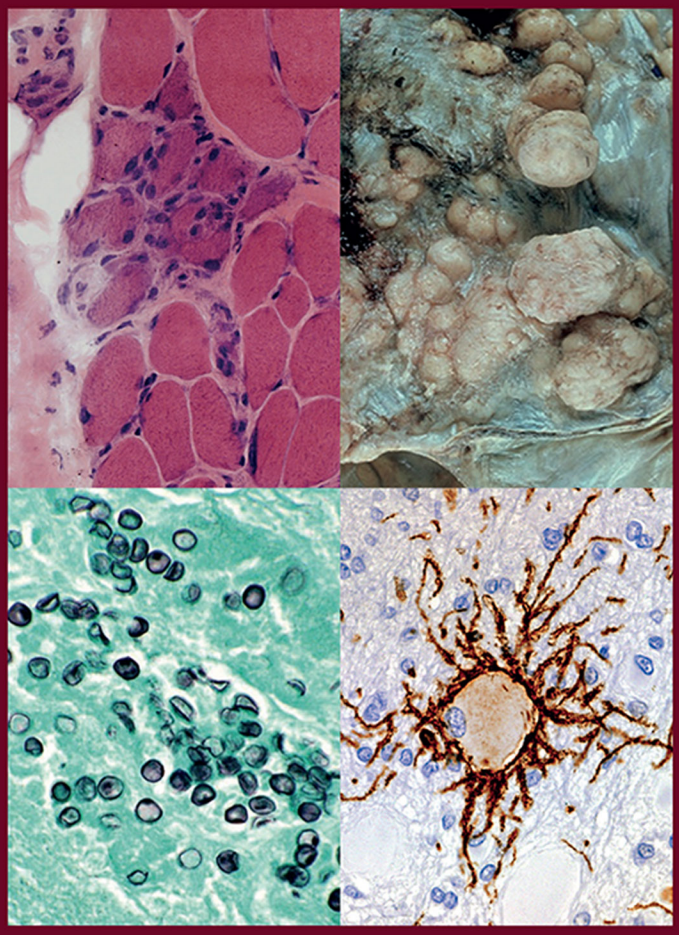
Greenfield's Neuropathology

NINTH EDITION

TWO VOLUME SET



EDITED BY
Seth Love, Arie Perry, James Ironside and Herbert Budka

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VOLUME 1

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Preface

Greenfield's Neuropathology holds a special place in the heart of most neuropathologists. It has long been a standard-bearer of our specialty. In 1921, Joseph Godwin Greenfield and Edward Farquhar Buzzard published *Pathology of the Nervous System*, which had a key role in defining neuropathology as a distinct specialty. The authors set out to 'describe clearly the anatomical changes which are associated with disorders of nervous function, to discuss briefly questions of pathogenesis, and to indicate in a few words, where it is possible, the relationship between structural alterations and clinical signs and symptoms.' In 1958, a book entitled simply *Neuropathology*, by Greenfield, William Blackwood, William McMenemy, Alfred Meyer and Ronald Norman, updated and greatly expanded on most of the content of *Pathology of the Nervous System*. Unlike *Pathology of the Nervous System*, however, *Neuropathology* did not cover neoplastic diseases (dealt with instead in a companion book, Russell and Rubinstein's *Pathology of Tumours of the Nervous System*). However, tumours of the nervous system have been included in *Greenfield's Neuropathology* since the seventh edition in 1997.

Readers of a succession of editions over many decades have dipped into this venerable reference book seeking definitive advice and instruction on all matters neuropathological. Producing a new edition of *Greenfield's Neuropathology* has therefore been both a huge privilege and a massive responsibility. It has also been a balancing act, in which we have had to reconcile the tension between the physical constraints of a two-volume book and the ever-expanding amount of information encompassed within our field. Indeed, this may be the last edition of *Greenfield's Neuropathology* that can be produced in hardcover printed format. Accommodating the additional information has largely involved a combination of reorganisation and restraint, together with considerably increased use of photographs and diagrams.

