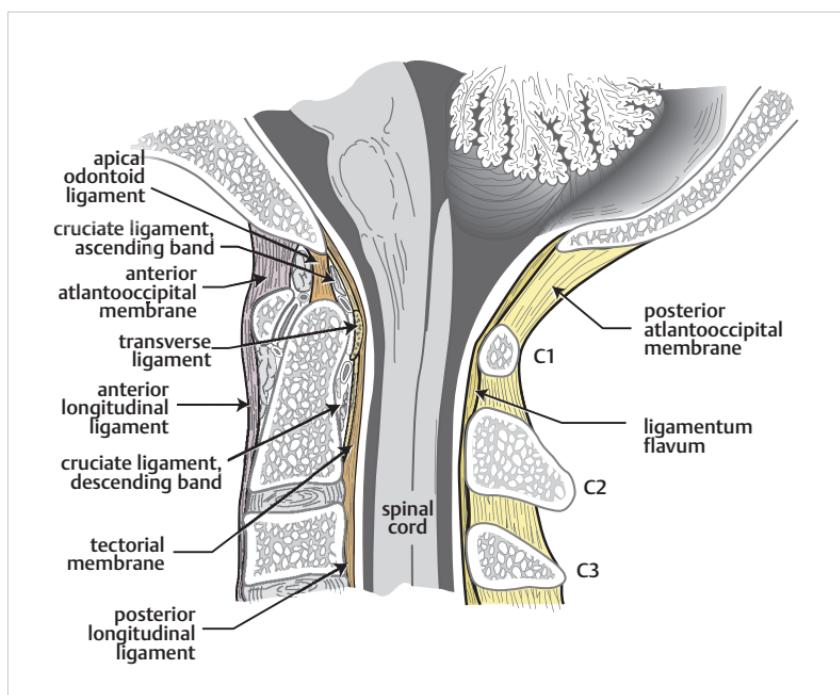
**Fig. 1.11** Right cerebellopontine angle. Normal anatomy viewed from behind (as in a suboccipital approach).<sup>25</sup>

## 1.8 Occipitoatlantoaxial-complex anatomy

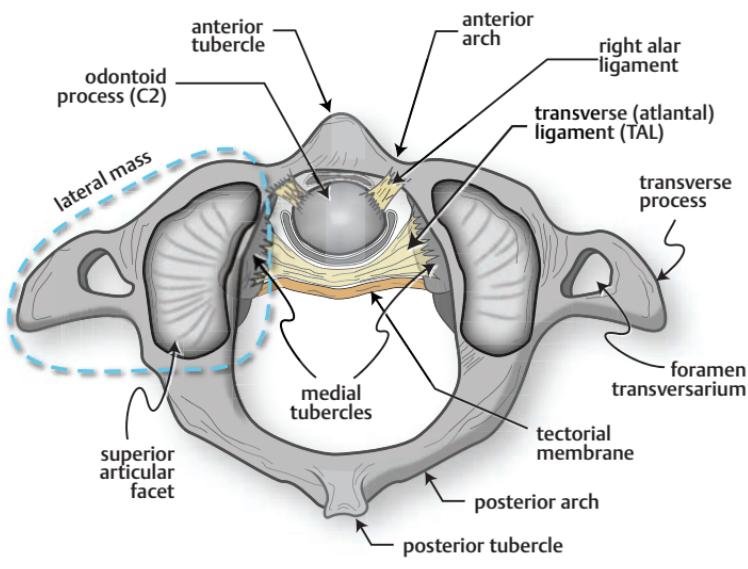
- **Ligaments of the occipitoatlantoaxial complex.** Stability of the occipitoatlantal joint is primarily due to ligaments, with little contribution from bony articulations and joint capsules (see ► Fig. 1.12, ► Fig. 1.13, ► Fig. 1.14):
  1. ligaments that connect the atlas to the occiput:
    - a) anterior atlantooccipital membrane: cephalad extension of the anterior longitudinal ligament. Extends from anterior margin of foramen magnum (FM) to anterior arch of C1
    - b) posterior atlantooccipital membrane: connects the posterior margin of the FM to posterior arch of C1
    - c) the ascending band of the cruciate ligament
  2. ligaments that connect the axis (viz. the odontoid) to the occiput:
    - a) tectorial membrane: some authors distinguish 2 components
      - superficial component: cephalad continuation of the posterior longitudinal ligament. A strong band connecting the dorsal surface of the dens to the ventral surface of the FM above, and dorsal surface of C2 & C3 bodies below
      - accessory (deep) portion: located laterally, connects C2 to occipital condyles
    - b) alar ligaments (AKA check ligaments of the odontoid)<sup>26</sup>
      - occipito-alar portion: connects side of the dens to occipital condyle
      - atlanto-alar portion: connects side of the dens to the lateral mass of C1



**Fig. 1.12 Cruciate and alar ligaments.** Dorsal view (with tectorial membrane removed). (Modified with permission from "In Vitro Cervical Spine Biomechanical Testing" BNI Quarterly, Vol. 9, No. 4, 1993.)



**Fig. 1.13 Ligaments of the craniocervical junction.** Sagittal view. (Modified with permission from "In Vitro Cervical Spine Biomechanical Testing" BNI Quarterly, Vol. 9, No. 4, 1993.)



**Fig. 1.14 C1 vertebral body.** Viewed from above, showing the transverse and alar ligaments, and the critically important transverse atlantal ligament (TAL) AKA transverse ligament. (Modified with permission from "In Vitro Cervical Spine Biomechanical Testing" BNI Quarterly, Vol. 9, No. 4, 1993.)

- c) apical odontoid ligament: connects tip of dens to the FM. Little mechanical strength
- 3. ligaments that connect the axis to the atlas:
  - a) transverse atlantal ligament (TAL) or (usually) just transverse ligament: the horizontal component of the cruciate ligament. Attaches at the medial tubercles of C1. Traps the dens against the anterior atlas via a strap-like mechanism (► Fig. 1.14). Provides the majority of the strength ("the strongest ligament of the spine"<sup>27</sup>)
  - b) atlanto-alar portion of the alar ligaments (see above)
  - c) descending band of the cruciate ligament

The most important structures in maintaining atlantoccipital stability are the tectorial membrane and the alar ligaments. Without these, the remaining cruciate ligament and apical dentate ligament are insufficient.

## 1.9 Spinal cord anatomy

### 1.9.1 Dentate ligament

The dentate ligament separates dorsal from ventral nerve roots in the spinal nerves. The spinal accessory nerve (Cr. N. XI) is dorsal to the dentate ligament.

### 1.9.2 Spinal cord tracts

#### Anatomy

- Fig. 1.15 depicts a cross-section of a typical spinal cord segment, combining some elements from different levels (e.g., the intermediolateral gray nucleus is only present from T1 to ≈ L1 or L2 where there are sympathetic [thoracolumbar outflow] nuclei). It is schematically divided into ascending and descending halves; however, in actuality, ascending and descending paths coexist on both sides.
- Fig. 1.15 also depicts some of the laminae according to the scheme of Rexed. Lamina II is equivalent to the substantia gelatinosa. Laminae III and IV are the nucleus proprius. Lamina VI is located in the base of the posterior horn.

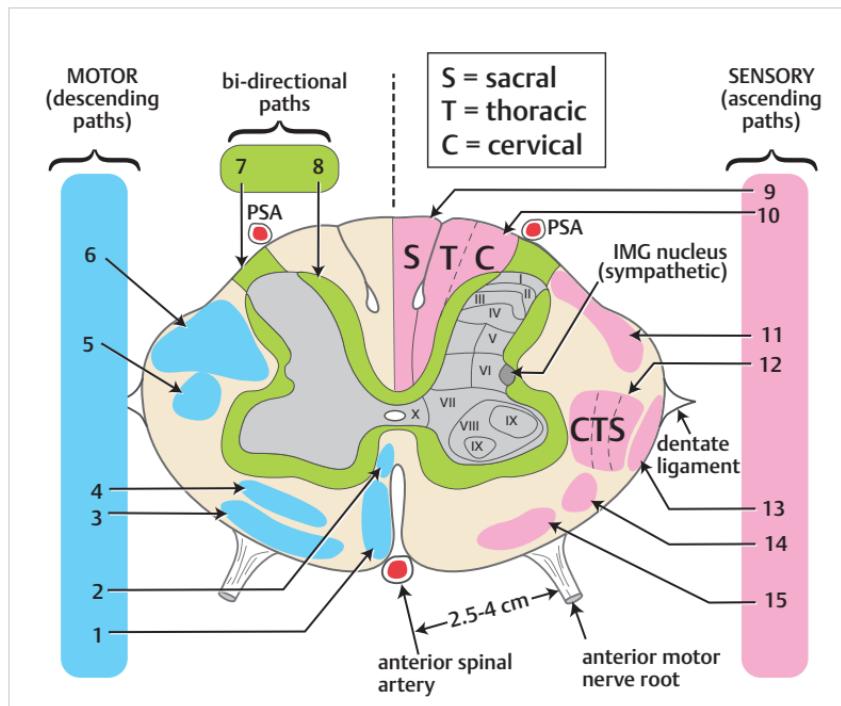


Fig. 1.15 Schematic cross-section of spinal cord. See ▶ Table 1.7, ▶ Table 1.8 and ▶ Table 1.9 for path names. Abbreviations: IMG = intermediolateral gray nucleus, PSA = posterior spinal artery. Roman numerals refer to laminae of Rexed.

Table 1.7 Descending (motor) tracts (↓) in ▶ Fig. 1.15

Number (▶ Fig. 1.15)	Path	Function	Side of body
1	anterior corticospinal tract	skilled movement	opposite <sup>a</sup>
2	medial longitudinal fasciculus	?	same
3	vestibulospinal tract	facilitates extensor muscle tone	same
4	medullary (ventrolateral) reticulospinal tract	automatic respirations?	same
5	rubrospinal tract	flexor muscle tone	same
6	lateral corticospinal (pyramidal) tract	skilled movement	same

<sup>a</sup>The terminal fibers of this uncrossed tract usually cross in the anterior white commissure to synapse on alpha motor neurons or on interneurons. A minority of the fibers do remain ipsilateral. Also, an anterior corticospinal tract is easily identified only in the cervical and upper thoracic regions.

## Motor

The lateral corticospinal tract (AKA pyramidal tract) is the largest and most significant motor tract of the spinal cord (often referred to simply as the corticospinal tract (CST) even though there is also an anterior CST). It consists of large axons of upper motor neuron (Betz cells) that originate in the motor cortex (precentral gyrus) in a somatotopic organization (p.58). The nerve fibers pass through the corona radiata and then the posterior limb of the internal capsule (IC), still somatotopically organized (▶ Fig. 1.10). The CST progressively loses its somatotopic organization as it passes through the cerebral peduncles and basis pontis.<sup>28</sup> About 10% of the fibers enter the ipsilateral anterior CST,

**Table 1.8** Bi-directional tracts in ► Fig. 1.15

Number (► Fig. 1.15)	Path	Function
7	dorsolateral fasciculus (of Lissauer)	?
8	fasciculus proprius	short spinospinal connections

**Table 1.9** Ascending (sensory) tracts (↑) in ► Fig. 1.15

Number (► Fig. 1.15)	Path	Function	Side of body
9	fasciculus gracilis	joint position, fine touch, vibration	same
10	fasciculus cuneatus		
11	posterior spinocerebellar tract	stretch receptors	same
12	lateral spinothalamic tract	pain & temperature	opposite
13	anterior spinocerebellar tract	whole limb position	opposite
14	spinothalamic tract	unknown, ? nociceptive	opposite
15	anterior spinothalamic tract	light touch	opposite

whereas the remaining fibers cross at the medullary decussation and continue as the lateral CST along with some fibers from the supplemental motor area (SMA) (Brodmann area 6, ► Fig. 1.1) and primary somatosensory cortex.

Contrary to classic teaching (which was that the CST is somatotopically organized with cervical fibers located medially, and thoracic and lumbar fibers situated progressively more laterally) evidence shows that the motor fibers of the CST in the spinal cord are diffusely distributed, unlike the situation with the sensory tracts (spinothalamic, and the gracilis and cuneatus fasciculi).<sup>28</sup> Axons of the CST terminate on alpha motor neurons (lower motor neurons) in the ventral gray horn of the spinal cord (Rexed lamina IX).

## Sensation

### Pain and temperature: body

Receptors: free nerve endings (probable).

1st order neuron: small, finely myelinated afferents; soma in dorsal root ganglion (no synapse). Enter cord at dorsolateral tract (zone of Lissauer). Synapse: substantia gelatinosa (Rexed II).

2nd order neuron: axons cross obliquely in the anterior white commissure ascending ≈ 1–3 segments while crossing to enter the lateral spinothalamic tract.

Synapse: VPL thalamus. 3rd order neurons pass through internal capsule to the postcentral gyrus (Brodmann's areas 3, 1, 2).

### Fine touch, deep pressure and proprioception: body

Fine touch AKA discriminative touch. Receptors: Meissner's & pacinian corpuscles, Merkel's discs, free nerve endings.

1st order neuron: heavily myelinated afferents; soma in dorsal root ganglion (no synapse). Short branches synapse in nucleus proprius (Rexed III & IV) of posterior gray; long fibers enter the ipsilateral posterior columns without synapsing (below T6: fasciculus gracilis; above T6: fasciculus cuneatus).

Synapse: nucleus gracilis/cuneatus (respectively), just above pyramidal decussation. 2nd order neuron axons form internal arcuate fibers, decussate in lower medulla as medial lemniscus.

Synapse: VPL thalamus. 3rd order neurons pass through IC primarily to postcentral gyrus.

### Light (crude) touch: body

Receptors: as fine touch (see above), also peritrichial arborizations.

1st order neuron: large, heavily myelinated afferents (Type II); soma in dorsal root ganglion (no synapse). Some ascend uncrossed in posterior columns (with fine touch); most synapse in Rexed VI & VII.

2nd order neuron: axons cross in anterior white commissure (a few don't cross); enter anterior spinothalamic tract.

Synapse: VPL thalamus. 3rd order neurons pass through IC primarily to postcentral gyrus.

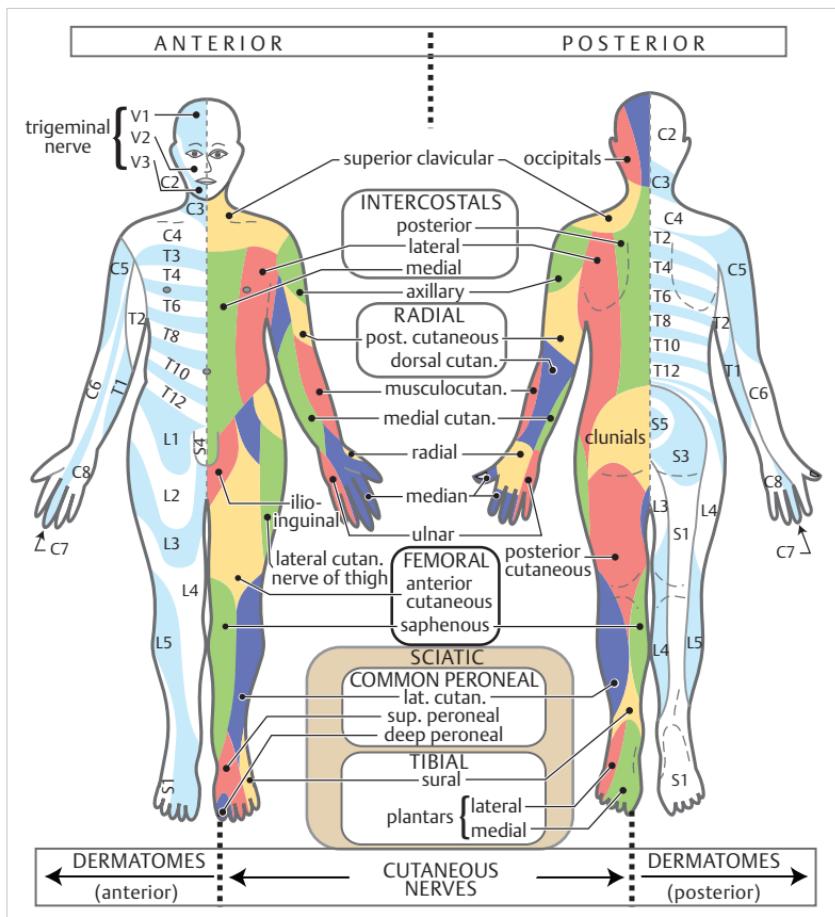
### 1.9.3 Dermatomes and sensory nerves

Dermatomes are areas of the body where sensation is subserved by a single nerve root.

Peripheral nerves generally receive contributions from more than one dermatome.

Lesions in peripheral nerves and lesions in nerve roots may sometimes be distinguished in part by the pattern of sensory loss. A classic example is splitting of the ring finger in median nerve or ulnar nerve lesions, which does not occur in C8 nerve root injuries.

► Fig. 1.16 shows anterior and posterior view, each schematically separated into sensory dermatomes (segmental) and peripheral sensory nerve distribution.



**Fig. 1.16 Dermatomal and sensory nerve distribution.** (Redrawn from "Introduction to Basic Neurology," by Harry D. Patton, John W. Sundsten, Wayne E. Crill and Phillip D. Swanson, © 1976, pp 173, W. B. Saunders Co., Philadelphia, PA, with permission.)

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## 2 Vascular Anatomy

### 2

### 2.1 Cerebral vascular territories

► Fig. 2.1 depicts approximate vascular distributions of the major cerebral arteries. There is considerable variability of the major arteries<sup>1</sup> as well as the central distribution.

Lenticulostriates may originate from different segments of the middle or anterior cerebral artery. Recurrent artery of Heubner (RAH) (AKA medial striate artery) origin: junction of the ACA and AComA in 62.3%, proximal A2 in 23.3%, A1 in 14.3%.<sup>2</sup>

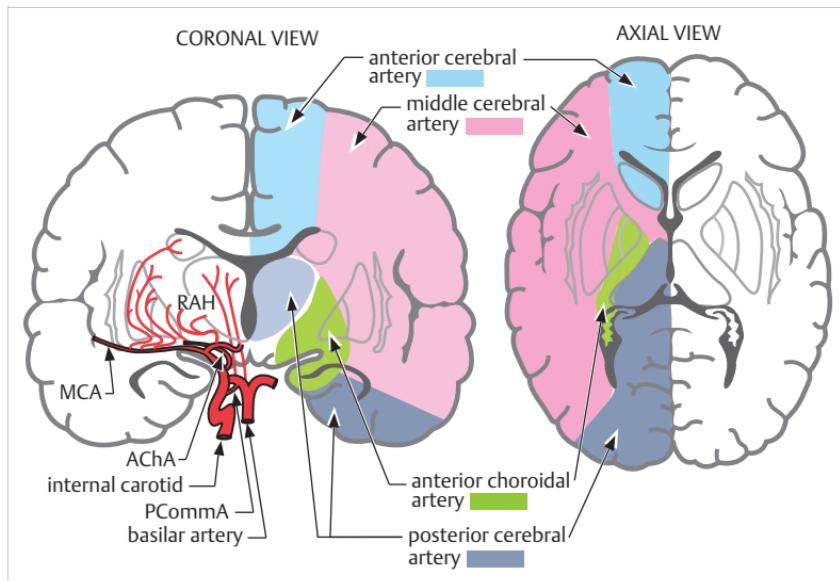


Fig. 2.1 Vascular territories of the cerebral hemispheres. RAH = recurrent artery of Heubner.

### 2.2 Cerebral arterial anatomy

#### 2.2.1 General information

The symbol “⇒” is used to denote a region supplied by the indicated artery. See Angiography (cerebral) (p.247) for angiographic diagrams of the following anatomy.

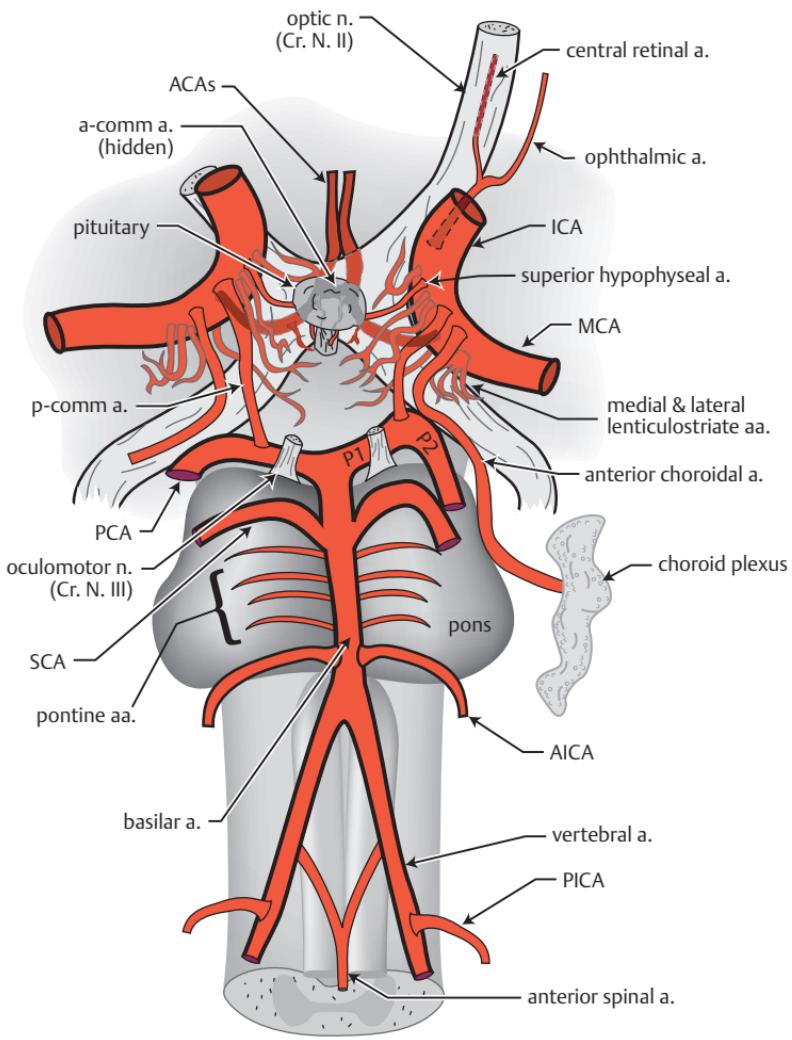
#### 2.2.2 Circle of Willis

See ► Fig. 2.2. A balanced configuration of the Circle of Willis is present in only 18% of the population. Hypoplasia of 1 or both PComAs occurs in 22–32%; absent or hypoplastic A1 segments occur in 25%.

Key point: the anterior cerebral arteries pass over the superior surface of the optic chiasm.

#### 2.2.3 Anatomical segments of intracranial cerebral arteries

1. carotid artery: see below for segments
2. anterior cerebral<sup>3</sup>:
  - a) A1 (precommunicating): ACA from origin to AComA
  - b) A2 (postcommunicating): ACA from AComA to branch-point of callosomarginal artery
  - c) A3 (precallosal): from branch-point of callosomarginal curving around the genu of the corpus callosum to superior surface of corpus callosum 3 cm posterior to the genu



**Fig. 2.2 Circle of Willis.** Viewed from anterior and inferior to the brain.

- d) A4: (supracallosal)
  - e) A5: terminal branch (postcallosal)
3. middle cerebral<sup>4</sup>:
- a) M1: MCA from origin to bifurcation (horizontal segment on AP angiogram). A classical bifurcation into relatively symmetrical superior and inferior trunks is seen in 50%, no bifurcation occurs in 2%, 25% have a very proximal branch (middle trunk) arising from the superior (15%) or the inferior (10%) trunk creating a "pseudo-trifurcation," a pseudo-tetrafurcation occurs in 5%
    - lateral fronto-orbital and prefrontal branches arise from M1 or superior M2 trunk
    - precentral, central, anterior and posterior parietal arteries arise from a superior (60%), middle (25%), or inferior (15%) trunk
    - the superior M2 trunk does not give any branches to the temporal lobe

- b) M2: MCA trunks from bifurcation to emergence from Sylvian fissure
  - c) M3–4: distal branches
  - d) M5: terminal branch
4. posterior cerebral (PCA) (several nomenclature schemes exist<sup>3,5</sup>):
- a) P1: PCA from the origin to posterior communicating artery (AKA mesencephalic, precommunicating, circular, peduncular, basilar...). The long and short circumflex and thalamoperforating arteries arise from P1
  - b) P2: PCA from origin of PComA to the origin of inferior temporal arteries (AKA ambient, post-communicating, perimesencephalic), P2 traverses the ambient cistern, hippocampal, anterior temporal, peduncular perforating, and medial posterior choroidal arteries arise from P2
  - c) P3: PCA from the origin of the inferior temporal branches to the origin of the terminal branches (AKA quadrigeminal segment). P3 traverses the quadrigeminal cistern
  - d) P4: segment after the origin of the parieto-occipital and calcarine arteries, includes the cortical branches of the PCA

## 2.2.4 Anterior circulation

### Anatomic variants

Bovine circulation: the common carotids arise from a common trunk off the aorta.

### External carotid

1. superior thyroid a.: 1st anterior branch
2. ascending pharyngeal a.
  - a) neuromeningeal trunk of the ascending pharyngeal a.: supplies IX, X & XI (important when embolizing glomus tumors, 20% of lower cranial nerve palsy if this branch is occluded)
  - b) pharyngeal branch: usually the primary feeder for jugular foramen tumors (essentially the only cause of hypertrophy of the ascending pharyngeal a.)
3. lingual a.
4. facial a.: branches anastomose with ophthalmic a.; important in collateral flow with ICA occlusion (p. 1537)
5. occipital a. → posterior scalp
6. posterior auricular
7. superficial temporal
  - a) frontal branch
  - b) parietal branch
8. (internal) maxillary a.—initially within parotid gland
  - a) middle meningeal a.
    - anterior branch
    - posterior branch
  - b) accessory meningeal
  - c) inferior alveolar
  - d) infra-orbital
  - e) others: distal branches of which may anastomose with branches of ophthalmic artery in the orbit

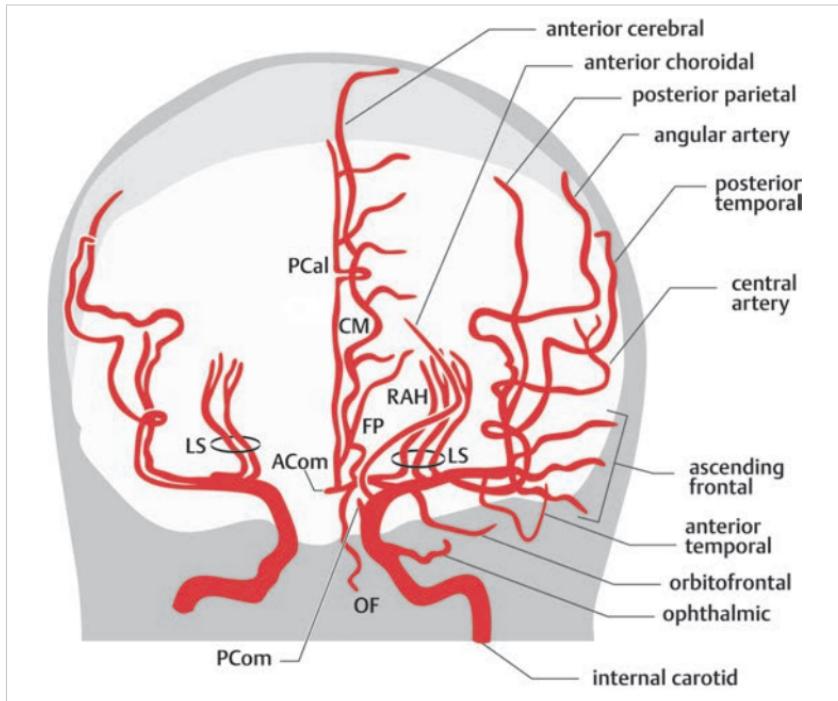
### Internal carotid artery (ICA)

Lies posterior & medial to the external carotid (ECA).

### Segments of the ICA and its branches

See ▶ Fig. 2.3 for angiographic appearance, and ▶ Fig. 2.4<sup>6</sup> for anatomic illustration.

1. **C1 (cervical):** begins in the neck at the carotid bifurcation where the common carotid artery divides into internal and external carotid arteries. Encircled with postganglionic sympathetic nerves (PGSN), the ICA travels in the carotid sheath with the IJV and vagal nerve. C1 ends where the ICA enters the carotid canal of the petrous bone. *No branches*
2. **C2 (petrous):** still surrounded by PGSNs. Ends at the posterior edge of the foramen lacerum (f-Lac) (inferomedial to the edge of the Gasserian ganglion in Meckel's cave). Three subdivisions:
  - a) vertical segment: ICA ascends then bends as the...
  - b) posterior loop: anterior to the cochlea, bends antero-medially becoming the...



**Fig. 2.3 Internal carotid arteriogram (AP view).**

ACom: anterior communicating artery

CM: callosomarginal artery

FP: frontopolar artery

LS: lenticulostriate arteries

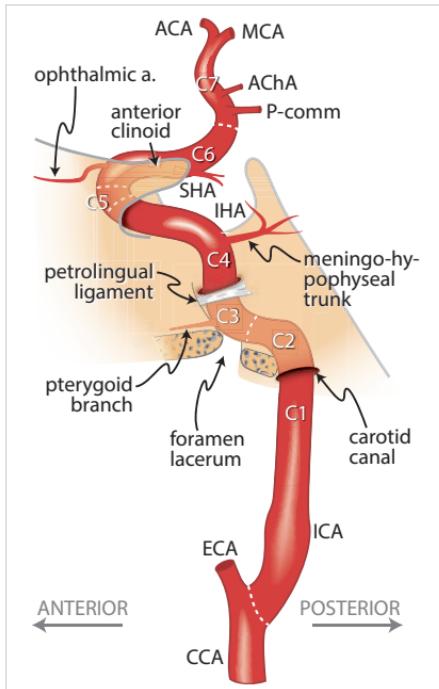
OF: orbitofrontal artery

PCal: pericallosal artery

PCom: posterior communicating artery

RAH: recurrent artery of Heubner (Reprinted courtesy of Eastman Kodak Company)

- c) horizontal segment: deep and medial to the greater and lesser superficial petrosal nerves, anterior to the tympanic membrane (TM)
- 3. C3 (lacerum): the ICA passes over (but not through) the foramen lacerum (f-Lac) forming the lateral loop. Ascends in the canalicular portion of the f-Lac to the juxtasellar position, piercing the dura as it passes the petroclival ligament to become the cavernous segment. Branches (usually not visible angiographically):
  - a) caroticotympanic (inconsistent)  $\Rightarrow$  tympanic cavity
  - b) pterygoid (vidian) branch: passes through the f-Lac, present in only 30%, may continue as the artery of the pterygoid canal
- 4. C4 (cavernous): covered by a vascular membrane lining the sinus, still surrounded by PGSNs. Passes anteriorly then supero-medially, bends posteriorly (medial loop of ICA), travels horizontally, and bends anteriorly (part of anterior loop of ICA) to the anterior clinoid process. Ends at the proximal dural ring (incompletely encircles ICA). Many branches, main ones include
  - a) meningohypophyseal trunk (MHT) (largest & most proximal). 2 causes of a prominent MHT:
    - (1) tumor (usually petroclival meningioma—see below), (2) dural AVM (p. 1514). 3 branches:
      - 1. a. of tentorium (AKA artery of Bernasconi & Cassinari): the blood supply of petroclival meningiomas
      - 2. dorsal meningeal a. (AKA dorsal clival a.)
      - 3. inferior hypophyseal a. ( $\Rightarrow$  posterior lobe of pituitary): post-partum occlusion causes pituitary infarcts (Sheehan's necrosis); however, DI is rare because the stalk is spared
    - b) anterior meningeal a.



**Fig. 2.4 Segments of the internal carotid artery (ICA).<sup>6</sup>**

Left ICA viewed from the left side.

Abbreviations: ACA = anterior cerebral artery; AChA = anterior choroidal artery; CCA = common carotid artery; ECA = external carotid artery; IHA = inferior hypophyseal artery; MCA = middle cerebral artery; P-comm = posterior communicating artery; SHA = superior hypophyseal artery.

- c) a. to inferior portion of cavernous sinus (present in 80%)
- d) capsular aa. of McConnell (in 30%): supply the capsule of the pituitary<sup>7</sup>
- 5. **C5 (clinoid):** begins at the proximal dural ring, ends at the distal dural ring (which completely encircles ICA) where the ICA becomes intradural
- 6. **C6 (ophthalmic):** begins at distal dural ring, ends just proximal to the PComA. Branches:
  - a) ophthalmic a.: the origin from the ICA is distal to the cavernous sinus in 89% (intracavernous in 8%, the ophthalmic artery is absent in 3%)<sup>8</sup> and can vary from 5 mm anterior to 7 mm posterior to the anterior clinoid.<sup>7</sup> Passes through the optic canal into the orbit (the intracranial course is very short, usually 1–2 mm<sup>7</sup>). Has a characteristic bayonet-like “kink” or “L” shape (depending on whether it passes above or below the optic nerve) on lateral angiogram
  - b) superior hypophyseal a. branches ⇒ anterior lobe of pituitary & stalk (1st branch of supraclinoid ICA)
- 7. **C7 (communicating):** begins just proximal to the PComA origin, travels between Cr. N. II & III, terminates just below anterior perforated substance where it bifurcates into the ACA & MCA
  - a) posterior communicating a. (PComA)
    - few anterior thalamoperforators (⇒ optic tract, chiasm & posterior hypothalamus): below
    - plexal segment: enters supracornual recess of temporal horn, ⇒ only this portion of choroid plexus
    - cisternal segment: passes through crural cistern
  - b) anterior choroidal artery<sup>9</sup>: takeoff 2–4 mm distal to PComA ⇒ (variable) portion of optic tract, medial globus pallidus, genu of internal capsule (IC) (in 50%), inferior half of posterior limb of IC, uncus, retro lenticular fibers (optic radiation), lateral geniculate body; for occlusion syndromes (p. 1539)
- 8. “Carotid siphon”: not a segment, but a region incorporating the cavernous, ophthalmic and communicating segments. Begins at the posterior bend of the cavernous ICA, and ends at the ICA bifurcation

## Differentiating PComA from ACh on arteriogram

1. PComA origin is proximal to that of the anterior choroidal artery (ACh)
2. PComA is usually larger than ACh
3. PComA usually goes up or down a little, then straight back & usually bifurcates
4. ACh usually has a superior "hump" (plexal point) where it passes through the choroidal fissure to enter the ventricle

2

### Anterior cerebral artery (ACA)

Passes between Cr. N. II and anterior perforated substance. See ▶ Fig. 2.5. Branches:

1. recurrent artery (of Heubner): typically arises from the area of the A1/A2 junction. Various statistics can be found in the literature regarding the percentage that arise from distal A1 vs. proximal A2.<sup>2</sup> It is most important to be mindful that the takeoff is variable, e.g., when treating aneurysms (one of the larger medial lenticulostriates, remainder of lenticulostriates may arise from this artery) ⇒ head of caudate, putamen, and anterior internal capsule
2. medial orbitofrontal artery
3. frontopolar artery
4. callosomarginal
  - a) internal frontal branches:
    - anterior
    - middle
    - posterior
  - b) paracentral artery
5. pericallosal artery (continuation of ACA)
  - a) superior internal parietal (precuneate) artery
  - b) inferior internal parietal artery

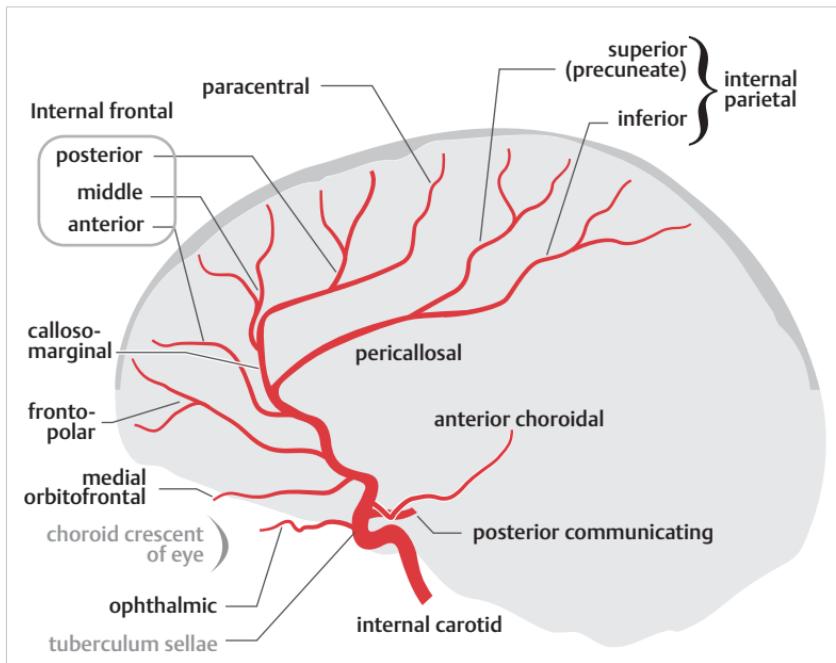


Fig. 2.5 Anterior cerebral arteriogram (lateral view). (Reprinted courtesy of Eastman Kodak Company.)

## Anatomic variants

Hypoid: having only one anterior cerebral artery (as in a horse).

## Middle cerebral artery (MCA)

See ▶ Fig. 2.6 and anatomy (p. 75). Branches vary widely, 10 common ones:

1. medial (3–6 per side) and lateral lenticulostriate arteries
2. anterior temporal
3. posterior temporal
4. lateral orbitofrontal
5. ascending frontal (candelabra)
6. precentral (prerolandic)
7. central (rolandic)
8. anterior parietal (postrolandic)
9. posterior parietal
10. angular

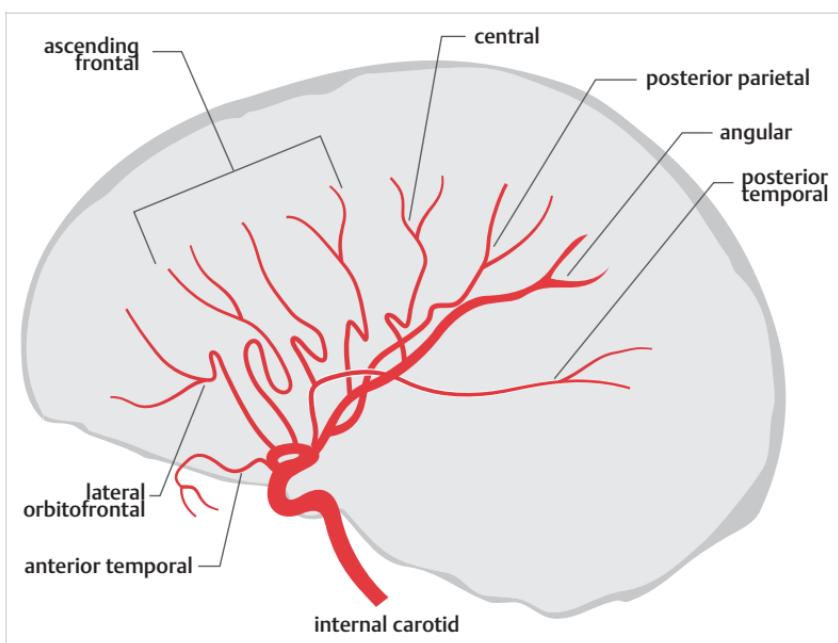


Fig. 2.6 Middle cerebral arteriogram (lateral view). (Reprinted courtesy of Eastman Kodak Company.)

## 2.2.5 Posterior circulation

### Anatomic variants

Fetal circulation: 15–35% of patients supply their posterior cerebral artery on one or both sides primarily from the carotid (via PComA) instead of via the vertebrobasilar system.

### Vertebral artery (VA)

The VA is the first and usually the largest branch of the subclavian artery. Variant: the left VA arises off the aortic arch in  $\approx$  4%. Diameter  $\approx$  3 mm. Mean blood flow  $\approx$  150 ml/min. The *left* VA is dominant in 60%. The right VA will be hypoplastic in 10%, and the left will be hypoplastic in 5%. The VA is atretic and does not communicate with the BA on the left in 3%, and on the right in 2% (the VA may terminate in PICA).

Four segments:

- **V1 prevertebral:** from subclavian artery, courses superiorly and posteriorly and enters the foramen transversarium, usually of the 6th vertebral body
- **V2** ascends vertically within the transverse foramina of the cervical vertebrae surrounded by sympathetic fibers (from the stellate ganglion) and a venous plexus. It is situated *anterior* to the cervical roots. It turns laterally to enter the foramen within the transverse process of the axis
- **V3** exits the foramen of the axis and curves posteriorly and medially in a groove on the upper surface of the atlas and enters the foramen magnum
- **V4** pierces the dura (location somewhat variable) and immediately enters the subarachnoid space. Joins the contralateral VA at the vertebral confluens located at the lower pontine border to form the basilar artery (BA)

## Branches

► **Anterior meningeal.** Arises at body of C2 (axis), may feed chordomas or foramen magnum meningiomas, may also act as collateral in vascular occlusion

► **Posterior meningeal.** May be a source of blood for some dural AVMs (p. 1514)

► **Medullary (bulbar) aa.**

► **Posterior spinal**

► **Posterior inferior cerebellar artery (PICA) (largest branch).** Usually arises  $\approx$  10 mm distal to point where VA becomes intradural,  $\approx$  15 mm proximal to the vertebrobasilar junction (► Fig. 2.7)

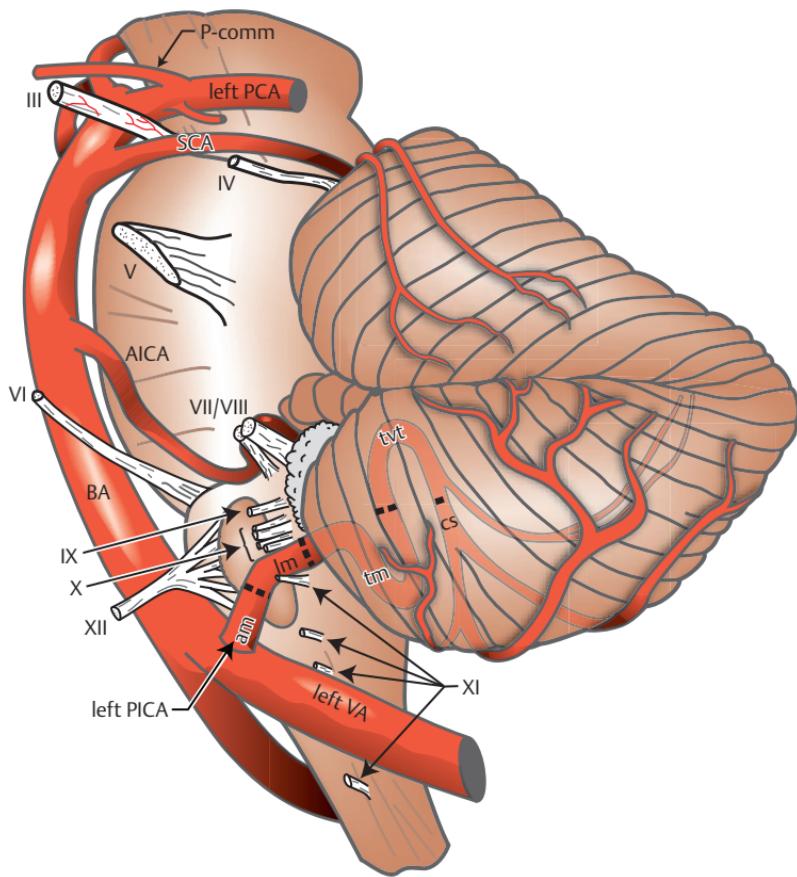
1. anatomic variants:
  - a) in 5–8% the PICA has an extradural origin
  - b) "AICA-PICA": origin is off basilar trunk (where AICA would usually originate)
2. 5 segments<sup>10</sup> (some systems describe only 4). During surgery, the first three must be preserved, but the last 2 may usually be sacrificed with minimal deficit<sup>11</sup>:
  - a) anterior medullary: from PICA origin to inferior olive prominence. 1 or 2 short medullary circumflex branches  $\Rightarrow$  ventral medulla
  - b) lateral medullary: to origin of nerves IX, X & XI. Up to 5 branches that supply brainstem
  - c) tonsillomedullary: to tonsillar midportion (contains *caudal loop* on angio)
  - d) telovelotonsillar (supratonsillar): ascends in tonsillomedullary fissure (contains *cranial loop* on angio)
  - e) cortical segments
3. 3 branches
  - a) choroidal a. (BRANCH 1) arises from cranial loop (*choroidal point*),  $\Rightarrow$  choroid plexus of 4th ventricle
  - b) terminal branches:
    - tonsillohemispheric (BRANCH 2)
    - inferior vermian (BRANCH 3) inferior inflection = *copular point* on angio

► **Anterior spinal**

## Basilar artery (BA)

Formed by the junction of the 2 vertebral arteries. Branches:

1. anterior inferior cerebellar artery (AICA): from lower part of BA, runs posterolaterally anterior to VI, VII & VIII. Often gives off a loop that runs into the IAC and gives off the labyrinthine artery and then emerges to supply the anterolateral inferior cerebellum and then anastomoses with PICA
  2. internal auditory (labyrinthine)
  3. pontine branches
  4. superior cerebellar a. (SCA)
    - a) sup. vermian
  5. posterior cerebral: joined by PComAs  $\approx$  1 cm from origin (the PComA is the major origin of the PCA in 15% and is termed "fetal" circulation, bilateral in 2%).
- 3 segments (named for surrounding cistern) and their branches:
- a) peduncular segment (P1)
    - mesencephalic perforating aa. ( $\Rightarrow$  tectum, cerebral peduncles, and these nuclei: Edinger-Westphal, oculomotor and trochlear)
    - interpeduncular thalamoperforators (1st of 2 groups of posterior thalamoperforating aa.)
    - medial post. choroidal (most from P1 or P2)



**Fig. 2.7 Intradural VA and PICA segments.** Lateral view. (Modified with permission from Lewis SB, Chang DJ, Peace DA, Lafrentz PJ, Day AL. Distal posterior inferior cerebellar artery aneurysms: clinical features and management. J Neurosurg 2002;97(4):756-66.)

- “artery of Percheron”: a rare anatomic variant<sup>12</sup> in which a solitary arterial trunk arising from the proximal segment of one PCA supplies the paramedian thalamus and rostral midbrain bilaterally
- b) ambient segment (P2)
  - lateral post. choroidal (most from P2)
  - thalamogeniculate thalamoperforators (2nd of 2 groups of posterior thalamoperforating aa.) → geniculate bodies + pulvinar
  - anterior temporal (anastomoses with anterior temporal br. of MCA)
  - posterior temporal
  - parieto-occipital
  - calcarine
- c) quadrigeminal segment (P3)
  - quadrigeminal & geniculate branches → quadrigeminal plate
  - post. pericallosal (splenial) (anastomoses with pericallosal of ACA)

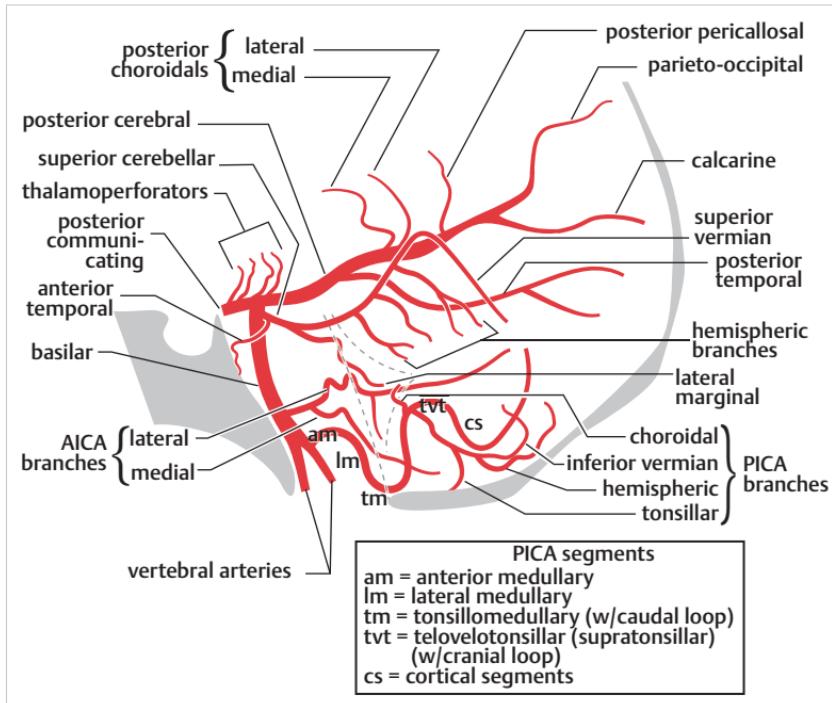


Fig. 2.8 Vertebrabasilar arteriogram. Lateral view. (Reprinted courtesy of Eastman Kodak Company.)