The reorganisation has involved the merging of vascular disease, hypoxia and related conditions into a single chapter; the subdivision of movement disorders into separate chapters on extrapyramidal disorders, ataxias and motor neuron diseases; the inclusion of separate chapters on ageing and dementia, the latter encompassing an expanded section on vascular dementia; and the further subdivision of the tumour section from two chapters in the previous edition to twenty-one in the present one, which we hope will make this part of the book easier to navigate. The total number of chapters in the book has increased from twenty-four to forty-six. Restraint has been applied in relation to the inclusion of references and of some very detailed molecular genetic and phenotypic information that is readily accessible through online resources such as OMIM, the database of Genotypes and Phenotypes (dbGaP), AlzGene and PDGene. We expect readers to look to *Greenfield's Neuropathology* for guidance and perspective rather than as a substitute for bibliographic databases and search engines.

The changes have involved a great deal of work on the part of our authors, who have shown unfailing courtesy and forbearance in responding to requests to condense prose, reorganise chapters and be selective in the inclusion of references. We are in their debt. Throughout, our objectives, much like those of Greenfield and Buzzard, have been to describe clearly the neuropathological changes that underlie neurological diseases, to discuss briefly their pathogenesis, and to try to relate molecular genetic, structural and biochemical alterations to clinical and neuroradiological manifestations.

Once a full account has been taken of the clinical and neuroradiological manifestations of neurological disease in a particular patient, a detailed visual examination of the diseased tissue is the starting point for almost all neuropathological investigations. Much of the excitement of neuropathology comes from discovering visual clues to disease, macroscopic or microscopic, whether in a section stained simply with haematoxylin and eosin, a series of confocal laser scanning images or a transmission electron micrograph. Neuropathology remains a highly visual specialty and most of us neuropathologists obtain immense aesthetic gratification from our work. Not surprisingly, therefore, we have placed a strong emphasis on visual aspects of this reference book, which includes over one thousand completely new photographs and drawings. It also incorporates new design elements such as the alternate colour coding of chapters that is intended to allow their easier navigation. To this same end, both volumes now include full indexes to the whole book. There are also improved search, annotation and bookmarking facilities in the bundled bonus e-book version of this edition. The e-book frees users from most of the physical limitations (not least of which are the size and weight) of the printed version and can be downloaded to a wide range of mobile and electronic devices, so that it is not necessary to be online to have full access to *Greenfield's Neuropathology*.

Publication of this ninth edition of *Greenfield's Neuropathology* would not have been possible without the support of many people, initially at Hodder Arnold and subsequently at Taylor and Francis. At Hodder Arnold, Joanna Koster, Editorial Director; Caroline

Makepeace, Head of Postgraduate and Professional Publishing; Mischa Barrett, Project Editor; and Miriam Trent, Editorial Assistant, were closely involved in the early stages. At Taylor and Francis, Barbara Norwitz, Executive Editor; Amy Blalock, Supervisor, Editorial Project Development; Rachael Russell, Senior Editorial Assistant; and Linda Van Pelt, Senior Project Manager, Medical, all worked on different stages of the title, and one person who merits special thanks is Sue Hodgson for her invaluable help as Executive Editor. Glenys Norquay provided freelance support and Jayne Jones designed the cover and interior pages.

We are pleased to present the ninth edition of *Greenfield's Neuropathology*. We hope you obtain as much satisfaction from reading this book as we have from editing it.

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November 2014

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Abbreviations

AA	anaplastic astrocytoma
AACD	age-associated cognitive decline
AAMI	age-associated memory impairment
ABC	ATP-binding cassette
ABCA1	ATP-binding cassette transporter 1
ABRA	Aβ-related angiitis
ACA	anterior cerebral artery
ACC	adrenocortical carcinoma
ACCIS	Automated Childhood Cancer Information System
ACh	acetylcholine
AChR	acetylcholine receptor
ACTH	adrenocorticotropin
AD	Alzheimer disease
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADC	apparent diffusion coefficient
ADCA	autosomal dominant cerebellar ataxia
ADEM	acute disseminated encephalomyelitis
ADK	adenosine kinase
ADNFLE	autosomal dominant nocturnal frontal lobe epilepsy
ADP	adenosine diphosphate
AFP	alpha-fetoprotein
AGA	aspartylglucosaminidase
AGE	advanced glycosylation end product
AGPS	alkylglycerone phosphate synthase
AGS	Aicardi-Goutières syndrome
AGU	aspartylglucosaminuria
AHLE	acute haemorrhagic leukoencephalitis
AHT	abusive head trauma
AIDP	acute inflammatory demyelinating polyneuropathy
AIDS	acquired immunodeficiency syndrome
AIP	aryl hydrocarbon receptor-interacting protein
AIS	axon initial segment
AISS	axonal index sector score
AL	amyloidosis
ALCL	anaplastic large cell lymphoma
ALD	adrenoleukodystrophy
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
ALT	alternative lengthening of telomeres
AMAN	acute motor axonal neuropathy
AMN	adrenomyeloneuropathy
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMSAN	acute motor sensory axonal neuropathy
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic autoantibody
ANCL	adult neuronal ceroid lipofuscinosis
Ang-1	angiopoietin-1
Ang-2	angiopoietin-2
ANI	asymptomatic neurocognitive impairment
AOA1	early-onset ataxia with oculomotor apraxia, type 1
APGBD	adult polyglucosan body disease
APLA	antiphospholipid antibody
ApoE	apolipoprotein E
APP	amyloid precursor protein
APrP	amyloid prion protein
APUD	amine precursor uptake and decarboxylation
AQP4	aquaporin-4
AR	androgen receptor
ARBD	alcohol-related brain damage
ARFGEF2	adenosine diphosphate (ADP)-ribosylation factor guanine exchange factor 2
ASA	arylsulfatase A
ASDH	acute subdural haematoma
ASE	acute schistosomal encephalopathy
ASL	arterial spin labelling
AT	ataxia telangiectasia
ATP	adenosine triphosphate
ATRT	atypical teratoid/rhabdoid tumour
ATTR	amyloid transthyretin
AVM	arteriovenous malformation
BA	Brodmann area
BACE	β-site APP-cleaving enzyme
BAC	bacterial artificial chromosome
BAV	Banna virus
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
BDV	Borna disease virus
BEAN	brain expressed protein associated with NEDD4
bFGF	basic fibroblast growth factor
BGC	basal ganglia calcification
BHC	benign hereditary chorea
BMAA	β-N-methylamino-L-alanine
BMD	Becker muscular dystrophy
BMP	bone morphogenetic protein
BOLD	blood oxygenation dependent
bp	base pair
BPAU	bromophenylacetylurea