### Posterior cerebral artery (PCA)

See ▶ Fig. 2.8.

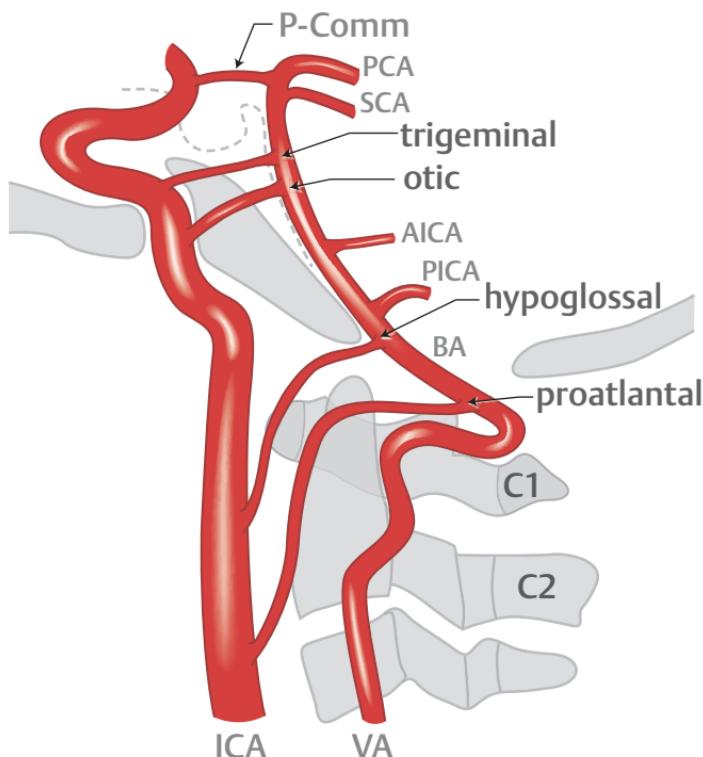
#### 2.2.6 Fetal carotid-vertebrobasilar anastomoses

PCoA artery: the “normal” (most common) anastomosis.

Persistent fetal anastomoses<sup>13</sup> (▶ Fig. 2.9) result from failure to involute as the VAs and PCoAs develop (order of involution: otic, hypoglossal, primitive trigeminal, proatlantal). Most are asymptomatic. However, some may be associated with vascular anomalies such as aneurysms or AVMs, and occasionally cranial nerve symptoms (e.g., trigeminal neuralgia with PPTA) can occur.

Four types (from cranial to caudal—the 1st 3 are named for the associated cranial nerve):

1. persistent primitive trigeminal artery (PPTA): seen in ≈ 0.6% of cerebral angiograms. The most common of the persistent fetal anastomoses (83%). May be associated with trigeminal neuralgia (p. 1857). Connects the cavernous carotid to the basilar artery. Arises from the ICA proximal to the origin of the meningohypophyseal trunk (50% go through sella, 50% exit the cavernous sinus & course with the trigeminal nerve) and connects to the upper basilar artery between AICA & SCA. The VAs may be small. Saltzman type 1 variant: the PCoAs are hypoplastic and the PPTA provides significant blood supply to the distributions of the distal BA, PCA and the SCAs (the basilar artery is often hypoplastic). Saltzman type 2: PCoA supplies PCA. Saltzman type 3: PPTA joins the SCA (instead of the BA). It is critical to recognize a PPTA before doing a Wada test (p. 1890) because of the risk of anesthetizing the brainstem, and in doing transsphenoidal surgery because of risk of arterial injury. May rarely be an explanation of posterior fossa symptoms in a patient with carotid disease
2. otic: the first to involute, and the rarest to persist (8 cases reported). Passes through IAC to connect petrous carotid to basilar artery



**Fig. 2.9 Fetal carotid-vertebrobasilar anastomoses.**

Normal adult arteries: P-Comm = posterior communicating, PCA = posterior cerebral, SCA = superior cerebellar, AICA = anterior inferior cerebellar, PICA = posterior inferior cerebellar, BA = basilar, ICA = internal carotid, VA = vertebral artery.

3. hypoglossal: connects petrous or distal cervical ICA (origin usually between C1–3) to VA. Travesses the hypoglossal canal. Does not cross foramen magnum
4. proatlantal intersegmental: connects cervical ICA to VA. May arise from: bifurcation of common carotid, ECA, or ICA from C2–4. Anastomosis with VA in suboccipital region. 50% have hypoplastic proximal VA. 40 cases reported

## 2.3 Cerebral venous anatomy

### 2.3.1 Supratentorial venous system

#### Major veins and tributaries

See ▶ Fig. 2.10 for angiogram and branches.

The left and right internal jugular veins (IJVs) are the major source of outflow of blood from the intracranial compartment. The right IJV is usually dominant. Other sources of outflow include orbital veins and the venous plexuses around the vertebral arteries. Diploic and scalp veins may act as collateral pathways, e.g., with superior sagittal sinus obstruction.<sup>14</sup> The following outline traces the venous drainage back from the IJVs.

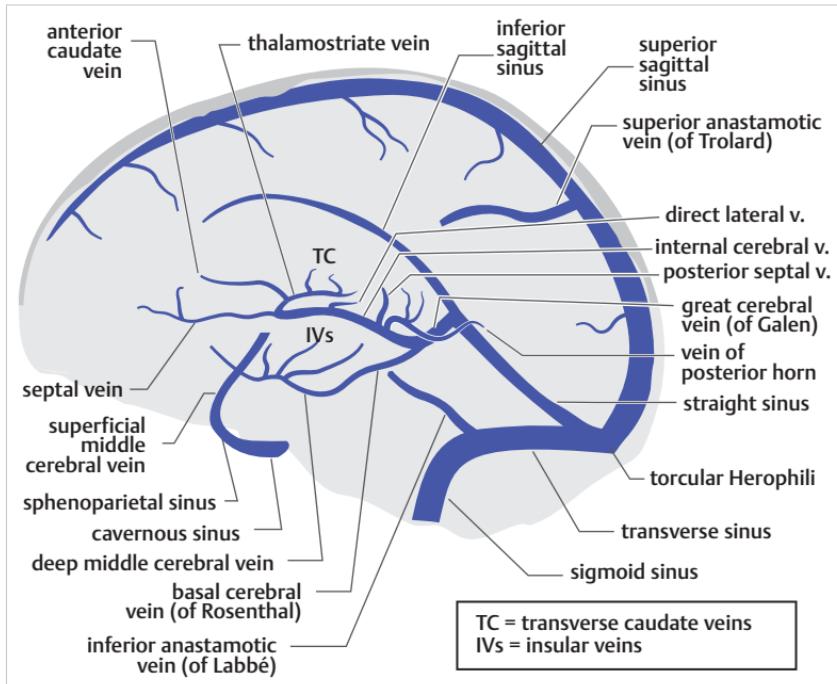


Fig. 2.10 Internal carotid venogram (lateral view). (Reprinted courtesy of Eastman Kodak Company.)

### Inferior petrosal sinus

Drains to IJV near junction with sigmoid sinus.

### Sigmoid sinus

#### Superior petrosal sinus

Terminates at sigmoid sinus within 1 cm of the junction of the sigmoid and transverse sinuses.

### Transverse sinus

The right transverse sinus is dominant (i.e., R > L) in 65%.

#### ► V. of Labbe. (Inferior anastomotic v.)

► **Confluence of sinuses.** (AKA torcular Herophili AKA torcula AKA confluens sinuum [TA]). Located at the internal occipital protuberance, a coming together of:

1. occipital sinus
2. superior sagittal sinus, fed by
  - a) v. of Trolard (superior anastomotic v.): the prominent superficial vein on the *non-dominant* side (Labbé is more prominent on the dominant side)
  - b) cortical veins
3. straight sinus, fed by
  - a) inferior sagittal sinus
  - b) great cerebral v. (of Galen)
    - pre-central cerebellar v.
    - basal vein of Rosenthal
    - internal cerebral v.: joined at the foramen of Monro (venous angle) by:
      - anterior septal v.
      - thalamostriate v.

## Cavernous sinus

2

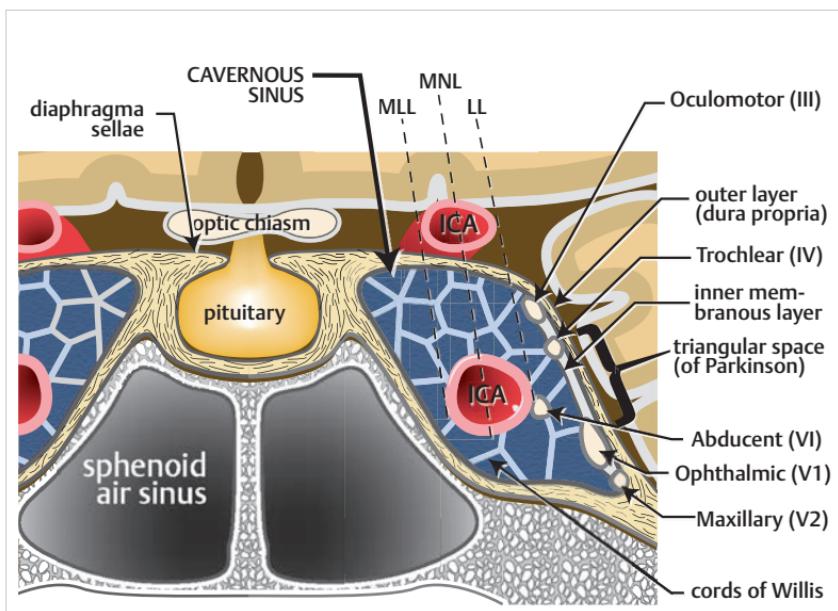


Fig. 2.11 Right cavernous sinus (colored in blue).

Stylized diagram of coronal cut through the cavernous sinuses.

3 lines passing through the intracavernous and supracavernous portion of the ICA may be used to classify the degree of tumor invasion: MLL (medial line) tangent to the medial borders of ICA cuts, MNL (median line) through middle of ICA cuts, & LL (lateral line) tangent to the lateral edges of ICA cuts (p. 884).

Originally named for its superficial resemblance to the corpora cavernosa. Although classical teaching depicts the cavernous sinus as a large venous space with multiple trabeculations, injection studies<sup>15</sup> and surgical experience<sup>16</sup> instead support the concept of the cavernous sinus as a plexus of veins. It is highly variable between individuals and from side-to-side. ► Fig. 2.11 is an oversimplified schematic of one section through the right cavernous sinus.

1. inflowing veins:
  - a) superior & inferior ophthalmic veins
  - b) superficial middle cerebral veins
  - c) sphenoparietal sinus
  - d) superior & inferior petrosal sinus
2. outflow:
  - a) sphenoparietal sinus
  - b) superior petrosal sinus
  - c) basilar plexus (which drains to the inferior petrosal sinus)
  - d) pterygoid plexus
  - e) the right and left cavernous sinuses communicate anteriorly and posteriorly via the circular sinus
3. contents<sup>17</sup>
  - a) oculomotor n. (cranial nerve III)
  - b) trochlear n. (IV)
  - c) ophthalmic division of trigeminal n. (V1)
  - d) maxillary division of trigeminal n. (V2): the only nerve of the cavernous sinus that doesn't exit the skull through the superior orbital fissure (it exits through foramen rotundum)
  - e) internal carotid artery (ICA). 3 segments within the cavernous sinus
    - posterior ascending segment: immediately after ICA enters the sinus

- horizontal segment: after ICA turns anteriorly (the longest segment of the intracavernous ICA)
- anterior ascending segment: ICA turns superiorly
- f) abducens n. (VI): the only nerve NOT attached to lateral dural wall, therefore sometimes considered as the only cranial nerve *inside* the cavernous sinus
- 4. triangular space (of Parkinson): superior border formed by Cr. N. III & IV, and the lower margin formed by V1 & VI (a landmark for surgical entrance to the cavernous sinus)<sup>18,19(p 3007)</sup>

### 2.3.2 Posterior fossa venous anatomy

See ▶ Fig. 2.12.

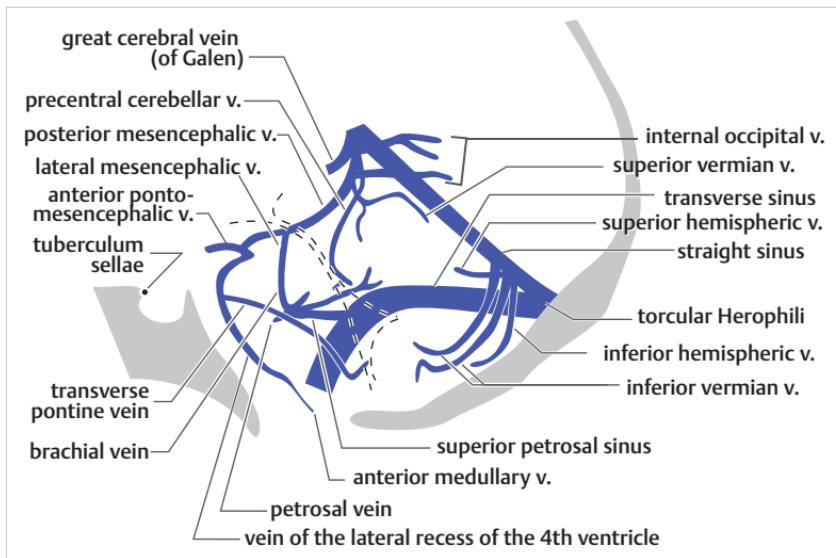
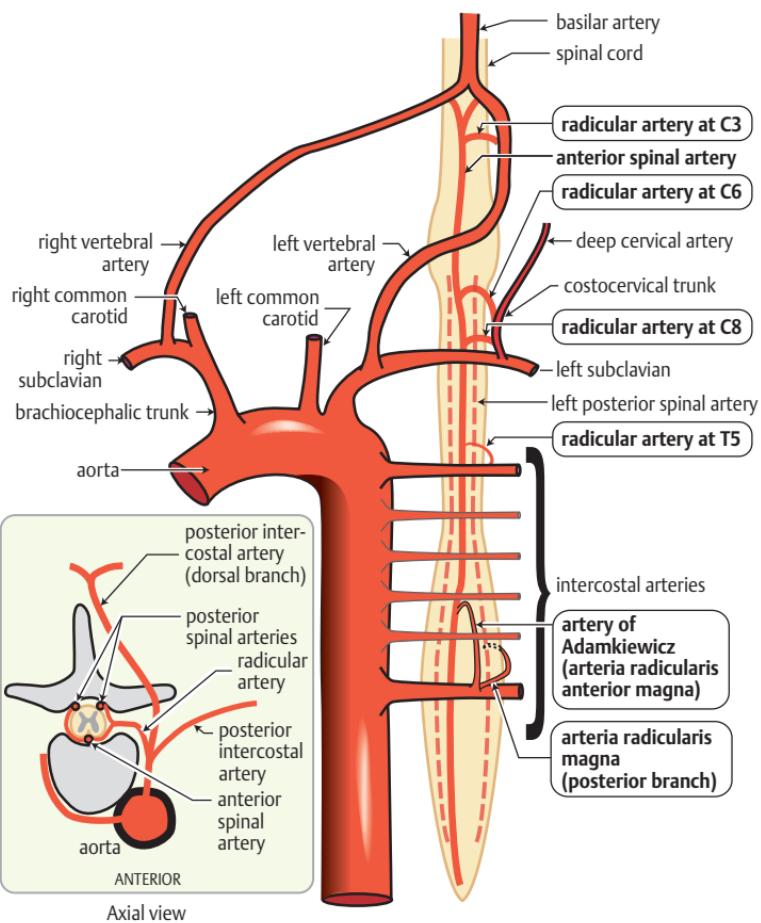


Fig. 2.12 Vertebrobasilar venogram. Lateral view. (Reprinted courtesy of Eastman Kodak Company.)

### 2.4 Spinal cord vasculature

See ▶ Fig. 2.13. Although a radicular artery from the aorta accompanies the nerve root at many levels, most of these contribute little flow to the spinal cord itself. The anterior spinal artery is formed from the junction of two branches, each from one of the vertebral arteries. It supplies blood to the anterior 2/3 of the spinal cord (▶ Fig. 2.14). Branches include sulcal arteries which also supply the anterior horns of the gray matter. Major contributions to the anterior spinal cord are from 6–9 radicular arteries in variable locations, which may include the following (“radiculomedullary arteries,” the levels listed are fairly consistent, but the side varies<sup>20(p 1180–1)</sup>):

1. C3—arises from vertebral artery
2. C6 and C8 (~ 10% of population lack an anterior radicular artery in lower cervical spine<sup>21</sup>)
  - a) C6—usually arises from deep cervical artery
  - b) C8—usually from costocervical trunk
3. T4 or T5
4. artery of Adamkiewicz AKA arteria radicularis anterior magna
  - a) the main arterial supply for the spinal cord from ~ T8 to the conus
  - b) located on the left in 80%<sup>22</sup>
  - c) situated between T9 & L2 in 85% (between T9 & T12 in 75%); in remaining 15% between T5 & T8 (in these latter cases, there may be a supplemental radicular artery further down)



**Fig. 2.13 Spinal cord arterial supply.** Schematic diagram. (Modified from Diagnostic Neuroradiology, 2nd ed., Volume II, pp. 1181, Taveras J M, Woods EH, editors, © 1976, the Williams and Wilkins Co., Baltimore, with permission.)

- d) usually fairly large, gives off cephalic and caudal branch (latter is usually larger) giving a characteristic hair-pin appearance on angiography

The paired posterior spinal arteries are less well-defined than the anterior spinal artery, and are fed by 10–23 radicular branches. Anastomotic vessels between the anterior and posterior spinal arteries are called vasocorona.

The midthoracic region has a tenuous vascular supply (“watershed zone”), possessing only the above noted artery at T4 or T5. It is thus more susceptible to vascular insults.

- **Anatomic variants.** Arcade of Lazorthes: normal variant where the anterior spinal artery joins with the paired posterior spinal arteries at the conus medullaris.

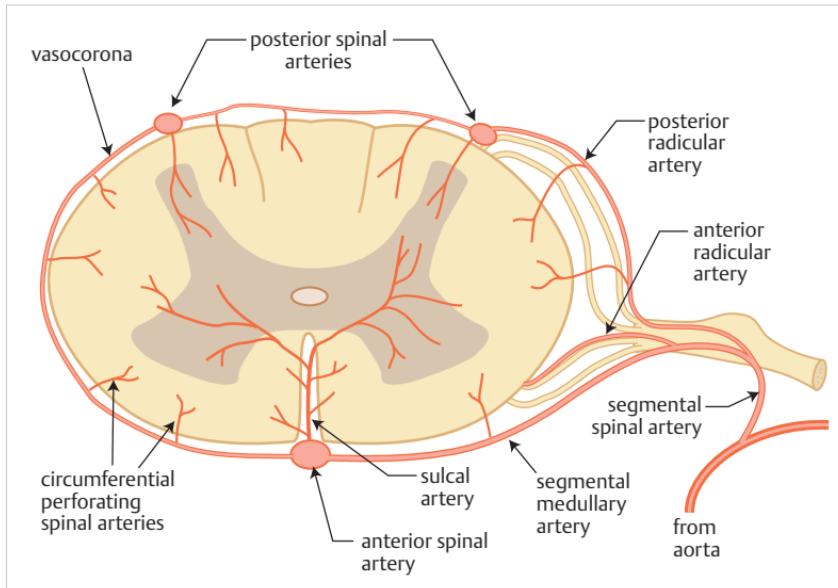


Fig. 2.14 Segmental blood supply to the spinal cord.

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## 3 Neurophysiology and Regional Brain Syndromes

3

### 3.1 Neurophysiology

#### 3.1.1 Blood-brain barrier

##### General information

The passage of water-soluble substances from the blood to the CNS is limited by tight junctions (zonulae occludentes) which are found between cerebral capillary endothelial cells, limiting penetration of the cerebral parenchyma (blood-brain barrier, BBB), as well as between choroid plexus epithelial cells (blood-CSF barrier).<sup>1</sup> A number of specialized mediated transport systems allow transmission of, among other things, glucose and certain amino acids (especially precursors to neurotransmitters).

The efficacy of the BBB is compromised in certain pathological states (e.g., tumor, infection, trauma, stroke, hepatic encephalopathy...), and can also be manipulated pharmacologically (e.g., hypertonic mannitol increases the permeability, whereas steroids reduce the penetration of small hydrophilic molecules).

The BBB is absent in the following areas: circumventricular organs<sup>2</sup> (area postrema, median eminence of the hypothalamus, neurohypophysis (posterior pituitary), pineal gland...) choroid plexus, tuber cinereum, and preoptic recess.

Means of assessing the integrity of the BBB:

- visible dyes: Evan's blue, fluorescein
- radioopaque dyes (imaged with CT scan<sup>3</sup>): iodine (protein-bound contrast agent)
- paramagnetic (imaged on MRI): gadolinium (protein-bound contrast agent)
- microscopic: horseradish peroxidase
- radiolabeled: albumin, sucrose

##### Cerebral edema and the blood-brain barrier

Two basic types of cerebral edema; diffusion-weighted MRI (p. 243) may be able to differentiate:

1. cytotoxic: BBB is closed, therefore no protein extravasation, therefore no enhancement on CT or MRI. Cells swell then shrink. Classic examples: cell death due to head trauma or stroke
2. vasogenic: BBB is disrupted. Protein (serum) leaks out of vascular system, and therefore may enhance on imaging. Extracellular space (ECS) expands. Cells are stable. Responds to corticosteroids (e.g., dexamethasone). Seen, e.g., surrounding metastatic brain tumor

Cerebral edema related to ischemia may be a combination of the above. BBB is closed initially, but then may open. ECS shrinks then expands. Fluid extravasates late. May cause delayed deterioration following intracerebral hemorrhage (p. 1615)

#### 3.1.2 Language and speech function

##### Localizing language function

Caveat: Language function cannot be reliably localized on anatomic grounds alone due to individual variability. In order to perform maximal brain resections (e.g., for tumor) while minimizing the risk of aphasia, techniques such as awake intraoperative brain mapping (p. 1735)<sup>4</sup> need to be employed.

##### Classic model

The model of speech and language function that was accepted for years was that of 2 primary areas, Wernicke's area (Brodmann area 40 and part of 39), which subserved language, and Broca's area (Brodmann area 44), which was considered the "motor speech" area, both located in the dominant hemisphere (► Fig. 1.1). These two areas were thought to communicate via the arcuate fasciculus (p. 246).

Lesions in Wernicke's area were classically thought to produce "receptive aphasia," wherein the patient could not understand language. Some of these patients demonstrated "fluent aphasia," in which they generated speech without content. Conversely, patients with lesions in Broca's area would exhibit "expressive aphasia," wherein they could comprehend language, but lacked the motor

ability to generate speech. "Conduction aphasia" was considered to be the result of damage to the arcuate fasciculus.

### Dual stream model of language

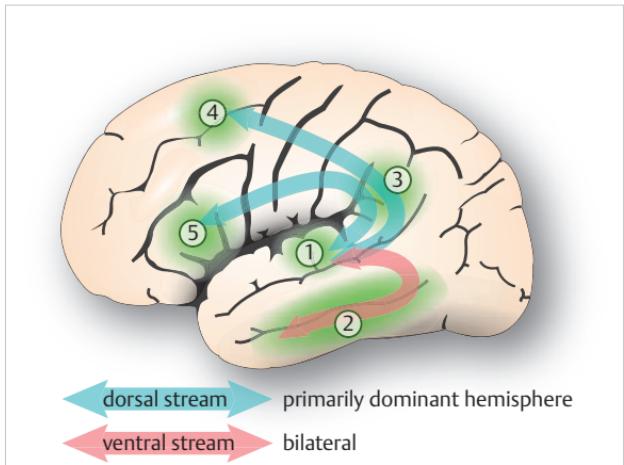
A model that incorporates current understanding of speech and language<sup>5</sup> (► Fig. 3.1).

Region 1: (primary auditory areas) initial processing of language.

The ventral stream flows from Region 1 to Region 2 (anterior and middle temporal lobe) and is involved in speech recognition and lexical concepts.

The dorsal stream maps phonological information onto motor areas (Regions 4 (premotor cortex) & 5 (~ Broca's area)).

Regions 3 (~ Wernicke's area), 4 & 5 are all involved in dorsal stream processing.



**Fig. 3.1** Dual stream model of language function.

See text for descriptions of numbered green shaded Regions 1–5.

### 3.1.3 Babinski sign and Hoffmann sign

#### Introduction

Although the Babinski sign is regarded as the most famous sign in neurology, there is still disagreement over what constitutes a normal response and when abnormal responses should occur.<sup>6</sup> The following represents one interpretation.

The plantar reflex (PR) (AKA Babinski sign after Joseph François Félix Babinski [1857–1932], a French neurologist of Polish descent) is a primitive reflex, present in infancy, consisting of extension of the great toe in response to a noxious stimulus applied to the foot. The small toes may fan, but this is not a consistent nor clinically important component. The PR disappears usually at ≈ 10 months of age (range: 6 mos to 12 yrs), presumably under inhibitory control as myelination of the CNS occurs, and the normal response then converts to plantarflexion of the great toe. An upper motor neuron (UMN) lesion anywhere along the pyramidal (corticospinal) tract from the motor strip down to ≈ L4 will result in a loss of inhibition, and the PR will be "unmasked" producing extension of the great toe. With such an UMN lesion, there may also be associated flexor synergy resulting in concurrent dorsiflexion of the ankle, and flexion of the knee and hip (AKA triple flexor response) in addition to extension of the great toe.

#### Neuroanatomy

The afferent limb of the reflex originates in cutaneous receptors restricted to the first sacral dermatome (S1) and travels proximally via the tibial nerve. The spinal cord segments involved in the reflex-arc lie within L4–2. The efferent limb to the toe extensors travels via the *peroneal nerve*.

**Table 3.1** Differential diagnosis of the plantar reflex (PR)**Etiologies**

- spinal cord injuries<sup>a</sup>
- cervical spinal myelopathy
- lesions in motor strip or internal capsule (stroke, tumor, contusion...)
- subdural or epidural hematoma
- hydranencephaly
- toxic-metabolic coma
- seizures
- trauma
- TIA
- hemiplegic migraine
- motor neuron disease (ALS)

<sup>a</sup>In spinal cord injuries, the PR may initially be absent during the period of spinal “shock” (p. 1119)

**Differential diagnosis****Etiologies**

Lesions producing a PR need not be structural, but may be functional and reversible. The roster of possible etiologies is extensive, some are listed in ► Table 3.1.

**Eliciting the plantar reflex, and variations**

The optimal stimulus consists of stimulation of the lateral plantar surface and transverse arch in a single movement lasting 5–6 seconds.<sup>7</sup> Other means for applying noxious stimuli may also elicit the plantar reflex (even outside the S1 dermatome, although these do not produce toe flexion in normals). Described maneuvers include Chaddock (scratch the lateral foot; positive in 3% where plantar stimulation was negative), Schaeffer (pinch the Achilles tendon), Oppenheim (slide knuckles down shin), Gordon (momentarily squeeze lower gastrocnemius), Bing (light pinpricks on dorsolateral foot), Gonda or Stronsky (pull the 4th or 5th toe down and out and allow it to snap back).

**Hoffmann's (or Hoffmann's or Hoffmann) sign**

Attributed to Johann Hoffmann, a German neurologist practicing in the late 1800s. May signify a similar UMN interruption to the upper extremities. Elicited by flicking downward on the nail of the middle or ring finger: a positive (pathologic) response consists of involuntary flexion of the adjacent fingers and/or thumb (may be weakly present in normals).<sup>8</sup> Differs from the plantar reflex since it is monosynaptic (synapse in Rexed lamina IX).

Can sometimes be seen as normal in a young individual with diffusely brisk reflexes & positive jaw jerk, usually symmetric. When present pathologically, represents disinhibition of a C8 reflex,  indicates lesion above C8.

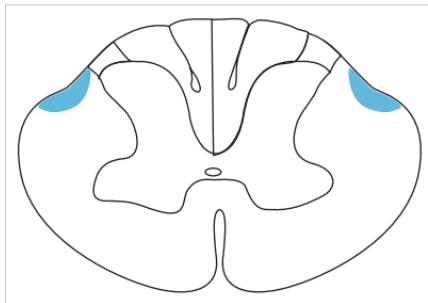
Hoffmann sign was observed in 68% of patients operated on for cervical spondylosis myelopathy.<sup>8</sup> In 11 patients presenting with lumbar symptoms but no myelopathy, a bilateral Hoffmann sign was associated with occult cervical spinal cord compression in 10 (91%).<sup>8</sup> The Hoffmann test has a sensitivity of 33–68%, a specificity of 59–78%, a positive predictive value of 26–62% and a negative predictive value of 67–75%.<sup>9</sup>

Conclusion: Hoffmann sign has too low a predictive value for it to be relied upon by itself as a screening tool for, or as an indication of the presence of, myelopathy.<sup>9,10</sup>

**3.1.4 Bladder neurophysiology****Central pathways**

The primary coordinating center for bladder function resides within the nucleus locus caeruleus of the pons. This center synchronizes bladder contraction with relaxation of the urethral sphincter during voiding.<sup>11</sup>

Voluntary cortical control primarily involves inhibition of the pontine reflex, and originates in the anteromedial portion of the frontal lobes and in the genu of the corpus callosum. In an uninhibited bladder (e.g., infancy), the pontine voiding center functions without cortical inhibition and the detrusor muscle contracts when the bladder reaches a critical capacity. Voluntary suppression from the cortex via the pyramidal tract may contract the external sphincter and may also inhibit detrusor contraction. Cortical lesions in this location → urgency incontinence with inability to suppress the micturition reflex.<sup>12</sup> (p 1031)



**Fig. 3.2 Location of spinal cord bladder efferents in the spinal cord (shaded).**

Efferents to the bladder travel in the dorsal portion of the lateral columns of the spinal cord (shaded areas in ► Fig. 3.2).

## Motor

There are two sphincters that prevent the flow of urine from the bladder: internal (autonomic, involuntary control), and external (striated muscle, voluntary control).

### Parasympathetics (PSN)

The detrusor muscle of the bladder contracts and the internal sphincter relaxes under PSN stimulation. PSN preganglionic cell bodies reside in the intermediolateral gray of spinal cord segments S2–4. Fibers exit as ventral nerve roots and travel via pelvic splanchnic nerves (*nervi erigentes*) to terminate on ganglia within the wall of the detrusor muscle in the body and dome of the bladder. These are the target receptors of anticholinergic medications and onabotulinumtoxinA (Botox™).<sup>13</sup>

### Sympathetics

Sympathetic cell bodies lie within the intermediolateral gray column of lumbar spinal cord from segments T12–L2. Preganglionic axons pass through the sympathetic chain (without synapsing) to the inferior mesenteric ganglion. Postganglionic fibers pass through the inferior hypogastric plexus to the bladder wall and internal sphincter. Sympathetics heavily innervate the bladder neck and trigone. Stimulation of alpha-1 adrenergic receptors results in bladder neck closure allowing bladder filling and urine storage. Beta-3 adrenergic receptor stimulation results in detrusor smooth muscle relaxation during bladder filling and storage.<sup>14</sup>

Pelvic nerve stimulation → increased sympathetic tone → detrusor relaxation & increased bladder neck tone (allowing a larger volume to be accommodated).

### Somatic nerves

Somatic voluntary control descends in the pyramidal tract to synapse on motor nerves in S2–4, and then travels via the pudendal nerve to the external sphincter. This sphincter may be voluntarily contracted, but relaxes reflexly with opening of the internal sphincter at the initiation of micturition. Primarily maintains continence during ↑ vesical pressure (e.g., Valsalva).

## Sensory

Bladder wall stretch receptors sense bladder filling and send afferent signals via myelinated A-delta fibers (aid sensation during filling and emptying) and unmyelinated C fibers (sense noxious stimuli, thought to be involved in involuntary detrusor overactivity in neurogenic bladder<sup>15</sup>). These fibers run through the pelvic, pudendal, and hypogastric nerves to spinal cord segments T10–2 & S2–4. Fibers ascend primarily in the spinothalamic tract.

## Urinary bladder dysfunction

### General information

Bladder management is vital to protect the kidneys from obstruction and subsequent loss of renal function.

**Neurogenic bladder:** bladder dysfunction due to lesions in the central or peripheral nervous systems. Clinical manifestations differ based on the location of the lesion.

- detrusor hyperreflexia (detrusor overactivity (DO)): involuntary contraction of the detrusor muscle → sensation of urgency & possible urge incontinence
- detrusor-sphincter dyssynergia (DSD): detrusor contraction with inappropriate activation of the external urethral sphincters
- detrusor areflexia: loss of bladder tone → inability to contract sufficient for micturition<sup>16</sup>

3

### Specific injuries affecting the bladder

Classic descriptions of location of lesions are described below; however, over 50% of patients do not have classic presentation or symptoms.

1. supraspinal (lesions above the brainstem): loss of centrally mediated inhibition of the pontine voiding reflex. Voluntary inhibition of micturition is lost. Coordination of detrusor filling and contraction with smooth and striated urinary sphincters is intact, allowing maintenance of normal bladder pressures with low risk of high pressure renal damage. Patients have DO without DSD. Detrusor hypertrophy is less pronounced. Symptoms: urinary frequency or urgency, urgency incontinence, and nocturia.<sup>11</sup> If sensory pathways are interrupted, unconscious incontinence occurs (insensate incontinence AKA incontinence of the unaware type). Voluntary bladder emptying may be maintained and timed voiding together with anticholinergic medications (see below) are used in management. Areflexia may sometimes occur
2. complete (or near complete) spinal cord lesions:
  - a) suprasacral (lesion *above* the S2 spinal cord level, which is ≈ T12/L1 vertebral body level in an adult): loss of innervation to the pontine micturition center results in reflexive voiding modulated by the sacral voiding center (located in the conus medullaris).<sup>17</sup>  
Etiologies: spinal cord injuries, tumors, transverse myelitis.
    - initially following spinal cord injury, there may be spinal shock. During spinal shock (p. 1119), the bladder is acontractile and areflexic (detrusor areflexia); sphincter tone usually persists and urinary retention is the rule (urinary incontinence generally does not occur except with overdistention). This requires catheter drainage (intermittent or indwelling) due to retention until the spinal shock resolves typically within 6 months<sup>17</sup>
    - after spinal shock subsides, most develop *detrusor hyperreflexia* – involuntary bladder contractions without sensation (automatic bladder), smooth sphincter synergy, but striated dyssynergy (involuntary contraction of the external sphincter during voiding which produces a functional outlet obstruction with poor emptying and high vesical pressures which is transmitted to the kidneys and may result in loss of renal function). Bladder fills and empties spontaneously due to reflexive voiding.<sup>17</sup> Bladder hypertrophy occurs due to contraction against a closed sphincter and bladder storage pressure increases. Patients have DO with DSD. Management goals: decrease bladder pressures and preserve renal function, usually with pharmaceuticals and intermittent catheterizations. The frequency of bladder drainage is determined by urodynamic pressures to ensure urine volumes consistent with safe storage pressures (see below).
  - b) infrasacral lesions (lesion *below* the S2 spinal cord level): includes injury to conus medullaris, cauda equina or peripheral nerves (formerly referred to as lower motor neuron lesions). Etiologies: large HLD, trauma with compromise of spinal canal or peripheral nerve injuries (traumatic or iatrogenic with pelvic surgery). Detrusor areflexia usually ensues, and do not have voluntary or involuntary bladder contractions. Reduced urinary flow rate or retention results, and voluntary voiding may be lost. Overflow incontinence develops. Usually associated with loss of bulbocavernosus (BCR) and anal wink reflexes (preserved in suprasacral lesions, except when spinal shock is present (p. 1119)) and perineal sensory loss. NB: up to 20% of neurologically normal patients do not exhibit a BCR<sup>18</sup>
3. specific disease processes
  - a) herniated lumbar disc (p. 1250): most consist initially of difficulty voiding, straining, or urinary retention. Later, irritative symptoms may develop
  - b) spinal stenosis (lumbar or cervical): urologic symptoms vary, and depend on the spinal level (s) involved and the type of involvement (e.g., in cervical spinal stenosis, detrusor hyperactivity or underactivity may occur depending on whether the involvement of the micturition neural axis is compression of the inhibitory reticulospinal tracts or myelopathy involving the posterior funiculus)
  - c) cauda equina syndrome (p. 1254): usually produces urinary retention, although sometimes incontinence may occur (some cases are overflow incontinence)

- d) peripheral neuropathies: such as with diabetes, usually produce impaired detrusor activity
- e) neurospinal dysraphism: most myelodysplastic patients have an areflexic bladder with an open bladder neck. The bladder usually fills until the resting residual fixed external sphincter pressure is exceeded and the leakage occurs
- f) multiple sclerosis: 50–90% of patients develop voiding symptoms at some point. The demyelination primarily involves the posterior and lateral columns of the cervical spinal cord. Detrusor hyperreflexia is the most common urodynamic abnormality (in 50–99% of cases), with bladder areflexia being less common (5–20%). Patients have DO with DSD without upper tract injury or loss of compliance
- g) tethered cord: urologic complaints are present on initial presentation 30–70% of the time. Most common urologic symptoms are urgency and incontinence. Urodynamic findings show DO with DSD.<sup>19</sup> Urinary dysfunction improves in more than half, but not all patients, after surgical correction<sup>20</sup>

3

## Urinary retention

Etiologies of urinary retention:

1. bladder outlet obstruction (a brief differential diagnosis list is presented here)
  - a) urethral stricture: retention tends to be progressive over time
  - b) prostatic enlargement in males:
    - benign prostatic hypertrophy (BPH) & prostate cancer: retention tends to be progressive over time
    - acute prostatitis: onset of retention may be sudden
  - c) women: bladder or vaginal prolapse which can produce a urethral kink
  - d) obstructing thrombus from hematuria (clot retention)
  - e) bladder calculi
  - f) bladder or urethral foreign bodies
  - g) urethral cancer: rare
2. detrusor areflexia or hypotonia
  - a) spinal cord lesion
    - trauma
    - tumor
    - myelomeningocele
  - b) cauda equina syndrome (p. 1254)
  - c) medications: anticholinergics, narcotics
  - d) diabetes mellitus (autonomic neuropathy)
  - e) herpes zoster at the level of the sacral dorsal root ganglia<sup>21</sup> (p 967)
3. postoperative urinary retention (POUR): occurs in ~ 4% of all surgeries, and 20–40% in neurosurgical patients after general anesthesia.<sup>22,23</sup> Felt to be secondary to combination of patient predisposition (eg BPH) along with anesthetic. Propofol, narcotics, benzodiazepines, inhaled anesthetics, and local intrathecal and epidural have all been shown to impact bladder contraction and coordination of micturition. POUR should be managed with CIC or indwelling catheterization along with alpha blockers (see below) in men. Voiding trial may be done as soon as postoperative day 1 to avoid prolonged catheterization but keeping the Foley for 3–4 days has been shown to decrease need for replacement of the catheter.<sup>23</sup> POUR may persist > 1 week. Preoperative use of alpha blockers in at risk patients has shown protective against POUR in some studies, but not significant difference in other studies.<sup>24</sup> Urgent intervention is recommended to avoid long term sequela of bladder distention

## Evaluation of bladder function

### Urodynamics (UDS)

Usually combined with X-ray (cystometrogram [CMG]) or fluoro (videourodynamics). Measures intravesicular pressures during retrograde bladder filling through a urethral catheter, usually combined with sphincter electromyography. Assesses intravesical pressures during filling and voiding. Objectively assesses detrusor muscle at time of sensation to void. Most importantly, assesses bladder compliance, bladder storage pressures and risk for long term upper tract deterioration. Bladder pressures: < 40 cm H<sub>2</sub>O is the cut off for safe storage pressures.<sup>25</sup> If bladder pressure > 40 cm H<sub>2</sub>O during storage of urine, there is a high risk of progressive CKD. Routine UDS can help ensure safe management of a neurogenic bladder. UDS can also be used in the neurologically intact patient to determine if urinary retention is secondary to obstruction versus bladder areflexia.<sup>26</sup>

## Voiding cystourethrogram and intravenous pyelography (IVP)

Voiding cystourethrogram (VCUG) detects urethral pathology (diverticula, strictures...), abnormalities of bladder (diverticula, detrusor trabeculations associated with long-standing contractions against high resistance...), and vesical-ureteral reflux. VCUG can be performed at the time of UDS (video urodynamics).

3

## Urologic follow-up

Routine follow-up is needed to ensure bladder pressures < 40 cm H<sub>2</sub>O, and subsequently for periodic renal imaging and monitoring of serum creatinine.

Changes in voiding symptoms should trigger prompt reevaluation.

NB: patient with indwelling catheters (Foley, suprapubic tube...) or intermittent catheterization will have colonization of their urine. Treatment for positive urine cultures is only indicated when related symptoms develop or when undergoing instrumentation.

## Pharmacologic treatment for bladder dysfunction

### Muscarinic anticholinergics

Bladder contraction is produced by ACh-mediated stimulation of postganglionic parasympathetic muscarinic cholinergic receptors on bladder smooth muscle. Anticholinergics bind M2 and M3 choline receptors and prevent stimulation. This increases bladder capacity by 50 ml and decreases bladder storage pressures by 15 cm H<sub>2</sub>O.<sup>27</sup> They are a pillar in treating neurogenic bladders.

All are contraindicated in glaucoma as anticholinergics induce mydriasis. Overdosage results in the classic anticholinergic symptoms ("red as a beet, hot as a stove, dry as a rock, mad as a hatter"). Use is often limited by side effects including dry mouth, constipation, dry eyes, blurry vision, urinary retention & indigestion.

Anticholinergics may negatively impact cognition and memory.<sup>28,29</sup> Newer agents (tolterodine, darifenacin) have less impact on memory. Trospium, a quaternary amine, crosses the blood-brain barrier less readily than other anticholinergics and may have less negative impact.<sup>29</sup>

### Drug info: Oxybutynin (Ditropan®)

Widely prescribed agent. Combines anticholinergic activity with independent musculotropic relaxant effect and local anesthetic activity. Immediate release (IR) produces the most side effects (including cognitive) in the class, which are better with extended release (ER).

**R** Adult IR: 5–30 mg divided TID. ER: 10–30 mg/d. Patch (Oxytrol) 3.7 mg q 3 d. **R** Peds: not recommended for age < 5 years; usual dose is 5 mg BID (maximum 5 mg TID). **Supplied:** 5 mg tablets, 5 mg/5 ml syrup.

### Drug info: Tolterodine (Detrol®)

Milder side effects than oxybutynin, but may also be less effective.<sup>30</sup> Side effects with IR > ER.

**R** IR: 2–8 mg PO divided BID. Can be lowered to 1 mg PO BID in some patients. ER: 2–8 mg qd. **Supplied:** 1 & 2 mg tablets. Detrol® LA 2 & 4 mg capsule

### Drug info: Solifenacin (Vesicare®)

Most constipation in class.

**R** 5–10 mg qd. **Supplied:** ER & 10 mg tablets.

### Drug info: Darifenacin (Enablex®)

**R** 5–10 mg po qd. **Supplied:** ER 7.5 & 15 mg tablets.

## Drug info: Fesoterodine (Toviaz®)

R4 mg PO qd, may increase up to 8 mg po qd PRN. Supplied: ER 4 & 8 mg tablets.

## Drug info: Trospium (Sanctura®, Sanctura® XR)

RIR: 20–60 mg po divided BID, ER: capsule 60 mg po qd. Supplied: IR: 20 mg tablets, ER: 60 mg capsule.

3

### Alpha blockers

Alpha-adrenoreceptor antagonists block alpha-1 receptors on the bladder neck which results in smooth muscles relaxation and decreased bladder outlet resistance. This increases bladder compliance and decreases storage pressures with neurogenic bladders. Terazosin also decreases the frequency and severity of symptoms of autonomic dysreflexia.<sup>27</sup> Side effects include postural hypotension, rhinitis and retrograde ejaculation. Hypotension is more common in less selective alpha blockers and therefore dose escalation is required with terazosin and doxazosin.

## Drug info: Tamsulosin (Flomax®)

A prostate alpha<sub>1A</sub> adrenoreceptor antagonist. Used to treat voiding difficulties resulting from outlet obstruction due to benign prostatic hypertrophy (BPH). Has some effectiveness in women via other mechanisms. Similar to terazosin (Hytrin®) and doxazosin (Cardura®), but has an advantage for acute relief because the dose of tamsulosin does not need to be gradually ramped up (it can be started at the therapeutic dose). It takes at least 5–7 days to work.

**Side effects :** very few. Rhinitis, retrograde or diminished ejaculation, or postural hypotension may occur.<sup>31</sup>

**R:** 0.4 mg PO qd (usually given 30 minutes after the same meal each day). If there is no response by 2–4 weeks, a dose of 0.8 mg PO qd can be tried.<sup>31</sup>

### Botulinum toxin (Botox™)

Botulinum toxin A (BTX-A) inhibits acetylcholine exocytosis from parasympathetic postganglionic nerves to the M2 and M3 receptors of the detrusor, inhibiting detrusor contraction. BTX-A (100–200u) is injected into the detrusor muscle during cystoscopy. It decreases overactivity, urgency, and storage pressures.<sup>32</sup> Efficacy lasts 3–12 months and repeat injections are required. Maximum Botox dose is 360 u per 90 day from all sources. Side effects include urinary tract infection and urinary retention. In patient not already managed with catheterization, must be aware of the risk of urinary retention and need for temporary catheterization in 2–20% of patients.<sup>32</sup> This is usually self-limited to weeks or months as the BTX-A wears off.

### Neuromodulation for bladder dysfunction

Permanent implantable neuromodulation (e.g., InterStim™ by Medtronic) is indicated for refractory urinary urgency, frequency, urge incontinence, non-obstructive urinary retention, and fecal incontinence. If a trial with a temporary lead placed adjacent to the sacral nerve via the S3 foramen produces > 50% reduction in symptoms, it is connected to an implantable pulse generator. Mechanism of action is poorly understood but may modulate the afferent signals of the micturition reflex.<sup>33</sup> Improvement in symptoms is seen in up to 70% of patients with complete resolution in incontinence around 39%.<sup>34</sup> Contraindications to implantation include failure to improve with trial and the likely need for repeated MRIs in the future (the device is MRI conditional for head only with ≤ 1.5 tesla MRI).

## Bladder management after acute urinary retention

In situations where there is urinary retention (e.g., following cauda equina compression) with some prospect of return of function (e.g., following surgery for acute cauda equina compression) the following bladder management regimen may be employed:

- early bladder management is key to avoid bladder overdistention & permanent injury to the detrusor
- use of intermittent catheterization (if able to be performed), or indwelling catheter (Foley or suprapubic) to drain bladder with a goal of < 400 ml each time (or volumes lower than patient's safe bladder capacity if known)
- initiate alpha blockers (e.g., tamsulosin (Flomax®) (p.97) 0.4 mg PO q d (see above))
- urology consultation for assistance with long-term follow-up & bladder management

## 3.2 Regional brain syndromes

This section serves to briefly describe typical syndromes associated with lesions in various areas of the brain. Unless otherwise noted, the described syndromes occur with *destructive* lesions.

### 3.2.1 Overview

1. frontal lobe
  - a) unilateral injury:
    - may produce few clinical findings except with very large lesions
    - bilateral or large unilateral lesions: apathy, abulia
    - the frontal eye field (for contralateral gaze) is located in the posterior frontal lobe (Br. area 8, shown as the striped area in ► Fig. 1.1). Destructive lesions impair gaze to the contralateral side (patient looks *toward* the side of the lesion), whereas irritative lesions (i.e., seizures) cause the center to activate, producing contralateral gaze (patient looks *away* from the side of the lesion). See also **Extraocular muscle (EOM) system** (p.596) for more details.
  - b) bilateral injury: may produce apathy, abulia
  - c) olfactory groove region: may produce Foster Kennedy syndrome (p. 100)
  - d) prefrontal lobes control "executive function": planning, prioritizing, organizing thoughts, suppressing impulses, understanding the consequences of decisions
2. parietal lobe: major features (see below for details)
  - a) either side: cortical sensory syndrome, sensory extinction, contralateral homonymous hemianopia, contralateral neglect
  - b) dominant parietal lobe lesion (left in most): language disorders (aphasias), Gerstmann syndrome (p.99), bilateral astereognosis
  - c) non-dominant parietal lobe lesions: topographic memory loss, anosognosia and dressing apraxia
3. occipital lobe: homonymous hemianopsia
4. cerebellum
  - a) lesions of the cerebellar hemisphere cause ataxia in the *ipsilateral* limbs
  - b) lesions of the cerebellar vermis cause truncal ataxia
5. brainstem: usually produces a mixture of cranial nerve deficits and long tract findings (see below for some specific brainstem syndromes)
6. pineal region
  - a) Parinaud's syndrome (p. 101)

### 3.2.2 Parietal lobe syndromes

See reference.<sup>35</sup> (p 308–12)

#### Parietal lobe anatomy

The parietal lobe is located behind the central sulcus, above the Sylvian fissure, merging posteriorly into the occipital lobe (the border on the medial surface of the brain is defined by a line connecting the parieto-occipital sulcus to the pre-occipital notch).

## Parietal lobe neurophysiology

- either side: anterior parietal cortex organizes tactile precepts (probably contralateral) and integrates with visual and auditory sensation to build awareness of body and its spatial relations
- dominant side (on left in 97% of adults): understanding language, includes “cross-modal matching” (auditory-visual, visual-tactile, etc.). Dysphasia present with dominant lobe lesions often impedes assessment
- non-dominant side (right in most): integrates visual and proprioceptive sensation to allow manipulation of body and objects, and for certain constructional activities

## Clinical syndromes of parietal lobe disease

### Overview

- unilateral* parietal lobe disease (dominant or non-dominant):
  - cortical sensory syndrome (see below) and sensory extinction (neglecting 1 of 2 simultaneously presented stimuli). Large lesion → hemianesthesia
  - congenital injury → mild hemiparesis & contralateral muscle atrophy
  - homonymous hemianopia or visual inattentiveness
  - occasionally: anosognosia
  - neglect of contralateral half of body and visual space (more common with right side lesions)
  - abolition of *optokinetic nystagmus* to one side
- additional effects of dominant parietal lobe lesion (left in most people):
  - language disorders (aphasias)
  - speech-related or verbally mediated functions, e.g., cross-modal matching (e.g., patient understands spoken words and can read, but cannot understand sentences with elements of relationships)
  - Gerstmann syndrome, named for Josef Gerstmann (1887-1969). Localizes to the angular and supramarginal gyrus (Brodmann area 39 & 40 respectively) of the dominant hemisphere.  
Classically:
    - agraphia without alexia (patients cannot write but can still read)
    - left-right confusion
    - digit agnosia: inability to identify finger by name
    - acalculia (or dyscalculia): difficulty with math
  - tactile agnosia (bilateral astereognosis)
  - bilateral ideomotor apraxia (inability to carry out verbal commands for activities that can otherwise be performed spontaneously with ease)
- additional effects of non-dominant parietal lobe lesions (usually right):
  - topographic memory loss
  - anosognosia and dressing apraxia

## Cortical sensory syndrome

Lesion of postcentral gyrus, especially area that maps to hand.

- sensory deficits:
  - loss of position sense and of passive movement sense
  - inability to localize tactile, thermal, and noxious stimuli
  - astereognosis (inability to judge object size, shape, and identity by feel)
  - agnosesthesia (cannot interpret numbers written on hand)
  - loss of two point discrimination
- preserved sensations: pain, touch, pressure, vibration, temperature
- other features
  - easy fatigability of sensory perceptions
  - difficulty distinguishing simultaneous stimulations
  - prolongation of superficial pain with hyperesthesia
  - touch hallucinations

## Anton-Babinski syndrome

A unilateral asomatognosia. May seem more common with non-dominant (usually right) parietal lesions because it may be obscured by the aphasia that occurs with dominant (left) sided lesions.

1. anosognosia (indifference or unawareness of deficits, patient may deny that paralyzed extremity is theirs)
2. apathy (indifference to failure)
3. allocheiria (one-sided stimuli perceived contralaterally)
4. dressing apraxia: neglect of one side of body in dressing and grooming
5. extinction: patient is unaware of contralateral stimulus when presented with double-sided simultaneous stimulation
6. inattention to an entire visual field (with or without homonymous hemianopia), with deviation of head, eyes, and torsion of body to unaffected side

### 3.2.3 Foster Kennedy syndrome

Named after neurologist Robert Foster Kennedy. Usually from olfactory groove or medial third sphe-noid wing tumor (usually meningioma). Now less common due to earlier detection by CT or MRI. Classic triad:

1. ipsilateral anosmia
2. *ipsilateral* central scotoma (with optic *atrophy* due to pressure on optic nerve)
3. *contralateral* papilledema (from elevated ICP)

Occasionally ipsilateral proptosis will also occur due to orbital invasion by tumor.

### 3.2.4 Cerebellar mutism & syndromes of the posterior fossa

#### General information

► **Cerebellar mutism (CM).** AKA mutism with subsequent dysarthria.

Definition: speechlessness that develops following various cerebellar injuries<sup>36</sup> including cerebellar trauma,<sup>37,38</sup> stroke,<sup>39</sup> hemorrhage,<sup>40</sup> and viral cerebellitis.<sup>41</sup> However, it is most frequently encountered in children subsequent to resection of posterior fossa brain tumors.

Essentially always improves, but almost never back to normal. The anatomical substrate has not been definitively identified

Cerebellar mutism (CM) may occur in isolation, or may be encountered as part of other more global syndromes that involve the posterior fossa:

1. cerebellar mutism syndrome: CM, ataxia, hypotonia & irritability, which may be encountered as part of #2 (the following item)<sup>42</sup>
2. posterior fossa syndrome: cerebellar mutism syndrome + cranial nerve deficits, neurobehavioral changes & urinary incontinence or retention

► **Cerebellar syndrome.** Ataxia, dysmetria & nystagmus.<sup>42</sup> CM is *not* part of the cerebellar syndrome.

#### Epidemiology

Incidence of CM: 11–29% of children following surgery for cerebellar tumors<sup>36</sup> including medulloblastoma (53%), ependymoma (33%) & pilocytic astrocytoma (11%).<sup>43</sup> Risk factors for post-op CM following surgery for medulloblastoma in children: brainstem involvement & midline location.<sup>44</sup>

Post-op CM has been observed in ≈ 1% of adults following p-fossa surgery.<sup>45</sup>

#### Clinical characteristics

CM is characterized by delayed onset (mean: 1.7 days post-op, range: 1–6 days),<sup>46</sup> limited duration (mean: 6.8 weeks, range: 4 d–4 months),<sup>46</sup> and long-term linguistic sequelae (in 98.8% of patients).<sup>47</sup>

#### Pathophysiological correlate

The underlying disease mechanism remains elusive. Theories include: postoperative vasospasm, cerebellar ischemia, and edema, as well as transient dysregulation of neurotransmitter release. However, the most widely accepted explanation is cerebellar diaschisis<sup>47</sup> (from the Greek: διάσχισις meaning “shocked throughout”): metabolic hypofunction in a brain region distant but connected to an area of brain injury. Specifically: CM has been linked to the disruption of cerebello-cerebral circuits, such as the dentate thalamocortical tract, which originates in the dentate nucleus, extends through the superior cerebellar peduncle, and decussates to the contralateral cerebral hemisphere,

where it connects the ventrolateral nucleus of the thalamus to diverse cortical areas.<sup>48</sup> SPECT scans demonstrated transient reduction of cerebral perfusion in frontal, parietal, and temporal cortices of patients with post-op CM.<sup>49,50</sup> In this manner, a supratentorial condition is provoked by disruption of connections to the cerebellum as a result of cerebellar injury.

### Treatment & prevention

Treatment is limited to supportive measures: speech & rehabilitation therapy.

Post-op CM may be prevented by avoiding midline splitting of the cerebellar vermis (e.g., by using the telovelar approach to the 4th ventricle). However, results are conflicting and general recommendation for surgical strategies to avoid CM cannot be made at this time.

## 3.2.5 Brainstem and related syndromes

### Weber's syndrome

Cr. N. III palsy with contralateral hemiparesis; also see Lacunar strokes (p. 1540). Third nerve palsies from parenchymal lesions may be relatively pupil sparing.

### Benedikt's syndrome

Similar to Weber's, plus red nucleus lesion. Cr. N. III palsy with contralateral hemiparesis except arm which has hyperkinesia, ataxia, and a coarse intention tremor. Lesion: midbrain tegmentum involving red nucleus, brachium conjunctivum, and fascicles of III.

### Millard-Gubler syndrome

Facial (VII) & abducens (VI) palsy + contralateral hemiplegia (corticospinal tract) from lesion in base of pons (usually ischemic infarct, occasionally tumor).

## 3.2.6 Parinaud's syndrome

### Definition

AKA dorsal midbrain syndrome, AKA pretectal syndrome. As originally described, a supranuclear paralysis of vertical gaze resulting from damage to the mesencephalon.<sup>51</sup>

There are a number of somewhat varying descriptions; however, most include:

- supranuclear upward gaze palsy (i.e., upgaze palsy affecting both voluntary saccadic and pursuit movements, with preservation of vestibulo-ocular or oculocephalic [doll's eyes] reflexes in most cases). Horizontal eye movements are spared
- lid retraction (Collier's sign): NB: upgaze palsy + lid retraction produces the "setting sun sign"
- convergence palsy
- accommodation palsy
- less common associations: pseudoabducens palsy (AKA thalamic esotropia), see-saw nystagmus, fixed pupils, dissociated light-near response (pseudo-Argyll Robertson), convergence spasm, nystagmus retractorius, internuclear ophthalmoplegia (INO)

Skew deviation may be a unilateral variant of Parinaud's syndrome.

Syndrome of the Sylvian aqueduct: Parinaud's syndrome (PS) combined with downgaze palsy.

### Differential diagnosis

#### Etiologies

1. masses pressing directly on quadrigeminal plate (e.g., pineal region tumors)
2. elevated ICP: secondary to compression of mesencephalic tectum by dilated suprapineal recess, e.g., in hydrocephalus
3. stroke or hemorrhage in upper brainstem
4. multiple sclerosis (MS)
5. occasionally seen with toxoplasmosis

Conditions affecting ocular motility that could mimic the upgaze palsy of PS:

1. Guillain-Barré syndrome
2. myasthenia gravis

3. botulism
4. hypothyroidism
5. there may be a gradual benign loss of upgaze with senescence

### 3.3 Jugular foramen syndromes

#### 3.3.1 Applied anatomy

The jugular foramen (JF) is one of a pair of openings between the lateral part of the occipital bone and the petrous part of the temporal bone. The foramen is usually divided in 2 by a bony spine from the petrous temporal bone that attaches via a fibrous bridge (which is bony in 26%) to the jugular process of the occipital bone.<sup>52</sup> The right JF is usually larger than the left.<sup>52,53</sup> The carotid ridge separates the JF from the nearby carotid canal. Contents of jugular foramen (JF): Cr. N. IX, X, XI, petrosal sinus, sigmoid sinus, some meningeal branches from the ascending pharyngeal and occipital arteries.<sup>54</sup>

Nearby: Cr. N. XII passes through the hypoglossal canal just above the occipital condyle. The carotid artery with the sympathetic plexus enters the carotid canal.

Compartmentalization of the jugular foramen remains controversial. As many as 4 foramina have been described over the years. Although it had been recognized previously, an early 2-compartment description was published in 1967 by Hovelacque.<sup>55</sup> In this, the bony spine ( $\pm$  its fibrous septum) divides the foramen into:

- pars vascularis: the larger posterolateral compartment containing the vagal nerve (and branching Arnold's nerve), spinal accessory nerve and the internal jugular vein
- pars nervosa: the smaller anteromedial compartment containing the glossopharyngeal nerve (and branching Jacobson's nerve), inferior petrosal sinus and meningeal branch of the ascending pharyngeal artery

A publication in 1997 described these 3 compartments<sup>56</sup>:

- sigmoid: large posterolateral compartment containing sigmoid sinus
- petrosal: smaller anteromedial compartment containing petrosal sinus
- intrajugular or neural: CN IX, X, and XI

#### 3.3.2 Clinical syndromes

##### General information

A number of eponymous syndromes with some conflicting findings in the literature have been described. See ▶ Table 3.2 for a summary and ▶ Fig. 3.3 for a schematic diagram of deficits in various jugular foramen syndromes.

**Table 3.2** Cranial nerve dysfunction in jugular foramen syndromes

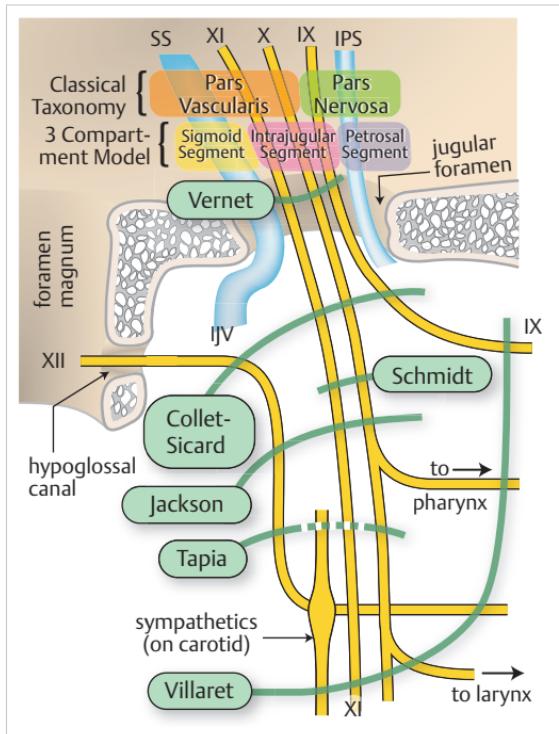
Nerve	Result of lesion	Syndrome					
		Vernet	Collet Sicard	Villaret	Tapia	Jackson	Schmidt
IX	loss of taste and sensation in posterior third of tongue	X	X	X			
X	paralysis of vocal cords & palate, anesthesia of pharynx & larynx	X	X	X	X	X	X
XI	weak trapezius & SCM	X	X	X	±	X	X
XII	tongue paralysis & atrophy		X	X	X	X	
sympathetics	Horner syndrome			X	±		

Key: X indicates dysfunction / deficit (lesion) of that nerve; ± indicates involvement may or may not occur

##### Vernet's syndrome: CN IX, X & XI palsy

AKA syndrome of the jugular foramen. Usually due to intracranial lesion.

Etiologies include: jugular foramen tumors, ICA dissections, mycotic aneurysms of the external carotid, thrombosis of the jugular vein, following carotid endarterectomy.



**Fig. 3.3 Jugular foramen.** Schematic diagram (coronal section through left jugular foramen viewed from the front). Includes the classic 2 compartment model and the 3 compartment classification of Katsuta et al.<sup>56</sup>

Jugular foramen syndromes are illustrated: a solid line through a nerve indicates a deficit, dashed line indicates  $\pm$  involvement.

Abbreviations: SS = sigmoid sinus; IJV = inferior jugular vein; IPS = inferior petrosal sinus; Roman numerals denote cranial nerve numbers.

Symptoms: unilateral paralysis of the palate, vocal cords, sternocleidomastoid, trapezius, with loss of taste in the posterior 1/3 tongue, anesthesia of the soft palate, larynx and pharynx.

### Collet-Sicard syndrome

Palsies of CN IX, X, XI & XII without sympathetic involvement. More likely with lesion outside skull. If caused by an intracranial lesion, it would have to be of such a large size that it would usually produce brainstem compression  $\rightarrow$  long tract findings.

Etiologies include condylar and Jefferson's fractures, internal carotid dissection, primary and metastatic tumors, Lyme disease, and fibromuscular dysplasia.

Symptoms: unilateral paralysis of the palate, vocal cords, sternocleidomastoid, trapezius, tongue, loss of taste in posterior 1/3 tongue, anesthesia of soft palate, larynx and pharynx.

### Villaret's syndrome: CN IX, X, XI & XII palsy + sympathetic dysfunction

AKA posterior retropharyngeal syndrome, AKA the nervous syndrome of the posterior retroparotid space). Collet-Sicard syndrome with sympathetic involvement. Usually due to retropharyngeal lesions.

Etiologies include: parotid tumors, metastases, external carotid aneurysm and osteomyelitis of the skull base.

Symptoms: as with Collet-Sicard + Horner syndrome.

### Tapia syndrome: CN X & XII palsy ( $\pm$ XI)

AKA Matador's disease (first described in a bullfighter by Antonio Garcia Tapia). Some authors describe an intracranial and extracranial form.<sup>57</sup>

Etiologies include: oral intubation (majority of cases prior to 2013), metastases, rarely associated with carotid or vertebral artery dissections.

Symptoms: hoarseness of voice, dysphagia secondary to incoordination of tongue and food bolus propulsion, unilateral atrophy and paralysis of the tongue, ± paralysis of sternocleidomastoid & trapezius, sparing the soft palate.

### (Hughlings) Jackson's syndrome: CN X, XI & XII palsy

First described in 1864 with unilateral paralysis of the soft palate, larynx, sternocleidomastoid, trapezius and tongue.

3

### Schmidt syndrome: CN X & XI

AKA vago-spinal syndrome. Schmidt first described this in 1892. Unilateral vocal cord and paralysis of sternocleidomastoid, soft palate, larynx and trapezius.

## References

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## **Part II**

### **General and Neurology**

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II

## 4 Neuroanesthesia

### 4.1 ASA classification

► Table 4.1 shows the American Society of Anesthesiologists (ASA) grading system to estimate anesthetic risk for various conditions.

4

**Table 4.1 ASA classification (modified<sup>1a</sup>)**

ASA class	Description	% mortality <48 hrs <sup>2</sup>	% mortality <7 days <sup>3</sup>
I	normally healthy patient	0.08	0.06
II	mild systemic disease; no functional limitation	0.27	0.4
III	severe systemic disease (SSD); definite functional limitation	1.8	4.3
IV	SSD that is a constant threat to life	7.8	23.4
V	moribund, expected to die in 24 hrs with or without surgery	9.4	50.7
VI	organ donor		
"e"	appended for emergency operation	triple that for elective	

<sup>a</sup>NB: in this study, no reference is made to type of operation (intracranial and abdominal vascular surgery have higher mortality)

### 4.2 Neuroanesthesia parameters

For issues related to intracranial pressure (ICP), cerebral perfusion pressure (CPP), intracranial constituents, etc., see ICP principles (p. 1036). For cerebral blood flow (CBF) and cerebral metabolic rate of oxygen consumption (CMRO<sub>2</sub>), see CBF and oxygen utilization (p.1536).

Parameters of primary relevance to neurological surgery that can be modulated by the anesthesiologist:

1. blood pressure: one of the factors that determines CPP as well as spinal cord perfusion. May need to be manipulated (e.g., reduced when working on an aneurysm, or increased to enhance collateral circulation during cross clamping). Measurement by arterial line is most accurate and depending on the patient's presentation and the planned procedure, often should be placed prior to induction of anesthesia. For intracranial procedures, the arterial line should be calibrated at the external auditory meatus to most closely reflect intracranial blood pressure
2. jugular venous pressure: one of the factors that influences ICP
3. arterial CO<sub>2</sub> tension (PaCO<sub>2</sub>): CO<sub>2</sub> is the most potent cerebral vasodilator. Hyperventilation reduces PaCO<sub>2</sub> (hypocapnia), which decreases CBV but also CBF. Goal is generally end tidal CO<sub>2</sub> (ETCO<sub>2</sub>) of 25–30 mm Hg with a correlating PaCO<sub>2</sub> of 30–35. Use with care for stereotactic procedures to minimize shift of intracranial contents when using this method to control ICP<sup>4</sup>
4. arterial O<sub>2</sub> tension
5. hematocrit: in neurosurgery it is critical to balance oxygen carrying capacity (decreased by anemia) against improved blood rheology (impaired by elevated Hct)
6. patient temperature: mild hypothermia provides some protection against ischemia by reducing the cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) by ≈ 7% for each 1 °C drop
7. blood glucose level: hyperglycemia exacerbates ischemic deficits<sup>5</sup>
8. CMRO<sub>2</sub>: reduced with certain neuro-protective agents and by hypothermia which helps protect against ischemic injury
9. in cases where a lumbar drain or a ventricular drain has been placed: CSF output
10. elevation of the head of the patient: lowering the head increases arterial blood flow, but also increases ICP by impairing venous outflow
11. intravascular volume: hypovolemia can impair blood flow in neurovascular cases. In surgery in the prone position, excessive fluids may contribute to facial edema which is one of the risk factors for PION (p. 1261)
12. positioning injuries: during the procedure, the patient's position may change and be unnoticed due to draping. Careful and frequent examination of the patient's position may prevent injuries associated with prolonged malpositioning
13. postoperative nausea and vomiting (PONV): may adversely affect ICP and may negatively impact recent cervical surgical procedures. Avoidance of anesthetic agents known to cause PONV or pretreatment to prevent PONV may be prudent

## 4.3 Drugs used in neuroanesthesia

### 4.3.1 Inhalational agents

#### General information

Most reduce cerebral metabolism (except nitrous oxide) by suppressing neuronal activity. These agents disturb cerebral autoregulation and cause cerebral vasodilatation, which increases cerebral blood volume (CBV) and can increase ICP. With administration > 2 hrs they increase CSF volume, which can also potentially contribute to increased ICP. Most agents increase the CO<sub>2</sub> reactivity of cerebral blood vessels. These agents affect intraoperative EP monitoring (p. 112).

#### Drug info: Nitrous oxide

A potent vasodilator that markedly increases CBF and minimally increases cerebral metabolism. Contributes to post-op N/V (PONV).

**Nitrous oxide, pneumocephalus and air embolism:** The solubility of nitrous oxide (N<sub>2</sub>O) is ≈ 34 times that of nitrogen.<sup>6</sup> When N<sub>2</sub>O comes out of solution in an airtight space it can increase the pressure which may convert pneumocephalus to “tension pneumocephalus.” It may also aggravate air embolism. Thus caution must be used especially in the sitting position where significant post-op pneumocephalus and air embolism are common. The risk of tension pneumocephalus may be reduced by filling the cavity with fluid in conjunction with turning off N<sub>2</sub>O about 10 minutes prior to completion of dural closure. See Pneumocephalus (p. 1067).

#### Halogenated agents

Agents in primary usage today are shown below. All suppress EEG activity and may provide some degree of cerebral protection.

#### Drug info: Isoflurane (Forane®)

Can produce isoelectric EEG without metabolic toxicity. Improves neurologic outcome in cases of incomplete global ischemia (although in experimental studies on rats, the amount of tissue injury was greater than with thiopental<sup>7</sup>).

#### Drug info: Desflurane (Suprane®)

A cerebral vasodilator, increases CBF and ICP. Decreases CMRO<sub>2</sub> which tends to cause a compensatory vasoconstriction.

#### Drug info: Sevoflurane (Ultane®)

Mildly increases CBP and ICP, and reduces CMRO<sub>2</sub>. Mild negative inotrope, cardiac output not as well maintained as with isoflurane or desflurane.

### 4.3.2 Intravenous anesthetic agents

#### Agents generally used for induction

1. propofol: exact mechanism of action unknown. Short half-life with no active metabolites. May be used for induction and as a continuous infusion during total intravenous anesthesia (TIVA). Causes dose dependent decrease in mean arterial blood pressure (MAP) and ICP. See also information other than use in induction (p. 110). Is more rapidly cleared than, and has largely replaced, thiopental

- 4**
2. barbiturates: produce significant reduction in CMRO<sub>2</sub> and scavenge free radicals among other effects (p. 1464). Produce dose-dependent EEG suppression which can be taken all the way to isoelectric. Minimally affect EPs. Most are anticonvulsant, but methohexitol (Brevital®) (p. 139) can lower the seizure threshold. Myocardial suppression and peripheral vasodilatation from barbiturates may cause hypotension and compromise CPP, especially in hypovolemic patients  
★ sodium thiopental (Pentothal®): the most common agent. Rapid onset, short acting. Minimal effect on ICP, CBF and CMRO<sub>2</sub>
  3. etomidate (Amidate®): a carboxylated imidazole derivative. Anesthetic and amnestic, but no analgesic properties. Sometimes produces myoclonic activity which may be confused with seizures. Impairs renal function and should be avoided in patients with known renal disease. May produce adrenal insufficiency. See Miscellaneous drugs in neuroanesthesia (p. 110) for information other than use in induction.
  4. ketamine: NMDA receptor antagonist. Produces a dissociative anesthesia. Maintains cardiac output. May slightly increase both heart rate and blood pressure. ICP increases in parallel with increased cardiac output.

### Narcotics in anesthesia

#### Nonsynthetic narcotics

Narcotics increase CSF absorption and minimally reduce cerebral metabolism. They slow the EEG but will not produce an isoelectric tracing. ✗ All narcotics cause dose-dependent respiratory depression which can result in hypercarbia and concomitant increased ICP in non-ventilated patients. Often also contribute to post-op N/V (PONV).

Morphine: does not significantly cross the BBB.

✗ Disadvantages in neuro patients:

1. causes histamine release which
  - a) may produce hypotension
  - b) may cause cerebrovascular vasodilation → increased ICP<sup>8</sup>(p 1593)
  - c) the above together may compromise CPP
2. in renal or hepatic insufficiency, the metabolite morphine-6-glucuronide can accumulate which may cause confusion

#### Synthetic narcotics

These do not cause histamine release, unlike morphine and meperidine.

★ Remifentanil (Ultiva®); see also detailed information (p.140): reduces CMRO<sub>2</sub>, CBV and ICP. Large doses may be neurotoxic to limbic system and associated areas. May be used for awake craniotomy (p.1732).

Fentanyl: crosses the BBB. Reduces CMRO<sub>2</sub>, CBV and ICP. May be given as bolus and/or as a continuous infusion.

Sufentanil: more potent than fentanyl. Does not increase CBF. ✗ Raises ICP (may be due to hypoventilation, which can occur with any narcotic) and is thus often not appropriate for neurosurgical cases. Expensive.

### 4.3.3 Miscellaneous drugs in neuroanesthesia

- **Benzodiazepines.** These drugs are GABA agonists and decrease CMRO<sub>2</sub>. They also provide antiseizure action and produce amnesia. See also agents and reversal (p.213).
- **Etomidate** (p. 110). Used primarily for induction.
- a cerebrovasoconstrictor which therefore: reduces CBF and ICP; reduces CMRO<sub>2</sub> but no longer promoted as a cerebral protectant based on experimental studies<sup>9</sup> and a drop in pBtO<sub>2</sub> with temporary MCA clipping<sup>10</sup>
- does not suppress brainstem activity
- suppresses adrenocortical function cortisol production. This usually occurs with prolonged administration, but can occur even after single dose for induction and may persist up to 8 hrs (no adverse outcomes from short-term suppression have been reported)
- increases activity of seizure foci which may be used for mapping foci during seizure surgery but may also induce seizures
- **Propofol.** A sedative hypnotic. Useful for induction (p.109). Reduces cerebral metabolism, CBF and ICP. Has been described for cerebral protection (p.1466) and for sedation (p.140). Short half-life permits rapid awakening which may be useful for awake craniotomy (p.1733). Not analgesic.

- **Lidocaine.** Given IV, suppresses laryngeal reflexes which may help blunt ICP elevations that normally follow endotracheal intubation or suctioning. Anticonvulsant at low doses; may provoke seizures at high concentrations.
- **Esmolol.** Selective beta-1 adrenergic antagonist, blunts the sympathetic response to laryngoscopy and intubation. Less sedating than equipotent doses of lidocaine or fentanyl used for the same purpose. Half life: 9 minutes. See also dosing, etc. (p.132).
- **Dexmedetomidine (Precedex®).** Alpha 2 adrenergic receptor agonist, used for control of hypertension post operatively, as well as for its sedating qualities during awake craniotomy either alone or in conjunction with propofol (p.109). Also used to help patients tolerate endotracheal tube without sedatives/narcotics to facilitate extubation.

#### 4.3.4 Paralytics for intubation

Paralytics (neuromuscular blocking agents [NMBA]): administered to facilitate tracheal intubation and to improve surgical conditions when indicated. Administration of paralytics ideally should always be guided by neuromuscular twitch monitoring. Also see Sedatives & paralytics (p.139). In addition to paralytics, all conscious patients should also receive a sedative to blunt awareness.

Paralytics should not be given until it has been determined that patient can be ventilated manually, unless treating laryngospasm (may be tested with thiopental). Use with caution in non-fixated patients with unstable C-spine.

Due to long action, pancuronium (Pavulon®) is not indicated as the primary paralytic for intubation, but may be useful once patient is intubated or in *low* dose as an adjunct to succinylcholine.

#### Drug info: Succinylcholine (Anectine®)

The only depolarizing agent. May be used to secure airway for emergency intubation, but due to possible side effects (p. 141), should not be used acutely following injury or in adolescents or children (a short acting nondepolarizing blocker is preferred). May transiently increase ICP. Prior dosing with 10% of the ED95 dose of a non-depolarizing muscle relaxant reduces muscle fasciculations.

R Intubating dose: 1–1.5 mg/kg (supplied as 20 mg/ml → 3.5–5 cc for a 70 kg patient), onset 60–90 sec, duration 3–10 min, may repeat same dose × 1.

#### Drug info: Rocuronium (Zemuron®)

Intermediate acting, aminosteroid, non-depolarizing muscle relaxant. The only nondepolarizing neuromuscular blocking agent approved for rapid sequence intubation (RSI). Duration of action and onset are dose dependent. R (p.142).

#### Drug info: Vecuronium (Norcuron®)

See details (p. 142).

Aminosteroid with activity similar to that of rocuronium, however, does not cause histamine release and is not approved for rapid sequence intubation. R.

#### Drug info: Cisatracurium (Nimbex®)

See details (p. 143).

Metabolized by Hoffman degradation (temperature dependent), intermediate acting, no significant increases in histamine. R

## 4.4 Anesthetic requirements for intraoperative evoked potential monitoring

For details of intraoperative evoked potential (EP) monitoring itself, see **Intraoperative evoked potentials** (p.251).

All volatile anesthetics produce dose-dependent reduction in SSEP peak amplitude and an increase in peak latency. Adding nitrous oxide increases this sensitivity to anesthetic agents.

Anesthesia issues related to intraoperative evoked potential (EPs) monitoring:

1. induction: minimize pentothal dose (produces  $\approx$  30 minutes of suppression of EPs), or use etomidate (which increases both SSEP amplitude and latency<sup>11</sup>)
2. total intravenous anesthesia (TIVA) is ideal (i.e., no inhalational agents)
3. nitrous/narcotic technique is a distant second choice
4. if inhalational anesthetic agents are required:
  - a) use < 1 MAC (maximal alveolar concentration), ideally < 0.5 MAC
  - b) avoid older agents such as Halothane
5. nondepolarizing muscle relaxants have little effect on EP (in monkeys<sup>12</sup>)
6. propofol has a mild effect on EP: total anesthesia with propofol causes less EP depression than inhalational agents at the same depth of anesthesia<sup>13</sup>
7. benzodiazepines have a mild-to-moderate depressant effect on EPs
8. continuous infusion of anesthetic drugs is preferred over intermittent boluses
9. SSEPs can be affected by hyper- or hypothermia, and changes in BP
10. hypocapnia (down to end tidal CO<sub>2</sub> = 21) causes minimal reduction in peak latencies<sup>14</sup>
11. antiseizure medications: phenytoin, carbamazepine and phenobarbital do not affect SSEP<sup>15</sup>

## 4.5 Malignant hyperthermia

### 4.5.1 General information

Malignant hyperthermia (MH) is a hypermetabolic state of skeletal muscle due to idiopathic block of Ca<sup>++</sup> re-entry into sarcoplasmic reticulum. Transmitted by a multifactorial genetic predisposition. Total body O<sub>2</sub> consumption increases  $\times$  2–3.

Incidence: 1 in 15,000 anesthetic administrations in peds, 1 in 40,000 adults. 50% had previous anesthesia without MH. Frequently associated with administration of halogenated inhalational agents and the use of succinylcholine (fulminant form: muscle rigidity almost immediately after succinylcholine, may involve masseters  $\rightarrow$  difficulty intubating). Initial attack and recrudescence may also occur post-op. 30% mortality.<sup>16</sup>

### 4.5.2 Presentation

1. earliest possible sign: *increase* in end-tidal pCO<sub>2</sub>
2. tachycardia (early) and other arrhythmias
3. with progression:
  - a) coagulation disorder (DIC) (bleeding from surgical wound and body orifices)
  - b) ABG: increasing metabolic acidosis & decreasing pO<sub>2</sub>
  - c) pulmonary edema
  - d) elevated body temperature (may reach  $\geq$  44 °C (113 °F) at rate of 1 °C/5-min) (normal patients become hypothermic with general anesthesia)
  - e) limb muscle rigidity (common, but late)
  - f) rhabdomyolysis  $\rightarrow$  elevated CPK & myoglobin (late)
4. terminal:
  - a) hypotension
  - b) bradycardia
  - c) cardiac arrest

### 4.5.3 Treatment

1. eliminate offending agents (stop the operation, D/C inhalation anesthesia and change tubing on anesthesia machine)
2. dantrolene sodium (Dantrium®) 2.5 mg/kg IV usually effective, infuse until symptoms subside, up to 10 mg/kg

3. hyperventilation with 100% O<sub>2</sub>
4. surface and cavity cooling: IV, in wound, per NG, PR
5. bicarbonate 1–2 mEq/kg for acidosis
6. IV insulin and glucose (lowers K<sup>+</sup>, glucose acts as energy substrate)
7. procainamide for arrhythmias
8. diuresis: volume loading + osmotic diuretics

#### 4.5.4 Prevention

1. identification of patients at risk:
  - a) only reliable test: 4 cm viable muscle biopsy for in-vitro tests at a few regional test centers (abnormal contracture to caffeine or halothane)
  - b) family history: any relative with syndrome puts patient at risk
  - c) related traits: 50% of MH patients have heavy musculature, Duchenne type muscular dystrophy, or scoliosis
  - d) patients who exhibit masseter spasm in response to succinylcholine
2. in patients at risk: avoid succinylcholine (nondepolarizing blockers preferred if paralysis essential), may safely have non-halogenated anesthetics (narcotics, barbiturates, benzodiazepines, droperidol, nitrous...)
3. prophylactic oral dantrolene: 4–8 mg/kg/day for 1–2 days (last dose given 2 hrs before anesthesia) is usually effective

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## 5 Sodium Homeostasis and Osmolality

### 5.1 Serum osmolality and sodium concentration

Clinical significance of various serum osmolality values is shown in ► Table 5.1.

- **Serum osmolality.** May be estimated using Eq (5.1).

$$\text{Osmolality (mOsm/kg)} = 2 \times \{ [\text{Na}^+] + [\text{K}^+] \} + \frac{[\text{BUN}]}{2.8} + \frac{[\text{glucose}]}{18} \quad (5.1)$$

5

(with  $[\text{Na}^+]$  in mEq/L or mmol/L, and glucose and BUN in mg/dl).

NB: terms in square brackets [] represent the serum concentrations (in mEq/L for electrolytes).

- **Sodium content.** In the diet: usually expressed in grams  $\text{Na}^+$  (not NaCl), a low sodium diet is considered 2 g of  $\text{Na}^+$  per day or less.

1 teaspoon of table salt (NaCl) has 2.3 gm of  $\text{Na}^+$ .

1 mg NaCl has 17 mEq  $\text{Na}^+$ . 1 mg  $\text{Na}^+$  has 43 mEq  $\text{Na}^+$ .

Normal saline has 0.9 gm of NaCl/100 ml. 3% NaCl has 3 gm NaCl/100 ml.

**Table 5.1** Clinical correlates of serum osmolality

Value (mOsm/kg)	Comment
282–295	normal
<240 or >321	panic values
>320	risk of renal failure
>384	produces stupor
>400	risk of generalized seizures
>420	usually fatal

### 5.2 Hyponatremia

#### 5.2.1 General information

##### Key concepts

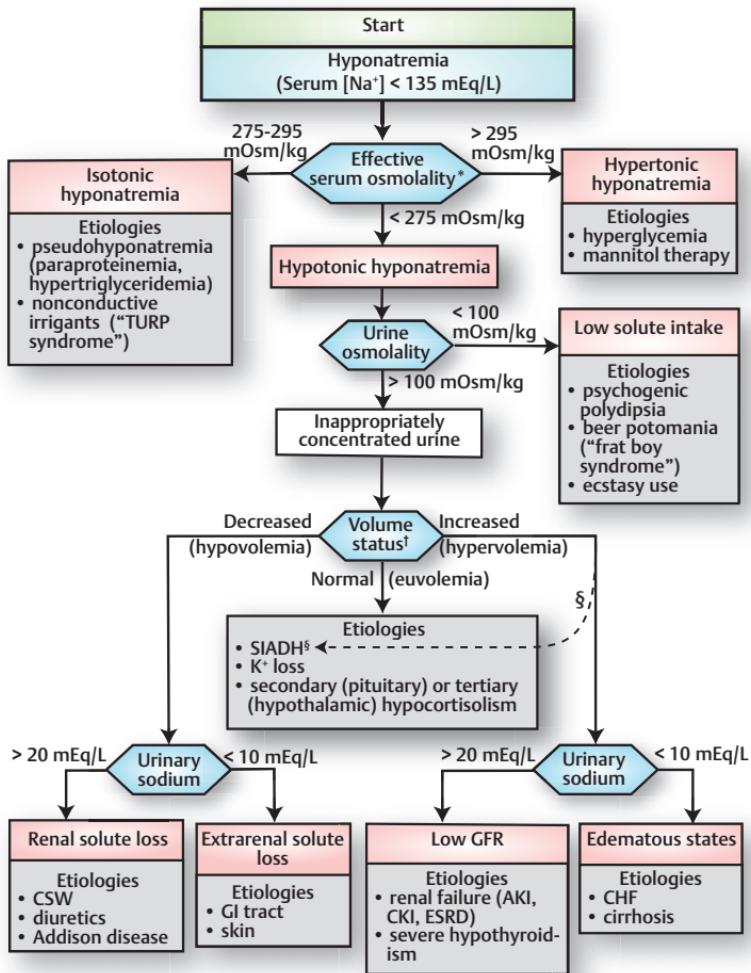
- definition: serum  $[\text{Na}^+] < 135$  mEq/L. Common etiologies:
  - SIADH: hypotonic hyponatremia (effective serum osmolality  $< 275$  mOsm/kg) with inappropriately high urinary concentration (urine osmolality  $> 100$  mOsm/kg) and euolemia or hypervolemia
  - cerebral salt wasting (CSW): similar to SIADH but with extracellular fluid volume depletion due to renal sodium loss (urinary  $[\text{Na}] > 20$  mEq/L)
- minimum W/U: ✓ serum  $[\text{Na}^+]$ , ✓ serum osmolality, ✓ urine osmolality, ✓ clinical assessment of volume status. If volume status is high or low: ✓ urinary  $[\text{Na}^+]$  ✓ TSH (to R/O hypothyroidism)
- treatment: based on acuity, severity, symptoms & etiology; see SIADH (p. 119) or CSW (p. 122) as appropriate
- risk of overly rapid correction: osmotic demyelination (including central pontine myelinolysis)

- **Classification.** Severity of hyponatremia:  $[\text{Na}^+] < 135$  mEq/L = mild,  $< 130$  = moderate,  $< 125$  = severe hyponatremia.

See ► Fig. 5.1 for flow chart.

- **Hyponatremia in neurosurgical patients.** Chiefly seen in:

- syndrome of inappropriate antidiuretic hormone secretion (SIADH) (p. 118): dilutional hyponatremia with normal or elevated intravascular volume. The most common type of hyponatremia.<sup>1</sup>



**Fig. 5.1** Etiologies of hyponatremia (adapted<sup>5,9</sup>).

\* effective serum osmolality = measured osmolality -  $[BUN]/2.8$  (see formula in text (p. 117)).

† volume status is usually assessed clinically, but this may be insensitive to volume depletion.

§ SIADH may be associated with euvoolemia or hypervolemia.

Abbreviations: AKI = acute kidney injury; CHF = congestive heart failure; CKI = chronic kidney injury; CSW = cerebral salt wasting;  $[Na^+]$ <sub>urine</sub> = urinary concentration of sodium; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Usually treated with *fluid restriction*. May be associated with numerous intracranial abnormalities (► Table 5.2) and following transsphenoidal surgery

- cerebral salt wasting (CSW): inappropriate natriuresis with *volume depletion*. Treated with *volume replacement* (opposite to SIADH) and *sodium*; symptoms from derangements due to CSW may be exacerbated by fluid restriction (p. 122).<sup>2</sup> It is the etiology of 6–23% of cases of moderate-to-severe hyponatremia following aneurysmal SAH<sup>3,4</sup> (compared to 35% for SIADH)

**Table 5.2 Etiologies of SIAD<sup>a</sup>****Malignant tumors**

1. especially bronchogenic small-cell Ca
2. tumors of GI or GU tract
3. lymphomas
4. Ewing's sarcoma

**CNS disorders**

1. infection:
  - a) encephalitis
  - b) meningitis: especially in peds
  - c) TB meningitis
  - d) AIDS
  - e) brain abscess
2. head trauma: 4.6% prevalence
3. increased ICP: hydrocephalus, SDH...
4. SAH
5. brain tumors
6. cavernous sinus thrombosis
7. ★ post craniotomy, especially following surgery for pituitary tumors, craniopharyngiomas, hypothalamic tumors
8. MS
9. Guillain-Barré
10. Shy-Drager
11. delirium tremens (DTs)

**Pulmonary disorders**

1. infection: pneumonia (bacterial & viral), abscess, TB, aspergillosis
2. asthma
3. respiratory failure associated with positive pressure respiration

**Drugs**

1. drugs that release ADH or potentiate it
  - a) chlorpropamide (Diabinese®): increases renal sensitivity to ADH
  - b) carbamazepine (Tegretol®), even more common with oxcarbazepine
  - c) HCTZ
  - d) SSRIs, TCAs
  - e) clofibrate
  - f) vincristine
  - g) antipsychotics
  - h) NSAIDs
  - i) MDMA ("ecstasy")
2. ADH analogues
  - a) DDAVP
  - b) oxytocin: ADH cross activity, may also be contaminated with ADH

**Endocrine disturbances**

1. adrenal insufficiency
2. hypothyroidism

**Miscellaneous**

1. anemia
2. stress, severe pain, nausea or hypotension (all can stimulate ADH release), postoperative state
3. acute intermittent porphyria (AIP)

<sup>a</sup>excerpted and modified<sup>1,11</sup>

► **Other forms of hyponatremia:**

1. isotonic hyponatremia (effective serum osmolality: 275–295 mOsm/kg):
  - a) pseudohyponatremia: an artifact of *indirect* lab techniques.<sup>5</sup> Unusually high levels of lipids (e.g., hypertriglyceridemia) or proteins (e.g., immunoglobulins as can occur in multiple myeloma<sup>6</sup>) reduce the aqueous fraction of plasma and produce artificially low sodium lab values. This error does not occur with direct measurement methods
  - b) nonconductive irrigants, e.g., as used in cystoscopy to allow coagulation, when large volumes are inadvertently absorbed through a severed vein ("TURP syndrome")

2. hypertonic hyponatremia (effective serum osmolality: > 295 mOsm/kg): excess of osmotically active solutes. Hyperglycemia is the most common example. For every 100 mg/dl increase of glucose, serum  $[Na^+]$  decreases by 1.6–2.4 mEq/L. Can also occur with mannitol
3. hypotonic hyponatremia (effective serum osmolality: typically < 275 mOsm/kg. Exceptions: in the presence of solutes with total body water distribution: e.g., EtOH, urea). Examples:
  - a) renal failure: associated with hypervolemia and  $[Na^+]_{urine} > 20$  mEq/L
  - b) CHF, cirrhosis: associated with hypervolemia and  $[Na^+]_{urine} < 10$  mEq/L
4. postoperative hyponatremia: a rare condition usually described in young, otherwise healthy women undergoing elective surgery<sup>7</sup> and may be related to administration of even only mildly hypotonic fluids (sometimes in modest amounts)<sup>8</sup> and the actions of ADH (which may be increased due to stress, pain, or medications)

### 5.2.2 Evaluation of hyponatremia

► Fig. 5.1 shows an algorithm for evaluating the etiology of hyponatremia<sup>9</sup> which drives treatment decisions. Work-up requires assessment of:

1. serum sodium: must be < 135 mEq/L to qualify as hyponatremia
2. the *effective* serum osmolality (AKA tonicity) is shown in this equation:

$$\text{effective serum osmolality} = \text{measured osmolality} - \frac{[BUN] (\text{mg/dL})}{2.8}$$

and should be used when the blood urea nitrogen (BUN) level is elevated (for a normal [BUN] of 7–18 mg/dL, just subtract 5 from the measured osmolality). Values < 275 mOsm/kg indicate hypotonic hyponatremia

3. urine osmolality: values > 100 mOsm/kg are inappropriately high if serum tonicity is < 275 mOsm/kg
4. volume status: differentiates SIADH from CSW
  - a) clinical assessment: better for hypervolemia (edema, upward trend in patient weights) but is insensitive in identifying extracellular fluid depletion as an etiology of hyponatremia<sup>10</sup> (look for dry mucous membranes, loss of skin turgor, orthostatic hypotension)
  - b) normal saline infusion test used in uncertain cases. If baseline urine osmolality is < 500 mOsm/kg, it is usually safe to infuse 2 L of 0.9% saline over 24–48 hours. Correction of the hyponatremia suggests extracellular fluid volume depletion was the cause
  - c) central venous pressure (CVP) may be used: CVP < 5–6 cm H<sub>2</sub>O suggests hypovolemia in patients with normal cardiac function<sup>3,9</sup>
5. check urinary  $[Na^+]$  if volume status is high or low
6. determine duration of hyponatremia:
  - a) duration documented as < 48 hours is considered acute
  - b) hyponatremia of > 48 hours duration or of unknown duration is chronic
  - c) hyponatremia that occurs outside the hospital is usually chronic and asymptomatic except in marathoners and MDMA ("ecstasy") drug users

### 5.2.3 Symptoms

Due to slow compensatory mechanisms in the brain, a gradual decline in serum sodium is better tolerated than a rapid drop. Symptoms of mild ( $[Na] < 130$  mEq/L) or gradual hyponatremia include: anorexia, headache, difficulty concentrating, irritability, dysgeusia, and muscle weakness. Severe hyponatremia (< 125 mEq/L) or a rapid drop (> 0.5 mEq/hr) can cause neuromuscular excitability, cerebral edema, muscle twitching and cramps, nausea/vomiting, confusion, seizures, respiratory arrest and possibly permanent neurologic injury, coma or death.

### 5.2.4 Syndrome of inappropriate antidiuresis (SIAD)

This term covers excess water retention in the face of hyponatremia, including cases due to inappropriate ADH secretion (SIADH) as well as others without increased circulating levels of ADH (e.g., heightened response to ADH, certain drugs...). A partial list of etiologies is shown in ► Table 5.2 (see references<sup>1,11</sup> for details).

The diagnostic criteria of SIAD is shown in ► Table 5.3. It is critical to *measure serum osmolality* to rule out pseudohyponatremia (p. 116), an artifact of indirect lab techniques.