BRC brain reserve capacity
BRRS Bannayan-Riley-Ruvalcaba syndrome
BSE bovine spongiform encephalopathy
CAA cerebral amyloid angiopathy
CADASIL cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAE childhood absence epilepsy
CAHS chronic acquired hepatocerebral syndrome
CAMTA1 calmodulin-binding transcription activator 1
c-ANCA cytoplasmic antineutrophil cytoplasmic antibody
CANOMAD chronic ataxic neuropathy, ophthalmoplegia, M-protein agglutination, disialosyl antibodies
CAR coxsackievirus and adenovirus receptor
CARASIL cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy
cART combined antiretroviral therapy
CASK calcium-dependent serine protein kinase
CBD corticobasal degeneration
CBF cerebral blood flow
CBS corticobasal syndrome
CBTRUS Central Brain Tumor Registry of the United States
CCM cerebral cavernous malformation
CCSVI chronic cerebrospinal venous insufficiency
CD Cowden disease
CDE common data elements
CDI conformation dependent immunoassay
CDK5 cyclin-dependent kinase 5
CDKI cyclin-dependent kinase inhibitor
CDKN2C cyclin-dependent kinase inhibitor 2C
CDV canine distemper virus
CEA carcinoembryonic antigen
CESD cholesteryl ester storage disease
CGH comparative genomic hybridization
cGMP cyclic guanosine monophosphate
CGRP calcitonin gene-related peptide
CHD5 chromodomain helicase DNA binding domain 5
CHN congenital hypomyelinating neuropathy
CHS classical hippocampal sclerosis
CIM critical illness myopathy
CIP critical illness polyneuropathy
CIPD chronic inflammatory demyelinating polyneuropathy
CIS clinically isolated syndrome
CISP chronic immune sensory polyradiculopathy
CK cytokeratin; creatine kinase
CLA2 X-linked cerebellar ataxia
CLL chronic lymphatic leukaemia
CM cerebral malaria
CMD congenital muscular dystrophy
CMRgl cerebral metabolic rate for glucose
$CMRO_2$ cerebral metabolic rate for oxygen
CMROGl cerebral metabolic rates of oxygen and glucose
CMT Charcot–Marie–Tooth
CMV cytomegalovirus
CN cystic nephroma
CNC Carney's complex
CNP 2′,3′-cyclic nucleotide 3′-phosphodiesterase
CNS central nervous system
CNS PNET central nervous system primitive neuroectodermal tumour
CNTF ciliary neurotrophic factor
CO carbon monoxide
COL4A1 collagen, type IV, alpha 1
COX cytochrome *c* oxidase
COX-2 cyclooxygenase-2
CP choroid plexus
CPCS chronic post-concussion syndrome
CPM central pontine myelinolysis
CPP cerebral perfusion pressure; central precocious puberty
CPT carnitine palmitoyltransferase
CR cognitive reserve
CR3 complement receptor type 3
CRABP cellular retinoic acid binding protein
CRBP cytoplasmic retinol binding protein
CREB cyclic adenine dinucleotide phosphate response element binding protein
CRH corticotropin-releasing hormone
CRIMYNE critical illness myopathy and neuropathy
CRMP-5 collapsing response mediator protein 5
CRV cerebroretinal vasculopathy
CSDH chronic subdural haematoma
CSF cerebrospinal fluid
CSPα cysteine string protein α
CT computed tomography
CTD connective tissue disease
CTE chronic traumatic encephalopathy
CTF Colorado tick fever
CTL cytotoxic lymphocyte
CUP cancer of unknown primary
CUTE corticotropin upstream transcription-binding element
CuZnSOD copper- and zinc-containing superoxide dismutase
CVD cardiovascular disease
CVS chorionic villus sampling
CVST cerebral venous sinus thrombosis
CVT cerebral venous thrombosis