**Table 5.3 Diagnostic criteria for SIAD<sup>1</sup>****Essential features**

- decreased effective serum osmolality<sup>a</sup> (< 275 mOsm/kg of water)
- simultaneous urine osmolality > 100 mOsm/kg of water
- clinical euolemia
  - no clinical signs of extracellular (EC) volume orthostatic hypotension (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes...)
  - no clinical signs of excess EC volume (edema, ascites...)
- urinary [Na] > 40 mEq/L with normal dietary Na intake
- normal thyroid and adrenal function
- no recent diuretic use

**Supplemental features**

- plasma [uric acid] < 4 mg/dl
- [BUN] < 10 mg/dl
- fractional Na excretion > 1%; fractional urea excretion > 55%
- NS infusion test: failure to correct hyponatremia with IV infusion of 2 L 0.9% saline over 24–48 hrs
- correction of hyponatremia with fluid restriction<sup>b</sup>
- abnormal result on water load test<sup>c</sup>:
  - < 80% excretion of 20 ml of water/kg body weight over 5 hours, or
  - inadequate urinary dilution (< 100 mOsm/kg of water)
- elevated plasma [ADH] with hyponatremia and euolemia

<sup>a</sup>effective osmolality (AKA tonicity) = (measured osmolality) – [BUN]/2.8 with [BUN] measured in mg/dl

<sup>b</sup>this test is used in uncertain cases (corrects volume depletion), and is usually safe when baseline urine osmolality is < 500 mOsm/L

<sup>c</sup>water load test & [ADH] levels are rarely recommended; see text for details (p. 119)

## 5.2.5 Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

### General information

#### Key concepts

- definition: release of ADH in the absence of physiologic (osmotic) stimuli
- results in hyponatremia with hypervolemia (occasionally with euolemia) with inappropriately high urine osmolality (> 100 mOsm/kg)
- may be seen with certain malignancies and many intracranial abnormalities
- critical to distinguish from cerebral salt wasting which produces hypovolemia
- treatment: initial guidelines in brief, see details (p. 119)
  - avoid rapid correction or overcorrection to reduce risk of osmotic demyelination (p. 119). Check serum [Na<sup>+</sup>] q 2–4 hours and do not exceed 1 mEq/L per hour, or 8 mEq/L in 24 hrs or 18 mEq/L in 48 hrs
  - severe ([Na<sup>+</sup>] < 125 mEq/L or < 48 hrs duration or with severe symptoms (coma, Sz): start 3% saline at 1–2 ml/kg body weight/hr + furosemide 20 mg IV qd
  - severe ([Na<sup>+</sup>] < 125 mEq/L of duration > 48 hours or unknown without severe symptoms: normal saline infusion @ 100 ml/hr + furosemide 20 mg IV qd
  - chronic or unknown duration and asymptomatic: fluid restriction (► Table 5.4) with dietary salt and protein, and, if necessary, adjuvant drugs (demeocycline, conivaptan...)

SIADH, AKA Schwartz-Bartter syndrome, was first described with bronchogenic cancer which is one cause of SIAD. SIADH is the release of antidiuretic hormone (ADH), AKA arginine vasopressin (AVP) (p.153), in the absence of physiologic (osmotic) stimuli. Result: elevated urine osmolality, and expansion of the extracellular fluid volume leading to a dilutional hyponatremia which can produce fluid overload (hypervolemia), but SIADH may also occur with euolemia. For unclear reasons, edema does not occur.

The hyponatremia of SIADH must be differentiated from that due to cerebral salt wasting (CSW) (p.122) because of differences in treatment recommendations.

Etiologies: ► Table 5.2.

**Table 5.4** Fluid restriction recommendations<sup>1</sup>

Solute ratio <sup>a</sup>	Recommended fluid intake
> 1	< 500 mL/d
1	500–700 mL/d
< 1	< 1 L/d

<sup>a</sup>solute ratio defined as:  $\frac{\text{urinary } [\text{Na}^+] + \text{urinary } [\text{K}^+]}{\text{plasma } [\text{Na}^+]}$

## Diagnosis of SIADH

In general, 3 diagnostic criteria are: hyponatremia, inappropriately concentrated urine, and no evidence of renal or adrenal dysfunction. In more detail:

1. low serum sodium (hyponatremia): usually < 134 mEq/L
2. low effective serum osmolality: < 275 mOsm/kg
3. high urinary sodium (salt wasting): at least > 18 mEq/L, often 50–150. Note: there has not been an adequate explanation of the high urinary sodium in SIADH
4. high ratio of urine:serum osmolality: often 1.5–2.5:1, but may be 1:1
5. normal renal function (check BUN & creatinine): BUN commonly < 10
6. normal adrenal function (no hypotension, no hyperkalemia)
7. no hypothyroidism
8. no signs of dehydration or overhydration (in many patients with acute brain disease, there is significant hypovolemia often due to CSW (p. 122) and as this is a stimulus for ADH secretion, the ADH release may be "appropriate"<sup>12</sup>). In uncertain cases, the normal saline infusion test (p. 117) may be used.

If further testing is required, the following are options, but are rarely recommended:

1. measure serum or urinary levels of ADH. Rarely indicated since urine osmolality > 100 mOsm/kg is usually sufficient to indicate excessive ADH.<sup>1</sup> ADH is normally undetectable in etiologies of hyponatremia other than SIADH
  2. water-load test: considered to be the definitive test.<sup>13</sup> The patient is asked to consume a water load of 20 mL/kg up to 1500 mL. In the absence of adrenal or renal insufficiency, the failure to excrete 65% of the water load in 4 hrs or 80% in 5 hrs indicates SIADH.
- ✖ CONTRAINDICATIONS: this test is dangerous if the starting serum  $[\text{Na}^+]$  is  $\leq 124$  mEq/L or if the patient has symptoms of hyponatremia

## Symptoms of SIADH

Symptoms of SIADH are those of hyponatremia (p. 117) and possibly fluid overload. If mild, or if descent of  $[\text{Na}^+]$  is gradual, it may be tolerated.  $[\text{Na}^+] < 120\text{--}125$  mEq/L is almost always symptomatic. These patients often have a paradoxical (inappropriate) thirst.

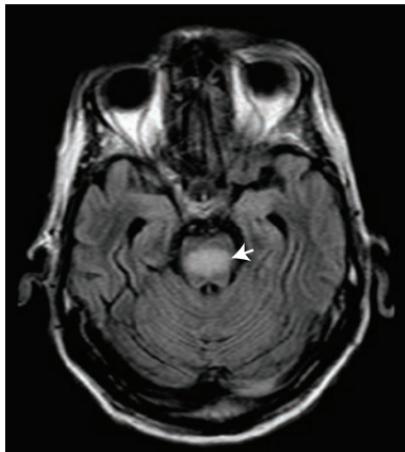
## Treatment of hyponatremia with SIADH

Management is based on the severity and duration of hyponatremia, and the presence of symptoms. Two caveats:

1. ✖ be sure that hyponatremia is not due to CSW (p. 122) before restricting fluids
2. avoid too rapid correction and avoid correcting to normal or supranormal (overcorrection) sodium to reduce the risk of osmotic demyelination syndrome

## Osmotic demyelination syndrome

A complication associated with some cases of treatment for hyponatremia. While excessively slow correction of acute hyponatremia is associated with increased morbidity and mortality,<sup>14</sup> some cases of inordinately rapid treatment have been associated with osmotic demyelination syndrome (which includes central pontine myelinolysis (CPM) a rare disorder of pontine white matter<sup>15</sup> (► Fig. 5.2) and extrapontine myelinolysis (► Fig. 5.3), as well as other areas of cerebral white matter). First described in alcoholics,<sup>16</sup> producing insidious flaccid quadriplegia, mental status changes, and cranial nerve abnormalities with a pseudobulbar palsy appearance. In one review,<sup>17</sup> no patient developed CPM when treated slowly as outlined below. And yet, the rate of correction correlates poorly with CPM; it may be that the magnitude is another critical variable.<sup>18</sup> Features common to patients who develop CPM are<sup>17</sup>:



**Fig. 5.2 Central pontine myelinolysis (arrowhead).**  
Image: axial FLAIR MRI.



**Fig. 5.3 Osmotic demyelination.** Seen in pons (black arrowhead) & thalamus (white arrowhead). Image: coronal T2WI MRI.

- delay in the diagnosis of hyponatremia with resultant respiratory arrest or seizure with probable hypoxicemic event
- rapid correction to normo- or hypernatremia (> 135 mEq/L) within 48 hours of initiating therapy
- increase of serum sodium by > 25 mEq/L within 48 hours of initiation of therapy
- over-correcting serum sodium in patients with hepatic encephalopathy
- NB: many patients developing CPM were victims of chronic debilitating disease, malnourishment, or alcoholism and never had hyponatremia. Many had an episode of hypoxia/anoxia<sup>18</sup>
- presence of hyponatremia >24 hrs prior to treatment<sup>18</sup>

The only definitive treatment is treatment of the underlying cause.

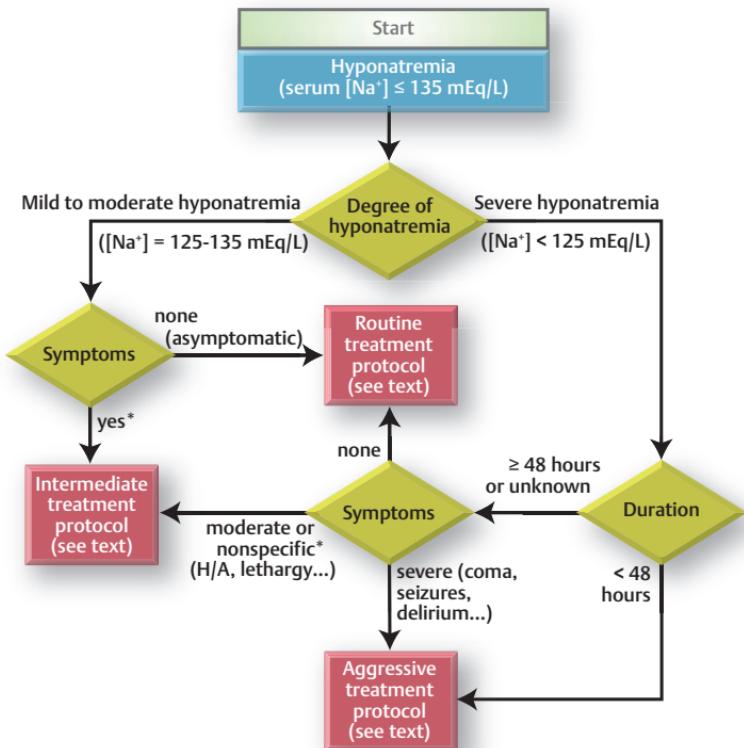
- if caused by anemia: usually responds to transfusion
- if caused by malignancy, may respond to antineoplastic therapy
- most drug-related cases respond rapidly to discontinuation of the offending drug

#### Treatment algorithms

► Fig. 5.4 is an algorithm for selecting the correct SIADH treatment protocol (detailed below).

► **Aggressive treatment protocol.** Indications (also refer to ► Fig. 5.4):

1. severe hyponatremia (serum  $[Na^+]$  < 125 mEq/L)



**Fig. 5.4 Treatment protocol selection for hyponatremia in SIADH (see text for protocol details).**

\* mild to moderate symptoms include: anorexia, headache, difficulty concentrating, irritability, dysgeusia, muscle weakness...

2. AND either
  - a) duration known to be < 48 hours
  - b) or severe symptoms (coma, seizures)

#### Treatment

- transfer patient to ICU
- interventions
  - 3% saline: start infusion 1–2 ml/kg body weight per hour (infusion rate may be doubled to 2–4 ml/kg/h for limited periods in patients with coma or seizures<sup>1</sup>)
  - and furosemide (Lasix®) 20 mg IV q d (furosemide accelerates the increase in [Na<sup>+</sup>] and prevents volume overload with subsequent increase in atrial natriuretic factor and resultant urinary dumping of the extra Na<sup>+</sup> being administered)
- monitoring and adjustments
  - check serum [Na<sup>+</sup>] every 2–3 hours and adjust infusion rate of 3% saline
    - goal: raise serum sodium by 1–2 mEq/L/hr<sup>20</sup> (use lower end of range for hyponatremia > 48 hours duration or unknown duration)
    - limits: do not exceed 8–10 mEq/L in 24 hrs and 18–25 mEq/L in 48 hrs<sup>1</sup> (use lower end of these ranges for hyponatremia > 48 hours duration or unknown duration) to reduce risk of CPM
  - measure K<sup>+</sup> lost in urine and replace accordingly

- if symptoms of osmotic demyelination occur (early symptoms are lethargy and affective changes, usually after initial improvement): deficits may improve by stopping treatment and modestly relowering the serum sodium e.g., with DDAVP<sup>21,22</sup>

► **Intermediate treatment protocol.** Indications (also refer to ► Fig. 5.4):

1. symptomatic nonsevere hyponatremia (serum  $[Na^+]$  = 125–135 mEq/L), or
2. severe hyponatremia (serum  $[Na^+]$  < 125 mEq/L), AND
  - a) duration > 48 hours or unknown AND
  - b) only moderate symptoms or nonspecific symptoms (e.g., H/A, or lethargy)

Treatment

1. interventions
  - a) 0.9% saline (normal saline) infusion
  - b) and furosemide (Lasix®) 20 mg IV q d
  - c) consider conivaptan for refractory cases
2. monitoring: check serum  $[Na^+]$  every 4 hours and adjust infusion rate of normal saline
3. goals:  $[Na^+]$  increase of 0.5–2 mEq/L/hr
4. limits: do not exceed 8–10 mEq/L in 24 hrs and 18–25 mEq/L in 48 hrs<sup>1</sup>

► **Routine treatment protocol and maintenance therapy.** Indications (also refer to ► Fig. 5.4):

1. asymptomatic nonsevere hyponatremia (serum  $[Na^+]$  = 125–135 mEq/L), or
2. severe hyponatremia (serum  $[Na^+]$  < 125 mEq/L) AND
  - a) duration > 48 hours or unknown AND
  - b) asymptomatic

Treatment

1. interventions
  - a) fluid restriction ► Table 5.4 for adults, for peds: 1 L/m<sup>2</sup>/day) while encouraging use of dietary salt and protein. Caution restricting fluids in hyponatremia following SAH (p. 1435).
  - b) for refractory cases, consider
    - demeclocycline: a tetracycline antibiotic that partially antagonizes the effects of ADH on the renal tubules.<sup>23,24,25</sup> Effects are variable, and nephrotoxicity may occur. R 300–600 mg PO BID
    - conivaptan (Vaprisol®): a nonpeptide antagonist of V1A & V2 vasopressin receptors. FDA approved for euvolemic and hypervolemic moderate-to-severe hyponatremia in hospitalized patients (NB: severe symptoms of seizures, coma, delirium... warrants aggressive treatment with hypertonic saline<sup>1</sup>). Use in the neuro-ICU has been described for treating elevated ICP when serum  $[Na]$  is not responding to traditional methods<sup>26</sup> (off-label use—use with caution). R loading dose 20 mg IV over 30 minutes, followed by infusions of 20 mg over 24 hours × 3 days. If serum  $[Na^+]$  are not rising as desired, the infusion may be increased to the maximal dose of 40 mg over 24 hours. Use is approved for up to 4 days total. Caution re drug interactions
    - lithium: not very effective and many side effects. Not recommended

## 5.2.6 Cerebral salt wasting

Cerebral salt wasting (CSW): renal loss of sodium as a result of intracranial disease, producing hyponatremia and a decrease in extracellular fluid volume.<sup>13</sup> CAUTION: CSW after aneurysmal SAH may mimic SIADH; however, there is usually also hypovolemia in CSW. In this setting, fluid restriction may exacerbate vasospasm induced ischemia.<sup>13,27,28,29</sup>

The mechanism whereby the kidneys fail to conserve sodium in CSW is not known, and may be either a result of a natriuretic factor or direct neural control mechanisms.

Laboratory tests (serum and urinary electrolytes and osmolalities) may be identical with SIADH and CSW.<sup>30</sup> Furthermore, hypovolemia in CSW may stimulate ADH release. To differentiate: CVP, PCWP, and plasma volume (a nuclear medicine study) are low in hypovolemia (i.e., CSW). ► Table 5.5 compares some features of CSW and SIADH, the two most important differences being extracellular volume and salt balance. An elevated serum  $[K^+]$  with hyponatremia is incompatible with the diagnosis of SIADH.

**Table 5.5** Comparison of CSW and SIADH<sup>13</sup>

Parameter	CSW	SIADH
★ Plasma volume	↓ (<35 mL/kg)	↑ or WNL
★ Salt balance	negative	variable
Signs & symptoms of dehydration	present	absent
Weight	↓	↑ or no Δ
PCWP	↓ (<8 mm Hg)	↑ or WNL
CVP	↓ (<6 mm Hg)	↑ or WNL
Orthostatic hypotension	+	±
Hematocrit	↑	↓ or no Δ
Serum osmolality	↑ or WNL <sup>a</sup>	↓
Ratio of serum [BUN]:[creatinine]	↑	WNL
Serum [protein]	↑	WNL
Urinary [Na <sup>+</sup> ]	↑↑	↑
Serum [K <sup>+</sup> ]	↑ or no Δ	↓ or no Δ
Serum [uric acid]	WNL	↓

Abbreviations: ↓ = decreased, ↑ = increased, ↑↑ = significantly increased, WNL = within normal limits, no Δ = no change, [ ] = concentration, + = present, ± = may or may not be present

<sup>a</sup>In reality, serum osmolality is usually ↓ in CSW

### Treatment of cerebral salt wasting (CSW)

✖ Caution! Restricting fluids (which is the treatment for SIADH) may be hazardous in the case of CSW (SIADH or CSW may occur after SAH) since dehydration increases blood viscosity, which exacerbates ischemia from vasospasm.<sup>28</sup> See Treatment of hyponatremia with SIADH (p. 119).

Treatment goals:

1. volume replacement to achieve *euvolemia* (avoid hypovolemia & induced hypervolemia)
2. positive salt balance
3. avoid excessively rapid correction of hyponatremia or overcorrection which may be associated with osmotic demyelination (p. 119) (as discussed under SIADH (p. 119))
4. ✖ avoid hyperchloremic acidosis due to overuse of NS or 3% sodium (see below)

Interventions:

1. treat hypovolemia aggressively
  - a) start with infusions of crystalloid, usually 0.9% NS at 100–125 mL/hr
  - b) for severe cases, 3% saline at 25–50 mL/hr is occasionally needed. It is effective in correcting hyponatremia<sup>31</sup> and appears to increase regional cerebral blood flow, brain tissue oxygen, and pH in patients with high-grade aSAH<sup>32</sup>
  - c) if fluid requirements remain large, switch to balanced crystalloid (e.g., Plasma-Lyte) to avoid hyperchloremic acidosis (see below)
  - d) PRBCs as needed (see discussion of optimal Hgb)
  - e) colloids may be used to supplement. Expensive as a replacement for crystalloids
2. ✖ do not give furosemide for CSW
3. salt may also be simultaneously replaced orally. Table salt is ≈ 99% NaCl: 1 tsp salt = 6 g salt = 2300 mg Na<sup>+</sup> = 100 mEq Na<sup>+</sup>. Salt tablets typically contain 1 g salt/tablet (other concentrations may be available) = 16.7 mEq Na<sup>+</sup>
4. blood products may be administered if anemia is present
5. medications
  - a) fludrocortisone acetate acts directly on the renal tubule to increase sodium absorption and helps correct hyponatremia, with a reduced need for fluids,<sup>33,34</sup> but significant complications of pulmonary edema, hypokalemia and HTN may occur. Dose: 0.2 mg IV or PO q d for CSW<sup>33</sup>
  - b) hydrocortisone administration has been associated with reduced natriuresis and a lower rate of hyponatremia<sup>35</sup>
  - c) urea: an alternative treatment using urea, may be applicable to the hyponatremia of either SIADH or CSW, and therefore may be used before the cause has been ascertained: urea

(Ureaphil®) 0.5 grams/kg (dissolve 40 gm in 100–150 ml NS) IV over 30–60 mins q 8 hrs.<sup>36</sup> Use NS + 20 mEq KCl/L at 2 ml/kg/hr as the main IV until the hyponatremia is corrected (unlike mannitol, urea does not increase ADH secretion). They supplemented with colloids (viz. 250 ml of 5% albumin IV q 8–12 hrs x 72 hrs)

► **Hyperchloremic acidosis.** The sodium burden accompanying NS and even hypertonic saline is usually better tolerated by post-aSAH patients than other critically ill patients because hyponatremia after aSAH is usually due to CSW, which is sodium losing. However, the chloride load associated with NS or 3% saline can produce hyperchloremic acidosis (HCA), a metabolic acidosis that augments the inflammatory response, decreases renal cortical blood flow,<sup>37,38</sup> reduces gastric mucosal perfusion, and → tachypnea → hypocapnia → ↑ risk of cerebral vasoconstriction. Rationale: normally serum Na<sup>+</sup> is 140 and Cl<sup>-</sup> is 100, but NS contains 154 mEq/L of Na<sup>+</sup> and Cl<sup>-</sup> (representing excess Cl<sup>-</sup>). Treating HCA is harder than prevention. To prevent HCA, avoid overuse of NS and reserve hypertonic saline for severe hyponatremia or acute increases in ICP. Consider using isotonic balanced crystalloid solutions, such as Plasma-Lyte A (pH = 7.4, osmolality = 294 mOsm/L, electrolytes (in mEq/L): Na<sup>+</sup> = 140, K<sup>+</sup> = 5, Cl<sup>-</sup> = 98, Mg<sup>2+</sup> = 1.5, acetate = 27, gluconate = 23) or Isolyte® for the main IV.

**Treatment of hyperchloremic acidosis:** substitute chlorine-free fluid for maintenance IV

- sodium bicarbonate (NaHCO<sub>3</sub>): 3 amps (150 mEq) in 1 L sterile water: produces a slightly hypertonic solution for sodium (1.26%), or
- sodium acetate: 140 mEq/L of sodium acetate is isotonic

## 5.3 Hypernatremia

### 5.3.1 General information

Definition: serum sodium > 150 mEq/L. In neurosurgical patients, this is most often seen in the setting of diabetes insipidus (DI).

Since normal total body water (TBW) is ≈ 60% of the patient's normal body weight, the patient's current TBW may be estimated by Eq (5.2).

$$\text{TBW}_{\text{current}} = \frac{[\text{Na}^+]_{\text{normal}} \times \text{TBW}_{\text{normal}}}{[\text{Na}^+]_{\text{current}}} = \frac{140 \text{mEq/L} \times 0.6 \times \text{usual body wt(kg)}}{[\text{Na}^+]_{\text{current}}} \quad (5.2)$$

The free water deficit to be replaced is given by Eq (5.3). Correction must be made slowly to avoid exacerbating cerebral edema. *One half* the water deficit is replaced over 24 hours, and the remainder is given over 1–2 additional days. Judicious replacement of deficient ADH in cases of true DI must also be made.

$$\begin{aligned} \text{free water deficit} &= 0.6 \times \text{usual body wt (kg)} - \text{TBW}_{\text{current}} \\ &= \frac{[\text{Na}^+]_{\text{current}} - 140 \text{mEq/L}}{[\text{Na}^+]_{\text{current}}} \times 0.6 \times \text{usual body wt (kg)} \end{aligned} \quad (5.3)$$

### 5.3.2 Diabetes insipidus

#### General information

#### Key concepts

- due to low levels of ADH (or, rarely, renal insensitivity to ADH)
- high output of dilute urine (< 300 mOsmol/kg or SG < 1.003) with normal or high serum osmolality and high serum sodium
- often accompanied by craving for water, especially ice-water
- if not managed carefully, there is a danger of severe dehydration, hypernatremia and, if severe, brain shrinkage with intracranial hemorrhage<sup>39</sup>

Diabetes insipidus (DI) is due to insufficient ADH activity at the kidneys, and results in the excessive renal loss of water (polyuria) and electrolytes. The name comes from the fact that the excessive urine is *insipid* (no taste) compared to the excessive urine of diabetes mellitus (mellitus meaning sweet, due to the spilling of sugar into the urine).

DI may be produced by two different etiologies:

- central or neurogenic DI: subnormal levels of ADH caused by hypothalamic-pituitary axis dysfunction. This is the type most often seen by neurosurgeons
- “nephrogenic DI”: due to relative resistance of the kidney to normal or supra-normal levels of ADH. Seen with some drugs (drugs: I)

Etiologies of DI<sup>40</sup>:

1. neurogenic (AKA central) diabetes insipidus: dysfunction of hypothalamus or pituitary
  - a) familial (autosomal dominant)
  - b) idiopathic
  - c) posttraumatic (brain injury, including surgery affecting the pituitary gland)
  - d) tumor: craniopharyngioma, metastasis, lymphoma...
  - e) granuloma: neurosarcoidosis, histiocytosis
  - f) infectious: hypophysitis, meningitis, encephalitis
  - g) autoimmune
  - h) vascular: aneurysm, Sheehan's syndrome (rarely causes DI)
  - i) dipsogenic DI: hypothalamic disorder that causes inappropriate thirst. Other causes include: psychogenic polydipsia (a mental health problem)
2. nephrogenic diabetes insipidus
  - a) familial (X-linked recessive)
  - b) hypokalemia
  - c) hypercalcemia
  - d) Sjögren's syndrome
  - e) drugs: lithium, demeclocycline, colchicine...
  - f) chronic renal disease: pyelonephritis, amyloidosis, sickle cell disease, polycystic kidney disease, sarcoidosis

## Central DI

85% of ADH secretory capacity must be lost before clinical DI ensues. Characteristic features: high urine output (polyuria) with low urine osmolality, and (in the conscious patient) craving for water (polydipsia), especially ice-water.

Differential diagnosis of DI:

1. (neurogenic) diabetes insipidus (true DI)
2. nephrogenic diabetes insipidus (see above)
3. psychogenic
  - a) idiopathic: from resetting of the osmostat (dipsogenic)
  - b) psychogenic polydipsia (excess free water intake)
4. osmotic diuresis: e.g., following mannitol, or with renal glucose spilling
5. diuretic use: furosemide, hydrochlorothiazide...

Central DI may be seen in the following situations:

1. following transsphenoidal surgery or removal of craniopharyngioma: (usually transient, therefore avoid long-acting agents until it can be determined if long-term replacement is required). Injury to the posterior pituitary or stalk usually causes one of three patterns of DI<sup>41</sup>:
  - a) transient DI: supra-normal urine output (UO) and polydipsia which typically normalizes ≈ 12–36 hrs post-op
  - b) “prolonged” DI: UO stays supra-normal either for a prolonged period (may be months – about two-thirds of these patients will return to near-normal at one year post-op due to release of ADH directly from the hypothalamus) or permanently
  - c) “triphasic response”: least common
    - phase 1: injury to pituitary reduces ADH levels for 4–5 days → DI (polyuria/polydipsia producing **hyponatremia**)
    - phase 2: cell death liberates ADH for the next 4–5 days → transient normalization or even SIADH-like water retention producing **normonatremia or hyponatremia**
    - (**NB:** there is a danger of inadvertently continuing vasopressin therapy beyond the initial phase 1 DI into this phase which can produce iatrogenic SIADH)

- phase 3: reduced or absent ADH secretion → DI (transient DI as in "a" above, or "prolonged" DI as in "b" above) producing **hypernatremia**
2. central herniation (p.325): shearing of pituitary stalk may occur
  3. brain death: hypothalamic production of ADH ceases
  4. with certain tumors:
    - a) PitNET/adenomas: DI is rare even with very large macroadenomas. DI may occur with pituitary apoplexy (p.865)
    - b) craniopharyngioma: DI usually only occurs postoperatively since damage to pituitary or lower stalk does not prevent production and release of ADH by hypothalamic nuclei
    - c) suprasellar germ cell tumors
    - d) rarely with a colloid cyst
    - e) hypothalamic tumors: Langerhans cell histiocytosis
  5. mass lesions pressing on hypothalamus: e.g., AComA aneurysm
  6. following head injury: primarily with basal (clival) skull fractures (p.1065)
  7. with encephalitis or meningitis
  8. drug induced:
    - a) ethanol and phenytoin can inhibit ADH release
    - b) exogenous steroids may seem to "bring out" DI because they may correct adrenal insufficiency (see below) and they inhibit ADH release
  9. granulomatous diseases
    - a) Wegener's granulomatosis (p.207): a vasculitis
    - b) sarcoidosis involving the hypothalamus (p.198)
  10. inflammatory: autoimmune hypophysitis (p.1656)<sup>42</sup> or lymphocytic infundibuloneurohypophysitis<sup>43</sup> (distinct conditions)

## Diagnosis

The following are usually adequate to make the diagnosis of DI, especially in the appropriate clinical setting:

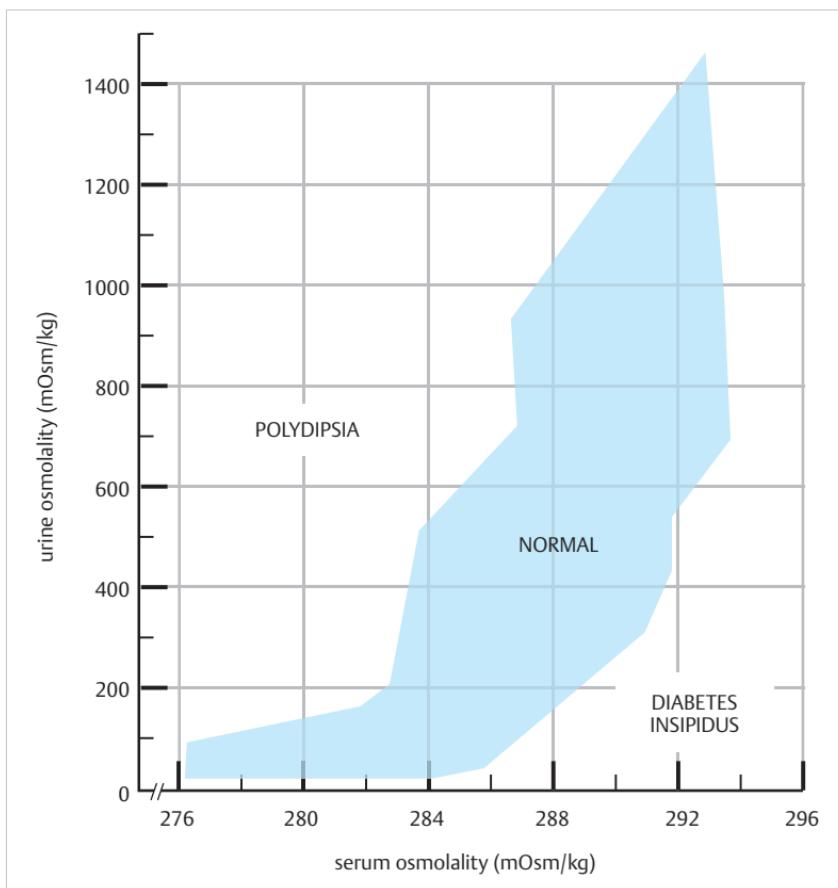
1. dilute urine:
  - a) urine osmolality < 300 mOsm/kg (usually 50–150). (NB: normally, urine osmolality averages between 500–800 mOsm/kg; extreme range: 50–1400). Urine osmolality > 800 mOsm/kg rules out DI and polydipsia
  - b) urine specific gravity (USG) in DI is usually < 1.003 (range: 1.001 to 1.005). USG is often used as a quick bedside test, but is not as accurate as urine osmolality since it can be affected by the size of the solute particles.  
NB: moieties that produce osmotic diuresis can falsely elevate USG and therefore mask DI by making the urine look more concentrated than it really is. Agents include: large doses of mannitol as may be used in head trauma, glucose (as in poorly controlled diabetes mellitus)
2. or the inability to concentrate urine to > 300 mOsm/kg in the presence of clinical dehydration
3. **polyuria:** urine output (UO) > 50 ml/kg/24 hours in adults and children ≥ 2 years (which is 3.5 L/day for a 70 kg patient).  
Pediatrics: > 150 ml/kg/24 hours at birth (gestational DI); > 100–110 ml/kg/24 hours up to age 2 years.
4. serum sodium: > 135 mmol/L (normal or above-normal)
5. normal adrenal function: DI cannot occur in primary adrenal insufficiency because a minimum of mineralocorticoid activity is needed for the kidney to make free water, thus steroids may "bring out" or "unmask" underlying DI by correcting adrenal insufficiency

### ► Interpretation

- absence of polyuria rules out DI and psychogenic polydipsia (pathological water drinking)
- polyuria with urine osmolality > 800 mOsm/kg also rules out DI and polydipsia
- polyuria with serum sodium < 135 mmol/L (normal or low normal) and plasma osmolality ≤ 280 mOsm/kg is diagnostic of primary polydipsia

Plotting simultaneous urine and serum osmolality on the graph in ► Fig. 5.5 may help.

1. low serum osmolality (≤ 280 mOsm/kg) usually indicates psychogenic polydipsia
2. if the point falls in the "normal" range, a *supervised* water deprivation test is needed to determine if the patient can concentrate their urine with dehydration (caution: see below)
3. high serum osmolality:
  - diagnosis of DI is established and no further testing to establish the diagnosis is required



**Fig. 5.5 Interpretation of simultaneous serum vs. urine osmolality in patients with polyuria.** (Provided by Arnold M. Moses, MD, used with permission.)

- further testing is only needed to differentiate central from nephrogenic DI.  
If desired to differentiate central from nephrogenic DI, give aqueous Pitressin® 5 U SQ; in central DI the urine osmolality should double within 1–2 hours
- 4. plotting more than one data point may help as some patients tend to “vacillate” around the border zones

#### Water deprivation test

For indeterminate cases, polyuria due to DI can be differentiated from psychogenic polydipsia by the water deprivation test (✖ CAUTION: perform only under close supervision as rapid and potentially fatal dehydration may ensue in DI). (Note: in compensated DI, serum osmolality is more likely to be lower and to overlap with normal.<sup>44</sup>) There is also a hypertonic saline infusion test (not covered here).

Water deprivation test protocol:

- stop IVs and make the patient NPO
- monitoring:
  - check urine osmolality q hr
  - check patient weight q 1 hr

- continue the test until one of the following occurs:
  - normal response occurs: urine output decreases, and urine osmolality rises to 600–850 mOsm/kg. Indicates primary polydipsia. Stop the test
  - 6–8 hours lapse
  - urine osmolality plateaus (i.e., changes < 30 mOsm in 3 consecutive hours)
  - patient loses 3% of body weight
- if the patient fails to demonstrate the normal response, then:
  - give exogenous ADH (5 U aqueous Pitressin® SQ), which normally increases urine osmolality to > 300 mOsm/kg
  - check urine osmolality 30 and 60 minutes later
  - compare highest urine osmolality after Pitressin® to the osmolality just before Pitressin® according to ► Table 5.6

5

**Table 5.6** Highest urinary osmolality after Pitressin in water deprivation test

$\Delta$ in urinary Osm	Interpretation
<5% increase	normal
6–67% increase	partial ADH deficiency
>67% increase	severe ADH deficiency

## Treatment of DI

### In conscious ambulatory patient

If DI is mild, and the patient's natural thirst mechanism is intact, instruct patient to drink *only* when thirsty and they usually "keep up" with losses and will not become overhydrated. Thirst is normally triggered when serum osmolality gets above  $\approx$  285 mOsm/kg.

If severe, the patient may not be able to maintain adequate intake of fluid or tolerate the frequent trips to bathroom. In these cases, treatment typically involves a vasopressin analogue. See below for a synopsis of vasopressin analogues. Typically start with either:

1. desmopressin (DDAVP®)
  - a) PO: 0.1 mg PO BID, adjust up or down PRN urine output (typical dosage range: 0.1–0.8 mg/d in divided doses)
  - b) nasal spray: 2.5 mcg (0.025 ml) by nasal insufflation BID, titrate up to 20 mcg BID as needed (the nasal spray may be used for doses that are multiples of 10 mcg)

OR
2. ADH enhancing medications (works primarily in chronic partial ADH deficiency. Will not work in total absence of ADH)
  - clofibrate (Atromid S®) 500 mg PO QJD
  - chlorpropamide: increases renal sensitivity to ADH
  - hydrochlorothiazide: thiazide diuretics may act by depleting  $\text{Na}^+$  which increases reabsorption in proximal tubules and shifting fluid away from distal tubules which is where ADH works. **R:** e.g., Dyazide® 1 PO q d (may increase up to 2 per day PRN)

### In conscious ambulatory patient with impaired thirst mechanisms

Conscious ambulatory patients whose thirst mechanism is *not* intact run the risk of dehydration (adipsic DI) or fluid overload. For these patients:

1. have patient follow UO and daily weights, balance fluid intake and output using antidiuretic medication as needed to keep UO reasonable
2. check serial labs (approximately q weekly) including serum sodium, BUN

### In non-ambulatory, comatose/stuporous, or brain-dead patient; see also Medical Management of the Potential Organ Donor (p. 336)

1. follow I's & O's q 1 hr, with urine specific gravity (SG) q 4 hrs and whenever urine output (UO)  $>$  250 ml/hr
2. labs: serum electrolytes with osmolality q 6 hrs
3. IV fluid management:  
BASE IV: D5 1/2 NS + 20 mEq KCl/L at appropriate rate (75–100 ml/hr)  
PLUS: replace UO above base IV rate ml for ml with 1/2 NS  
NB: for post-op patients, if the patient received significant intraoperative fluids, then they may have an *appropriate* post-op diuresis, in this case use 1/2 NS to replace only  $\approx$  2/3 of UO that exceeds the basal IV rate

4. if unable to keep up with fluid loss with IV (or NG) replacement (usually with UO > 300 ml/hr), then EITHER
- 5 U arginine vasopressin (aqueous Pitressin®) IVP/IM/SQ q 4–6 hrs (avoid tannate oil suspension due to erratic absorption and variable duration)  
OR
  - vasopressin IV drip: start at 0.2 U/min & titrate (max: 0.9 U/min)  
OR
  - desmopressin injection SQ/IV titrated to UO, usual adult dose: 0.5–1 ml (2–4 mcg) daily in 2 divided doses

### Vasopressin analogues

► Table 5.7 and ► Table 5.8 show dosing forms and duration of action of vasopressin analogues. Pitressin® is aqueous solution of 8-arginine vasopressin and should be used with caution in patients with vascular disease (especially coronary arteries). ✖ Caution – soundalikes: sometimes pitocin is confused with pitressin because of similarities of the names.

DDAVP (1-deamino-8-D-arginine vasopressin) AKA desmopressin. More potent and longer acting than vasopressin.

**Table 5.7 Available preparations of vasopressin analogues**

Generic name	Trade name	Route	Concentration	Availability	Manufacturer
desmopressin	DDAVP®	SQ, IM, IV	4 mcg/ml	1 & 10 ml	Aventis
desmopressin	DDAVP® Nasal Spray	nasal spray	100 mcg/ml, each spray delivers 10 mcg	50 doses per bottle	Aventis
desmopressin	DDAVP® Tablets	PO		0.1 & 0.2 mg	Aventis
arginine vasopressin	aqueous Pitressin®	SQ, IM	20 U/ml (50 mcg/ml)	0.5 and 1 ml	Parke-Davis

**Table 5.8 Mean time of hypertonic urine<sup>a</sup> (relative to plasma)<sup>b</sup>**

Generic name	Route	Dose	Mean duration of action <sup>c</sup>
desmopressin	SQ, IM, IV	0.5 mcg	8 hrs
desmopressin <sup>d</sup>	SQ, IM, IV	1.0 mcg	12 hrs
desmopressin	SQ, IM, IV	2.0 mcg	16 hrs
desmopressin	SQ, IM, IV	4.0 mcg	20 hrs
desmopressin	intranasal	10 mcg (0.1 ml)	12 hrs
desmopressin	intranasal	15 mcg (0.15 ml)	16 hrs
desmopressin	intranasal	20 mcg (0.2 ml)	20 hrs
arginine vasopressin	SQ, IM	5 U (12.5 mcg)	4 hrs (range: 4–8)

<sup>a</sup>provided by Arnold M. Moses, M.D., used with permission

<sup>b</sup>onset of antidiuretic action of these preparations is 30–45 minutes following administration (except pituitary powder in oil which takes 2–4 hrs to start working)

<sup>c</sup>times may vary from patient to patient, but are usually consistent in any individual

<sup>d</sup>Note: 1 mcg BID of desmopressin is as effective as 4 mcg q d, but would obviously be less expensive

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## 6 General Neurocritical Care

### 6.1 Parenteral agents for hypertension

#### Drug info: ★ Nicardipine (Cardene®)

Calcium channel blocker (CCB) that may be given IV. Does not require arterial line, *does not raise ICP*. Does not reduce heart rate, but may be used in conjunction with, e.g., labetalol or esmolol if that is desired. **Side effects:** H/A 15%, nausea 5%, hypotension 5%, reflex tachycardia 3.5%.

**R** start at 5 mg/hr IV (off label: 10 mg/hr may be used in situations where urgent reduction is needed). Increase by 2.5 mg/hr every 5–15 minutes up to a maximum of 15 mg/hr. Decrease to 3 mg/hr once control is achieved. **✗** Ampules contain 25 mg and *must be diluted* before administration.

#### Drug info: ★ Clevidepine (Cleviprex®)

IV calcium channel blocker (CCB) that is selective for vascular smooth muscle, with minimal effect on myocardial contractility or cardiac conduction. Reduces MAP by decreasing systemic vascular resistance. Is rapidly degraded by esterases in blood and extravascular tissues. **.** dosing does not need to be adjusted for liver or renal insufficiency. It is even metabolized rapidly in pseudocholinesterase deficient patients. Onset and end time are rapid which is an advantage for finely titrating blood pressure. Does not require arterial line, *does not raise ICP*. Does not reduce heart rate, but may be used in conjunction with, e.g., labetalol or esmolol if that is desired. **Side effects:** H/A 15%, nausea 5%, hypotension 5%, reflex tachycardia 3.5%. It is a lipid emulsion, with milky white appearance similar to propofol (possible confusion) and may induce hypertriglyceridemia when used simultaneously.<sup>1</sup>

In perioperative setting there is a 4–5% reduction in SBP within 4–5 minutes after infusion is started, and BP fully recovers in 5–15 minutes in most patients.

**R** start at 1–2 mg/hr IV. Titrate up by doubling the dose every 90 seconds until nearing the desired BP then smaller increments are made less frequently up to a maximum of 32 mg/hr (control is usually achieved at ≤ 16 mg/hr). The drug is *not diluted* before administration. **✗** Because of lipid loading, it is recommended to limit infusion to ≤ 1000 ml per 24 hours (an average of 21 mg/hr). There is little information regarding infusions > 72 hours.

#### Drug info: Nitroglycerin (NTG)

Raises ICP (less than with nitroprusside due to preferential venous action<sup>2</sup>). Vasodilator, venous > arterial (large coronaries > small). Result: decreases LV filling pressure (pre-load). Does not cause "coronary steal" (cf nitroprusside).

**R** 10–20 mcg/min IV drip (increase by 5–10 mcg/min q 5–10 min). For angina pectoris: 0.4 mg SL q 5 min × 3 doses, check BP before each dose.

#### Drug info: Labetalol (Normodyne®, Trandate®)

Blocks α<sub>1</sub> selective, β non-selective (potency < propranolol). ICP reduces or no change.<sup>3</sup> Pulse rate: decreases or no change. Cardiac output does not change. Does not exacerbate coronary ischemia. May be used in controlled CHF, but not in overt CHF. Contraindicated in asthma. Renal failure: same dose. **Side effects:** fatigue, dizziness, orthostatic hypotension.

##### Intravenous (IV)

Onset 5 mins, peak 10 mins, duration 3–6 hrs.

**R** IV: patient supine; check BP q 5 min; give each dose slow IVP (over 2 min) q 10 minutes until desired BP achieved; dose sequence: 20, 40, 80, 80, then 80 mg (300 mg total). Once controlled, use ≈ same total dose IVP q 8 hrs.

**R IV drip** (alternative): add 40 ml (200 mg) to 160 ml of IVF (result: 1 mg/ml); run at 2 ml/min (2 mg/min) until desired BP (usual effective dose = 50–200 mg) or until 300 mg given; then titrate rate (bradycardia limits dose, increase slowly since effect takes 10–20 minutes).

### Oral (PO)

Undergoes first pass liver degradation, therefore requires higher doses PO. PO onset: 2 hrs, peak: 4 hrs.

**R PO:** to convert IV → PO, start with 200 mg PO BID. To start with PO, give 100 mg BID, and increase 100 mg/dose q 2 day; max. = 2400 mg/day.

## Drug info: Enalaprilat (Vasotec®)

An angiotensin-converting enzyme (ACE) inhibitor. The active metabolite of the orally administered drug enalapril (see below). Acts within ≈ 15 mins of administration.

**Side effects:** hyperkalemia occurs in ≈ 1%. Do not use during pregnancy.

**R IV:** start with 1.25 mg slow IV over 5 mins, may increase up to 5 mg q 6 hrs PRN.

## Drug info: Esmolol (Brevibloc®)

Cardioselective short-acting beta blocker.<sup>4</sup> Being investigated for hypertensive emergencies. Metabolized by RBC esterase. Elimination half-life: 9 mins. Therapeutic response (> 20% decrease in heart rate, HR < 100, or conversion to sinus rhythm) in 72%. **Side effects:** dose related hypotension (in 20–50%), generally resolves within 30 mins of D/C. Bronchospasm less likely than other beta blockers. Avoid in CHF.

**R** 500 mcg/kg loading dose over 1 min, follow with 4 min infusion starting with 50 mcg/kg/min. Repeat loading dose and increment infusion rate by 50 mcg/kg/min q 5 mins. Rarely > 100 mcg/kg/min required. Doses > 200 mcg/kg/min add little.

## Drug info: Fenoldopam (Corlopam®)

Vasodilator. Onset of action < 5 minutes, duration 30 mins.

**R IV infusion** (no bolus doses): start with 0.1–0.3 mcg/kg/min, titrate by 0.1 mcg/kg/min q 15 min up to a maximum of 1.6 mcg/kg/min.

## Drug info: Propranolol (Inderal®)

Main use IV is to counteract tachycardia with vasodilators (usually doesn't lower BP acutely when used alone), but esmolol and labetalol are more commonly used for this.

**R IV:** load with 1–10 mg slow IVP, follow with 3 mg/hr. PO: 80–640 mg q d in divided doses.

## 6.2 Hypotension (shock)

### 6.2.1 Classification

- hypovolemic: first sign usually tachycardia. > 20–40% of blood volume loss must occur before perfusion of vital organs is impaired. Includes:
  - hemorrhage (external or internal)
  - bowel obstruction (with third spacing)

2. septic: most often due to gram-negative sepsis
3. cardiogenic: includes MI, cardiomyopathy, dysrhythmias (including A-fib)
4. neurogenic: e.g., paralysis due to spinal cord injury. Blood pools in venous capacitance vessels
5. miscellaneous
  - a) anaphylaxis
  - b) insulin reaction

## 6.2.2 Cardiovascular agents for shock

Plasma expanders. Includes:

1. crystalloids: normal saline has less tendency to promote cerebral edema than others; see IV fluids (p. 1050), under control of elevated ICP
2. colloids: e.g., hetastarch (Hespan®). **\* CAUTION:** repeated administration over a period of days may prolong PT/PTT and clotting times and may increase the risk of rebleeding in aneurysmal SAH (p. 1437).<sup>5</sup>
3. blood products: expensive. Risk of transmissible diseases or transfusion reaction

6

### Drug info: Dopamine

See ▶ Table 6.1 for a summary of the effects of dopamine (DA) at various dosages. DA is primarily a vasoconstrictor ( $\beta_1$  effects usually overridden by  $\alpha$ -activity). 25% of dopamine given is rapidly converted to norepinephrine (NE). At doses  $> 10$  mcg/kg/min one is essentially giving NE. May cause significant hyperglycemia at high doses.

R Start with 2–5 mcg/kg/min and titrate.

Table 6.1 Dopamine dosage

Dose (mcg/kg/min)	Effect	Result
0.5–2.0 (sometimes up to 5)	dopaminergic	renal, mesenteric, coronary, & cerebral vasodilatation, (+) inotrope
2–10	$\beta_1$	positive inotrope
$> 10$	$\alpha$ , $\beta$ & dopaminergic	releases nor-epi (vasoconstrictor)

### Drug info: Dobutamine (Dobutrex®)

Vasodilates by  $\beta_1$  (primary) and by increased CO from (+) inotropy ( $\beta_2$ ); result: little or no fall in BP, less tachycardia than DA. No alpha release nor vasoconstriction. May be used synergistically with nitroprusside. Tachyphylaxis after  $\approx 72$  hrs. Pulse increases  $> 10\%$  may exacerbate myocardial ischemia, more common at doses  $> 20$  mcg/kg/min. Optimal use requires hemodynamic monitoring. Possible platelet function inhibition.

R usual range 2.5–10 mcg/kg/min; rarely doses up to 40 used (to prepare: put 50 mg in 250 ml D5 W to yield 200 mcg/ml).

### Drug info: Amrinone (Inocor®)

Nonadrenergic cardiotonic. Phosphodiesterase inhibitor, effects similar to dobutamine (including exacerbation of myocardial ischemia). 2% incidence of thrombocytopenia.

R 0.75 mg/kg initially over 2–3 min, then drip 5–10 mcg/kg/min.

## Drug info: Phenylephrine (Neo-Synephrine®)

Pure alpha sympathomimetic. Useful in hypotension associated with tachycardia (atrial tachyarrhythmias). Elevates BP by increasing SVR via vasoconstriction, causes reflex increase in parasympathetic tone (with resultant slowing of pulse). Lack of  $\beta$  action means non-inotropic, no cardiac acceleration, and no relaxation of bronchial smooth muscle. Cardiac output and renal blood flow may decrease. Avoid in spinal cord injuries (p. 1139).

R pressor range: 100–180 mcg/min; maintenance: 40–60 mcg/min. To prepare: put 40 mg (4 amps) in 500 ml D5 W to yield 80 mcg/ml; a rate of 8 ml/hr = 10 mcg/min.

## Drug info: Norepinephrine

Primarily vasoconstrictor (? counterproductive in cerebral vasospasm, ? decreases CBF).  $\beta$ -agonist at low doses. Increases pulmonary vascular resistance.

## Drug info: Epinephrine (adrenalin globally)

R 0.5–1.0 mg of 1:10,000 solution IVP; may repeat q 5 minutes (may bolus per ET tube). Drip: start at 1.0 mcg/min, titrate up to 8 mcg/min (to prepare: put 1 mg in 100 ml NS or D5W).

## Drug info: Isoproterenol (Isuprel®)

Positive chronotropic and inotropic,  $\rightarrow$  increased cardiac O<sub>2</sub> consumption, arrhythmias, vasodilatation (by  $\beta_1$  action) skeletal muscle > cerebral vessels.

## Drug info: Levophed

Direct  $\beta$  stimulation (positive inotropic and chronotropic).

R start drip at 8–12 mcg/min; maintenance 2–4 mcg/min (0.5–1.0 ml/min) (to prepare: put 2 mg in 500 ml NS or D5 W to yield 4 mcg/cc).

## 6.3 Acid inhibitors

### 6.3.1 Stress ulcers in neurosurgery

See reference.<sup>6</sup>

The risk of developing stress ulcers (SU) AKA Cushing's ulcers is high in critically ill patients with CNS pathology. These lesions are AKA Cushing's ulcers due to Cushing's classic treatise.<sup>7</sup> 17% of SUs produce clinically significant hemorrhage. CNS risk factors include intracranial pathology: brain injury (especially Glasgow Coma scale score <9), brain tumors, intracerebral hemorrhage, SIADH, CNS infection, ischemic stroke, as well as spinal cord injury. The odds are increased with the coexistence of extra-CNS risk factors including long-term use of steroids (usually > 3 weeks), burns > 25% of body surface area, hypotension, respiratory failure, coagulopathies, renal or hepatic failure and sepsis.

The pathogenesis of SUs is incompletely understood, but probably results from an imbalance of destructive factors (acid, pepsin & bile) relative to protective factors (mucosal blood flow, mucus-bicarbonate layer, endothelial cell replenishment & prostaglandins).<sup>6</sup> CNS pathology, especially that involving the diencephalon or brainstem, can lead to reduction of vagal output which leads to hypersecretion of gastric acid and pepsin. There is a peak in acid and pepsin production 3–5 days after CNS injury.

### 6.3.2 Prophylaxis for stress ulcers

There is strong evidence that reduction of gastric acid (whether by antacids or agents that inhibit acid secretion) reduces the incidence of GI bleeding from stress ulcers in critically ill patients. Elevating gastric pH > 4.5 also inactivates pepsin.

Other therapies that don't involve alterations of pH that may be effective include sucralfate (see below) and enteral nutrition (controversial).<sup>6</sup> Titrated antacids or sucralfate appear to be superior to H2 antagonists in reducing the incidence of SU's.

Routine prophylaxis when steroids are used is not warranted unless one of the following risk factors are present: prior PUD, concurrent use of NSAIDs, hepatic or renal failure, malnourishment, or prolonged steroid therapy > 3 weeks.

### 6.3.3 Possible increased pneumonia and mortality from altering gastric pH

Whereas bringing gastric pH to a more neutral level reduces the risk of SU's, pH > 4 permits bacterial colonization of the normally sterile stomach. This may increase the risk of pneumonia from aspiration, and there is a suggestion that mortality may also be increased.<sup>8</sup> Sucralfate may be as effective in reducing bleeding, but may be associated with lower rates of pneumonia and mortality. There is insufficient data to determine the net result of sucralfate compared to no treatment.<sup>8</sup>

### 6.3.4 Histamine2 (H2) antagonists

#### Drug info: Ranitidine (Zantac®)

**R** Adult age ≤ 65 yrs: 150 mg PO BID, or 50 mg IVPB q 8 hrs. For age > 65 with normal renal function: 50 mg IV q 12 hrs.

IV drip (provides a more consistently higher pH without peaks and troughs; some controversy that this may increase gastric bacterial concentration with increased risk of aspiration pneumonia has not been borne out): 6.25 mg/hr (e.g., inject 150 mg into 42 ml of IVF yielding 3.125 mg/ml, run at 2 ml/hr).

#### Drug info: Famotidine (Pepcid®)

**R** Adult: 20 mg PO q hs for maintenance; 40 mg PO q hs for active ulcer therapy; IV: 20 mg q 12 hrs (for hypersecretory conditions, 20 mg IVPB q 6 hrs).<sup>9</sup> **Supplied:** 20 & 40 mg tablets, 40 mg/5 ml suspension, and 20 & 40 mg orally disintegrating tablets as Pepcid RPD. Available OTC in 10 mg tablets as Pepcid AC. Available IV.

#### Drug info: Nizatidine (Axic®)

**R** 300 mg PO q d or 150 mg PO BID. **Supplied:** 150 & 300 mg pulvules. Available OTC in 75 mg tablets as Axic AR.

### 6.3.5 Gastric acid secretion inhibitors (proton pump inhibitors)

These agents reduce gastric acid by specific inhibition of the final step in acid secretion by gastric parietal cells (by inhibiting the (H<sup>+</sup>, K<sup>+</sup>)-ATPase enzyme system on the cell surface, the so-called "acid pump"). They block acid secretion regardless of the stimulus (Zollinger-Ellison syndrome, hypergastrinemia...). Full recovery of acid secretion upon discontinuation may not occur for weeks. **X** Not indicated for long-term treatment as the trophic effects of the resultant elevated levels of gastrin may lead to gastric carcinoid tumors.

## Drug info: Omeprazole (Prilosec®)

Inhibition of some hepatic P-450 enzymes results in reduced clearance of warfarin and phenytoin. Decreases the effectiveness of prednisone.

**R** Adult: for peptic ulcers and gastro-esophageal reflux disease (GERD) 20–40 mg PO daily. For Zollinger-Ellison syndrome: 20 mg PO q d to 120 mg PO TID (dose adjusted to keep basal acid output <60 mEq/hr). **Side effects:** N/V, H/A, diarrhea, abdominal pain, or rash in 1–5% of patients. **Supplied:** 10, 20 & 40 mg delayed-release capsules. Available OTC in 20.6 mg tablets as Prilosec OTC.

## Drug info: ★ Lansoprazole (Prevacid®)

Found not to have an affect on a number of other drugs metabolized by cytochrome P-450 including phenytoin, warfarin, and prednisone.

**R** Adult: 15 mg (for duodenal ulcer, GERD, or maintenance therapy) or 30 mg (for gastric ulcer or erosive esophagitis) PO q d, short-term treatment × 4 wks. **Supplied:** 15 & 30 mg delayed-release capsules.

## Drug info: Pantoprazole (Protonix®)

**R** PO: 40 mg PO q d for up to 8 wks. IV: 40 mg IV q d × 7–10 d. **Supplied:** PO: 40 mg delayed-release capsules.

### 6.3.6 Miscellaneous

## Drug info: Sucralfate (Carafate®)

Minimally absorbed from GI tract. Acts by coating ulcerated areas of mucosa, does not inhibit acid secretion. This may actually result in a lower incidence of pneumonia and mortality than agents that affect gastric pH (see above).

**R** 1 gm PO QID on an empty stomach. Do not give antacids within one half-hour of sucralfate.

## 6.4 Rhabdomyolysis

### 6.4.1 Background and pathophysiology

1. **rhabdomyolysis (RM):** a syndrome caused by injury to skeletal muscle → leakage of intracellular contents (potassium, phosphate, CPK, urate, and myoglobin) into plasma that may be toxic to kidneys
2. **clinical triad:** muscle weakness, myalgias, and dark urine
3. **myoglobin (Mgb)** is an oxygen binding protein in muscle that accepts oxygen from circulating hemoglobin. After muscle injury, plasma Mgb levels may exceed the capacity of the normal clearing mechanisms (which includes haptoglobin binding) and Mgb can precipitate in glomerular filtrate causing renal tubular obstruction, direct nephrotoxicity, intrarenal vasoconstriction, and acute kidney injury. Mgb appears quickly in the blood and is rapidly cleared within 24 hours. If Mgb spills into the urine (myoglobinuria) it can cause urine to test positive for "blood." Reference blood levels: 0–85 ng/ml.
4. **creatine phosphokinase (CPK)** AKA creatine kinase (CK) is found mainly in the brain (CK-BB), skeletal muscle (CK-MM) and cardiac muscle (CK-MB & CK-MM). In muscle, CPK replenishes ATP by catalyzing a reaction between creatine phosphate and ADP. The appearance of CPK in the blood lags behind Mgb by a few hours, peaks in 24–36 hours, decreases at 30–40% per day, and

remains elevated for several days. It is used as a marker for the diagnosis and assessment of the severity of muscular injury. Reference range: 60–174 IU/L

5. acute kidney injury (AKI) is due to:
  - a) decreased extracellular volume + vasoactive substances → renal vasoconstriction and
  - b) ferrihemate, which is formed from myoglobin at a pH < 5.6
6. vasoconstriction/ischemia deplete renal tubular ATP formation, enhancing tubular cell damage and myoglobin precipitation causes formation of obstructive casts
7. risk of renal injury is low when initial CPK levels are < 15,000–20,000 U/L (though may occur at lower levels in patients with sepsis, dehydration, or acidosis)

## 6.4.2 Etiology and epidemiology

1. trauma & muscle compression/crush → direct injury to sarcolemma & occlusion of muscular vessels
2. excluding trauma, neurosurgeons are most likely to encounter RM in the setting of prolonged operations, especially spine surgery in the prone position, but also possibly even with minimally invasive lateral approach<sup>10</sup>
3. other nontraumatic etiologies: infection, metabolic derangement, neuroleptic malignant syndrome, malignant hyperthermia, drugs, EtOH, environmental toxins, extreme muscular activity, sickle cell trait
4. incidence of myoglobin-induced AKI in adult rhabdomyolysis (all causes) ranges from 17–35%
5. ≈ 28–37% of adult patients require short-term hemodialysis
6. rhabdomyolysis accounts for 5–20% of all adult cases of AKI

## 6.4.3 Management and treatment

**Proactive intervention:** for patients at risk for rhabdomyolysis (e.g., spine surgery lasting > 5 hours), it may be helpful to proactively check CPK & myoglobin (Mgb) levels post-op, and, when elevated, to aggressively hydrate before the full-blown syndrome develops

Predictors of potential AKI include<sup>11</sup>:

1. peak CPK level > 6000 IU/L, and especially if > 15,000 IU/L
2. dehydration: hematocrit > 50, serum sodium level > 150 mEq/L, orthostatic hypotension, pulmonary capillary wedge pressure < 5 mm Hg, urinary fractional excretion of sodium < 1%
3. sepsis
4. hyperkalemia or hyperphosphatemia on admission
5. hypoalbuminemia

**Treatment:** there is no Level 1 evidence for the treatment of rhabdomyolysis (RM).<sup>12</sup> Traditionally, RM has been treated with IV fluids with bicarbonate (in an effort to alkalinize the urine) along with PRN diuretics. These adjuncts to IV hydration have been called into question,<sup>13</sup> and it appears that prompt recognition and appropriate volume replacement may be all that is needed to avoid AKI in most patients.

The following is one possible protocol for adults (modified<sup>12</sup> available online).

In an adult with RM and CPK ≥ 5000 IU/L AND acute renal failure (Cr ≥ 2.9 mg/dL):

1. general measures:
  - a) ABCs, I/O monitoring (foley catheter), correction of electrolyte abnormalities, correction of underlying cause if possible to prevent end organ complications, invasive hemodynamic monitoring may be needed to ensure adequate volume resuscitation
  - b) minimize other potential renal stressors: nephrotoxic antibiotics, iodinated IV contrast, ACE inhibitors, NSAIDs... (Level III<sup>12</sup>)
  - c) EKG if hyperkalemia present
2. the mainstay of treatment is expansion of extracellular volume → increased glomerular filtration rate (GFR), oxygen delivery and dilution of myoglobin and other renal tubular toxins
3. start with IV fluid (IVF): lactated ringers (LR) is preferred over NS (Level II<sup>12</sup>) to maintain urine output (UO) ≥ 1 ml/kg/hr
4. if this not possible with IVF alone, add sodium bicarbonate (NaHCO<sub>3</sub>) and mannitol as follows until CPK shows a steady downtrend or falls below 5000 IU/L or UO averages > 100 ml/hr for 12 consecutive hours
  - a) if serum sodium ≤ 147 mEq/L: use 1/2 NS + 100 mEq NaHCO<sub>3</sub>/L @ 125 ml/hr
  - b) if serum sodium > 147 mEq/L: use D5W + 100 mEq NaHCO<sub>3</sub>/L @ 125 ml/hr
  - c) mannitol: 12.5 g IV q 6 hours

5. in patients receiving NaHCO<sub>3</sub>, check daily ABG & electrolytes
  - a) if serum pH < 7.15 or serum NaHCO<sub>3</sub> ≤ 15 mg/dL: bolus with 100 mEq NaHCO<sub>3</sub> and recheck ABG in 3 hours, repeat until pH is > 7.5 AND serum NaHCO<sub>3</sub> is > 15
  - b) discontinue bicarbonate if pH ≥ 7.5
  - c) hold NaHCO<sub>3</sub> for hypernatremia
6. serial CPK measurements are not required after the peak is passed (Level III<sup>12</sup>)
7. dialysis may be required in patients with oliguric renal failure, persistent hyperkalemia, pulmonary edema, congestive heart failure, or persistent metabolic acidosis

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# 7 Sedatives, Paralytics, Analgesics

## 7.1 Sedatives and paralytics

### 7.1.1 Richmond agitation-sedation scale (RASS)

A validated scale<sup>1,2</sup> for quantitating the level of sedation, e.g., when titrating sedatives for agitated patients (► Table 7.1). Positive numbers = agitation, negative numbers = sedation

Procedure for performing RASS assessment:

1. on observation, patient is alert, restless or agitated: score 0 to +4
2. if patient is not alert, state patient's name and verbally instruct to open eyes and look at speaker: score -1 to -3
3. if no response to verbal stimulus, physically stimulate by shaking shoulder and/or sternal rub: score -4 or -5

**Table 7.1** Richmond agitation-sedation scale

	Score	Term	Description	
Agitation	+ 4	combative	overly combative, violent, immediate danger to staff	
	+ 3	very agitated	pulls or removes tubes or catheters; aggressive	
	+ 2	agitated	frequent non-purposeful movements, fights ventilator	
	+ 1	restless	anxious, but movements not aggressive/vigorous	
	0	alert & calm		
Sedation	-1	drowsy	not fully alert, but has sustained awakening (eye-opening/contact) to voice ( $\geq 10$ seconds)	verbal stimulation
	-2	light sedation	briefly awakens with eye contact to voice ( $< 10$ seconds)	
	-3	moderate sedation	movement or eye opening to voice (no eye contact)	
	-4	deep sedation	no response to voice, but movement or eye-opening to physical stimulation	physical stimulation
	-5	unarousable	no response to voice or physical stimulation	

### 7.1.2 Conscious sedation

Use of these agents requires ability to provide immediate emergency ventilatory support (including intubation). Agents include:

1. midazolam (Versed®) (p. 1050) with fentanyl
2. fentanyl
3. pentobarbital (Nembutal®): a barbiturate. **R** for 70 kg adult: 100 mg slow IVP

### Drug info: Methohexitol (Brevital®)

More potent and shorter acting than thiopental (useful e.g., for percutaneous rhizotomy where patient needs to be sedated and awakened repeatedly). Lasts 5–7 min. Similar cautions with the added problem that methohexitol may *induce* seizures. May no longer be available in the U.S.

**R** Adult: 1 gm% solution (add 50 ml diluent to 500 mg to yield 10 mg/ml), 2 ml test dose, then 5–12 ml IVP at rate of 1 ml/5 secs, then 2 to 4 ml q 4–7 min PRN.

### 7.1.3 Sedation

Generally requires intubation and mechanical ventilatory support in the ICU. Doses are generally lower than those used by anesthesiologists for general anesthesia.

## Drug info: Thiopental (Pentothal®)

A short acting barbiturate. 1st dose causes unconsciousness in 20–30 secs (circulation time), depth increases up to 40 secs, duration = 5 mins (terminated by redistribution), consciousness returns over 20–30 mins.

**Side effects:** dose-related respiratory depression, irritation if extravasated, intra-arterial injection → necrosis, agitation if injected slowly, an *antianalgesic*, myocardial depressant, hypotension in hypovolemic patients.

R: Adult: initial concentration should not exceed 2.5%, give 50 mg test dose moderately rapid IVP, then if tolerated give 100–200 mg IVP over 20–30 secs (500 mg may be required in large patient).

## Drug info: ★ Remifentanil (Ultiva®)

Ultrashort acting micro-opioid receptor agonist. Potency similar to fentanyl. Rapidly crosses BBB. Onset: < 1 min. Offset: 3–10 mins. *Lowers ICP*. Metabolism: non-hepatic hydrolysis by nonspecific blood and tissue esterases, ↘ no accumulation. Synergy with thiopental, propofol, isoflurane, midazolam requires reducing doses of these agents by up to 75%. **Side effects:** bradycardia, hypotension (these side effects may be blunted by pretreatment with anticholinergics), N/V, muscle rigidity, pruritus (especially facial) dose-dependent respiratory depression at doses > 0.05 mcg/kg/min.

R: Adult: avoid bolus doses. Start with drip of 0.05 mcg/kg/min. Titrate in 0.025 mcg/kg/min increments to a maximum of 0.1–0.2 mcg/kg/min. Add a sedative if adequate sedation not achieved at maximum dose. Wean infusion in 25% decrements over 10 minutes after extubation. **Supplied:** vials of 1, 2 or 5 mg powder to be reconstituted to 1 mg/ml solution.

## Drug info: Fentanyl (Sublimaze®)

Narcotic, potency ≈ 100 × morphine. High lipid solubility → rapid onset. Offset (small doses): 20–30 mins. Unlike morphine and meperidine, does not cause histamine release. *Lowers ICP*. **Side effects:** dose dependent respiratory depression, large doses given rapidly may cause chest wall rigidity. Repeated dosing may cause accumulation. Diminished sensitivity to CO<sub>2</sub> stimulation, may persist longer than the depression of respiratory rate (up to 4 hours).

R: Adult: 25–100 mcg (0.5–2 ml) IVP, repeat PRN. **Supplied:** 50 mcg/ml; requires refrigeration.

## Drug info: ★ Propofol (Diprivan®)

A sedative hypnotic. Also useful in high doses during aneurysm surgery as a neuroprotectant (p. 1466). Protection seems to be less than with barbiturates. Offset time increases after ≈ 12 hours of use.

R for sedation: start at 5–10 mcg/kg/min. Increase by 5–10 mcg/kg/min q 5–10 minutes PRN desired sedation (up to a max of 50 mcg/kg/min).

**Side effects:** include Propofol infusion syndrome: hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, myocardial failure, rhabdomyolysis, renal failure and sometimes death.<sup>3</sup> First identified in children, but may occur at any age. NB: *metabolic acidosis* of unknown etiology in a patient on propofol is propofol infusion syndrome until proven otherwise. Use with caution at doses > 50 mcg/kg/min or at any dose for > 48 hrs. Also note that the lipid carrier provides 1.1 kCal/ml and hypertriglyceridemia may occur.

**Supplied:** 500 mg suspended in a 50 ml bottle of fat emulsion. The bottle and tubing must be changed every 12 hours since it contains no bacteriostatic agent.

## Drug info: ★ Precedex® (Dexmedetomidine)

An alpha-2 adrenoceptor agonist. Acts in locus ceruleus and dorsal root ganglia. Has both sedative and analgesic properties and dramatically reduces the risk of respiratory depression and the amount of narcotic analgesics required. Reduces shivering.

**R:** usual loading dose is 1 mcg/kg IV over 10 minutes (loading dose not needed if patient already sedated with other agents), followed by continuous IV infusion of 0.2–1.0 mcg/kg/hr titrated to desired effect, not to exceed 24 hours (for short sedation or use as a “transition” drug). **Side effects:** clinically significant bradycardia and sinus arrest have occurred in young, healthy volunteers with increased vagal tone (anticholinergics such as atropine 0.2 mg IV or glycopyrrolate 0.2 mg IV may help). Use with caution in patients with advanced heart block, baseline bradycardia, using other drugs that lower heart rate, and hypovolemia. **Supplied:** 2 ml vials of 100 mcg/ml to be diluted in 48 ml NS for a final concentration of 4 mcg/ml for IV use.

## 7.2 Paralytics (neuromuscular blocking agents)

### 7.2.1 General information

**CAUTION:** requires ventilation (intubation or Ambu-bag/mask). Reminder: paralyzed patients may still be conscious and therefore able to feel pain, thus the simultaneous use of sedation is required for conscious patients.

Early routine use in head-injured patients lowers ICP (e.g., from suctioning<sup>4</sup>) and mortality, but does not improve overall outcome.<sup>5</sup>

Neuromuscular blocking agents (NMBAs) are classified clinically by time to onset and duration of paralysis as shown in ► Table 7.2. Additional information for some agents follows the table along with some considerations for neurosurgical patients.

Table 7.2 Onset and duration of muscle relaxants

Clinical class	Agent	Trade name (®)	Onset (min)	Duration (min)	Spontaneous recovery (min)	Comment
Ultra-short	succinylcholine	Anectine	1	5–10	20	shortest onset and duration; plasma cholinesterase dependent; many side effects
Short	rocuronium	Zemuron	1–1.5	20–35	40–60	close to succinylcholine in onset in large doses; some vagolytic action in children
Intermediate	vecuronium	Norcuron	3–5	20–35	40–60	minimal cardiovascular side effects (bradycardia reported); no histamine release
	cisatracurium	Nimbex	1.5–2	40–60	60–80	no histamine release at recommended doses

### 7.2.2 Ultra-short acting paralytics

## Drug info: Succinylcholine (Aneccine®)

The only depolarizing ganglionic blocker (the rest are competitive blockers). Rapidly inactivated by plasma pseudocholinesterases. A single dose produces fasciculations then paralysis. Onset: 1 min. Duration of action: 5–10 min.

## Indications

Due to significant side effects (see below), use is now limited primarily to the following indications.  
 Adults: generally recommended only for emergency intubations where the airway is not controlled.  
 In children: only when intubation is needed with a full stomach, or if laryngospasm occurs during attempted intubation using other agents.

## Side effects

✖ CAUTIONS: usually increases serum K<sup>+</sup> by 0.5 mEq/L (on rare occasion causes severe *hyperkalemia* ([K<sup>+</sup>] up to 12 mEq/L) in patients with neuronal or muscular pathology, causing cardiac complications which cannot be blocked), therefore contraindicated in acute phase of injury following major burns, multiple trauma or extensive denervation of skeletal muscle or upper motor neuron injury. Do not use for routine intubations in adolescents and children (may cause cardiac arrest even in apparently healthy youngsters, many of whom have undiagnosed myopathies). Linked to malignant hyperthermia (p. 112).

May cause dysrhythmias, especially sinus bradycardia (treat with atropine). May get autonomic stimulation from ACh-like action → HTN, and brady- or tachycardia (especially in pediatrics with repeated doses). The fasciculations may increase ICP, intragastric pressure, and intraocular pressure (contraindicated in penetrating eye injury, especially to anterior chamber; OK in glaucoma).

Precarization with a “priming dose” of a nondepolarizing blocker (usually ≈ 10% of the intubating dose, e.g., *pancuronium* 0.5–1 mg IV 3–5 minutes prior to succinylcholine) in patients with elevated ICP or increased intraocular pressure (to ameliorate further pressure increases during fasciculation phase) and in patients who have eaten recently (controversial<sup>6</sup>). Phase II block (similar to nondepolarizing blocker) may develop with excessive doses or in patients with abnormal pseudocholinesterase.

## Dosing

R Adult: 0.6–1.1 mg/kg (2–3 ml/70 kg) IVP (err on high side to allow time for procedure & to avoid multi-dosing complications), may repeat this dose × 1.

R Peds (CAUTION: Not recommended for routine use, see above) Children: 1.1 mg/kg. Infants (< 1 month): 2 mg/kg.

Supplied: 20 mg/ml concentration.

## 7.2.3 Short acting paralytics

### Drug info: Rocuronium (Zemuron®)

In large doses, has speed of onset that approaches succinylcholine. However, in these doses, paralysis usually lasts ≈ 1–2 hrs. Expensive.

R Adult: initial dose 0.6–1 mg/kg. May be used as infusion of 10–12 mcg/kg/min.

## 7.2.4 Intermediate acting paralytics

### Drug info: ★ Vecuronium (Norcuron®)

Nondepolarizing (competitive) NMBA. Adequate paralysis for intubation within 2.5–3 minutes of administration. About one-third more potent than *pancuronium*, shorter duration of action (lasts ≈ 30 minutes after initial dose). Unlike *pancuronium*, very little vagal (i.e., cardiovascular) effects. No CNS active metabolites. Does not affect ICP or CPP. Hepatically metabolized. Due to active metabolites, paralysis has been reported to take 6 hrs to 7 days to recede following discontinuation of the drug after ≥ 2 days use in patients with renal failure.<sup>7</sup> Must be mixed to use.

## Dosing

Supplied: 10 mg freeze-dried cakes requiring reconstitution. Use within 24 hrs of mixing.

R Adult and children > 10 years of age: 0.1 mg/kg (for most adults use 8–10 mg as initial dose).

May repeat q 1 hr PRN. Infusion: 1–2 mcg/kg/min.

R Pediatric: children (1–10 yrs) require slightly higher dose and more frequent dosing than adult.

Infants (7 weeks–1 yr): slightly more sensitive on a mg/kg basis than adults, takes ≈ 1.5 × longer to recover. Use in neonates and continuous infusion in children is insufficiently studied.

## Drug info: ★ Cisatracurium (Nimbex®)

Nondepolarizing (competitive) blocker. This isomer of atracurium does not release histamine unlike its parent compound (see below). Provides about 1 hour of paralysis. Also undergoes Hofmann degradation, with laudanosine as one of its metabolites.

R Adult and children > 12 years of age: 0.15 or 0.2 mg/kg as part of propofol/nitrous oxide/oxygen induction-intubation technique produces muscle paralysis adequate for intubation within 2 or 1.5 minutes, respectively. Infusion: 1–3 mcg/kg/min.

R Pediatric: children (2–12 yrs): 0.1 mg/kg given over 5–10 seconds during inhalational or opioid anesthesia.

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### 7.2.5 Reversal of competitive muscle blockade

Reversal is usually not attempted until patient has at least 1 twitch to a train of 4 stimuli, otherwise reversal may be incomplete if patient is profoundly blocked and blockade may reoccur as the reversal wears off (a response of 1/4 indicates 90% muscle blockade).

- neostigmine (Prostigmin®): R 2.5 mg (minimum) to 5 mg (maximum) IV  
(start low, no efficacy from > 5 mg and can produce severe weakness especially if the maximum dose is exceeded in the absence of neuromuscular blockade)
- PLUS (to prevent bradycardia...),
  - EITHER
    - atropine R 0.5 mg for each mg of neostigmine
  - OR
    - glycopyrrolate (Robinul®) R 0.2 mg for each mg of neostigmine

► **Reversal of rocuronium or vecuronium.** Sugammadex (Bridion®) is the first selective relaxant binding agent and is specific for aminosteroid non-depolarizing NMBA (e.g., rocuronium or vecuronium). In the European Union, in children & adolescents, sugammadex should be only used to reverse rocuronium. Sugammadex encapsulates the NMBA molecule so that it is unable to bind to the acetylcholine receptor at the neuromuscular junction. Unlike neostigmine, sugammadex does not inhibit acetylcholinesterase which would produce cholinergic side effects, so co-administration of antimuscarinic agents (e.g., atropine or glycopyrrolate) is not required except for the rare occasion when clinically significant bradycardia follows administration.

- Dosing: sugammadex is given as an IV bolus over 10 secs
- for moderate block (reappearance of the second twitch in TOF): R 2 mg/kg IV bolus over 10 secs
  - for deep block (1-2 posttetanic count (PTC) but no twitch response to TOF): R 4 mg/kg IV bolus

## 7.3 Analgesics

### 7.3.1 General information

For a discussion of types of pain and pain procedures (p. 518).

Three types of pain medication

1. non-opioid pain medication (see below)
  - a) nonsteroidal anti-inflammatory drugs: aspirin, ibuprofen...
  - b) acetaminophen
2. opioids (p. 146)
  - a) agonists
  - b) partial agonists
  - c) mixed agonist/antagonists
3. drugs that are not strictly analgesics, but which act as adjuvants (p. 149) when added to any of the above: tricyclic antidepressants, antiseizure medications, caffeine, hydroxyzine, corticosteroids (p. 149)

### 7.3.2 Guiding principles

The key to good pain control is the early use of adequate levels of effective analgesics. For cancer pain, scheduled dosing is superior to PRN dosing, and “rescue” medication should be available.<sup>8</sup>

Nonopioid analgesics should be continued as more potent medications and invasive techniques are utilized.

### 7.3.3 Analgesics for some specific types of pain

#### Visceral or deafferentation pain

May sometimes be effectively treated with tricyclic antidepressants (p. 519).

Tryptophan may be effective (p. 149).

Carbamazepine (Tegretol®) may be useful for paroxysmal, lancinating pain.

#### Pain from metastatic bone disease

Steroids, aspirin, or NSAIDs are especially helpful, probably by reducing prostaglandin mediated sensitization of A-delta and C fibers, and therefore may be preferred to APAP.

### 7.3.4 Nonopioid analgesics

#### Acetaminophen

For dosing information, see ► Table 7.3.

**Table 7.3 Acetaminophen dosing**

Medication	Dosage
acetaminophen (APAP) (Tylenol®)	<ul style="list-style-type: none"> <li>• adult dose: 650 or 1000 mg PO/PR q 4–6 hrs, not to exceed 4000 mg/day<sup>a</sup></li> <li>• pediatric dose:           <ul style="list-style-type: none"> <li>◦ infants: 10–15 mg/kg PO/PR q 4–6 hrs</li> <li>◦ children: 1 grain/yr of age (= 65 mg/yr up to 650 mg) PO/PR q 4–6 hrs not to exceed 15 mg/kg q 4 hrs</li> </ul> </li> </ul>

<sup>a</sup>hepatic toxicity from APAP: usually with doses  $\geq$  10 gm/day, rare at doses  $<$  4000 mg. However, may occur at lower doses (even at high therapeutic doses) in alcoholics, fasting patients, and those taking cytochrome P-450 enzyme-inducing drugs

#### Nonsteroidal anti-inflammatory drugs (NSAIDs)

The anti-inflammatory properties of NSAIDs is primarily due to inhibition of the enzyme cyclooxygenase (COX) which participates in the synthesis of prostaglandins and thromboxanes.<sup>9</sup> For dosage information, see ► Table 7.4.

Characteristics of nonselective nonsteroidal anti-inflammatory drugs:

1. all are given orally except ketorolac tromethamine (Toradol®) (see below)
2. no dependence develops
3. additive effect improves the pain relief with opioid analgesics
4. NSAIDs (and APAP) demonstrate a ceiling effect: a maximum dose above which no further analgesia is obtained. For aspirin and APAP, this is usually between 650–1300 mg, and is often higher for other NSAIDs which may also have a longer duration of action
5. risk of GI upset is common, more serious risks of hepatotoxicity,<sup>10</sup> or GI ulceration, hemorrhage, or perforation are less common
6. taking medication with meals or antacids has not been proven effective in reducing GI side effects. Misoprostol (Cytotec®), a prostaglandin, may be effective in mitigating NSAID-induced gastric erosion or peptic ulcer. Contraindicated in pregnancy. **R** 200 mcg PO QID with food as long as patient is on NSAIDs. If not tolerated, use 100 mcg. **\* CAUTION:** an abortifacient. Should not be given to pregnant women or women of childbearing potential
7. most reversibly inhibit platelet function and prolong bleeding time (nonacetylated salicylates have less antiplatelet action, e.g., salsalate, trisalicylate, nabumetone). Aspirin, unlike all other NSAIDs, irreversibly binds to cyclooxygenase and thus inhibits platelet function for the 8–10 day life of the platelet
8. all cause sodium and water retention and carry the risk of NSAID-induced nephrotoxicity<sup>11</sup> (by reducing synthesis of renal vasodilator prostaglandins → reduced renal blood flow which can → renal insufficiency, interstitial nephritis, nephrotic syndrome, hyperkalemia)
9. non-aspirin NSAIDs increase the risk of heart attack or stroke<sup>12</sup>

**Table 7.4** Nonsteroidal anti-inflammatory drugs (NSAIDs)<sup>a</sup>

Generic name (proprietary name [®])	Typical adult oral dose <sup>b</sup>	Tabs/caps availability (mg) <sup>c</sup>	Daily maximum dose (mg)
aspirin <sup>d</sup> (many)	500–1000 mg PO q 4–6 hrs (ceiling dose ≈ 1 gm)	325, 500	4000
diclofenac (Voltaren, Cataflam)	start at 25 mg QID; additional dose q hs PRN; increase up to 50 mg TID or QID, or 75 mg BID	25, 50, 75	200
etodolac	for acute pain: 200–400 mg q 6–8 hrs	200, 300 caps, 400 tabs	1200
fenoprofen (Nalfon)	200 mg q 4–6 hrs; for rheumatoid arthritis 300–600 mg TID-QID	200, 300, 600	3200
flurbiprofen (Ansaid)	50 mg TID-QID or 100 mg TID	50, 100	300
ketoprofen	immediate release: start at 75 mg TID or 50 mg QID, ↑ to 150–300 mg daily DIV TID-QID	25, 50, 75	300
	extended release: 150 mg q d	ER <sup>e</sup> 150	
ketorolac	see below	see below	
ibuprofen <sup>e</sup> (Motrin)	400–800 mg QID (ceiling dose: 800 mg)	300, 400, 600, 800	3200
indomethacin	25 mg TID, ↑ by 25 mg total per day PRN	25, 50, SR 75	150–200
meclofenamate	50 mg q 4–6 hrs; ↑ to 100 mg QID if needed	50, 100	400
mefenamic (Ponstel)	500 mg initial; then 250 mg q 6 hrs	250	
nabumetone <sup>f</sup> (Relafen)	1000–2000 mg/d given in 1 or 2 doses	500, 750	2000
naproxen (Naprosyn)	500 mg, then 250 mg q 6–8 hrs	250, 375, 500	<1250
naproxen sodium (Anaprox)	550 mg, followed by 275 mg q 6–8 hrs	275, DS = 550	1375
oxaprozin (Daypro)	1200 mg q d (1st day may take 1800)	600	1800
piroxicam (Feldene)	10–20 mg q d (steady state takes 7–12 d)	10, 20	
sulindac	200 mg BID; ↓ to 150 BID when pain controlled	150, 200	400
salsalate	3000 mg divided BID-TID (e.g., 500 mg 2-tabs TID)	500, 750	
tolmetin	400 mg TID (bioavailability is reduced by food)	200, DS = 400, 600	1800

<sup>a</sup>NSAIDs increase the risk of cardiovascular thrombotic events (heart attack or stroke)<sup>12</sup><sup>b</sup>when dosage ranges are given, use the smallest effective dose<sup>c</sup>abbreviations: DS = double strength; SR = slow release; ER = extended release; DOC = drug of choice<sup>d</sup>aspirin: has unique effectiveness in pain from bone metastases<sup>e</sup>ibuprofen: is available as a suspension (PedialProfen®) 100 mg/ml; dose for children 6 mos to 12 yrs of age is 5–10 mg/kg with a maximum of 40 mg/kg/day (not FDA approved for children because of possible Reye's syndrome)<sup>f</sup>unlike most NSAIDs, nabumetone does not interfere with platelet function

## Drug info: Ketorolac tromethamine (Toradol®)

The only parenteral NSAID approved for use in pain control in the U.S. Analgesic effect is more potent than anti-inflammatory effect. Half-life ≈ 6 hrs. May be useful to control pain in the following situations:

1. where the avoidance of sedation or respiratory depression is critical
2. when constipation cannot be tolerated
3. for patients who are nauseated by narcotics
4. where narcotic dependency is a serious concern
5. when epidural morphine has been used and further analgesia is needed without risk of respiratory depression (agonist type narcotics are contraindicated)
6. cautions:
  - a) not indicated for use > 72 hrs (complications have been reported primarily with prolonged use of the oral form)

- b) use with caution in postoperative patients since (as with most NSAIDs) bleeding time is prolonged by platelet function inhibition (risk of GI or op-site hemorrhage is small, but is increased in patients > 75 yrs old, when used > 5 days, and when used in higher doses<sup>13)</sup>
- c) even though IM dosing circumvents the GI system, gastric mucosal irritation and erosions may occur as with all NSAIDs (avoid use with PUD)
- d) as with all NSAIDs, use with caution in patients at risk for renal side effects

**R** Parenteral: For single dose administration: 30 mg IV or 60 mg IM in healthy adult. For multiple dosing: 30 mg IV or IM q 6 hrs PRN. Maximum dosage: 120 mg/day. Parenteral use should not exceed 5 days (3 days may be a better guideline).

For patient weight < 50 kg, age > 65 yrs, or reduced renal function (creatinine clearance < 50 ml/min), all of the above dosages are halved (max daily dose: 60 mg). Creatinine clearance can be estimated using the Cockcroft-Gault equation<sup>14</sup> shown in Eq (7.1), with normal values  $\geq 60 \text{ ml/min}$ .

$$\text{Creatinine clearance}(\text{ml/min}) = \frac{[140 - \text{age}(\text{years})] \times \text{ideal wt}(\text{kg})}{72 \times \text{serum creatinine} (\text{mg/dl})} \times (0.85 \text{ for females}) \quad (7.1)$$

**R** PO: Indicated only as a continuation of IV or IM therapy, not for routine use as an NSAID. Switching from IM to PO: start with 10 mg PO q 4–6 hrs (combined PO and IM dose should be  $\leq 120 \text{ mg}$  on the day of transition). **Supplied:** 10 mg tablets.

### 7.3.5 Opioid analgesics

#### General information

Narcotics are most commonly used for moderate to severe acute pain or cancer pain (some experts characterize cancer pain as recurrent acute pain and not chronic pain).

Characteristics of narcotics:

1. no ceiling effect (p.144): i.e., increasing dosage increases the effectiveness (although with weak opioids for moderate pain, side effects may limit dosages to relatively low levels<sup>8)</sup>)
2. with chronic use, tolerance develops (physical and psychological)
3. overdose possible (p.215), with the potential for respiratory depression with all, and seizures with some

#### Mild to moderate pain

Some useful medications are shown in ► Table 7.5.

Codeine and congener pentazocine, are usually no more effective than ASA or APAP and are usually combined with these drugs.

Table 7.5 Weak opioids for mild to moderate pain

Medication	Dosage	
codeine	usual adult dose: 30–60 mg IM/PO q 3 hrs PRN; use with caution in nursing mothers <sup>a</sup> and children (30 mg PO is equivalent to 300 mg aspirin) pediatric dose: 0.5–1 mg/kg/dose q 4–6 hrs PO or IV PRN	
pentazocine	pentazocine is a mixed agonist-antagonist	
	Talwin®	→ 12.5 mg pentazocine, 325 mg ASA. <b>R:</b> 2 PO TID-QID PRN
with naloxone		→ 50 mg pentazocine, 0.5 mg naloxone. <b>R:</b> 1–2 PO q 3–4 hrs PRN up to 12 tabs/day
tramadol (Ultram®)	(see below)	

<sup>a</sup>1–28% of women are ultrafast metabolizers of codeine and the resultant morphine may be passed on to the infant via the breast milk

## Drug info: Tramadol (Ultram®)

An oral opioid agonist that binds to  $\mu$ -opioid receptors, and is also a centrally acting analgesic that inhibits reuptake of norepinephrine and serotonin. For acute pain, 100 mg is comparable to codeine 60 mg with ASA or APAP.<sup>15,16</sup> There has been no report of respiratory depression when oral dosing recommendations are followed. Seizures and opioid-like dependence have been reported.<sup>16</sup>

**R** 50 to 100 mg PO q 4–6 hrs PRN pain up to a maximum of 400 mg/day (or 300 mg/d for older patients). For moderately severe acute pain, an initial dose of 100 mg followed by 50 mg doses may suffice. **Supplied:** 50 mg tabs.

### Moderate to severe pain

See ▶ Table 7.6.

**Table 7.6** Opioids for moderate to severe pain

Medication	Dosage		
hydrocodone	(Vicodin®, Lorcet®, Lortab®...): 5 mg hydrocodone + 500 mg acetaminophen; (Vicodin ES®, Lortab 7.5/500®): 7.5 mg hydrocodone + 500 mg APAP; <b>R</b> 1 tab PO q 6 hrs PRN (may increase up to 2 tabs PO q 3–4 hrs not to exceed 8 pills/24 hrs).		
	(Lorcet® Plus, Lorcet® 10/650): 7.5 or 10 mg hydrocodone (respectively) + 650 mg APAP; <b>R</b> 1 tab PO q 6 hrs PRN (not to exceed 6 tabs in 24 hrs).		
	(Lortab® 10/500: 10 mg. hydrocodone + 500 mg APAP); <b>R</b> : 1–2 PO q 4 hrs PRN up to 6 tabs/day.		
	(Norco®): 10 mg hydrocodone + 325 mg APAP scored tabs; <b>R</b> : 1 PO q 4 hrs PRN up to 6 tabs/day.		
oxycodone	<b>Supplied:</b> usually available in combination as: aspirin 325 mg with oxycodone 5 mg (Percodan®) or acetaminophen (APAP) (Tylox® = APAP 500 mg + oxycodone 5 mg) (Percocet® = oxycodone/APAP in 2.5/325, 5/325, 7.5/500, 10/650) dose: 1 PO q 3–4 hrs PRN (may increase up to 2 PO q 3 hrs <sup>a</sup> ) <b>Supplied:</b> also available alone as OxyIR® 5 mg, OxyFast® oral solution of 20 mg/ml, or in controlled-release tablets as OxyContin® 10, 20, 40, 80 <sup>b</sup> & 160 <sup>b</sup> mg (which last 12 hours, achieving steady state in 24–36 hours). <b>R</b> Adult: OxyContin® tablets are taken whole and are not to be divided, chewed or crushed. It is intended for management of moderate to severe pain when continuous around-the-clock analgesic is needed for an extended period of time and is not intended for use as a PRN analgesic. For opiate naïve patients, start with 10 mg PO q 12 hrs. For patients on narcotic medications, a conversion table is provided below for some medications. Titrate dose every 1–2 days, increasing dose by 25–50% q 12 hrs.		
	<b>Conversion table for starting OxyContin®</b>		
	Preparation currently being used	Dose	Suggested starting dose of OxyContin®
	oxycodone combination pills (Tylox, Percodan...) or Lortab, Vicodin or Tylenol #3	1–5 pills/day	10–20 mg PO q 12 hrs
		6–9 pills/day	20–30 mg PO q 12 hrs
		10–12 pills/day	30–40 mg PO q 12 hrs
	IV PCA morphine	determine total MSO <sub>4</sub> dose used per 24 hrs	multiply total MSO <sub>4</sub> dose in 24 hrs $\times$ 1.3 for total OxyContin dose in 24 hrs
hydromorphone	Dilaudid®: (see ▶ Table 7.7)		
morphine	used in low doses (see ▶ Table 7.7)		

<sup>a</sup>not to exceed 4000 mg of acetaminophen/24 hrs (see footnote to ▶ Table 7.3)

<sup>b</sup>for use only in opioid-tolerant patients

### Severe pain

See ▶ Table 7.7 and ▶ Table 7.8.

**Table 7.7** Equianalgesic doses for SEVERE pain, AGONIST opioids (parenteral route is referenced to 10 mg IM morphine)

Drug name: generic (proprietary®)	Route	Dose (mg)	Peak (hrs)	Duration (hrs)	Comments
morphine	IM	10	0.5–1	4–6	respiratory depression long acting PO forms: MS Contin®, Avinza® (see below)
	PO	20–60 <sup>a</sup>	1.5–2	4–7	
codeine (not recommended at these doses)	IM	130		3–5	these high doses cause unacceptable side effects
	PO	200			
methadone <sup>b</sup> (Dolophine®)	IM	10	0.5–1	4–6	long half-life <sup>b</sup>
	PO	20	1.5–2	4–7	
oxycodone (e.g., Tylox® <sup>c</sup> ) (OxyContin®)	IM	15			combination (Tylox®) or liquid <i>OxyContin</i> , see ► Table 7.6
	PO	30	1	3–4	
	PO	30–40		12	
oxymorphone	IM	1		3–5	available as suppository
	PR	10			
hydromorphone (Dilaudid®)	IM	1.5	0.5–1	3–4	supplied: 1, 2, 3, & 4 mg tabs
	PO	7.5	1.5–2	3–4	
fentanyl (Sublimaze®)	IV	0.1		1–2	not recommended for acute pain control, esp. in narcotic naive pts.
transdermal fentanyl patch (Duragesic®) <sup>d</sup>	transdermal	e	12–24	72	patches of 25, 50, 75, 100 or 125 mcg/hr (use lowest effective)

<sup>a</sup>IM:PO potency ratio for morphine is 1:6 for single doses, but changes to 1:2–3 with chronic dosing<sup>b</sup>due to long half-life, repeated dosing can lead to accumulation and CNS depression (must reduce dose after ≈ 3 days, even though the analgesic half-life does not change), especially in the elderly or debilitated patient. Use should be limited to physicians with experience using these drugs<sup>c</sup>may not be practical for use in severe pain since 1 Tylox® contains only 5 mg oxycodone (the acetaminophen limits the dosage), may use OxyContin® for higher doses of oxycodone<sup>d</sup>✖ should not be used as routine post-op analgesic (risk of respiratory depression). Apply 1 patch to upper torso, replace q 72 hrs PRN.<sup>e</sup>conversion from total daily parenteral morphine as follows:

8–27 mg MSO<sub>4</sub>/day → Duragesic 25 mcg/hr  
 28–37 mg MSO<sub>4</sub>/day → Duragesic 50 mcg/hr  
 38–52 mg MSO<sub>4</sub>/day → Duragesic 75 mcg/hr  
 53–67 mg MSO<sub>4</sub>/day → Duragesic 100 mcg/hr  
 68–82 mg MSO<sub>4</sub>/day → Duragesic 125 mcg/hr

**Table 7.8** Equianalgesic doses for SEVERE pain, AGONIST/ANTAGONIST opioids (referenced to 10 mg IM morphine)

Drug name: generic (proprietary®)	Route	Dose (mg)	Peak (hrs)	Duration (hrs)	Comments
buprenorphine (Buprenex®)	IM	0.4			partial agonist
	SL	0.3			
<b>Mixed agonist/antagonist<sup>a</sup></b>					
butorphanol	IM	2	0.5–1	4–6	
nalbuphine	IM	10	1	3–6	no sigma receptor occupation <sup>b</sup>
	IV	140 mcg/kg	0.5	2–5	
pentazocine (Talwin® <sup>c</sup> )	IM <sup>b</sup>	20–40	0.5–1	4–6	
	PO <sup>b</sup>	180 (start @ 50)	1.5–2	4–7	

<sup>a</sup>all can precipitate withdrawal symptoms in patients physically dependent on agonists<sup>b</sup>most agonist/antagonist drugs occupy sigma receptors (Stadol>Nubain), which may cause hallucinations<sup>c</sup>Talwin injectable (for IM use) contains only pentazocine. Talwin® Compound tablets contain ASA; therefore for high PO doses, use Talwin Nx, which contains no ASA (► Table 7.5)

## Drug info: Avinza® (extended release morphine)

Once daily oral morphine formulation using a spherical oral drug absorption system (SODAS) (numerous ammonio-methacrylate copolymer beads,  $\approx 1$  mm dia.). Potential for overdosage and/or abuse.

**R:** Dosage is titrated based on patient's opioid tolerance and degree of pain. Taken as 1 capsule PO q d. Not to be taken "PRN." Not for post-op pain. **\* CAUTION:** To prevent potentially fatal doses of morphine, capsules are to be swallowed whole, and are not to be chewed, crushed or dissolved. However, the contents of the capsule (the beads) may be sprinkled on apple-sauce for those unable to swallow the capsules, but the beads are not to be chewed or crushed. **Side effects:** Due to the potentially nephrotoxic effect of fumaric acid used in SODAS, the maximum dose of Avinza is 1600 mg/d. Doses  $\geq 60$  mg are for opioid tolerant patients only. **Supplied:** 30, 60, 90 & 120 mg capsules.

### 7.3.6 Adjuvant pain medications

The following may enhance the effectiveness of opioid analgesics (and thereby may reduce the required dose).

#### Tricyclic antidepressants:

Tryptophan: an amino acid and a precursor of serotonin, may work by increasing serotonin levels. Requires high doses and has hypnotic effects; therefore 1.5–2 g given usually q hs. Must give daily MVI as chronic tryptophan therapy depletes vitamin B6.

Antihistamines: histamines play a role in nociception. Antihistamines, which are also anxiolytic, antiemetic, and mildly hypnotic, are effective as analgesics or as adjuvants. Hydroxyzine (Atarax®, Vistaril®): **R:** start with 50 mg PO q AM and 100 mg PO q hs. May increase up to  $\sim 200$  mg daily.

Antiseizure medication-class drugs: carbamazepine, clonazepam, phenytoin, gabapentin or pregabalin tend to be more effective in neuropathic pain, e.g., from diabetic neuropathy, trigeminal neuralgia, post-herpetic neuralgia, glossopharyngeal neuralgia, and neuralgias due to nerve injury or infiltration with cancer.<sup>16</sup> See index for entries.

Phenothiazines: some cause mild reduction in nociception. Most are tranquilizing and antiemetic. Best known for this use is fluphenazine (Prolixin®), usually given with a tricyclic antidepressant for neuropathic pain, **Diabetic neuropathy, Treatment** (p.572). Phenothiazines may reduce the seizure threshold.

Corticosteroids: in addition to the reduction of toxic effects of radiation or chemotherapy, they may potentiate narcotic analgesics. There are also a number of nonspecific beneficial effects: increased appetite, sense of well being, antiemetic. Steroid side effects (p. 156) may limit usefulness.

Caffeine: although it possesses no intrinsic analgesic properties, doses of 65–200 mg enhance the analgesic effect of APAP, ASA, or ibuprofen for pain including H/A, oral surgery pain, and post-partum pain.

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## 8 Endocrinology

### 8.1 Pituitary embryology and neuroendocrinology

#### 8.1.1 Embryology and derivation of the pituitary gland

The posterior pituitary (neurohypophysis AKA pars nervosa) derives from downward evagination of neural crest cells (brain neuroectoderm) from the floor of the third ventricle. The residual recess in the floor of the third ventricle is called the median eminence. The anterior pituitary gland (adenohypophysis) develops from an upward evagination of epithelial ectoderm of the oropharynx, the evagination is known as Rathke's pouch and is eventually separated from the oropharynx by the sphenoid bone. Failure of this separation results in a craniopharyngeal duct which can be a source of recurrent meningitis. The posterior surface of Rathke's pouch forms the pars intermedia, while the anterior portion forms the pars distalis. Remnants of Rathke's pouch may persist (Rathke's cleft [► Fig. 8.1]) in the pars intermedia. The adenohypophysis is comprised of the pars distalis (anterior lobe), the pars intermedia (intermediate lobe) and the pars tuberalis (extension of adenohypophyseal cells surrounding the base of the pituitary stalk<sup>1</sup>). The pituitary gland is functionally *outside* the blood-brain barrier.

#### 8.1.2 Pituitary hormones, their targets and their controls

##### General information

The pituitary gland releases 8 hormones, 6 from the anterior pituitary and 2 from the posterior pituitary (► Fig. 8.1).

The anterior pituitary is one of only two sites in the body having a portal circulation (the other being the liver). Six hypothalamic hormones are released in a pulsatile fashion from neurons of the tuber cinereum (a hypothalamic nucleus) that are conveyed via the tubero-hypophyseal tract (a parvocellular system) to their terminus in the median eminence of the pituitary stalk. These hypophyseal hormones are released into capillaries of the hypophyseal portal circulation, which carries them via the pituitary stalk to a second capillary bed in the anterior pituitary where they control release of hormones by adenohypophyseal gland cells.<sup>1</sup>

Posterior pituitary hormones (ADH & oxytocin) are synthesized in magnocellular neuroendocrine neurons (*not* gland cells) in the supraoptic and paraventricular nuclei of the hypothalamus and are conveyed along their axons in the supraoptic-hypophyseal tract, also via the pituitary stalk, to the posterior pituitary gland where they are released into the circulation.

The complete homeostatic loops (including negative feedback involving hypothalamic hormones) will not be covered here, and the reader is referred to physiology texts.

##### Propiomelanocortin (POMC), AKA proopiomelanocortin

241 amino acid polypeptide hormone precursor synthesized primarily in corticotroph cell of the anterior pituitary (but also found in the hypothalamus). Contains amino acid sequences for ACTH, alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH),  $\beta$ -lipotropin,  $\gamma$ -lipotropin,  $\beta$ -endorphin and met-enkephalin.

##### Corticotropin AKA adrenocorticotropic hormone (ACTH)

A 39 amino acid trophic hormone synthesized from POMC. The first 13 amino acids at the amino terminal of ACTH are identical to  $\alpha$ -MSH. Active half-life is  $\approx$  10 minutes. Produces a diurnal peak in cortisol (the highest peak occurs in the early morning, with a second, lesser peak in the late afternoon) and also increases in response to stress.

**Control:** CRH from the hypothalamus stimulates the release of ACTH.

##### Prolactin

AKA somatomammotropin. 199 amino-acid protein weighing 23,000 daltons. Levels are higher in females than males, and are higher still in pregnancy (see ► Table 52.3). Secreted in pulsatile fashion with a frequency and amplitude that varies during menstrual cycle (range: 5–27 ng/ml) ( $\approx$  9 pulses/24 hours in the late luteal phase,  $\approx$  14 pulses/24 hours in the late follicular phase, the pulse amplitude increases from early to late follicular and luteal phases). There is also diurnal variation: levels begin to

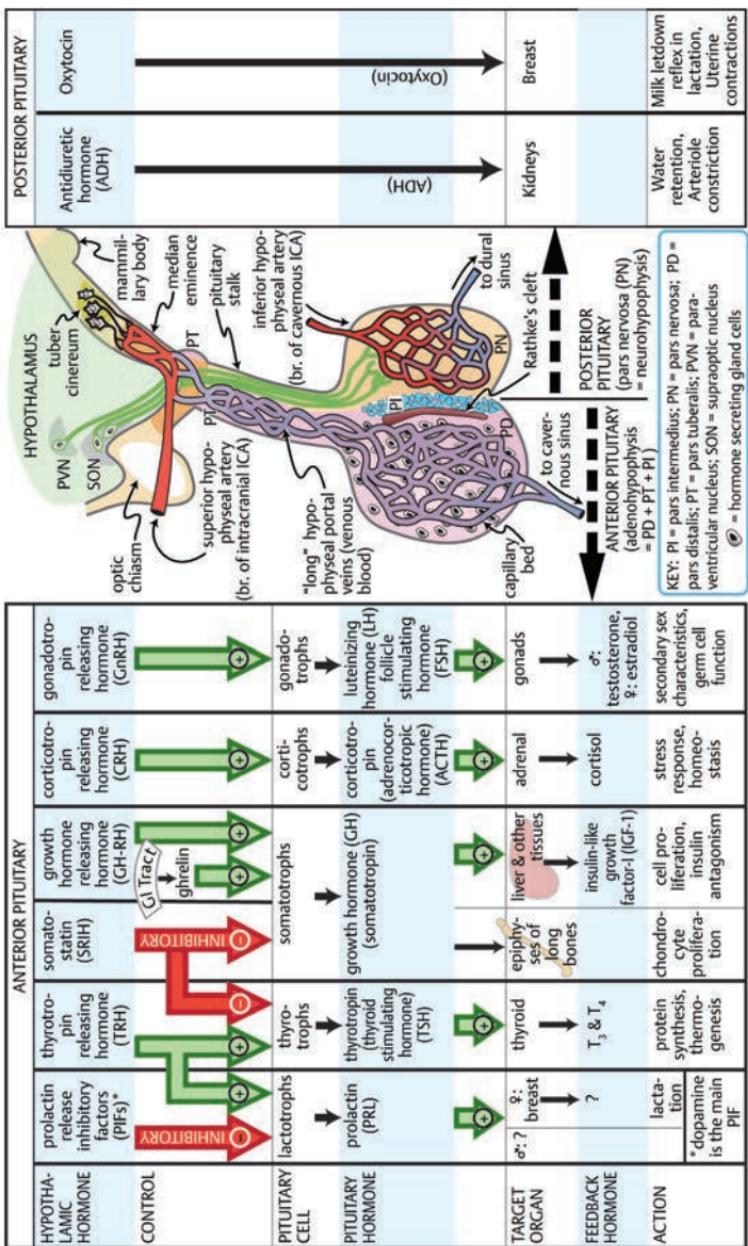


Fig. 8.1 Pituitary neuroendocrinology.

rise 1 hour after the onset of sleep, peak  $\approx$  5:00–7:00 AM, and nadir in midmorning after awakening. Heterogeneity of the molecule may produce different results between bioassays and immunoassays.

**Control:** prolactin is the only pituitary hormone predominantly under *inhibitory* control from the hypothalamus by prolactin releasing inhibitory factors (PIFs), with dopamine being the primary PIF. Prolactin releasing factors (PRFs) include thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP). The physiologic role of PRFs is not established. For DDx of hyperprolactinemia see ► Table 52.4.

### Growth hormone (GH)

A 191 amino-acid polypeptide trophic hormone. GH normally has pulsatile secretion ( $\approx$  5–10 pulses/24 hours, primarily at night, up to 30 mcg/L), levels may be undetectable ( $<0.2$  mcg/L) by standard assays between pulses.<sup>2</sup> Insulin-like growth factor-1 (IGF-1) (formerly known as somatomedin-C) is the protein secreted primarily by the liver in response to GH that is responsible for most of GH's systemic effects (see levels (p.881)). GH also acts directly on epiphyseal endplates of long bone to stimulate chondrocyte proliferation.

**Control:** GH is under dual hypothalamic control via the hypophysial portal system. GH-releasing hormone (GHRH) from the arcuate nucleus stimulates pituitary *secretion* and *synthesis* of GH and induces GH gene transcription. Somatostatin from the periventricular nucleus suppresses GH *release* only, and has no effect on synthesis. GH *release* is also stimulated by ghrelin,<sup>3</sup> a peptide synthesized primarily in the GI tract in response to certain nutrients (may act partially or totally via hypothalamic GHRH).

### Thyrotropin AKA thyroid stimulating hormone (TSH)

Glycoprotein trophic hormone secreted by thyrotroph cells of the anterior pituitary.

**Control:** TSH is also under dual hypothalamic control. TRH stimulates production and release of TSH. Somatostatin inhibits the release of TSH.

### Gonadotropins

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) (AKA lutropin) are released from the pituitary in response to gonadotropin releasing hormone 1 (GnRH, formerly luteinizing hormone releasing hormone LH-RH) synthesized primarily in the preoptic area of the hypothalamus.

### Antidiuretic hormone (ADH)

AKA arginine vasopressin (AVP). The major source of this nanopeptide hormone is the magnocellular portion of the supraoptic nucleus of the hypothalamus. It is conveyed along *axons* in the supraoptic-hypophyseal tract to the posterior pituitary gland where it is released into the systemic circulation. All actions of ADH result from binding of the hormone to specific membrane-bound receptors on the surface of target cells.<sup>4</sup> One of the major effects of ADH is to increase the permeability of the distal renal tubules resulting in increased reabsorption of water, diluting the circulating blood and producing a concentrated urine. The most powerful physiologic stimulus for ADH release is an increase in serum osmolality; a less potent stimulus is a reduction of intravascular volume. ADH is also released in glucocorticoid deficiency, and is inhibited by exogenous glucocorticoids and adrenergic drugs. ADH is also a potent vasoconstrictor.

### Oxytocin

A nonapeptide. Oxytocin is a neurotransmitter as well as a hormone. The hypothalamus is the main source of pituitary oxytocin which is stored in nerve endings in the neurohypophysis and is involved in the milk letdown reflex for breastfeeding as well as in uterine contraction during labor.

## 8.2 Corticosteroids

### 8.2.1 General information

Under normal, basal conditions, the zona fasciculata of the adrenal cortex secretes 15–25 mg/day of cortisol (hydrocortisone is the name for the identical pharmaceutical compound for administration), and 1.5–4 mg/day of corticosterone. Cortisol has a half-life of  $\approx$  90 minutes. The release of cortisol by the adrenal glands is stimulated by adrenocorticotrophic hormone (ACTH) from the pituitary which in turn is stimulated by corticotropin releasing hormone (CRH) from the hypothalamus.

## 8.2.2 Replacement therapy

In primary adrenocortical insufficiency (Addison's disease), both glucocorticoids and mineralocorticoids must be replaced. In secondary adrenal insufficiency caused by deficient corticotropin (ACTH) release by the pituitary, mineralocorticoid secretion is usually normal and only glucocorticoids need to be replaced.

► Table 8.1 shows equivalent daily corticosteroid doses for replacement therapy.

**Table 8.1** Equivalent corticosteroid doses<sup>a</sup>

Steroid: generic (proprietary)	Equiv dose (mg)	Route	Dosing	Mineralocorticoid potency	Oral dosing forms
cortisone acetate	25	PO, IM	2/3 in AM, 1/3 in PM	2+	tabs: 5, 10 & 25 mg
hydrocortisone AKA cortisol (Cortef®) (Solu-Cortef®)	20	PO	2/3 in AM, 1/3 in PM	2+	tabs: 5, 10 & 20 mg
		IV, IM <sup>b</sup>			
prednisone	5	PO only	divided BID-TID	1+	tabs: 1, 2.5, 5, 10, 20, 50 mg <sup>c</sup>
methylprednisolone	4	PO, IV, IM		0	tabs <sup>d</sup> : 2, 4, 8, 16, 24, 32 mg
dexamethasone	0.75	PO, IV	divided BID-QID	0	scored tabs: 0.25, 0.5, 0.75, 1.5, 4, 6 mg

<sup>a</sup>doses given are daily doses. Steroids listed are used primarily as glucocorticoids: equivalent glucocorticoid PO or IV dose is given; IM may differ

<sup>b</sup>IM route recommended only for emergencies where IV access cannot be rapidly obtained

<sup>c</sup>steraped Uni-Pak® contains 21 tabs of 5 mg prednisone and tapers dosage from 30 to 5 mg over 6 days; "DS" contains 10 mg tabs and tapers from 60 mg to 10 mg over 6 days; "DS 12-Day" contains 48 10 mg tabs and tapers from 60 mg to 20 mg over 12 days

<sup>d</sup>Medrol Dosepak® contains 21 tabs of 4 mgs methylprednisolone and tapers dosage from 24 mg/d to 4 mg/d over 6 days

Physiologic replacement (in the absence of stress) can be accomplished with either:

1. hydrocortisone: 20 mg PO q AM and 10 mg PO q PM
2. or prednisone: 5 mg PO q AM and 2.5 mg PO q PM

Cortisol and cortisone are useful for chronic primary adrenocortical insufficiency or for Addisonian crisis. Because of mineralocorticoid activity, use for chronic therapy of other conditions (e.g., hypopituitarism) may result in salt and fluid retention, hypertension, and hypokalemia.

## 8.2.3 Hypothalamic-pituitary-adrenal axis suppression

### General information

Chronic steroid administration suppresses the hypothalamic-pituitary-adrenal (HPA) axis, and eventually causes adrenal atrophy. When the HPA is suppressed, if exogenous steroids are abruptly stopped or if acute illness develops (which increases the steroid requirements), symptoms of adrenocortical insufficiency (AI) may ensue (► Table 8.2). Severe cases of AI may progress to Addisonian crisis (p. 157). Recovery of adrenal cortex lags behind the pituitary, so basal ACTH levels increase before cortisol levels do.

**Table 8.2** Symptoms of adrenal insufficiency (AI)

- fatigue
- weakness
- arthralgia
- anorexia
- nausea
- hypotension
- orthostatic dizziness
- hypoglycemia
- dyspnea
- Addisonian crisis (p. 157) (if severe; with risk of death)

HPA suppression depends on the specific glucocorticoid used, the route, frequency, time, and duration of treatment. Suppression is unlikely with <40 mg prednisone (or equivalent) given in the morning for less than  $\approx$  7 days, or with every-other-day therapy of <40 mg for  $\approx$  5 weeks.<sup>5</sup> Some adrenal atrophy may occur after 3–4 days of high dose steroids, and some axis suppression will almost certainly occur after 2 weeks of 40–60 mg hydrocortisone (or equivalent) daily. After a month or more of steroids, the HPA axis may be depressed for as long as one year.

Measuring morning plasma hydrocortisone can evaluate the degree of recovery of basal adrenocortical function, but does *not* assess adequacy of stress response.

### Steroid withdrawal

See reference<sup>5</sup>

In addition to the above dangers of hypocortisolism in the presence of HPA suppression, too rapid a taper may cause a flare-up of the underlying condition for which steroids were prescribed.

When the risk of HPA suppression is low (as is the case with short courses of steroids for less than  $\approx$  5–7 days<sup>6</sup> generally prescribed for most neurosurgical indications) abrupt discontinuation usually carries a low risk of AI. For up to  $\approx$  2 weeks of use, steroids are usually safely withdrawn by tapering over 1–2 weeks. For longer treatment, or when withdrawal problems develop, use the following *conservative taper*:

1. make small decrements (equivalent to 2.5–5 mg prednisone) every 3–7 d. Patient may experience mild withdrawal symptoms of<sup>7</sup>:
  - a) fatigue
  - b) anorexia
  - c) nausea
  - d) orthostatic dizziness
2. “backtrack” (i.e., increase the dose and resume a more gradual taper) if any of the following occur:
  - a) exacerbation of the underlying condition for which steroids were used
  - b) evidence of steroid withdrawal symptoms (► Table 8.2)
  - c) intercurrent infection or need for surgery; see Stress doses (p.155)
3. once “physiologic” doses of glucocorticoid have been reached (about 20 mg hydrocortisone/day or equivalent (► Table 8.1)):
  - a) the patient is switched to 20 mg hydrocortisone PO q AM (do not use long acting preparations)
  - b) after  $\approx$  2–4 weeks, a morning cortisol level is checked (prior to the AM hydrocortisone dose), and the hydrocortisone is tapered by 2.5 mg weekly until 10 mg/d is reached (lower limits of physiologic)
  - c) then, every 2–4 weeks, the AM cortisol level is drawn (prior to AM dose) until the 8 AM cortisol is  $>$  10 mcg/100 ml, indicating return of baseline adrenal function
  - d) when this return of baseline adrenal function occurs:
    - daily steroids are stopped, but stress doses must still be given when needed (see below)
    - monthly cosyntropin stimulation (p.880) tests are performed until normal. The need for stress doses of steroids ceases when a positive test is obtained. The risk for adrenal insufficiency persist  $\approx$  2 years after cessation of chronic steroids (especially the first year)

### Steroid stress doses

During physiologic “stress” the normal adrenal gland produces  $\approx$  250–300 mg hydrocortisone/day. With chronic glucocorticoid therapy (either at present, or within last 1–2 yrs), suppression of the normal “stress-response” necessitates supplemental doses.

In patients with a suppressed HPA axis:

- for mild illness (e.g., UTI, common cold), single dental extraction: double the daily dose (if off steroids, give 40 mg hydrocortisone BID)
- for moderate stress (e.g., flu), minor surgery under local anesthesia (endoscopy, multiple dental extractions...): give 50 mg hydrocortisone BID
- for major illness (pneumonia, systemic infections, high fever), severe trauma, or emergency surgery under general anesthesia: give 100 mg hydrocortisone IV q 6–8 hrs for 3–4 days until the stress is resolved
- for elective surgery, see ► Table 8.3 for guidelines

**Table 8.3** Steroid stress doses for elective surgery

Post-op day	Hydrocortisone (mg)		
	8 AM	4 PM	10 PM
1	50	50	50
2	50	25	25
3	40	20	20
4	30	20	10
5	25	20	5
6	25	15	–
7	20	10	–

### 8.2.4 Steroid side effects

Although deleterious side effects of steroids are more common with prolonged administration,<sup>8</sup> some can occur even with short treatment courses. Some evidence suggests that low-dose glucocorticoids ( $\leq 10$  mg/d of prednisolone or prednisone equivalent) for rheumatoid arthritis does not increase osteoporotic fractures, blood pressure, cardiovascular disease, or peptic ulcers,<sup>9</sup> but weight gain and skin changes are common. Possible side effects include<sup>7,10</sup>:

- cardiovascular and renal
  - hypertension
  - sodium and water retention
  - hypokalemic alkalosis
- CNS
  - progressive multifocal leukoencephalopathy (PML) (p. 354)
  - mental agitation or “steroid psychosis”
  - spinal cord compression from spinal epidural lipomatosis (p. 1381): rare
  - pseudotumor cerebri (p. 955)
- endocrine
  - caution: because of growth suppressant effect in children, daily glucocorticoid dosing over prolonged periods should be reserved for the most urgent indications
  - secondary amenorrhea
  - suppression of hypothalamic-pituitary-adrenal axis: reduces endogenous steroid production → risk of adrenal insufficiency with steroid withdrawal (see above)
  - Cushingoid features with prolonged usage (iatrogenic Cushing’s syndrome): obesity, hypertension, hirsutism...
- GI: risk increased only with steroid therapy  $> 3$  weeks duration and regimens of prednisone  $> 400$ – $1000$  mg/d or dexamethasone  $> 40$  mg/d<sup>11</sup>
  - gastritis and steroid ulcers: incidence lowered with the use of antacids and/or H2 antagonists (e.g., cimetidine, ranitidine...)
  - pancreatitis
  - intestinal or sigmoid diverticular perforation<sup>12</sup>: incidence  $\approx 0.7\%$ . Since steroids may mask signs of peritonitis, this should be considered in patients on steroids with abdominal discomfort, especially in the elderly and those with a history of diverticular disease. Abdominal X-ray usually shows free intraperitoneal air
- inhibition of fibroblasts
  - impaired wound healing or wound breakdown
  - subcutaneous tissue atrophy
- metabolic
  - glucose intolerance (diabetes) and disturbance of nitrogen metabolism
  - hyperosmolar nonketotic coma
  - hyperlipidemia
  - tend to increase BUN as a result of protein catabolism
- ophthalmologic
  - posterior subcapsular cataracts
  - glaucoma
- musculoskeletal

- avascular necrosis (AVN) of the hip or other bones: usually with prolonged administration → cushingoid habitus and increased marrow fat within the bone<sup>13</sup> (prednisone 60 mg/d for several months is probably the minimum necessary dose, whereas 20 mg/d for several months will probably *not* produce AVN<sup>14</sup>). Many cases blamed on steroids may instead be due to alcohol use, cigarette smoking,<sup>15</sup> liver disease, underlying vascular inflammation...
- osteoporosis: may predispose to vertebral compression fractures which occur in 30–50% of patients on prolonged glucocorticoids. Steroid induced bone loss may be reversed with cyclical administration of etidronate<sup>16</sup> in 4 cycles of 400 mg/d × 14 days followed by 76 days of oral calcium supplements of 500 mg/d (not proven to reduced rate of VB fractures)
- muscle weakness (steroid myopathy): often worse in proximal muscles
- infectious
  - immunosuppression: with possible superinfection, especially fungal, parasitic
  - possible reactivation of TB, chickenpox
- hematologic
  - hypercoagulopathy from inhibition of tissue plasminogen activator
  - steroids cause demargination of white blood cells, which may artifactually elevate the WBC count even in the absence of infection
- miscellaneous
  - hiccups: may respond to chlorpromazine (Thorazine®) 25–50 mg PO TID-QID × 2–3 days (if symptoms persist, give 25–50 mg IM)
  - steroids readily cross the placenta, and fetal adrenal hypoplasia may occur with the administration of large doses during pregnancy

## 8.2.5 Hypocortisolism

### General information

AKA adrenal insufficiency.

Assessment: 8 A.M. serum cortisol level is the best way to test for hypocortisolism. Each lab should provide a lower limit of normal for their lab, which may be broken down further by age and gender.

### Addisonian crisis

#### General information

AKA adrenal crisis. An adrenal insufficiency emergency.

Symptoms: mental status changes (confusion, lethargy, or agitation), muscle weakness.

Signs: postural hypotension or shock, hyperthermia (as high as 105 °F, 45.6 C)

#### Labs

Hyponatremia, hyperkalemia, hypoglycemia.

#### Treatment of Addisonian crisis

If possible, draw serum for cortisol determination (do not wait for these results to institute therapy). Give fluids sufficient for dehydration and shock.

For “glucocorticoid emergency”

- hydrocortisone sodium succinate (Solu-Cortef®): 100 mg IV STAT and then 50 mg IV q 6 hrs AND
- cortisone acetate 75–100 mg IM STAT, and then 50–75 mg IM q 6 hrs

#### For “mineralocorticoid emergency”

Usually not necessary in secondary adrenal insufficiency (e.g., panhypopituitarism)

- desoxycorticosterone acetate (Doxa®): 5 mg IM BID OR
- fludrocortisone (Florinef®): 0.05- 0.2 mg PO q d

\* methylprednisolone is NOT recommended for emergency treatment.

## 8.3 Hypothyroidism

### 8.3.1 General information

Chronic primary hypothyroidism may result in (non-pathologic) enlargement of the pituitary gland. Plasma TSH determination will distinguish primary hypothyroidism (high TSH) from secondary hypothyroidism (low TSH). Wound healing and cardiac function may be compromised, and surgery under general anesthesia should be postponed if possible until thyroid levels are normalized. Effects of anesthesia may be markedly prolonged, and dosages should be adjusted accordingly.

### 8.3.2 Thyroid replacement

#### Caution in patients with adrenal insufficiency

Primary hypothyroidism may be associated with immunologic destruction of adrenal cortex (Schmidt syndrome). Secondary hypothyroidism may be associated with and may mask reduced adrenal function. **✗** Thyroid replacement without adrenal replacement in patients with adrenal insufficiency (as may occur in panhypopituitarism) may precipitate adrenal crisis (thus give  $\approx 300\text{--}400$  mg hydrocortisone IV over 24 hrs in addition to thyroid replacement).

8

### 8.3.3 Routine thyroid replacement dosing

#### Drug info: Levothyroxine (Synthroid®)

Almost pure T4 (contains no T3 as most T3 is produced peripherally from T4).

Dose required to prevent myxedema coma (not to achieve euthyroidism):

- Maintenance: **R** 0.05 mg po q d
- when patient has been hypothyroid: **R** start at 0.05 mg po q d and increase by 0.025 mg every 2–3 weeks

For euthyroidism (approximate dose, follow levels and clinical evaluation):

- for most adults < 60 years of age: **R** 0.18 mg/day
- for elderly patients: **R** 0.12 mg/day

#### Drug info: Desiccated thyroid (e.g., Armour thyroid®)

Typical dose: **R** 60 mg (1 grain) to 300 mg daily.

#### Thyroid replacement in myxedema coma

Myxedema coma is an emergency of hypothyroidism and carries 50% mortality.

Symptoms: altered mental status or unresponsiveness.

Signs: hypotension, bradycardia, hyponatremia, hypoglycemia, hypothermia, hypoventilation, occasionally seizures.

#### Treatment

Drugs may need to be given IV due to reduced gastric motility.

1. general supportive care:

- a) hypotension: treat with IV fluids (responds poorly to pressors until thyroid replacement accomplished)
- b) hyponatremia: will correct with thyroid replacement; avoid hypertonic saline
- c) hypoglycemia: IV glucose
- d) symptoms of hypocortisolism: thyroid replacement may precipitate adrenal crisis (*see caution above*); give 300–400 mg hydrocortisone IV over 24 hrs
- e) hypothermia: avoid active warming since this increases metabolic demand, use blankets to warm gradually
- f) hypoventilation: check ABG, intubate if necessary

2. thyroid replacement (for average-sized adult):
  - a) IV replacement: **R** 0.5 mg of levothyroxine IV, followed by 0.05–0.2 mg/d IV until patient is able to tolerate PO or NG meds
  - b) nasogastric replacement: liothyronine (Cytomel®) is primarily T<sub>3</sub>, has a rapid onset of action, much shorter half-life than T<sub>4</sub>, and should be reserved for emergencies.  
**R**: liothyronine 0.05–0.1 mg per NG initially, followed by 0.025 mg BID per NG

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## 9 Hematology

### 9.1 Circulating blood volume

Circulating blood volumes for adults and pediatrics are shown in ► Table 9.1.

**Table 9.1** Circulating blood volume

Age	Vol (cc/kg <sup>a</sup> )
premature infant	85–100
term infant < 1 month	85
age > 1 mo (including adult)	75
<sup>a</sup> cc per kg of body weight	

### 9.2 Blood component therapy

#### 9.2.1 Massive transfusions

Definition: replacement of > 1 blood volume (in average adult ≈ 20 U) in < 24 hrs for adult, or > 2 × circulating blood volume in pediatrics, may cause dilution of effective platelets and coagulation factors, which requires platelet transfusion and fresh frozen plasma (FFP). When operating on a pediatric patient, you can usually safely replace up to 1.5 × the circulating blood volume before problems with coagulopathy ensue.

Blood component therapy required for massive transfusions:

#### 9.2.2 Cellular component

##### Red blood cell therapy

###### General information

Major histocompatibilities of blood are shown in ► Table 9.2.

**Table 9.2** Blood compatibility (ABO)

Blood type	Antibody present	Compatible blood (PRBC)	Compatible plasma	Compatible platelets or cryoprecipitate
A	B	A, O	A, AB	The same ABO type as the patient is preferred, but any ABO type may be used
B	A	B, O	B, AB	
AB	none	AB, A, B, O	AB	
O	A, B	O	AB, A, B, O	

##### Whole blood

1 U (≈ 510 cc) = 450 cc blood + 63 cc preservative.

Recommended transfusion criteria:

- exchange transfusions in neonates
- acute burn debridement and grafting in children

##### Packed red blood cells (PRBCs)

Recommended transfusion criteria:

1. acute blood loss ≥ 15% of patient's blood volume
2. in asymptomatic patient: hemoglobin (Hb) ≤ 8 gm or Hct ≤ 24%
3. symptoms of anemia at rest
4. preoperative Hb ≤ 15 gm or Hct < 45% in the neonate

Amount to transfuse:

Adult: 1 U (250–300 cc) raises Hct by 3–4%.

For peds, use Eq (9.1).

$$\text{ml of PRBC to transfuse} = \frac{(\text{estimated blood volume [ml]} \times (\text{Hct increment desired [%]})}{70\%} \quad (9.1)$$

(where the Hct of PRBCs ranges 70–80%)

Give no faster than 2–3 cc/kg/hr.

### Autologous blood transfusion

Predonated whole blood may be stored 35 days. PRBCs may be stored 42 days.

Patients may donate every 3 days to 1 week as long as they maintain  $\text{Hct} \geq 34\%$  (supplement with ferrous sulfate). The following patients require physician release before donating: patients with coronary artery disease, angina, cerebrovascular disease, seizure disorder, pregnancy (because of possible vasovagal episode) or patients with malignancy.

Try to time last donation > 72 hrs prior to surgery to allow patient to replenish some of the depleted RBCs before surgery.

## 9.2.3 Platelets

### General information

Normal platelet count (PC) is 150K–400K (abbreviation used here:  $150\text{K} = 150,000/\text{mm}^3 = 150 \times 10^9/\text{l}$ ). Thrombocytopenia is defined as  $\text{PC} < 150\text{K}$ . Bleeding (spontaneously or with invasive procedures) is rarely a problem with  $\text{PC} > 50\text{K}$ . Spontaneous hemorrhage is very likely with  $\text{PC} < 5\text{K}$ . Spontaneous intracranial hemorrhage is uncommon with  $\text{PC} > 30\text{K}$ , and is more common in adults than children. Based on patients with ITP, the risk of fatal hemorrhage in patients with  $\text{PC} < 30\text{K}$  is 0.0162–0.0389 cases per patient-year<sup>1</sup> (risk of death from infection is higher). Intracranial bleeding is usually subarachnoid or intraparenchymal, with petechial hemorrhages common.

1 unit of platelets contains  $5.5 \times 10^{10}$  (minimum) to  $10 \times 10^{10}$  platelets. The volume of 6 units is 250–300 ml. Platelets may be stored up to 5 days.

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### Recommended platelet transfusion criteria

Indications for platelet transfusion<sup>2</sup>:

- thrombocytopenia due to ↓ production (with or without increased destruction) (the most common causes are aplastic anemia and leukemia)
  - $\text{PC} < 10\text{K}$  even if no bleeding (prophylactic transfusion to prevent bleeding)
  - $\text{PC} < 20\text{K}$  and bleeding
  - $\text{PC} < 30\text{K}$  and patient at risk for bleeding: complaints of H/A, presence of confluent (c.f. scattered) petechiae, continuous bleeding from a wound, increasing retinal hemorrhage
  - $\text{PC} < 50\text{K}$  AND
    - major surgery planned within 12 hours
    - PC rapidly falling
    - patient <48 hours post-op
    - patient requires lumbar puncture
    - acute blood loss of > 1 blood volume in < 24 hours
- platelet transfusions have limited usefulness when thrombocytopenia is due to platelet destruction (e.g., by antibodies as in ITP) or consumption (if production is adequate or increased, platelet transfusion usually will not be useful)
- documented platelet dysfunction in a patient scheduled for surgery or in a patient with advanced hepatic and/or renal insufficiency (consider pharmacologic enhancement of platelet function, e.g., desmopressin<sup>3</sup>)

Other indications for platelet transfusion:

- patients who have been on Plavix® or aspirin who need urgent surgery that cannot be postponed for ≈ 5 days to allow new platelets to be synthesized

### Dosage

Approximately 25% of platelets are lost just with transfusion.

Peds: 1 U/m<sup>2</sup> raises PC by ≈ 10K, usually give 4 U/m<sup>2</sup>.

Adult: 1 U raises platelet count by  $\approx$  5–10K. Typical dose for thrombocytopenic bleeding adult: 6–10 U (usual order: “8-pack”). Alternatively, 1 U ofpheresed platelets may be given (obtained from a single donor by apheresis, equivalent to 8–10 U of pooled donor platelets).

Check PC 1–2 hrs after transfusion. The increase in PC will be less in DIC, sepsis, splenomegaly, with platelet antibodies, or if the patient is on chemotherapy. In the absence of increased consumption, platelets will be needed q 3–5 days.

## 9.2.4 Plasma proteins

### FFP (fresh frozen plasma)

#### General information

1 bag = 200–250 ml (usually referred to as a “unit,” not to be confused with 1 unit of factor activity which is defined as 1 ml). FFP is plasma separated from RBCs and platelets, and contains all coagulation factors and natural inhibitors. FFP has an out-date period of 12 months. The risk of AIDS and hepatitis for each unit of FFP is equal to that of a whole unit of blood.

#### Recommended transfusion criteria

Recommendations (modified<sup>2</sup>):

1. history or clinical course suggestive of coagulopathy due to congenital or acquired coagulation factor deficiency with active bleeding or pre-op, with PT > 18 sec or APTT > 1.5  $\times$  upper limit of normal (usually > 55 sec), fibrinogen functioning normally and level > 1 g/l, and coagulation factor assay < 25% activity
2. proven coagulation factor deficiency with active bleeding or scheduled for surgery or other invasive procedure
  - a) congenital deficiency of factor II, V, VII, X, XI or XII
  - b) deficiency of factor VIII or IX if safe replacement factors unavailable
  - c) von Willebrand's disease unresponsive to DDAVP
  - d) multiple coagulation factor deficiency as in hepatic dysfunction, vitamin K depletion or DIC
3. reversal of warfarin (Coumadin®) (p. 174) effect (PT > 18 sec, or INR > 1.6) in patient actively bleeding or requiring emergency surgery or procedure with insufficient time for vitamin K to correct (which usually requires > 6–12 hrs)
4. deficiency of antithrombin III, heparin cofactor II, or protein C or S
5. massive blood transfusion: replacement of > 1 blood volume ( $\approx$  5 L in 70 kg adult) within several hours with evidence of coagulation deficiency as in (1) and with continued bleeding
6. treatment of thrombotic thrombocytopenic purpura, hemolytic uremic syndrome
7. **\* because of associated hazards and suitable alternatives, the use of FFP as a volume expander is relatively contraindicated**

#### Dosage

Usual starting dose is 2 bags of FFP (400–600 ml). If PT is 18–22 secs or APTT is 55–70 secs, 1 bag may suffice. Doses as high as 10–15 ml/kg may be needed for some patients. Monitor PT/PTT (or specific factor assay) and clinical bleeding. Since factor VII has a shorter half-life ( $\approx$  6 hrs) than the other factors, PT may become prolonged before APTT.

Remember: if patient is also receiving platelets, that for every 5–6 units of platelets the patient is also receiving coagulation factors equivalent to  $\approx$  1 bag of FFP.

### Albumin and plasma protein fraction (PPF, AKA Plasmanate®)

Usually from outdated blood, treated to inactivate hepatitis B virus. Ratio of albumin:globulin percentage in “albumin” is 96%:4%, in PPF it is 83%:17%. Available in 5% (oncotically and osmotically equivalent to plasma) and 25% (contraindicated in dehydrated patients). 25% albumin may be diluted to 5% by mixing 1 volume of 25% albumin to 4 volumes of D5 W or 0.9% NS (**\*** caution: mixing with sterile water will result in a hypotonic solution that can cause hemolysis and possible renal failure).

Expensive for use simply as a volume expander ( $\approx$  \$60–80 per unit). Indicated only when total protein < 5.2 gm% (otherwise, use crystalloid which is equally effective). Rapid infusion (> 10 cc/min) has been reported to cause hypotension (due to Na-acetate and Hageman factor fragments). Use in ARDS is controversial. In neurosurgical patients, may be considered as an adjunct for volume expansion (along with crystalloids) for hyperdynamic therapy (p.1447) when the hematocrit is <40% following SAH where there is concern about increasing the risk of rebleeding e.g., with the use of hetastarch (p.1434).

## Cryoprecipitate

Recommended transfusion criteria:

1. hemophilia A
2. von Willebrand disease
3. documented fibrinogen/factor VIII deficiency
4. documented disseminated intravascular coagulation (DIC): along with other modes of therapy

## Prothrombin complex concentrate (PCC) (Kcentra® and others)

Derived from fresh-frozen human plasma, contains clotting factors II, VII, IX and X, with protein C & S to prevent thrombosis. Primary indication is to be given IV to reverse warfarin in emergency situations. However it is also used in other settings. Requires much lower volume than FFP to work. Also, when the INR gets down to about 1.4, PCC will continue to reduce the INR whereas FFP will have little or no benefit (the INR of FFP itself is  $\approx 1.3\text{--}1.4$ ).

Optimal dosing is not known. Doses of 15–50 IU/kg have been given to hemophiliacs, but the clotting deficit differs in vitamin-K depletion than in clotting factor absence. A reasonable dose that is often used is 25 IU/kg.

## 9.3 Anticoagulation considerations in neurosurgery

### 9.3.1 General information

Most of these issues have not been studied in a rigorous, prospective fashion. Yet, these questions frequently arise. The following is to be considered a framework of guidelines, and is not to be construed as a standard of care. ► Table 9.3 acts as an index to the topics discussed below.

Choice of oral anticoagulant: compared to vitamin K antagonists (VKAs) (e.g., warfarin), the novel oral anticoagulants (NOACs) dabigatran, rivaroxaban & edoxaban are at least as effective in preventing ischemic stroke and systemic embolization in patient with atrial fibrillation. And compared to warfarin, NOACs reduce ICH by about 50%,<sup>4</sup> have a more rapid onset of action, a shorter half-life, more predictable pharmacokinetics, fewer drug-drug interactions, and do not require routine monitoring.<sup>5</sup>

**Table 9.3** Anticoagulation issues in neurosurgery

**General neurosurgical contraindications to full anticoagulation with heparin (p. 163)**

**Starting/continuing anticoagulation in the presence of the following neurosurgical conditions**

- incidental aneurysm (p. 164)
- subarachnoid hemorrhage (p. 164)
- brain tumor (p. 164)
- following craniotomy (p. 164)
- acute epidural/subdural hematoma
- chronic subdural hematoma
- ischemic stroke
  - after tPA (p. 1564)
  - for prevention of (p. 1543)
- intracerebral hemorrhage (p. 1622)

**Managing patients who are already anticoagulated who need a neurosurgical procedure**

- warfarin (Coumadin®) (p. 164)
- heparin (p. 168)
- LMW-heparin (p. 168)
- antiplatelet drugs (aspirin, Plavix, NSAIDs) (p. 168)

**Recommendations for DVT prophylaxis in neurosurgical patients (p. 177)**

### 9.3.2 Contraindications to heparin

Contraindications to heparin therapy are constantly being reevaluated. Massive PE producing hemodynamic compromise should be treated with anticoagulation in most cases despite intracranial risks. Contraindications to full anticoagulation with heparin include:

- recent severe head injury
- recent craniotomy: see below
- patients with coagulopathies
- hemorrhagic infarction
- bleeding ulcer or other inaccessible bleeding site
- uncontrollable hypertension

- severe hepatic or renal disease
- <4–6 hours before an invasive procedure (see below)
- brain tumor: see below

### 9.3.3 Patients with unruptured (incidental) cerebral aneurysms

Anticoagulation may not increase the risk of hemorrhage (i.e., rupture); however, should rupture occur, anticoagulation would most likely increase volume of hemorrhage and thus increase morbidity and mortality.

The decision to start/continue anticoagulant depends on the indication for the drugs, the size of the aneurysm (a small aneurysm <4 mm is not as worrisome). Patients needing antiplatelet therapy (e.g., Plavix®) for drug-eluting cardiac stents should probably be left on their drugs.

### 9.3.4 Patients on anticoagulation/antiplatelet drugs who develop SAH

Coumadin and antiplatelet drugs are usually reversed.

### 9.3.5 In patients with brain tumor

Some authors are reluctant to administer full-dose heparin to a patient with a brain tumor,<sup>6</sup> although a number of studies found no higher risk in these patients when treated with heparin or oral anticoagulation<sup>7,8,9</sup> (PT should be followed very closely, one study recommended maintaining PT ≈ 1.25 × control<sup>9</sup>).

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### 9.3.6 Postoperatively following craniotomy

Requires individualization based on the reason for the craniotomy. Surgery for parenchymal lesions where the surgery disrupts small vessels (e.g., brain tumor) is probably higher risk for hemorrhage than, e.g., aneurysm surgery (expert opinion). Options:

Full anticoagulation: most neurosurgeons would probably not fully anticoagulate patients <3–5 days following craniotomy,<sup>10</sup> and some recommend at least 2 weeks. However, one study found no increased incidence of bleeding when anticoagulation was resumed 3 days post craniotomy.<sup>11</sup>

Low-dose (prophylactic) anticoagulation: either with mini-dose heparin (5000 U SQ 2 hrs prior to craniotomy and continuing q 12 hrs post-op × 7 d) or enoxaparin (Lovenox) (30 mg SQ BID or as a single dose of 40 MG SQ q d). RPDB study<sup>12</sup>: assessed safety (not efficacy), 55 patients undergoing craniotomy for tumor received mini-dose heparin as indicated had no increased bleeding tendency by any of the parameters measured. RPNB study<sup>13</sup>: incidence of post-op hemorrhage increased to 11% with enoxaparin.

### 9.3.7 Management of anticoagulants prior to neurosurgical procedures

Preoperative laboratory assessment of the coagulation pathway and platelet function is routinely used even though these studies rarely contribute critical information in the patient with a negative history for bleeding tendencies. There are no randomized studies to assess the value of coagulation laboratory measurements to patient care. This section encompasses the use of antiplatelet and anti-coagulation medicines, their monitoring, and their reversal.

► Table 9.4 summarizes this information.

## Warfarin

### Management guidelines

Patients on warfarin who must be anticoagulated as long as possible (e.g., mechanical heart valves) may be “bridged” to LMW heparin injections (e.g., Lovenox (p. 173)), as follows: stop warfarin at least 3 days prior to the procedure, and begin self-administered LMW heparin injections which are discontinued, as outlined in ► Table 9.4.

Patients with less critical anticoagulation needs (e.g., chronic a-fib) can usually stop the warfarin at least 4–5 days before the procedure, and a PT/INR is then checked on admission to the hospital. Patients must be advised that during the time that they are not anticoagulated, they are at risk of possible complications from the condition for which they are receiving the agents (*annual* risk for mechanical valve: ≈ 6%; for a-fib: depends on several factors including age and history of prior stroke, an average for patients >65 years of age is ≈ 5–6%; see details (p.1590).

Table 9.4 Anticoagulants

Drug Name (Brand)	Administration	Mechanism	Monitoring	Metabolism	Reversal strategy	Hold time <sup>a</sup>	Comments
Unfractionated heparin	IV for therapeutic anticoagulation; SQ for prophylaxis	Binds antithrombin III. Inhibits conversion of prothrombin → thrombin and fibrinogen → fibrin	aPTT, ACT, or antifactor Xa	Liver; excreted in urine; $T_{1/2}$ 60–90 min	1 mg protamine sulfate/100 u heparin administered	Full anticoagulation 4–6 hrs; consider repeat aPTT; SQ “mini-dose” 12 hrs	Heparin produced since 2009 is 10% less potent; incidence of HIT is variable; “heparin rebound” may occur 8–9 hrs after protamine infusion <sup>33,34</sup>
Enoxaparin (Lovenox, Sanofi Aventis) (an LMWH)	SQ for DVT prophylaxis and therapeutic anti-coagulation	Binds antithrombin III and accelerates activity; inhibits thrombin and factor Xa	Antifactor Xa (therapeutic level 0.4–0.8 units/ml)	Liver; renal clearance, caution in patients with CrCl < 30 ml/min	protamine sulfate (1 mg/1 mg enoxaparin given in last 8 hrs); will only partially reverse effects (60%)	12 hrs after prophylactic dose; 2 hrs after therapeutic dose	more selective inhibitor of factor Xa than thrombin <sup>33,34,35</sup>
Fondaparinux (Arixtra, GlaskoSmithKline)	SQ for DVT prophylaxis and therapeutic anti-coagulation	Inhibits factor Xa	Antifactor Xa: Prophylactic dose (0.4–0.5 mg/l); Therapeutic dose (1.2–1.26 mg/l)	Unknown; Excreted in urine; $T_{1/2}$ 17–21 hrs	No approved antidote; consider rVIIa, but no studies examining the role of rVIIa in reversing fondaparinux in the setting of bleeding; hemodialysis reduces ≈ 20%	2–4 days in patients with normal renal function	Does not cause HIT; useful in patients with HIT; recommend 50% dose reduction if CrCl 30–50, contraindicated if CrCl < 30 <sup>33,34,35</sup>
Warfarin (Coumadin, Bristol-Myers Squibb)	PO	Vitamin K antagonist. (Vitamin K dependent factors are II, VII, IX, X, protein C & S)	PT; INR (goal varies with indication)	Liver; excreted in urine ≈ 92%; bile; $T_{1/2}$ 20–60 hrs (highly variable)	Vitamin K 10 mg IV x 3 days and/or PCC (25–100 U/kg) or FFP (15 ml/kg) <sup>33</sup>	5 days	Consider decreasing dose with hepatic impairment
Argatroban (GlaskoSmithKline)	IV for prophylaxis and treatment of thrombosis in patients with HIT	Direct thrombin inhibitor	aPTT (goal 1.5–3x normal); ACT	Liver; excreted in feces ≈ 65% and urine ≈ 22%; $T_{1/2}$ 39–51 min	No reversal agent; supportive care; Hemodialysis can remove some drug from bloodstream, but unknown effect on bleeding, consider FFP or cryoprecipitate	2–4 hrs	Liver disease, consider decreasing start dose and titrate slowly <sup>30,34</sup>
Dabigatran (Pradaxa®, Boehringer Ingelheim)	PO, BID dosing	Direct thrombin inhibitor, reversible	No routine monitoring; normal aPTT implies no effect	Liver; renal clearance in urine; $T_{1/2}$ 12–17 hrs	idarucizumab (Praxbind®) (see text below)	1–2 days, longer if renal CrCl < 50 ml/min see ▶ Table 9.5	For prevention of stroke with atrial fibrillation (afib); PCC shown to be most effective but unproven in human studies <sup>33,34,36</sup>

(continued)

Table 9.4 continued

Drug Name (Brand)	Administration	Mechanism	Monitoring	Metabolism	Reversal strategy	Half time <sup>a</sup>	Comments
Rivaroxaban (Xarelto®, Bayer HealthCare)	PO daily dosing	Factor Xa inhibitor	No routine monitoring; normal antifactor Xa indicates no effect	Liver: renal clearance ≈ 66%; feces ≈ 28%; $T_{1/2}$ 5–9 h	Andexxa® (p. 175), if not available, consider rVlla (partial reversal in animals)	24 hrs (see ▶ Table 9.5)	For prevention of stroke in afib and DVT treatment; Caution: use with CrCl 15–50; CrCl < 30 avoid use. <sup>35,37</sup> Not dialyzable <sup>33</sup>
Apixaban (Eliquis®, Bristol-Myers Squibb)	PO, BID dosing	Factor Xa inhibitor	No routine monitoring; normal antifactor Xa indicates no effect	Liver ≈ 75% renal clearance ≈ 25%; $T_{1/2}$ 12 h	Andexxa® (p. 175), if not available, consider PCC, or rVlla. rVlla decreases bleeding time in animal model but does not reverse anticoagulant effect.	48 hrs (see ▶ Table 9.5)	For prevention of stroke in afib and DVT prophylaxis after orthopedic surgery. Decrease dose if Cr > 1.5; do not use with severe hepatic impairment. <sup>35,36</sup> Not dialyzable <sup>33</sup>
Edoxaban (Savaysa™, Daiichi Sankyo Co.)	PO, daily dosing. Do not use if CrCl > 95 mL/min	Factor Xa inhibitor	No routine monitoring. Changes in PT & INR are small and not useful. Normal antifactor Xa indicates no effect	renal ≈ 50% (unchanged drug). Remainder: biliary/intestinal excretion & minimal metabolism. $T_{1/2}$ 10–14 h	No specific antagonist	48 hrs	For DVT & PE after 5–10 d of parenteral anticoagulant; to reduce risk of stroke and embolism in nonvalvular afib
Antithrombin, recombinant (Atryn, Lundbeck)	IV	Inhibits thrombin and factor Xa	AT levels	$T_{1/2}$ 11.6–17.7 h			For thromboembolism prophylaxis in hereditary antithrombin deficiency
Antithrombin III (Thrombate III, Grifols)	IV	Forms bond with thrombin	AT levels	$T_{1/2}$ 2–3 days			For thromboembolism prophylaxis in hereditary antithrombin deficiency
Dalteparin (Fraxiparin, Eisai)	SQ for DVT prophylaxis and therapeutic anti-coagulation	Accelerates activity of antithrombin III (inhibits thrombin and factor Xa)		Liver, urine; $T_{1/2}$ 3–5 h (longer with renal impairment)			Caution when use with CrCl < 30; caution with hepatic impairment
Bivalirudin (Angiomax®, The Medicines Company)	IV	Direct thrombin inhibitor (reversible)	ACT	Plasma; excreted in urine; $T_{1/2}$ 25 min (longer with renal impairment)	None		Caution when use with CrCl < 30

Table 9.4 continued

Drug Name (Brand)	Administration	Mechanism	Monitoring	Metabolism	Reversal strategy	Hold time <sup>a</sup>	Comments
Desirudin (Iprivask®, Canyon)	SC	Direct thrombin inhibitor selectively inhibits free and clot-bound thrombin	aPTT	Kidney; excreted in urine; $T_{1/2}$ 2h (longer with renal impairment)	None		CrCl < 60 use caution, decrease initial dose <sup>33</sup>

Abbreviations: PCC = prothrombin complex concentrate; IV = intravenous; SQ = subcutaneous; aPTT = partial thromboplastin time; DVT = deep venous thrombosis; HIT = heparin induced thrombocytopenia; ACT = activated clotting time; AT = anti-thrombin; CrCl = creatinine clearance.

<sup>a</sup>Hold time is the recommended time to wait after discontinuing the drug before doing an elective operation in order to eliminate the effects of the drug  
bintravenous vitamin K has a more rapid onset than subcutaneous vitamin K and current formulations, made with micelles of lecithin and glycol, seem to have a lower complication profile than older formulations containing polyethylated castor oil.<sup>38</sup>

Table 9.5 Recommendations for holding oral anticoagulants prior to invasive procedures related to renal function.<sup>33</sup>

	dabigatran (Pradaxa®)	apixaban (Eliquis®)	rivaroxaban (Xarelto®)
CrCl > 80 ml/min	≥ 72 hr	≥ 48 hr	≥ 48 hr
CrCl 50–80 ml/min	≥ 72 hr	≥ 48 hr	≥ 48 hr
CrCl 30–49 ml/min	≥ 96 hr	≥ 72 hr	≥ 72 hr
CrCl < 30 ml/min	≥ 120 hr	≥ 96 hr	≥ 96 hr

The recommended minimum interval between last dose and procedure is based on renal function and procedure risk. Generally, neurosurgical procedures including minor procedures such as LPs are considered interventions with a high bleeding risk

### For non-emergent neurosurgical procedures

For procedures where post-op mass effect from bleeding would pose serious risk (which includes most neurosurgical operations), it is recommended that the PT should be  $\approx \leq 13.5$  sec (i.e.,  $\leq$  upper limits of normal) or the INR should be  $\approx \leq 1.4$  (e.g., for reference, this INR is considered safe for performing a percutaneous needle liver biopsy). See also reversal of anticoagulation (p. 174).

### For emergent neurosurgical procedures

Give FFP (start with 2 units) and vitamin K (10–20 mg IV at  $\leq 1$  mg/min) as soon as possible; see also reversal of anticoagulation (p. 174). The timing of surgery is then based on the urgency of the situation and the nature of the procedure (e.g., the decision might be to evacuate a spinal epidural hematoma in an acutely paralyzed patient before anticoagulation is fully reversed).

### Heparin

For emergencies: if it would be deleterious to wait 4–6 hours after discontinuing heparin and then repeating the PTT to verify that anticoagulation has been corrected, then heparin can be reversed with protamine (p. 174).

### For non-emergencies

IV heparin: stop the drip  $\approx 4\text{--}6$  hours prior to the planned procedure. Option: recheck PTT just prior to starting the procedure.

"Mini-dose" SQ heparin: not mandatory to stop for craniotomy, but if desired to discontinue, then give last dose  $\geq 12$  hours prior to surgery.

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### Low-molecular weight heparins (LMWH)

For emergencies: can be reversed with protamine (p. 174).

Non-emergencies: See ▶ Table 9.4. Longer times are needed in renal failure. A factor Xa level can be used to check anticoagulation status, but this usually must be sent out, making it unsuitable for acute management.

### Antiplatelet drugs and neurosurgical procedures

#### Platelet mechanistics and platelet function tests

Platelets are important for maintaining vascular endothelial integrity and are involved with hemostasis in conjunction with coagulation factors. Severe thrombocytopenia can result in petechial hemorrhages or spontaneous intracerebral hemorrhage (ICH). Vascular wall disturbance is the initial stimulus for platelet deposition and activation. Platelets adhere to collagen via surface receptors GPIb-V-IX and von Willebrand factor. This adhesion sets off a cascade of reactions, which result in platelet aggregation forming a hemostatic plug. Historically, bleeding time (BT) was used as the screening test for abnormalities of platelet function. Due to unreliability, many institutions have replaced the BT with the platelet function assay (PFA) using the PFA-100 (platelet function analyzer). There are limited studies confirming its use according to the International Society of Thrombosis and Hemostasis.<sup>14,15</sup>

In the PFA-100, primary hemostasis is simulated under "high-shear" flow by movement of citrated blood through a membrane-impregnated capillary in two collagen-coated cartridges; one stimulates platelets with adenosine diphosphate (ADP) and the other with epinephrine.<sup>16</sup> This interaction with the collagen induces a platelet plug, which closes an aperture. Results are reported as closure time in seconds. This method is eligible as a screening test for primary hemostatic disease such as von Willebrand disease as well as for monitoring the effect of antiplatelet therapy. The PFA-100 works for testing with aspirin but not with thienopyridine drug class (e.g., clopidogrel). Newly available PFA cartridges detect P2Y12 receptor blockade in patients on theinopyridine drugs.<sup>17</sup> VerifyNow® measures agonist-induced aggregation as an increase in light transmittance. The system contains a preparation of human fibrinogen-coated beads, which cause a change in light transmittance by ADP-induced platelet aggregation.<sup>17</sup> There is little correlation between the PFA-100 results and VerifyNow Assay.

## Agents

► **Plavix® (clopidogrel) (p. 1548) and aspirin.** Cause permanent inhibition of platelet function that persists  $\approx$  5 days after discontinuation of the drug and can increase the risk of bleeding. For elective cases, 5–7 days off these drugs is recommended (surveys of German neurosurgeons<sup>18,19</sup>; an average of 7 days was used for low-dose ASA, with a few who do spine surgery even while the patient is on ASA).

Cardiac stents: dual antiplatelet therapy (e.g., ASA + Plavix®) are mandatory for 4 weeks (90 days is preferable<sup>20</sup>) after placement of a bare metal cardiac stent, and for at least 1 year with drug-eluting stents (DES) (the risk declines from  $\approx$  6% to  $\approx$  3%).<sup>21</sup> Even short gaps in drug therapy (e.g., to perform neurosurgical procedures) is associated with significant risk of acute stent occlusion (and therefore elective surgery during this time is discouraged<sup>22</sup>). DES are so effective in suppressing endothelialization that lifetime dual antiplatelet therapy may be required. Bridging DES patients with antithrombin, anticoagulants, or glycoprotein IIb/IIIa agents has not been proven effective.<sup>22</sup>

**Reversal of antiplatelet drugs:** While heparin and warfarin can be reliably and measurably reversed, the situation is less clear with antiplatelet agents.<sup>23</sup> Agents used pre-op to reverse these drugs include Desmopressin (p. 175) (DDAVP<sup>®</sup>)<sup>18,19</sup> and FFP.<sup>18</sup>

Reversal of Plavix for emergency surgery (p. 161): platelets may be given; however, the Plavix effect persists for up to a couple of days after the last dose, and can actually inhibit platelets given after the drug is discontinued (the half-life of aspirin is lower and should not be an issue after 1 day). In cases with continued oozing in the first day or so after discontinuing Plavix, the following regimen is an option:

1. recombinant activated coagulation factor VII (rFVIIa): even though the defect is in the platelets, rFVIIa works, via a mechanism not mediated by protein clotting factors. Very expensive ( $\approx$  \$10,000 per dose), but this must be balanced against the cost of repeat craniotomy, increased ICU stay and additional morbidity
  - a) initial dose<sup>24</sup>: 90–120 mcg/kg
  - b) same dose 2 hrs later
  - c) 3rd dose 6 hrs after initial dose
2. platelets every 8 hours for 24 hours, either
  - a) 6 U of regular platelets
  - b) if patient is on fluid or volume restriction: 1 unit of pheresed platelets

► **Herbal products and supplements.** Herbal products and supplements often affect platelet aggregation and the coagulation cascade by means that cannot be detected by laboratory tests. The increasing popularity of these unregulated products requires screening patients for their use. There are limited studies regarding the use of herbal supplements in neurosurgery and, as a precaution for an elective operation, waiting 7–14 days after cessation of their use is suggested.

**Fish Oil** (Omega-3 Fatty Acids) is used for treatment of dyslipidemia and hypertriglyceridemia. Fish oil may affect platelet aggregation by a reduction in arachidonic acid and thromboxane and adenosine diphosphate receptor blockade. Fish oil may also potentially lengthen bleeding times.<sup>25,26,27</sup>

**Garlic** (*Allium sativum*): purported benefits include lowering blood pressure, preventing infection and myocardial infarction, and treating hypercholesterolemia. Garlic has an antiplatelet effect through ADP receptor blockade, and reducing calcium and thromboxane.<sup>28</sup> Garlic may potentiate the antiplatelet or anticoagulant effect of aspirin or warfarin.<sup>29</sup>

**Ginkgo** (*Ginkgo biloba*) is found in many formulations from capsules to energy drinks. It has been used to treat memory loss, depression, anxiety, dizziness, claudication, erectile dysfunction, tinnitus and headache. Ginkgo affects bleeding via an antiplatelet effect and antagonism of platelet-activating factor.<sup>30,31</sup> See *Ginkgo biloba* under Spontaneous subdural hematoma (p. 1085).

**Ginseng** (*Panax ginseng*) also has antiplatelet activity through thromboxane inhibition and platelet-activating factor.<sup>32</sup>

Some authors also advocate cautious use of ginger and vitamin E when planning surgery, but the exact antiplatelet mechanism is unclear.<sup>27</sup>

### 9.3.8 Anticoagulants

See also ► Table 9.6 for platelet function inhibitors.

Table 9.6 Platelet function inhibitors

Drug Name (Brand)	Mechanism	Administration	Monitoring	Metabolism	Reversal strategy	Hold time <sup>a</sup>	Comments
Aspirin (Acetylsalicylic acid)	COX-1 Direct action, irreversible	PO	PFA, Arachidonic acid-based tests (VerifyNow)	Gut, plasma, and liver; renal clearance; $T_{1/2}$ 15–20 min	Platelet transfusion; Desmopressin	7–10 days	Prevalence of aspirin resistance is 5–60%; therapeutic effect for lifetime of platelets (9 days), 10% of circulating platelets are replaced in 24-hr period <sup>33,34,39</sup>
Clopidogrel (Plavix®, Sanofi Aventis)	Thienopyridines/P2Y <sub>12</sub> Prodrug, irreversible	PO	PFA, VerifyNow P2Y12 (PRU Test)	Liver; renal clearance $T_{1/2}$ 8 hrs	Platelet transfusion (10 concentrate units every 12 hrs for 48 hrs); Desmopressin <sup>b</sup>	7–10 day	Prevalence of clopidogrel resistance is 8–35% <sup>33,34,39</sup>
Ticlodipine (Ticlid®, Roche)	Thienopyridines/P2Y <sub>12</sub> Prodrug, irreversible	PO	Bleeding time	Liver; renal clearance; $T_{1/2}$ 4–5 days	NA	Effective in ≈ 96% of patients with clopidogrel resistance	
Prasugrel (Effient®, Eli Lilly)	Thienopyridines/P2Y <sub>12</sub> Prodrug, irreversible	PO	PFA, VerifyNow P2Y12 (PRU Test)	Liver; renal clearance ≈ 68%; feces ≈ 27%; $T_{1/2}$ 3.7 hrs	Platelet transfusion; active metabolite not removed by dialysis	Used for coronary artery disease <sup>33</sup>	
Ticagrelor (Brilinta®, AstraZeneca)	Cyclopentyltriaxopyrimidine/P2Y <sub>12</sub> Direct-acting, reversible	PO	NA	Liver; excreted in bile primarily; $T_{1/2}$ 9 hrs (active metabolite)	NA, not removed by dialysis	5 days <sup>40</sup>	
Dipyridamole (Persantine®, Boehringer Ingelheim)	cGMP V Prodrug, reversible	PO	NA	Liver; excretion in bile; $T_{1/2}$ 10–12 hrs	Dialysis is no benefit		
Abciximab (ReoPro®, Eli Lilly)	GPⅡb/Ⅲa Reversible	IV	aPTT, ACT, VerifyNow IIb/IIIa test	Proteolytic cleavage; $T_{1/2}$ 30 min	Platelet transfusion, no antagonist	Platelet function returns to ≈ 50% of baseline 24 hrs after infusion; low-level inhibition may continue for up to 7 weeks <sup>34</sup>	

Table 9.6 continued

Drug Name (Brand)	Class/Target	Mechanism	Administration	Monitoring	Metabolism	Reversal strategy	Hold time <sup>a</sup>	Comments
Epifibatide (Integrenil, Millennium/ Merck)	GPIIb/IIIa	Reversible	IV	aPTT, ACT, VerifyNow lib/IIa test	Renal clearance 75%; $T_{1/2}$ 2.5 hrs	May be removed by dialysis		CrCl < 50 adjust infusion rate; platelet function returns to ≈ 50% 4hrs after infusion D/C <sup>b34</sup>
Tirofiban (Aggrastat, Medicure)	GPIIb/IIIa	Reversible	IV		Renal clearance 65%; feces 25%; $T_{1/2}$ 2-3 hrs	May be removed by dialysis		CrCl < 30 adjust infusion rate; platelet coagula- tion is inhibited within 5 min, and remains inhibited for 3-8h <sup>b34</sup>

Abbreviations: PCC = prothrombin complex concentrate; IV = intravenous; SQ = subcutaneous; aPTT = partial thromboplastin time; ACT = activated clotting time; CrCl = creatinine clearance; D/C = discontinue.

<sup>a</sup>Hold time is the recommended time to wait after discontinuing the drug before doing an elective operation in order to eliminate the effects of the drug.

<sup>b</sup>Desmopressin enhances platelet adhesion to vessel wall by increased concentrations of factor VIII and von Willebrand factor. Desmopressin increased platelet adhesion in randomized trial in both aspirin group and control group.<sup>41</sup>

## Warfarin

### Drug info: Warfarin (Coumadin®)

An oral vitamin K antagonist. To anticoagulate average-weight patient, give 10 mg PO q d  $\times$  2–4 days, then  $\approx$  5 mg q d. Follow coagulation studies, titrate to  $PT = 1.2\text{--}1.5 \times$  control (or  $INR \approx 2\text{--}3$ ) for most conditions (e.g., DVT, single TIA). Higher  $PT$  ratios of  $1.5\text{--}2 \times$  control ( $INR \approx 3\text{--}4$ ) may be needed for recurrent systemic embolism, mechanical heart valves... (the recommended ranges for the International Normalized Ratio (INR) are shown in ► Table 9.7).

\* Contraindicated in pregnancy: in addition to risk of bleeding, warfarin is associated with spontaneous abortion and stillbirth. Warfarin also crosses the placenta and is teratogenic, causing birth defects in 5–30%, including fetal warfarin syndrome during 1st trimester (including scoliosis, brachydactyly, vertebral column calcifications, ventriculomegaly, agenesis of the corpus callosum) and spasticity/seizures and eye defects after the 1st trimester.

Starting warfarin: During the first  $\approx$  3 days of warfarin therapy, patients may actually be hypercoagulable (secondary to reduction of vitamin-K dependent anticoagulation factors protein C and protein S), putting them at risk of "Coumadin necrosis." Therefore patients should be "bridged" by starting either Lovenox (p. 173) which can be self-administered as an outpatient, or heparin (with a therapeutic PTT).

**Supplied:** scored tabs of 1, 2, 2.5, 5, 7.5 and 10 mg. IV form: 5 mg/vial.

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**Table 9.7** Recommended INRs<sup>42</sup>

Indication	INR
• mechanical prosthetic heart valve • prevention of recurrent MI	2.5–3.5
antiphospholipid antibody syndrome (p. 1542) <sup>43</sup>	$\geq 3$
all other indications (DVT prophylaxis and treatment, PE, atrial fibrillation, recurrent systemic embolism, tissue heart valves)	2–3

## Heparin

### Drug info: Heparin

R Full anticoagulation in an average-weight patient, give 5000 U bolus IV, follow with 1000 U/hr IV drip. Titrate to therapeutic anticoagulation of  $APTT = 2\text{--}2.5 \times$  control (for DVT, some recommend  $1.5\text{--}2 \times$  control<sup>44</sup>).

R prophylactic AKA low-dose ("mini-dose") heparin: 5000 IU SQ q 8 or 12 hrs. Routine monitoring of  $APTT$  is usually not done, although occasionally patients may become fully anticoagulated on this regimen.

**Side effects:** (see Anticoagulant considerations in neurosurgery above): hemorrhage, thrombosis<sup>45</sup> (heparin activates anti-thrombin III and can cause platelet aggregation) which can result in MIs, DVTs, PEs, strokes, etc. Heparin induced thrombocytopenia (HIT): transient mild thrombocytopenia is fairly common in the first few days after initiating heparin therapy; however, severe thrombocytopenia occurs in 1–2% of patients receiving heparin > 4 days (usually has a delayed onset of 6–12 days, and is due to consumption in heparin-induced thrombosis or to antibodies formed against a heparin-platelet protein complex). The incidence of HIT in SAH is 5–6% and was similar with enoxaparin.<sup>46</sup> Consider use of fondaparinux in thrombocytopenic patients. Chronic therapy may cause osteoporosis.

## Low molecular weight heparins

See references.<sup>47,48</sup>

Low molecular weight heparins (LMWH) (average molecular weight = 3000–8000 daltons) are derived from unfractionated heparin (average MW = 12,000–15,000 daltons). LMWHs differ from unfractionated heparin because they have a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity which theoretically should produce antithrombotic effects with fewer hemorrhagic complications. Realization of this benefit has been very minor in clinical trials. LMWH have greater

bioavailability after sub-Q injection leading to more predictable plasma levels which eliminates the need to monitor biologic activity (such as APTT). LMWH have a longer half-life and therefore require fewer doses per day. LMWH have a lower incidence of thrombocytopenia. More effective in DVT prophylaxis than warfarin in orthopedic surgery.<sup>49</sup>

**Spinal epidural hematomas:** There have been a number of case reports of spinal epidural hematomas occurring in patients on LMWH (primarily enoxaparin) who also underwent spinal/epidural anesthesia or lumbar puncture, primarily in elderly women undergoing orthopedic surgery. Some have had significant neurologic sequelae, including permanent paralysis.<sup>50</sup> The risk is further increased by the use of NSAIDs, platelet inhibitors, or other anticoagulants, and with traumatic or repeated epidural or spinal puncture.

► **Available low molecular weight heparins.** Drugs include:

- enoxaparin (Lovenox®): see below
- dalteparin (Fragmin®): R 2500 anti-Xa U SQ q d
- ardeparin (Normiflo®): half-life = 3.3 hrs. R 50 anti-Xa U/kg SQ q 12 hrs
- danaraparoid (Orgaran®): a heparinoid. Even higher anti-Xa:anti-IIa ratio than LMWHs. Does not require laboratory monitoring. R 750 anti-Xa U SQ BID
- tinzaparin (Lopiparin®, Innohep®): not available in U.S. R 175 anti-Xa U per kg SQ once daily

### Drug info: Enoxaparin (Lovenox®)

R dosage established following hip replacement is 30 mg SQ BID × 7–14 days (alternative: 40 mg SQ q d). **Pharmacokinetics:** After SQ injection, peak serum concentration occurs in 3–5 hrs. Half-life: 4.5 hrs.

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### Direct thrombin inhibitors

### Drug info: Dabigatran (Pradaxa®, Rendix®)

An oral anticoagulant in the class of direct thrombin inhibitors. Administered as the prodrug dabigatran etexilate. Must be stopped 24 hrs prior to surgery.

**Reversal of anticoagulation:** Praxbind® (idarucizumab) IV for emergencies. Pradaxa reversal begins within 12 minutes, maximum reversal within 4 hrs, lasts 24 hrs.<sup>51</sup>

### Drug info: Bivalirudin (Angiomax® or Angiox®)

A reversible direct thrombin inhibitor (DTI) that increases the rapidity of plasminogen activator-mediated recanalization. No effective reversal.

R: IV loading dose of 0.5 mg/kg IV, followed by continuous infusion of 1.75 mg/kg/hr. Intra-arterial: inject 15 mg in 10 ml of heparinized saline via a microcatheter.

### Factor Xa inhibitors

### Drug info: Fondaparinux (Arixtra®)

A synthetic analog of the pentasaccharide binding sequence of heparin. Increases factor Xa inhibition without affecting factor IIa (thrombin).<sup>52</sup> Unlike heparin, fondaparinux does not bind to other plasma proteins or platelet factor-4 and does not cause heparin-induced thrombocytopenia (HIT) and can therefore be used in patients with HIT. May be more effective than enoxaparin (Lovenox®) for preventing post-op DVTs. **Side effects:** Bleeding is the most common side effect (may be increased by concurrent NSAID use). ✖ Contraindicated with severe renal impairment ( $\text{CrCl} < 30 \text{ ml/min}$ ).<sup>53</sup>

**R:** 2.5 mg SQ injection q d. **Supplied:** 2.5 mg single-dose syringes. **Pharmacokinetics:** Peak activity occurs in 2–3 hrs. Half-life: 17–21 hrs. Anticoagulation effect lasts 3–5 half-lives. Elimination: in urine (in renal insufficiency reduce dose by 50% for CrCl 30–50 ml/min). **STOP:** 2–4 days pre-op (longer with kidney dysfunction)

### 9.3.9 Coagulopathies

#### Correction of coagulopathies or reversal of anticoagulants

Also refer to recommended normal values for coagulation studies in neurosurgery (p. 164).

##### Platelets

See indications and administration guidelines (p. 161).

##### Fresh frozen plasma

To reverse warfarin anticoagulation, use the following as a starting point and recheck PT/PTT afterward:

- when patient is “therapeutically anticoagulated” start with 2–3 units FFP (approximately 15 ml/kg is usually needed)
- for severely prolonged PT/PTT, start with 6 units FFP

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##### Prothrombin complex concentrate (PCC)

Warfarin induced anticoagulation may be reversed up to 4 or 5 times more quickly with PCC (Kcentra®) (contains coag factors II, IX, and X) compared to FFP.<sup>54</sup> Patient may become hyperthrombotic with PCC.

### Drug info: Vitamin K (Mephyton®)

To reverse elevated PT from *warfarin*, give aqueous colloidal solution of vitamin K1 (phytonadione, Mephyton®). Doses > 10 mg may produce warfarin resistance for up to 1 week. FFP may be administered concurrently for more rapid correction (see above). See recommended levels of PT (p. 164).

**R** adult: start with 10–15 mg IM; the effect takes 6–12 hrs (in absence of liver disease). Repeat dose if needed. The average total dose needed to reverse therapeutic anticoagulation is 25–35 mg.

IV administration has been associated with severe reactions (possibly anaphylactic), including hypotension and even fatalities (even with proper precautions to dilute and administer slowly), therefore IV route is reserved only for situations where other routes are not feasible and the serious risk is justified. **R** IV (when IM route not feasible): 10–20 mg IV at a rate of injection not to exceed 1 mg/min (e.g., put 10 mg in 50 ml of D5 W and give over 30 minutes).

### Drug info: Protamine sulfate

For heparin: 1 mg protamine reverses ≈ 100 U *heparin* (give slowly, not to exceed 50 mg in any 10 min period). Therapy should be guided by coagulation studies.

**Reversal of low molecular weight heparins (LMWH):** slow IV injection of a 1% solution of protamine can also be used to reverse LMWHs as follows:

Enoxaparin (Lovenox®): ≈ 60% of Lovenox can be reversed with 1 mg of protamine for every mg of Lovenox given (maximum dose = 50 mg) within the last 8 hrs, and 0.5 mg of protamine for every mg of Lovenox given from 8–12 hrs prior. Protamine is probably not needed for Lovenox given > 12 hrs earlier.

Dalteparin (Fragmin®) or ardeparin (Normiflo®): 1 mg of protamine for every 100 anti-Xa IU of LMWH (maximum dose = 50 mg) with a second infusion of 0.5 mg protamine for every 100 anti-Xa IU of LMWH if the APTT remains elevated 2–4 hours after the first dose is completed.

Danaparoid and Hirudin: no known reversing agent.

## Drug info: Andexanet alfa (AndexXa®)

A recombinant DNA manufactured derivative of clotting factor Xa (fXa) that binds to certain fXa-inhibitors inhibiting their action. FDA-approved for reversal of rivaroxaban (Xarelto®) or apixaban (Eliquis®) for life-threatening or uncontrolled bleeding.<sup>55</sup>

Reduces anti-fXa activity in healthy volunteers, but improvement in hemostasis has not been established (studies ongoing). ✗ Has not been shown effective for, and is not indicated for, reversal of other fXa inhibitors (e.g., fondaparinux).

- Use low dose regimen described below for:
  - rivaroxaban dose ≤ 10 mg (any timing from last dose)
  - apixaban dose ≤ 5 mg (any timing from last dose)
  - rivaroxaban dose > 10 mg or dose unknown (≥ 8 hrs from last dose)
  - apixaban dose > 5 mg or dose unknown (≥ 8 hrs from last dose)
- Use high dose regimen described below for:
  - rivaroxaban dose > 10 mg or dose unknown (< 8 hrs from last dose or unknown)
  - apixaban dose > 5 mg or dose unknown (< 8 hrs from last dose or unknown)

Dosing regimens

- R Low dose regimen
  - Initial IV bolus: 400 mg IV. Target infusion rate: 10 mg/min.
  - Follow with 4 mg/min IV infusion for up to 120 min
- R High dose regimen
  - Initial IV bolus: 800 mg IV. Target infusion rate: 10 mg/min.
  - Follow with 8 mg/min IV infusion for up to 120 min

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## Drug info: Desmopressin (DDAVP®)

Causes an increase in factor III coagulant activity and von Willebrand factor which helps coagulation and platelet activity in mild hemophilia A and in von Willebrand's disease Type I (where the factors are normal in makeup but low in concentration, ✗ but may cause thrombocytopenia in von Willebrand's disease Type IIb where factors may be abnormal or missing). May prevent abnormal bleeding in minor procedures. Not all patients with mild hemophilia A or von Willebrand disease respond to DDAVP.

R 0.3 mcg/kg (use 50 ml of diluent for doses ≤ 3 mcg, use 10 ml for doses > 3 mcg) given over 15–30 minutes, 30 minutes prior to a surgical procedure.

### Elevated pre-op PTT

In a patient with no history of coagulopathy, a significantly elevated pre-op PTT is commonly due to either a factor deficiency or to lupus anticoagulant. Work-up:

1. mixing study
2. check serum lupus coagulant

If the mixing study corrects the elevated PTT, then there is probably a factor deficiency. Consult a hematologist.

**Lupus anticoagulant:** If the test for lupus anticoagulant is positive, then the major risk to the patient with surgery is *not* bleeding, rather it is thromboembolism. Management recommendations:

1. as soon as feasible post-op, start patient on heparin (p. 172) or LMW heparin (p. 172), e.g., Lovenox
2. at the same time start warfarin, and maintain therapeutic anticoagulation for 3–4 weeks (the risk of DVT/PE is actually highest in the first few weeks post-op)
3. mobilize as soon as possible post-op
4. consider vena-cava interruption filter in patients for whom anticoagulation is contraindicated

### Disseminated intravascular coagulation (DIC)

#### General information

Abnormal intravascular coagulation which consumes clotting factors and platelets, coupled with abnormal activation of fibrinolytic system. Head trauma is an independent risk factor for DIC,

possibly because the brain is rich in thromboplastin which may be released into systemic circulation with trauma.<sup>56</sup> Other risk factors: shock, sepsis.

### Presentation

Diffuse bleeding, cutaneous petechia, shock.

### Labs

1. fibrinogen degradation products (FDP) > 16 mcg/ml (1–8 = normal; 8–16 = borderline; 32 = definitely abnormal; some labs require > 40 for diagnosis of DIC) (the most common abnormality)
2. fibrinogen < 100 mcg/dl (some use 130)
3. PT > 16; PTT > 50
4. platelets < 50,000 (relatively uncommon)

### Chronic DIC

PT & PTT may be normal; platelet & fibrinogen low, fibrin split products elevated.

#### Treatment

1. remove inciting stimulus if possible (treat infections, debride injured tissue, stop transfusions if suspected)
2. vigorous fluid resuscitation
3. anticoagulants, if not contraindicated (p. 163)
4. FFP if PT or PTT elevated, or fibrinogen < 130
5. platelet transfusion if platelet count < 100 K

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### Pseudo-DIC

Increased fibrin split products, normal fibrinogen.

Seen in conditions such as liver failure.

## 9.3.10 Thromboembolism in neurosurgery

### Deep-vein thrombosis (DVT)

DVT is of concern primarily because of the potential for material (clot, platelet clumps...) to dislodge and form emboli (including pulmonary emboli [PE]) which may cause pulmonary infarction, sudden death (from cardiac arrest), or cerebral infarction (from a paradoxical embolus, which may occur in the presence of a patent foramen ovale, see Cardiogenic brain embolism (p. 1590)). The reported mortality from DVT in the LEs ranges from 9–50%.<sup>57</sup> DVT limited to the calf has a low threat (< 1%) of embolization; however, these clots later extend into the proximal deep veins in 30–50% of cases,<sup>57</sup> from where embolization may occur (in 40–50%), or they may produce postphlebitic syndrome.

Neurosurgical patients are particularly prone to developing DVTs (estimated risk: 19–50%), due at least in part to the relatively high frequency of the following:

1. long operating times of some procedures
2. prolonged bed rest pre- and/or post-op
3. alterations in coagulation status
  - a) in patients with brain tumors (see below) or head injury<sup>58</sup>
    - related to the condition itself
    - due to release of brain thromboplastins during brain surgery
  - b) increased blood viscosity with concomitant "sludging"
    - from dehydration therapy sometimes used to reduce cerebral edema
    - from volume loss following SAH (cerebral salt wasting)
  - c) use of high-dose glucocorticoids

Specific "neurological" risk factors for DVT and PE include<sup>57</sup>:

1. spinal cord injury (p. 1141)
2. brain tumor: autopsy prevalence of DVT = 28%, of PE = 8.4%. Incidence using 125I-fibrinogen<sup>59</sup>: meningioma 72%, malignant glioma 60%, metastasis 20%. Risk may be reduced by pre-op use of aspirin<sup>60</sup>
3. subarachnoid hemorrhage
4. head trauma: especially severe TBI (p. 1106)
5. stroke: incidence of PE = 1–19.8%, with mortality of 25–100%
6. neurosurgical operation: risk is higher following craniotomy for supratentorial tumors (7% of 492 patients) than p-fossa tumors (0 out of 141)<sup>61</sup>

## Prophylaxis against DVT

Options include:

1. general measures
  - a) passive range of motion
  - b) ambulate appropriate patients as early as possible
2. mechanical techniques (minimal risk of complications):
  - a) pneumatic compression boots<sup>62</sup> (PCBs) or sequential compression devices (SCDs): reduces the incidence of DVTs and probably PEs. Do not use if DVTs already present. Continue use until patient is able to walk 3–4 hrs per day
  - b) TED Stockings®: (TEDS) applies graduated pressure, higher distally. As effective as PCB. No evidence that the benefit is additive.<sup>57</sup> Care should be taken to avoid a tourniquet effect at the proximal end (note: TEDS® is a registered trademark. "TED" stands for thromboembolic disease)
  - c) electrical stimulation of calf muscles
  - d) rotating beds
3. anticoagulation; see also contraindications and considerations of anticoagulation in neurosurgery (p. 163)
  - a) full anticoagulation is associated with perioperative complications<sup>63</sup>
  - b) "low-dose" anticoagulation<sup>64</sup> (low-dose heparin): 5000 IU SQ q 8 or 12 hrs, starting 2 hrs pre-op or on admission to hospital. Potential for hazardous hemorrhage within brain or spinal canal has limited its use
  - c) low molecular weight heparins and heparinoids (p. 172): not a homogeneous group. Efficacy in neurosurgical prophylaxis has not been determined
  - d) aspirin: role in DVT prophylaxis is limited because ASA inhibits platelet aggregation, and platelets play only a minor role in DVT
4. combination of PCBs and "mini-dose" heparin starting on the morning of post-op day 1 (with no evidence of significant complications)<sup>65</sup>

## Recommendations

Recommended prophylaxis varies with the risk of developing DVT, as illustrated in ► Table 9.8.<sup>57</sup> See also details of prophylaxis in cervical spinal cord injuries (p. 1141).

**Table 9.8** Risk & prophylaxis of DVT in neurosurgical patients<sup>a</sup>

Risk group	Estimated risk of calf DVT	Typical neurosurgical patients	Treatment recommendation
low risk	<10%	age <40 yrs, minimal general risk factors, surgery with < 30 minutes general anesthesia	no prophylaxis, or PCB/ TEDS
moderate risk	10–40%	age ≥ 40 yrs, malignancy, prolonged bed rest, extensive surgery, varicose veins, obesity, surgery > 30 minutes duration (except simple lumbar discectomy), SAH, head injury	PCB/TEDs; or for patients without ICH or SAH, mini-dose heparin
high risk	40–80%	history of DVT or PE, paraplsis <sup>b</sup> (para- or quadriplegia or hemiparesis), brain tumor (especially meningioma or malignant glioma)	PCB/TEDS + (in patients without ICH or SAH) mini-dose heparin

<sup>a</sup>abbreviations: DVT = deep venous thrombosis, PCB = pneumatic compression device, TEDS = TED (thromboembolic disease) Stockings®, ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage

<sup>b</sup>see specifics regarding DVT prophylaxis in cervical SCI (p. 1141)

## Diagnosis of DVT

(For PE, see below). The clinical diagnosis of DVT is very unreliable. A patient with the "classic signs" of a hot, swollen, and tender calf, or a positive Homans' sign (calf pain on dorsiflexion of the ankle) will have a DVT only 20–50% of the time.<sup>57</sup> 50–60% of patients with DVT will not have these findings.

## Laboratory tests

- contrast venography: the "gold standard," however it is invasive and carries risk of iodine reaction, occasionally produces phlebitis, not readily repeated
- Doppler ultrasound with high-resolution real-time B-mode imaging: 95% sensitive and 99% specific for proximal DVT. Less effective for calf DVT.<sup>66</sup> As a result, it is recommended that patients with initially negative studies undergo repeat studies over the next 7–10 days to R/O proximal

- extension. Requires more skill on the part of the tester than IPG. May be used in immobilized or casted LE (unlike IPG). Widely accepted as the non-invasive test of choice for DVT<sup>67</sup>
- impedance plethysmography (IPG): looks for reduced electrical impedance produced by blood flow from the calf following relaxation of a pneumatic tourniquet. Good in detecting proximal DVT, not sensitive for calf DVT. A positive study indicates DVT that should be treated, a negative study can occur with non-occlusive DVT or with good collaterals, and should be repeated over a 2 week period
  - 125I-fibrinogen: radiolabeled fibrinogen is incorporated into the developing thrombus. Better for calf DVT than proximal DVT. Expensive, and many false positives. Risk of HIV transmission has resulted in withdrawal of use
  - D-dimer (a specific fibrin degradation product): high levels are associated with DVT and PE<sup>68</sup>

### Treatment of DVT

1. bed rest, with elevation of involved leg(s)
2. unless anticoagulation is contraindicated (p. 163): start heparin as outlined in Anticoagulation (p. 163), aim for APTT = 1.5–2 × control; or fixed dose of LMW heparinoids, e.g., tinzaparin (Logiparin®,<sup>69</sup> or in the U.S. enoxaparin (Lovenox®) (p. 173). Simultaneously initiate warfarin therapy. Heparin can be stopped after ≈ 5 days<sup>70</sup>
3. in patients where anticoagulation is contraindicated, consider inferior vena cava interruption or placement of a filter (e.g., Greenfield filter)
4. in non-paralyzed patients, cautiously begin to ambulate after ≈ 7–10 days
5. wear anti-embolic stocking on affected LE indefinitely (limb is always at risk of recurrent DVT)

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### Pulmonary embolism (PE)

See reference.<sup>71</sup>

#### Prevention of PE

Prevention of PE is best accomplished by prevention of DVT (p. 177).<sup>72</sup>

#### Presentation of PE

Post-op PE generally occurs 10–14 days following surgery.<sup>72</sup> The reported incidence<sup>72</sup> ranges from 0.4–5%. A series (on a service with routine use of elastic stockings and, in high risk patients, “mini-dose” heparin) found a post-op incidence of ≈ 0.4%, with a doubling of this number if only patients with major pathology (brain tumor, head trauma, or cerebrovascular or spinal pathology) were considered<sup>72</sup> (another series dealing only with brain tumors found a 4% incidence<sup>61</sup>).

Clinical diagnosis is nonspecific (differential diagnosis of symptoms is large, and ranges from atelectasis to MI or cardiac tamponade).

Common findings: sudden dyspnea (the most frequent finding), tachypnea, tachycardia, fever, hypotension, 3rd or 4th heart sound. *Triad* (rare): hemoptysis, pleuritic chest pain, dyspnea. Auscultation: pleuritic friction rub or rales (rare). Shock and CHF (mimics MI) indicates massive life-threatening PE. Mortality reported ranges from 9–60%,<sup>72</sup> with a significant number of deaths within the first hour.

#### Diagnosis of PE

A negative D-dimer test (see above) reliably excludes PE in patients with a low clinical probability of PE<sup>73</sup> or in those with nondiagnostic VQ scan.<sup>68</sup>

Alternatively, one can check for DVT utilizing IPG, Doppler, or venography (see above). If positive, this indicates a possible source of PE, and since the treatment is similar for both, no further search for PE need be made and treatment is started. If negative, further testing may be needed (e.g. VQ scan, see below).

#### Laboratory tests

D-dimer: see above.

#### General diagnostic tests

None are very sensitive or specific.

- EKG: “classic” S1Q3T3 is rare. Usually just nonspecific ST & T changes occur. Tachycardia may be the only finding

- CXR: normal in 25–30%. When abnormal, usually shows infiltrate and elevated hemidiaphragm
- ABG: not very sensitive.  $\text{pO}_2 > 90$  on room air virtually excludes massive PE

Specific radiographic evaluation

- **test of choice:** contrast enhanced chest CT. Occasionally chest CTA may be employed. Can provide insight into alternate diagnoses
- pulmonary angiogram: historically, the “gold standard.” Invasive, expensive, and labor intensive. 3–4% risk of significant complications. Not indicated in most cases
- ventilation-perfusion scan (VQ scan): CXR is also needed. A perfusion defect with no ventilation defect in a patient with no previous history of PE strongly suggests acute PE. Equivocal studies occur when an area of malperfusion corresponds to an area of reduced ventilation (on ventilation scan) or infiltrate (on CXR). Probabilities of PE based on VQ scan are shown in ► Table 9.9.<sup>74</sup> A technically adequate normal VQ scan virtually rules out PE. Patients with low or intermediate probability scans should have a test for DVT or quantitative D-dimer (see above). If test for DVT is positive, treat; if it is negative, the choice is to follow serial IPG or Doppler studies for 2 weeks, or (rarely) to do a pulmonary angiogram
- thin-section contrast-enhanced chest CT: more accurate in patients with COPD who often have an indeterminate VQ scan

**Table 9.9** Probability of PE based on VQ scan

Scan results	Incidence of PE
high probability	90–95%
intermediate probability or indeterminate	30–40%
low probability	10–15%
normal	0–5%

### Treatment

If diagnosis is seriously entertained, start **heparin** –unless contraindicated (p. 163)—without waiting for results of diagnostic studies. For an average 70 kg patient, begin with 5000–7500 unit IV bolus, followed by 1000 U/hr drip (less for smaller patient). Follow PTT and titrate drip rate for PTT 1.5 to 2 × control.

The use of heparin shortly after surgery and in patients with brain tumors is controversial, and vena caval interruption may be an alternate consideration (e.g., Greenfield filter).

Patients with massive PEs may be hemodynamically unstable. They usually require ICU care, often with PA catheter and pressors.

## 9.4 Extramedullary hematopoiesis

### 9.4.1 General information

In chronic anemias (especially thalassemia major, AKA Cooley's anemia), low hematocrit results in chronic overstimulation of bone marrow to produce RBCs. This results in systemic bony abnormalities, cardiomyopathy (due to hemochromatosis caused by increased breakdown of defective RBCs).

Pertinent to the CNS, there are three sites where extramedullary hematopoiesis (EMH) can cause findings:

- skull: produces “hair-on-end” appearance on skull X-ray
- vertebral bodies: may result in epidural cord compression<sup>75</sup> (see below)
- choroid plexus

### 9.4.2 Epidural cord compression from EMH

The exuberant tissue is very radiosensitive; however, the patient may be somewhat dependent on the hematopoietic capacity of the tissue.

### 9.4.3 Treatment

Surgical excision followed by radiation therapy has been the recommended treatment. Repeated blood transfusions may help reduce EMH and may be useful post-op instead of RTX except for refractory cases.<sup>75</sup>

Surgery on these patients is difficult because of:

1. low platelet count
2. poor condition of bone
3. cardiomyopathy: increased anesthetic risk
4. anemia, coupled with the fact that most of these patients are "iron-toxic" from multiple previous transfusions
5. total removal of the mass is not always possible

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# 10 Neurology for Neurosurgeons

## 10.1 Dementia

► **Definition.** Loss of intellectual abilities previously attained (memory, judgment, abstract thought, and other higher cortical functions) severe enough to interfere with social and/or occupational functioning.<sup>1</sup> Memory deficit is the cardinal feature; however, the DSM-IV definition requires impairment in at least one other domain (language, perception, visuospatial function, calculation, judgment, abstraction, problem-solving skills). Affects 3–11% of community-dwelling adults > 65 yrs of age, with a greater presence among institutionalized residents.<sup>2</sup>

Risk factors: advanced age, family history of dementia, and apolipoprotein E-4 allele.

► **Delirium vs. dementia (critical distinction).** Delirium AKA acute confusional state. Distinct from dementia; however, patients with dementia are at increased risk of developing delirium.<sup>3,4</sup> A primary disorder of attention that subsequently affects all other aspects of cognition.<sup>5</sup> Often represents life-threatening illness, e.g., hypoxia, sepsis, uremic encephalopathy, electrolyte abnormality, drug intoxication, MI. 50% of patients die within 2 yrs of this diagnosis.

Unlike dementia, delirium has acute onset, motor signs (tremor, myoclonus, asterixis), slurred speech, altered consciousness (hyperalert/agitated or lethargic, or fluctuations), hallucinations may be florid. EEG shows pronounced diffuse slowing.

► **Brain biopsy for dementia.** Clinical criteria are usually sufficient for the diagnosis of most dementias. Biopsy should be reserved for cases of a chronic progressive cerebral disorder with an unusual clinical course where all other possible diagnostic methods have been exhausted and have failed to provide adequate diagnostic certainty.<sup>6</sup> Biopsy may disclose CJD, low grade astrocytoma, and AD among others. The high incidence of CJD among patients selected for biopsy under these criteria necessitates appropriate precautions; see Creutzfeldt-Jakob disease (p.399). In a report of 50 brain biopsies performed to assess progressive neurodegenerative disease of unclear etiology,<sup>7</sup> the diagnostic yield was only 20% (6% were only suggestive of a diagnosis, 66% were abnormal but nonspecific, 8% were normal). The yield was highest in those with focal MRI abnormalities. Among the 10 patients with diagnostic biopsies, the biopsy result led to a meaningful therapeutic intervention in only 4.

► **Recommendations.** Based on the above, the following recommendations are made for patients with an otherwise unexplained neurodegenerative disease:

1. those with a focal abnormality on MRI: stereotactic biopsy
2. those without focal abnormality (possibly including SPECT or PET scan): brain biopsy should only be performed within an investigative protocol

► **Recommendations for specimen.** Ideally the biopsy specimen should<sup>8</sup>:

1. be large enough (usually 1 cm<sup>3</sup>)
2. be taken from an affected area
3. include gray and white matter, pia and dura
4. be handled carefully to minimize artifact (electrocautery should not be used on the specimen side of the incision)

## 10.2 Headache

### 10.2.1 General information

Headache (H/A) may be broadly categorized as follows:

1. chronic recurring headaches
  - a) vascular type (migraine): see below
  - b) muscle contraction (tension) headaches
2. headache due to pathology
  - a) systemic pathology
  - b) intracranial pathology: a wide variety of etiologies including:
    - subarachnoid hemorrhage: sudden onset, severe, usually with vomiting, apoplexy, focal deficits possible; see differential diagnosis of paroxysmal H/A (p.1418)
    - increased intracranial pressure from any cause (tumor, communicating hydrocephalus, inflammation, pseudotumor cerebri...)

- irritation or inflammation of meninges: meningitis
- tumor (p.623); with or without elevated ICP
- c) local pathology of the eye, nasopharynx, or extracranial tissues (including giant cell arteritis (p.203)
- d) following head trauma: postconcussive syndrome (p.1111)
- e) following craniotomy: "syndrome of the trephined" (p.1763)

A severe new H/A, or a change in the pattern of a long-standing or recurrent H/A (including developing associated N/V, or an abnormal neurologic exam) warrants further investigation with CT or MRI.<sup>9</sup>

Unilateral H/A that never changes side over a period  $\geq 1$  year warrants an MRI; this would be atypical in migraine and may be a presentation of an occipital AVM.

## 10.2.2 Migraine

### General information

Migraine attacks usually occur in individuals predisposed to the condition, and may be activated by factors such as bright light, stress, diet changes, trauma, administration of radiologic contrast media (especially angiography) and vasodilators.

### Classification

Based on the 1962 ad hoc committee on headache (H/A). See also index under Headache, e.g., for crash migraine (thunderclap headache) (p. 1418), post-myelogram headache (p. 1816).

#### Common migraine

Episodic H/A with N/V and photophobia, without aura or neurologic deficit.

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#### Classic migraine

Common migraine + aura. May have H/A with occasional focal neurologic deficit(s) that resolve completely in  $\leq 24$  hrs.

Over half of the transient neurologic disturbances are visual, and usually consist of positive phenomena (spark photopsia, stars, complex geometric patterns, fortification spectra) which may leave negative phenomena (scotoma, hemianopia, monocular or binocular visual loss...) in their wake. The second most common symptoms are somatosensory involving the hand and lower face. Less frequently, deficits may consist of aphasia, hemiparesis, or unilateral clumsiness. A *slow march-like progression* of deficit is characteristic. The risk of stroke is probably increased in patients with migraine.<sup>10</sup>

#### Complicated migraine

Occasional attacks of classic migraine with minimal or no associated H/A, and complete resolution of neurologic deficit in  $\leq 30$  days.

#### Migraine equivalent

Neurologic symptoms (N/V, visual aura, etc.) without H/A (acephalic migraine). Seen mostly in children. Usually develops into typical migraine with age. Aura may be shortened by opening and swallowing contents of a 10 mg nifedipine capsule.<sup>11</sup>

#### Hemiplegic migraine

H/A typically precedes hemiplegia which may persist even after H/A resolves.

#### Cluster headache

AKA histaminic migraine. Actually a neurovascular event, distinct from true migraine. Recurrent unilateral attacks of severe pain. Usually oculofrontal or oculotemporal with occasional radiation into the jaw, usually recurring on the same side of the head. Ipsilateral autonomic symptoms (conjunctival injection, nasal congestion, rhinorrhea, lacrimation, facial flushing) are common. Partial Horner syndrome (ptosis and miosis) sometimes occurs. Male:female ratio is  $\approx 5:1$ . 25% of patients have a personal or family history of migraine.

Headaches characteristically have no prodrome, last 30–90 minutes, and recur one or more times daily, usually for 4–12 weeks, often at a similar time of day, following which there is typically a remission for an average of 12 months.<sup>12</sup>

Prophylaxis for cluster H/A is only minimally effective:

1.  $\beta$ -adrenergic blockers are less effective
2. lithium: becoming drug of choice (response rate 60–80%). 300 mg PO TID and follow levels (desired: 0.7–1.2 mEq/L)
3. occasionally ergotamines are used
4. naproxen (Naprosyn®)
5. methysergide (Sansert®) 2–4 mg PO TID is effective in 20–40% of cases, must cycle patient off the drug to prevent retroperitoneal fibrosis, etc. (also see below)

Treatment for cluster H/A (prophylaxis is only minimally effective):

Treatment is difficult because there is no prodrome and the H/A often stops after 1–2 hrs. Treatment of acute attacks includes:

- 100% O<sub>2</sub> by face mask with patient sitting for  $\leq$  15 min or until attack aborted
- ergotamine: see below
- SQ sumatriptan: usually aborts attack within 15 minutes (see below)
- steroids: see below
- refractory cases may be considered for:
  - percutaneous radiofrequency sphenopalatine ganglion blockade<sup>13</sup>
  - occipital nerve stimulation<sup>14</sup>
  - hypothalamic deep brain stimulation

### **Basilar artery migraine**

Essentially restricted to adolescence. Recurrent episodes lasting minutes to hours of transient neurologic deficits in distribution of vertebrobasilar system. Deficits include vertigo (most common), gait ataxia, visual disturbance (scotomata, bilateral blindness), dysarthria, followed by severe H/A and occasionally nausea and vomiting.<sup>15</sup> Family history of migraine is present in 86%.

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## **10.3 Parkinsonism**

### **10.3.1 General information**

Parkinsonism may be primary or secondary to other conditions. All result from a relative loss of dopamine mediated inhibition of the effects of acetylcholine in the basal ganglia.

### **10.3.2 Idiopathic paralysis agitans (IPA)**

#### **Clinical**

Classical Parkinson's disease AKA shaking palsy. Affects  $\approx$  1% of Americans > age 50 yrs,<sup>16</sup> it is frequently underdiagnosed.<sup>17</sup> Male:female ratio is 3:2. Not clearly environmentally or genetically induced, but may be influenced by these factors.

The classic triad is shown in ► Table 10.1. Other signs may include: postural instability, micrographia, mask-like facies. Gait consists of small, shuffling steps (marche à petits pas) or festinating gait.

**Table 10.1** Classic triad of Parkinson's disease

- tremor (resting, 4–7/second)
- rigidity (cogwheel)
- bradykinesia

#### **Clinically distinguishing IPA from secondary parkinsonism (see below)**

May be difficult early. IPA generally exhibits gradual onset of bradykinesia with tremor that is often asymmetrical, and initially responds well to levodopa. Other disorders are suggested with rapid progression of symptoms, when the initial response to levodopa is equivocal, or when there are early midline symptoms (ataxia or impairment of gait and balance, sphincter disturbance...), or with the presence of other features such as early dementia, sensory findings, profound orthostatic hypotension, or abnormalities of extraocular movements.<sup>18,19</sup>

## Pathophysiology

Degeneration primarily of pigmented (neuromelanin-laden) dopaminergic neurons of the pars compacta of the substantia nigra, resulting in reduced levels of dopamine in the neostriatum (caudate nucleus, putamen, globus pallidus). This decreases the activity of inhibitory neurons with predominantly D2 class of dopamine receptors, which project directly to the internal segment of the globus pallidus (GPi), and also increases (by loss of inhibition) activity of neurons with predominantly D1 receptors which project indirectly to the globus pallidus externa (GPe) and subthalamic nucleus.<sup>20</sup> The net result is increased activity in GPi which has inhibitory projections to the thalamus which then suppresses activity in the supplemental motor cortex among other locations.

Histologically: Lewy bodies (eosinophilic intraneuronal hyaline inclusions) are the hallmark of IPA.

### 10.3.3 Secondary parkinsonism

#### General information

The differential diagnosis of Parkinson's disease includes the following etiologies of secondary parkinsonism or Parkinson-like conditions (these are sometimes referred to as "Parkinson plus" syndromes or parkinsonian disorders) (see above for distinguishing features):

1. olivopontocerebellar degeneration (OPC)
2. striato-nigral degeneration (SND): more aggressive than parkinsonism
3. postencephalitic parkinsonism: followed an epidemic of encephalitis lethargica (von Economo disease) in the 1920s, victims are no longer living. Distinguishing features: oculogyric crisis, tremor involves not only extremities but also trunk and head, asymmetrical, no Lewy bodies
4. progressive supranuclear palsy (PSNP): impaired vertical gaze (see below)
5. multiple system atrophy (Shy-Drager syndrome): see below
6. drug induced: includes:
  - a) prescription drugs (elderly females seem more susceptible)
    - antipsychotics (AKA neuroleptics): haloperidol (Haldol®) which works by blocking postsynaptic dopamine receptors
    - phenothiazine antiemetics: prochlorperazine (Compazine®)
    - metoclopramide (Reglan®)
    - reserpine
  - b) MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine): a commercially available chemical intermediate which is also a by-product of the synthesis of MPPP (a meperidine analog) that was synthesized and self-injected by a graduate student,<sup>21</sup> and later produced by illicit drug manufacturers to be sold as "synthetic heroin" and unwittingly injected by some IV drug abusers in northern California in 1983<sup>22</sup> (there is also a case report of a chemist who worked with MPTP who developed parkinsonism).<sup>23</sup> MPTP was subsequently discovered to be a potent neurotoxin for dopaminergic neurons (with continued toxic effects that persisted for years<sup>24</sup>). As a rule, the response to levodopa is dramatic, but short-lived with frequent side effects. In contrast to classic IPA, the locus caeruleus and dorsal motor vagus nucleus were essentially normal, and the symptoms differ slightly
  - c) there is an as yet unproven assertion that methylenedioxymethamphetamine (MDMA) AKA "ecstasy" (on the street), may hasten the onset of Parkinsonism (a study demonstrating a link had to be withdrawn because of a mislabeling of drugs)
7. toxic: poisoning with
  - a) carbon monoxide: symmetric low densities in the globus pallidus on CT
  - b) manganese: may be seen in miners, welders, and pyrotechnics workers. Manganese is excreted by the liver; people with hepatic insufficiency are more susceptible. Imaging: symmetrical high signal abnormalities on T1WI primarily in the globus pallidus with essentially no findings on T2WI or T2\* GRE (almost pathognomonic)
8. ischemic (lacunes in basal ganglia): produces so-called arteriosclerotic parkinsonism AKA vascular parkinsonism: "lower-half" parkinsonism (gait disturbance predominates<sup>17</sup>). Also causes pseudobulbar deficits, emotional lability. Tremor is rare
9. posttraumatic: parkinsonian symptoms may occur in chronic traumatic encephalopathy, see dementia pugilistica (p. 1112). There are usually other features not normally present in IPA (e.g., cerebellar findings)
10. normal pressure hydrocephalus (NPH) (p.439): urinary incontinence...
11. neoplasm in the region of the substantia nigra
12. Riley-Day (familial dysautonomia)

13. parkinson-dementia complex of Guam: classic IPA + amyotrophic lateral sclerosis (ALS). Pathologically has features of parkinsonism and Alzheimer's disease but no Lewy bodies nor senile plaques
14. Huntington's disease (HD): whereas adults typically show chorea, when HD manifests in a young person it may resemble IPA
15. (spontaneous) intracranial hypotension (p.421) may present with findings mimicking IPA

### Multiple system atrophy (MSA)

AKA Shy-Drager syndrome. Parkinsonism (indistinguishable from IPA), PLUS idiopathic orthostatic hypotension, PLUS other signs of autonomic nervous system (ANS) dysfunction (ANS findings may precede parkinsonism and may include urinary sphincter disturbance and hypersensitivity to norepinephrine or tyramine infusions). Degeneration of preganglionic lateral horn neurons of thoracic spinal cord. Unlike IPA, most do not respond to dopa therapy. NB: classic IPA may eventually produce orthostatic hypotension from inactivity or as a result of progressive autonomic failure.

### Progressive supranuclear palsy (PSNP)

AKA Steele-Richardson-Olszewski syndrome.<sup>25</sup>

Triad:

1. progressive supranuclear ophthalmoplegia (chiefly vertical gaze): paresis of voluntary vertical eye movement, but still moves to vertical doll's eyes maneuver
2. pseudobulbar palsy (mask-like facies with marked dysarthria and dysphagia, hyperactive jaw jerk, emotional incontinence usually mild)
3. axial dystonia (especially of neck and upper trunk)

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Associated findings: subcortical dementia (inconstant), motor findings of pyramidal, extrapyramidal and cerebellar systems. Average age of onset: 60 yrs. Males comprise 60%. Response to anti-parkinson drugs is usually very short-lived. Average survival after diagnosis: 5.7 yrs.

► **Differentiating from Parkinson's disease (IPA).** Patients with PSNP have a pseudo-parkinsonism. They have mask facies, but do not walk bent forward (they walk erect), and they do not have a tremor. They tend to fall backwards.

### Course

1. early:
  - a) many falls: due to dysequilibrium + downgaze palsy (can't see floor)
  - b) eye findings may be normal initially, subsequently may develop difficulty looking down (especially to command, less to following), calorics have normal tonic component but absent nystagmus (cortical component)
  - c) slurred speech
  - d) personality changes
  - e) difficulty eating: due to pseudobulbar palsy + inability to look down at food on plate
- late:
  - a) eyes fixed centrally (no response to oculocephalics or oculovestibulars): ocular immotility is due to frontal lobe lesions
  - b) neck stiffens in extension (retrocollis)

### Treatment for Parkinson's disease

Medical treatment for Parkinson's disease is beyond the scope of this book.

### Surgical treatment

Before the introduction of L-dopa in the late 1960s, stereotactic thalamotomy was widely used for Parkinson's disease. The location ultimately targeted for lesioning was the ventrolateral nucleus. The procedure worked better for relieving the tremor than for the bradykinesia; however, it was the latter symptom that was most disabling. This procedure cannot be done bilaterally without significant risk to speech function. The procedure fell out of favor when more effective drugs became available.<sup>26</sup>

See Surgical treatment of Parkinson's disease (p.1840) for further information.

## 10.4 Multiple sclerosis

### Key concepts

- an idiopathic demyelinating disease of the CNS producing exacerbating and remitting symptoms disseminated in space and time
- classic clinical findings: optic neuritis, paresthesias, INO and bladder symptoms
- diagnostic criteria (McDonald criteria) use clinical and/or lab results (MRI, CSF...) to stratify patients as: MS, probable MS, or not MS
- MRI: multiple usually enhancing lesions involving optic nerves & white matter of brain (especially periventricular white matter), cerebellum and spinal cord

#### 10.4.1 General information

An idiopathic demyelinating disease (thus affecting only white matter) of the cerebrum, optic nerves, and spinal cord (especially the corticospinal tracts and the posterior columns). Does *not* affect peripheral myelin. Pathologically produces multiple plaques of various age in diffuse locations in the CNS, especially in the periventricular white matter. Lesions initially evoke an inflammatory response with monocytes and lymphocytic perivascular cuffing, but with age settle down to glial scars.

#### 10.4.2 Epidemiology

Usual age of onset: 10–59 years, with the greatest peak between ages 20–40 years. The female:male incidence is approximately 2:1.<sup>27</sup>

Prevalence varies with latitude, and is <1 per 100,000 near the equator, and is ≈ 30–80 per 100,000 in the northern U.S. and Canada.

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#### 10.4.3 Classification

Typically causes exacerbations and remissions in various locations in the CNS (*dissemination in space and time*). Common symptoms: visual disturbances (diplopia, blurring, field cuts or scotoma), spastic paraparesis, and bladder disturbances. Nomenclature for the time course of MS is shown in ► Table 10.2.<sup>28</sup> Relapsing-remitting MS is the most common pattern (≥ 70%) at onset, and has the best response to therapy, but > 50% of cases eventually become secondary progressive MS. Only 10% have primary progressive MS, and these patients tend to be older at onset (40–60 years) and frequently develop progressive myelopathy.<sup>29</sup> Progressive relapsing MS is very uncommon. Deficits present > 6 months usually persist.

**Table 10.2** Clinical categories of MS

Category	Definition
relapsing-remitting	episodes of acute worsening with recovery and a stable course between relapses
secondary progressive	gradual neurologic deterioration ± superimposed acute relapses in a patient who previously had relapsing-remitting MS
primary progressive	gradual, nearly continuous neurologic deterioration from the onset of symptoms
progressive relapsing	gradual neurologic deterioration from the onset of symptoms, but with subsequent superimposed relapses

#### 10.4.4 Clinical signs and symptoms

##### Visual disturbances

Disturbances of visual acuity may be caused by optic or retrobulbar neuritis which is the presenting symptom of MS in 15% of cases, and which occurs at some time in 50% of MS patients. The percentage of patients with an attack of optic neuritis and no prior attack that will go on to develop MS ranges from 17–87%, depending on the series.<sup>30</sup> Symptoms: acute visual loss in one or both eyes with mild pain (often on eye movement).

Diplopia may be due to internuclear ophthalmoplegia (INO) (p.596) from a plaque in the MLF. INO is an important sign because it rarely occurs in other conditions besides MS or brainstem stroke.

### **Motor findings**

Extremity weakness (mono, para, or quadriparesis) and gait ataxia are among the most common symptoms of MS. Spasticity of the LEs is often due to pyramidal tract involvement. Scanning speech results from cerebellar lesions.

### **Sensory findings**

1. involvement of the posterior column of the spinal cord often causes loss of proprioception
2. paresthesias of extremities, trunk, or face
3. Lhermitte's sign (p.1712) (electric shock-like pain radiating down the spine on neck flexion) is common, but is not pathognomonic as it can occur in other conditions
4. trigeminal neuralgia occurs in  $\approx 2\%$ . It is more often bilateral and occurs at a younger age than in patients without MS<sup>31</sup>

### **Mental disturbances**

Euphoria (la belle indifference) and depression occur in  $\approx 50\%$  of patients.

### **Reflex changes**

Hyperreflexia and Babinski signs are common. *Abdominal cutaneous reflexes* disappear in 70–80%.

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### **GU symptoms**

Urinary frequency, urgency, and incontinence are common. Impotence in males and reduced libido in either sex is often seen.

### **10.4.5 Differential diagnosis**

The plethora of possible signs and symptoms in MS causes the differential diagnosis to extend to almost all conditions causing focal or diffuse dysfunction of the CNS. Conditions that may closely mimic MS clinically and on diagnostic testing include:

1. acute disseminated encephalomyelitis (ADEM) (p.190): generally monophasic. May also have CSF-OCB (p.190). Corpus callosum involvement is uncommon
2. CNS lymphoma (p.840)
3. other closely related demyelinating diseases: e.g., Devic syndrome (p.1698)
4. vasculitis
5. encephalitis: patients are usually very ill
6. chronic white matter changes: seen in older patients

### **10.4.6 Diagnostic criteria**

No single clinical feature or diagnostic test is adequate for the accurate diagnosis of MS. Therefore, clinical information is integrated with paraclinical studies. Diagnosing MS after a single, acute remitting clinically isolated syndrome (CIS) is very risky. 50–70% of patients with a CIS suggestive of MS will have multifocal MRI abnormalities characteristic of MS. The presence of these MRI abnormalities increases the risk of developing MS in 1–3 years (with greater prognostic significance than CSF-OCB). The more MRI lesions, the higher the risk.<sup>32</sup> Criteria for the diagnosis of MS<sup>33</sup> follows.

### **Definitions**

See references.<sup>33,34</sup>

The following definitions are used in the classification system that follows:

1. attack (exacerbation, relapse): neurologic disturbance lasting  $> 24$  hrs<sup>35</sup> typical of MS when clinical-pathological studies determine that the cause is demyelinating or inflammatory lesions
2. remission:  $\geq 30$  days should separate the onset of the first attack from the onset of a second

3. historical information: reporting of symptoms by the patient (confirmation by observer desirable), adequate to locate a lesion of MS, and has no other explanation (i.e., manifestations must not be attributable to another condition)
4. clinical evidence (signs): neuro dysfunction recorded by competent examiner
5. paraclinical evidence: tests or procedures demonstrating CNS lesion which has not produced signs; e.g., Uhthoff phenomenon or sign (worsening of symptoms with hot bath or shower), BAER, imaging procedures (CT, MRI), expert urological assessment
6. typical of MS: signs & symptoms (S/S) known to occur frequently in MS. Thus excludes gray matter lesions, peripheral nervous system lesions, and non-specific complaints such as H/A, depression, convulsive seizures, etc.
7. separate lesions: S/S cannot be explained on basis of single lesion (optic neuritis of both eyes simultaneously or within 15 days represents single lesion)
8. laboratory support: in this study, the only considerations were CSF oligoclonal bands (CSF-OCB) (see below) (OCB must not be present in serum) or increased CSF IgG production (CSF-IgG) (serum IgG must be normal). This assumes that syphilis, SSPE, sarcoidosis, etc. have been ruled out

## Diagnosis of MS

The 2010 "McDonald MS Diagnostic criteria"<sup>36</sup> are shown in ► Table 10.3.

**Table 10.3** 2010 McDonald MS Diagnostic Criteria<sup>36</sup>

**The diagnosis of MS requires elimination of more likely diagnoses and demonstration of lesions disseminated in space (DIS) and time (DIT)**

Clinical (attacks)	Lesions	Additional criteria to make the diagnosis
≥ 2	Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. If additional tests are done, results must still be consistent with MS
≥ 2	Objective clinical evidence of 1 lesion	DIS; or wait for further clinical attack implicating a different CNS location
1	Objective clinical evidence of ≥ 2 lesions	DIT; or wait for a second clinical attack
1	Objective clinical evidence of 1 lesion	DIS or wait for further clinical attack implicating a different CNS location and DIT; or wait for a second clinical attack
0 (progression from onset)		One year of disease progression (retrospective or prospective) and at least 2 of: <ul style="list-style-type: none"> <li>• DIS in the brain based on ≥ 1 T2 MRI lesion in periventricular, juxtacortical or infratentorial regions</li> <li>• DIS in the spinal cord based on ≥ 2 T2 MRI lesions</li> <li>• or positive CSF</li> </ul>
<b>Paraclinical evidence in diagnosis of MS</b>		
Evidence for DIS <sup>37</sup>	≥ 1 T2 MRI lesion in at least 2 out of 4 areas of the CNS: periventricular, juxtacortical, infratentorial or spinal cord <ul style="list-style-type: none"> <li>• Gadolinium enhancement of lesions is not required</li> <li>• If the patient has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count</li> </ul>	
Evidence for DIT <sup>38</sup>	<ul style="list-style-type: none"> <li>• New T2 and/or gadolinium-enhancing MRI lesion(s) on follow-up MRI, with reference to a baseline study, irrespective of the timing of the baseline MRI or</li> <li>• Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time</li> </ul>	
Evidence for positive CSF	Oligoclonal bands in CSF (and not serum) or elevated IgG index	

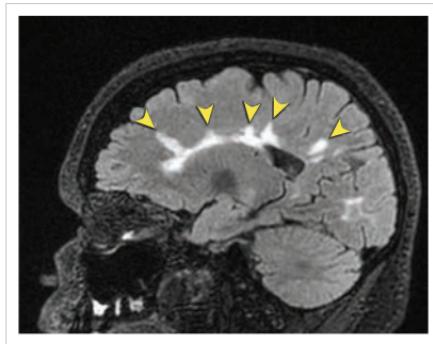
## MRI

MRI is the preferred imaging study in evaluating MS<sup>39</sup> and can demonstrate dissemination of lesions in time and space. Recommended<sup>33</sup> brain MRI criteria for diagnosing MS are shown in ► Table 10.3.<sup>40,41</sup> Lesions are normally  $> 3$  mm diameter.<sup>33</sup> MRI shows multiple white matter abnormalities in 80% of patients with MS (compared to 29% for CT).<sup>42,43</sup> Lesions are high signal on T2, and acute lesions tend to enhance with gadolinium more than old lesions do. Periventricular lesions may blend in with the signal from CSF in the ventricles on T2; these lesions are shown to better advantage on FLAIR (fluid attenuation) MRI (p.240). These lesions are ovoid, are oriented perpendicular to the ependymal surface (► Fig. 10.1), and are sometimes called Dawson's fingers (after neuropathologist James Dawson).

Spinal cord lesions normally show little or no swelling, should be  $\geq 3$  mm but  $< 2$  vertebral segments, occupy only a portion of the cross-section of the cord, and must be hyperintense on T2.<sup>44</sup>

Specificity of MRI is  $\approx 94\%$ <sup>45</sup>; however, encephalitis as well as UBOs seen in aging may mimic MS lesions. DWI should be normal; however, plaques can sometimes exhibit "shine through" (p.243), so the ADC map must be checked to rule out infarct.

Focal tumefactive demyelinating lesions (TDL) may occur in isolation or, more commonly, in patients with established MS (often blotchy in appearance, but may appear as bull's-eye targets in Balo's disease AKA concentric sclerosis of Balo). TDL may represent an intermediate position between MS and ADEM (p. 190).<sup>46</sup> TDLs tend to be symmetric. TDLs may enhance, and show perilesional edema (but less than MS) and thus be mistaken for neoplasms. Biopsy results may be confusing. MRS may not be able to differentiate from neoplasm.<sup>47</sup>



**Fig. 10.1** Dawson's fingers (yellow arrowheads) in patient with multiple sclerosis (MS). Sagittal FLAIR MRI.

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## CSF

CSF analysis can support the diagnosis in some cases, but cannot document dissemination of lesions in time or space. The CSF in MS is clear and colorless. The OP is normal. Total CSF protein is  $< 55$  mg/dl in  $\approx 75\%$  of patients, and  $< 108$  mg/dl in 99.7% (values near 100 should prompt a search for an alternative diagnosis). The WBC count is  $\leq 5$  cells/mcl in 70% of patients, and only 1% have a count  $> 20$  cells/mcl (high values may be seen in the acute myelitis).

In  $\approx 90\%$  of patients with MS, CSF-IgG is increased relative to other CSF proteins, and a characteristic pattern occurs. Agarose gel electrophoresis shows a few IgG bands in the gamma region (oligoclonal bands) that are not present in the serum (higher resolution isoelectric focusing can demonstrate 10–15 bands). CSF-OCB are not specific for MS, and can occur in CNS infections and less commonly with strokes or tumors. The predictive value of the absence of IgG in a patient with suspected MS has not been satisfactorily elucidated.

Recommended criteria have been published,<sup>48</sup> most of which pertain to specifics of laboratory analysis, pertinent clinical excerpts are shown in ► Table 10.4.

## 10.5 Acute disseminated encephalomyelitis

AKA ADEM. Acute demyelinating condition, has been associated with relatively recent history of vaccination. Like MS, may also demonstrate oligoclonal bands in CSF. ADEM is generally monophasic, and lesions occur within a couple of weeks. There is usually a good response to high-dose IV corticosteroids.

**Table 10.4** CSF criteria for MS

1. qualitative assessment of IgG is the most informative analysis and is best performed using IEF with some form of immunodetection (blotting or fixation)
2. analysis should be performed on unconcentrated CSF and must be compared to simultaneously run serum sample in the same assay
3. runs should use the same amount of IgG from serum and CSF
4. each run should contain positive and negative controls
5. quantitative analysis should be made in terms of one of the 5 recognized staining patterns for OCB
6. an individual experienced in the techniques should report the results
7. all other tests performed on the CSF (including WBC, protein & glucose, lactate) should be taken into consideration
8. evaluation using light chains for immunodetection may be helpful in certain cases to resolve equivocal oligoclonal IgG patterns
9. if clinical suspicion is high but CSF results are equivocal, negative or show only a single band, consider repeating the LP
10. to measure IgG levels, nonlinear formulas that consider integrity of the blood-CSF barrier should be used (e.g., the ratio of CSF to serum albumin [AKA Qalb] is a measure of leakiness)
11. labs analyzing CSF should have internal as well as external quality assessment controls
12. quantitative IgG is a complementary test, but is not a substitute for qualitative IgG testing, which has the highest sensitivity and specificity

## 10.6 Motor neuron diseases

### 10.6.1 General information

Degenerative diseases of motor neurons. See also comparison of upper motor neurons (UMN) with lower motor neurons (LMN) (p.531) and the paralysis they produce. There are five subtypes of degenerative motor neuron diseases, of which ALS is the most common (see below).

Three patterns of involvement:

1. mixed UMN & LMN degeneration: amyotrophic lateral sclerosis (ALS) (see below). The most common of the motor neuron diseases
2. UMN degeneration: primary lateral sclerosis. Rare, onset after age 50. No LMN signs. Slower progression than ALS (yrs to decades). Pseudobulbar palsy is common.<sup>49</sup> Usually does not shorten longevity. May present with falling due to balance problems or low back and neck pain due to axial muscle weakness
3. LMN degeneration: progressive muscular atrophy (PMA) and spinal muscular atrophy (SMA)

### 10.6.2 Amyotrophic lateral sclerosis

#### Key concepts

- degeneration of anterior horn cells and corticospinal tracts in the cervical spine and medulla (bulb) of unknown etiology
- a mixed upper and lower motor neuron disease (UMN → mild spasticity in LEs; LMN → atrophy and fasciculations in UEs)
- clinically: progressive muscle wasting, weakness, and fasciculations
- no cognitive, sensory, nor autonomic dysfunction

In the U.S. amyotrophic lateral sclerosis (ALS) is AKA Lou Gehrig's disease, named after the New York Yankees first baseman who announced that he had the disease in 1939. AKA motor neuron disease (singular).

#### Epidemiology

See reference.<sup>30</sup>

Prevalence: 4–6/100,000. Incidence: 0.8–1.2/100,000.

Familial in 8–10% of cases. Familial cases usually follow autosomal dominant inheritance, but occasionally demonstrate a recessive pattern.

Onset usually after 40 years of age.

## Pathology

Etiology is not known with certainty. Histology: degeneration of anterior horn alpha-motoneurons (in the spinal cord *and* in brainstem motor nuclei) (LMNs) and corticospinal tracts (UMNs). Produces mixed UMN & LMN findings, with a great deal of variability depending on which predominates at any given time.

## Clinical

Characterized by progressive muscle wasting, weakness, and fasciculations.

Involvement is of voluntary muscles, sparing the voluntary eye muscles and urinary sphincter.

Classically, presents initially with weakness and atrophy of the hands (lower motor neuron) with spasticity and hyperreflexia of the lower extremities (upper motor neuron). However, LEs may be hyporeflexic if the lower motor neuron deficits predominate.

Dysarthria and dysphagia are caused by a combination of upper and lower motor neuron pathology. Tongue atrophy and fasciculations may also occur.

Although cognitive deficits are generally considered to be absent in ALS, in actuality 1–2% of cases are associated with dementia, and cognitive changes may occasionally predate the usual features of ALS.<sup>50</sup>

## Differential diagnosis

At times, it may be very difficult to distinguish ALS from cervical spondylotic myelopathy; see discussion of differentiating features (p. 1301).

## Diagnostic studies

### EMG

Not absolutely necessary to make diagnosis in most cases. Fibrillations and positive sharp waves are found in advanced cases (may be absent early, especially if upper motor neuron pathology predominates). LMN findings in the LE in the absence of lumbar spine disease, or fibrillation potentials in the tongue are suggestive of ALS.

### LP (CSF)

May have slightly elevated protein.

## Treatment

Much of care is directed toward minimizing disability:

1. risk of aspiration may be reduced with
  - a) tracheostomy
  - b) gastrostomy tube to allow continued feeding
  - c) vocal cord injection with Teflon
2. noninvasive ventilation: e.g., BiPAP spasticity that occurs when upper motor neuron deficits predominate may be treated (usually with short-lived response) with:
  - a) baclofen (p. 1846): also may relieve the commonly occurring cramps
  - b) diazepam
3. riluzole (Rilutek®): inhibits presynaptic release of glutamate. Doses of 50–200 mg/d increases tracheostomy-free survival at 9 & 12 months, but the improvement is more modest or may be non-existent by ≈ 18 months<sup>51,52</sup>

## Prognosis

Most patients die within 5 years of onset (median survival: 3–4 yrs). Those with prominent oropharyngeal symptoms may have a shorter life-span usually due to complications of aspiration.

## 10.7 Guillain-Barré syndrome

### 10.7.1 General

#### Key concepts

- acute onset of peripheral neuropathy with progressive muscle weakness (more severe *proximally*) with areflexia, reaches maximum over 3 days to 3 weeks
- cranial neuropathy: also common, may include facial diplegia, ophthalmoplegia
- little or no sensory involvement (paresthesias are not uncommon)
- onset often 3 days-5 weeks following viral URI, immunization, *Campylobacter jejuni enteritis*, or surgery
- pathology: focal segmental demyelination with endoneurial monocytic infiltrate
- elevated CSF protein without pleocytosis (albuminocytologic dissociation)

Guillain-Barré syndrome (GBS) AKA acute polyradiculoneuritis, among others, is actually a collection of syndromes having inflammatory polyradiculoneuropathy in common. Its most frequent form is acute inflammatory demyelinating polyradiculoneuropathy (AIDP). First described as an ascending paralysis, most forms are characterized by *symmetric* weakness and areflexia. Mild cases may present only with ataxia, whereas fulminant cases may ascend to complete tetraparesis with paralysis of respiratory muscles and cranial nerves. There are also a number of variants (p. 194).

GBS is the most common acquired demyelinating neuropathy. Incidence is  $\approx$  1–3/100,000. The lifetime risk for any one individual getting GBS is  $\approx$  1/1,000.

GBS is triggered by both humoral and cell mediated autoimmune response to an immune sensitizing event. Frequent (but not essential) antecedents: viral infection, surgery, immunization, mycoplasma infection, enteral infection with *Campylobacter jejuni* ( $\approx$  4 days of intense diarrhea). Higher frequency in the following conditions than in general population: Hodgkin's disease, lymphoma, lupus.

Most cases involve antibodies to gangliosides and glycolipids in peripheral myelin (axon antibodies occur in some forms). For unknown reasons serum creatine kinase can be mildly elevated, and may correlate with muscle type pain.<sup>53</sup>

### 10.7.2 Diagnostic criteria

See reference.<sup>54</sup>

Features required for diagnosis:

- progressive motor weakness of more than 1 limb (from minimal weakness  $\pm$  ataxia to paralysis, may include bulbar or facial or EOM palsy). Unlike most neuropathies, proximal muscles are affected more than distal
- areflexia (usually universal, but distal areflexia with definite hyporeflexia of biceps and knee jerks suffices if other features are consistent)

Features strongly supportive of diagnosis:

- clinical features (in order of importance)
  - progression: motor weakness peaks at 2 wks in 50%, by 3 wks in 80%, and by 4 wks in > 90%
  - relative symmetry
  - mild sensory symptoms/signs (e.g., mild paresthesias in hands or feet)
  - cranial nerve involvement: *facial weakness* in 50%, usually *bilateral*. GBS presents initially in EOMs or other Cr. N. in < 5% of cases. Oropharyngeal muscles may be affected
  - recovery usually by 2–4 wks after progression stops, may be delayed by months (most patients recover functionally)
  - autonomic dysfunction (may fluctuate): tachycardia and other arrhythmias, postural hypotension, HTN, vasomotor symptoms
  - afebrile at onset of neuritic symptoms
  - variants (not ranked):
    - fever at onset of neuritic symptoms
    - severe sensory loss with pain
    - progression > 4 wks
    - cessation of progression without recovery

- sphincter dysfunction (usually spared): e.g., bladder paralysis
- CNS involvement (controversial): e.g., ataxia, dysarthria, Babinski signs
- CSF: albuminocytologic dissociation ( $\uparrow$  protein without pleocytosis)
  - protein: elevated after 1 wk of symptoms,  $> 55 \text{ mg/dl}$
  - cells: 10 or fewer mononuclear leukocytes/ml
  - variants
    - no CSF protein rise 1–10 wks after onset (rare)
    - 11–50 monocytes/ml
    - electrodiagnostics: 80% have NCV slowing or block at some time (may take several weeks in some). NCV usually  $< 60\%$  of normal, but not in all nerves

Features casting doubt on diagnosis:

- marked, persistent asymmetry of weakness
- persistent bowel or bladder dysfunction
- $> 50$  monocytes/ml CSF
- PMNs in CSF
- sharp sensory level
- features of conditions in the differential diagnosis (see below)

### 10.7.3 Guillain-Barré variants

#### General information

A number of variants have been described (some may simply be incomplete forms of typical Guillain-Barré). Autonomic dysfunction may occur in some.

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#### Miller-Fisher variant of GBS

Ataxia, areflexia and ophthalmoplegia. May also have ptosis. 5% of cases of GBS. Serum marker: anti-GQ1b antibodies.

#### Acute motor axonal neuropathy (AMAN)

This variant and AIDP are the most common to follow *Campylobacter jejuni* enteritis.

#### Pharyngeal-cervical-brachial variant

Facial, oropharyngeal, cervical, and UE weakness, sparing the LEs.

#### Pure sensory variant

Sensory loss accompanied by areflexia.

#### Atypical GBS

May be accompanied by rhabdomyolysis.<sup>55</sup>

### 10.7.4 Differential diagnosis

Also see conditions in the differential diagnosis under Myelopathy (p. 1696)

1. Guillain-Barré syndrome (including one of its variants)
2. critical illness polyneuropathy (p. 569): EMG:  $\downarrow$  CMAP & SNAP
3. current hexacarbon abuse: volatile solvents (n-hexane, methyl n-butyl ketone), glue sniffing
4. acute intermittent porphyria (AIP): a disorder of porphyrin metabolism. CSF protein is not elevated in AIP. Recurrent painful abdominal crises are common. Check urine delta-aminolevulinic acid or porphobilinogen
5. recent diphtheritic infection: diphtheritic polyneuropathy has a longer latency and a slower crescendo of symptoms
6. lead neuropathy: UE weakness with wrist drop. May be asymmetrical
7. poliomyelitis: usually *asymmetric*, has meningeal irritation
8. hypophosphatemia (may occur in chronic IV hyperalimentation)
9. botulism: difficult to distinguish clinically from GBS. Normal NCV and a facilitating response to repetitive nerve stimulation on electrodiagnostics

10. toxic neuropathy (e.g., from nitrofurantoin, dapsone, thallium or arsenic)
11. tick paralysis: may cause an ascending motor neuropathy without sensory impairment. Careful examination of the scalp for tick(s)
12. chronic immune demyelinating poly(radiculo)neuropathy (CIDP) AKA chronic relapsing GBS, chronic relapsing polyneuritis<sup>56</sup> AKA chronic immune demyelinating polyradiculoneuropathy. Similar to GBS, but longer time course (symptoms must be present > 2 mos). CIDP produces progressive, symmetrical, proximal & distal weakness, depression of muscle stretch reflexes, and variable sensory loss. Cranial nerves are usually spared (facial muscles may be involved). Balance difficulties are common. Need for respiratory support is rare. Peak incidence: age 40–60 yrs. Electrodiagnostics and nerve biopsy findings are indicative of demyelination. CSF findings are similar to GBS (see above). Most respond to immunosuppressive therapy (especially prednisolone & plasmapheresis) but relapses are common. Refractory cases may be treated with IV gamma-globulin, cyclosporin-A,<sup>57</sup> total body lymphoid irradiation or interferon- $\alpha$ <sup>58</sup>
13. critical illness myopathy: chronic illness myopathy. Muscles not excitable with direct stimulation. EMG: low or normal CMAP with normal SNAP. Muscle biopsy: abnormalities may range from Type II fiber atrophy to necrosis (severe necrosis may not recover)
14. motor neuron disease (p. 191): AKA ALS. Hyperreflexia in LEs
15. myasthenia gravis: weakness worsens towards the end of the day and with repeat efforts. Positive assay for circulating anti-acetylcholine receptor antibodies
16. spinal cord injury

### 10.7.5 Imaging

No characteristic finding; however, diffuse enhancement of cauda equina and nerve roots occurs in up to 95% of cases.<sup>59</sup> Thought to be due to disruption of the blood-nerve barrier from inflammation. Conspicuous nerve root enhancement correlates with pain, GBS disability grade, and duration of recovery.<sup>59</sup>

### 10.7.6 Treatment

Immunoglobulins may be helpful. In severe cases, early plasmapheresis hastens the recovery and reduces the residual deficit. Its role in mild cases is uncertain. Steroids are not helpful.<sup>60</sup> Mechanical ventilation and measures to prevent aspiration are used as appropriate. In cases of facial diplegia, the eyes must be protected from exposure (neuroparalytic) keratitis.

### 10.7.7 Outcome

Recovery may not be complete for several months. 35% of untreated patients have residual weakness and atrophy. Recurrence of GBS after achieving maximal recovery occurs in  $\approx$  2%.

## 10.8 Myelitis

### 10.8.1 General information

AKA acute transverse myelitis (ATM). The terminology is confusing: myelitis overlaps with "myelopathy." Both are pathologic conditions of the spinal cord. Myelitis indicates inflammation, and etiologies include infectious/post-infectious, autoimmune, and idiopathic. Myelopathy is generally reserved for compressive, toxic, or metabolic etiologies<sup>61</sup>; see also differential diagnosis (p. 1696).

### 10.8.2 Etiology

Many so-called "causes" remain unproven. Immunologic response against the CNS (most likely via cell mediated component) is the probable common mechanism. Animal model: experimental allergic encephalomyelitis (requires myelin basic protein of CNS, not peripheral).

Generally accepted etiologies include (items with an asterisk \* may be more properly associated with myelopathy rather than myelitis):

1. infectious and post-infectious
  - a) primary infectious myelitis
    - viral: poliomyelitis, myelitis with viral encephalomyelitis, herpes zoster, rabies
    - bacterial: including tuberculoma of spinal cord
    - spirochetal: AKA syphilitic myelitis. Causes syphilitic endarteritis

- fungal (aspergillosis, blastomycosis, cryptococcosis)
  - parasitic (Echinococcus, cysticercosis, paragonimiasis, schistosomiasis)
- b) post-infectious: including post-exanthematous, influenza
2. posttraumatic
  3. physical agents
    - a) decompression sickness (dysbarism)
    - b) electrical injury\*
    - c) post-irradiation
  4. paraneoplastic syndrome (remote effect of cancer): most common primary is lung, but prostate, ovary and rectum have also been described<sup>62</sup>
  5. metabolic
    - a) diabetes mellitus\*
    - b) pernicious anemia\*
    - c) chronic liver disease\*
  6. toxins
    - a) cresyl phosphates\*
    - b) intra-arterial contrast agents\*
    - c) spinal anesthetics
    - d) myelographic contrast agents
    - e) following chemonucleolysis<sup>63</sup>
  7. arachnoiditis
  8. autoimmune
    - a) multiple sclerosis (MS), especially neuromyelitis optica (NMO) (p. 1698)
    - b) following vaccination (smallpox, rabies)
  9. collagen vascular disease
    - a) systemic lupus erythematosus
    - b) mixed connective tissue disease

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### 10.8.3 Clinical

#### Presentation

34 patients with ATM<sup>64</sup>: age of onset ranged 15–55 yrs, with 66% occurring in 3rd and 4th decade. 12 patients (35%) had a viral-like prodrome. Presenting symptoms are shown in ► Table 10.5, with other presenting symptoms of unspecified frequency including<sup>65</sup>: fever and rash.

**Table 10.5** Presenting symptoms in myelitis

Symptom	Series A <sup>a</sup>	Series B <sup>b</sup>
pain (back or radicular)	35%	35%
muscle weakness	32%	13%
sensory deficit or paresthesias	26%	46%
spincter disturbance	12%	6%

<sup>a</sup>series A: 34 patients with ATM<sup>64</sup>

<sup>b</sup>series B: 52 patients with acute or subacute transverse myelitis<sup>66</sup>

#### Presenting level

The levels at presentation in 62 patients with ATM are shown in ► Table 10.6.<sup>65</sup> The thoracic level is the most common sensory level. Infrequently, ATM is the presenting symptom of MS ( $\approx$  3–6% of patients with ATM develop MS).

**Table 10.6** Level of sensory deficit

Level	%
cervical	8
high thoracic	36
low thoracic	32
lumbar	8
unknown	16

## Progression

Progression is usually rapid, with 66% reaching maximal deficit by 24 hrs; however, the interval between first symptom and maximal deficit varies from 2 hrs-14 days.<sup>65</sup> Findings at the time of maximal deficit are shown in ► Table 10.7.

**Table 10.7** Symptoms at time of *maximal* deficit (62 patients with ATM<sup>65</sup>)

Symptom	%
sensory deficit or paresthesias	100
muscle weakness	97
sphincter disturbance (hesitancy, retention, overflow incontinence)	94
pain in back, abdomen, or limbs	34
fever	27
nuchal rigidity	13

### 10.8.4 Evaluation

Imaging should be done to rule out a compressive lesion. MRI or CT/myelogram: no characteristic finding. One paper reports 2 patients with fusiform cord enlargement.<sup>67</sup> MRI may be able to demonstrate the area of involvement within the cord. MRI may show the "central dot sign,"<sup>68</sup> an area of high signal on axial T2WI usually centrally located with a small dot of isointense signal in the core of the hyperintensity.

CSF: normal during acute phase in 38% of LPs. Remainder (62%) had elevated protein (usually >40 mg%) or pleocytosis (lymphocytes, PMNs, or both) or both.

#### Evaluation scheme

In a patient developing acute myelopathy/paraparesia, especially when ATM is considered likely, the first test of choice is an emergency MRI. If not readily available, a myelogram (with CT to follow) directed at the region of the sensory level is performed (CSF may be sent in this circumstance once block is ruled out).

### 10.8.5 Treatment

No treatment has been studied in a randomized controlled trial.

1. steroids: not beneficial for some types of myelitis,<sup>69</sup> especially with ASIA A (complete paralysis); see ► 68.8.7 "ASIA impairment scale."<sup>70</sup> Rx: high-dose IV methylprednisolone 3–5 days (doses quoted include 500 mg/d, and 1000 mg/d<sup>71</sup>). The decision to introduce additional treatment measures is based on the response to steroids and the MRI appearance after ≈ 5 days of steroids
2. plasma exchange (PLEX) for patients that do not respond to steroids within 3–5 days
3. other forms of immune suppression may be attempted for failure of above therapies, including: cyclophosphamide (usually under the direction of an oncologist)
4. in cases of focal spinal cord enlargement, surgical decompression may be considered in cases that fail to respond to the above

### 10.8.6 Prognosis

In a series of 34 ATM patients with ≥ 5 yrs follow-up (F/U)<sup>64</sup>: 9 patients (26%) had good recovery (ambulate well, mild urinary symptoms, minimal sensory and UMN signs); 9 (26%) had fair recovery (functional gait with some degree of spasticity, urinary urgency, obvious sensory signs, paraparesis); 11 (32%) had poor recovery (paraplegic, absent sphincter control); 5 (15%) died within 4 mos of illness. 18 patients (62% of survivors) became ambulatory (in these cases, all could walk with support by 3–6 mos).

In a series of 59 patients<sup>65</sup> (F/U period unspecified): 22 (37%) had good recovery; 14 (24%) had poor recovery; 3 died in acute stage (respiratory insufficiency in 2, sepsis in 1). Recovery occurred between 4 weeks and 3 mos after onset (no improvement occurred after 3 mos).

## 10.9 Neurosarcoidosis

### 10.9.1 General information

#### Key concepts

- neurologic involvement of sarcoidosis (a systemic granulomatous disease)
- may produce multiple cranial nerve palsies
- the most common neurologic manifestation is diabetes insipidus
- immunosuppressants (including corticosteroids) can improve systemic as well as neurologic symptoms

Sarcoidosis is a granulomatous disease that is usually systemic, and may include the CNS (so-called neurosarcoidosis AKA neurosarcoid). Only 1–3% of cases have CNS findings without systemic manifestations.<sup>72</sup> The cause of the disease is unknown. An exaggerated cellular immune response for unknown reasons is the currently favored hypothesis. Organs commonly involved include lungs, skin, lymph nodes, bones, eyes, muscles, and parotid glands.<sup>30</sup>

### 10.9.2 Pathology

#### Gross involvement

CNS sarcoidosis primarily involves the leptomeninges; however, parenchymal invasion often occurs. Adhesive arachnoiditis with nodule formation may also occur (nodules have a predilection for the posterior fossa). Diffuse meningitis or meningoencephalitis may occur, and may be most pronounced at the base of the brain (basal meningitis) and in the subependymal region of the third ventricle (including the hypothalamus).

Spinal involvement may include arachnoiditis, and lesions that may be intramedullary, extramedullary intradural and extramedullary extradural.

#### Microscopic features

Constant microscopic features of neurosarcoidosis include noncaseating granulomas with lymphocytic infiltrates. Langhans giant cells may or may not be present.

### 10.9.3 Epidemiology

Incidence of sarcoidosis is  $\approx$  3–50 cases/100,000 population; neurosarcoidosis occurs in  $\approx$  5% of cases (reported range: 1–27%). In one series, the median age of onset of neurologic symptoms was 44 years.

The spinal cord is involved in < 1% of patients with sarcoidosis,<sup>73</sup> and in 16% of these, the spinal cord was the only identifiable site of involvement.

### 10.9.4 Clinical findings

Clinical findings include multiple cranial nerve palsies in 50–70% (particularly facial n., including diplopia), peripheral neuropathy, and myopathy.<sup>74</sup> Occasionally the lesions may produce mass effect,<sup>75</sup> and hydrocephalus may result from adhesive basal arachnoiditis. Patients may have low grade fever. Intracranial hypertension is common and may be dangerous. Hypothalamic involvement may produce disorders of ADH (diabetes insipidus, disordered thirst...). Rare involvement of the pituitary may produce pituitary insufficiency. Seizures occur in 15%.

Spinal cord involvement may produce myelopathy.

### 10.9.5 Laboratory

CBC: mild leukocytosis and eosinophilia may occur.

Serum angiotensin-converting enzyme (ACE): abnormally elevated in 83% of patients with active pulmonary sarcoidosis, but in only 11% with inactive disease.<sup>76</sup> False positive rate: 2–3%; may also be elevated in primary biliary cirrhosis.