CWD chronic wasting disease
CX32 connexin 32
DAB diaminobenzidine
DAG dystrophin-associated glycoprotein
DAI diffuse axonal injury
DAPAT dihydroxyacetonephosphate acyltransferase
DASE developmentally arrested structural elements
DAWM diffusely abnormal white matter
DCX doublecortin
DEHSI diffuse excessive high-signal intensity
DFFB DNA fragmentation factor subunit beta
DHA docosahexaenoic acid
DHAP dihydroxyacetone phosphate
DHPR dihydropyridine receptor
DiI dioctadecyl-tetramethylindocarbacyanine perchlorate
DILS diffuse infiltrative lymphocytosis syndrome
DIR double inversion recovery
DLB dementia with Lewy bodies
DLBCL diffuse large B cell lymphoma
DLK dual leucine kinase
DM dermatomyositis
DMD Duchenne muscular dystrophy
DMNV dorsal motor nucleus of the vagus
DMPK dermatomyositis protein kinase
DNER delta/notch-like epidermal growth factor-related receptor
DNL disseminated necrotizing leukoencephalopathy
DNMT DNA methyltransferase
DNT dysembryoplastic neuroepithelial tumour
DPR dipeptide repeat
DPX di-n-butylphthalate-polystyrene-xylene
DRD dopa-responsive dystonia
DRPLA dentatorubropallidoluysian atrophy
DSD Dejerine-Sottas disease
DSPN diffuse sensory polyneuropathy
DTI diffusion tensor imaging
DTICH delayed traumatic intracerebral haemorrhage
DWI diffusion weighted imaging
DXC doublecortin
EA episodic ataxia
EAAT excitatory amino acid transporter
EAN experimental allergic neuritis
EBP elastin-binding protein
EBV Epstein-Barr virus
EC endothelial cell; entorhinal cortex
ECGF1 endothelial cell growth factor 1 (platelet-derived)
ECM extracellular matrix
ECMO extracorporeal membrane oxygenation
EDH extradural haematoma
EEE eastern equine encephalitis
EEG electroencephalogram
EET epoxyeicosatrienoic acid
EF HS end folium hippocampal sclerosis
EGA estimated gestational age
EGB eosinophilic granular body
EGFR epidermal growth factor receptor
EGL external granule cell layer
EGR2 early growth response 2 gene
EIEE early infantile epileptic encephalopathy
EL encephalitis lethargica
ELBW extreme low birth weight
ELISA enzyme-linked immunosorbent assay
EM electron microscopy
EMA epithelial membrane antigen
EME early myoclonic encephalopathy
EMG electromyography
EMT epithelial-mesenchymal transition
eNSC embryonic neural stem cell
ENU ethylnitrosourea
EPC endothelial progenitor cell
EPMR epilepsy with mental retardation
ER endoplasmic reticulum
ERG electroretinogram
ERK extracellular signal-regulated kinase
ERM ezrin, radixin and moesin
ESAM endothelial cell-selective adhesion molecule
ESR erythrocyte sedimentation rate
ETANTR embryonal tumour with abundant neuropil and true rosettes
ETMR embryonal tumor with multilayered rosettes
EVOH ethylene-vinyl alcohol copolymer
FA Friedreich's ataxia
FACS fluorescence-activated cell sorting
FAD familial Alzheimer's disease
FAF familial amyloidosis of the Finnish type
FAK focal adhesion kinase
FALS familial amyotrophic lateral sclerosis
FAP familial amyloid polyneuropathy; familial polyposis
FBD familial British dementia
FBXO7 F-box only protein 7
FCD focal cortical dysplasia; follicular dendritic cell
FCE fibrocartilaginous embolism
fCJD familial Creutzfeldt-Jakob disease
FDD familial Danish dementia
FDF-2 fibroblast growth factor 2
FFI fatal familial insomnia
FFPE formalin-fixed paraffin-embedded tissue

FG fast-twitch glycolytic
FGF fibroblast growth factor
FHL1 four and a half LIM domains protein 1
FILIP filamin-A-interacting protein
FIPA familial isolated pituitary adenoma
FISH fluorescence *in situ* hybridization
FKRP fukutin-related protein
FLAIR fluid-associated inversion recovery
FLNA filamin A
FMD fibromuscular dysplasia; Fukuyama muscular dystrophy
fMRI functional magnetic resonance imaging
FOG fast-twitch oxidative glycolytic
FPS fasciitis-panniculitis syndrome
FR fatigue resistant
FS febrile seizure
FSH follicle stimulating hormone
FSHD facioscapulohumeral muscular dystrophy
FTBSI focal traumatic brain stem injury
FTD frontotemporal dementia
FTL ferritin light
FTLD frontotemporal lobar degeneration
FUPB1 far-upstream element binding protein 1
FUS fused-in-sarcoma protein
FXTAS fragile X tremor/ataxia syndrome
G-CIMP glioma CpG island methylator phenotype
GABA gamma-aminobutyric acid
GAD gracile axonal dystrophy; glutamic acid decarboxylase
GAG glycosaminoglycan
GALT gut-associated lymphoid tissue
GAP-43 growth-associated protein 43
GAT1 glutaric aciduria type 1
Gb Ose3 Cer globotriaosylceramide
GBE glycogen branching enzyme
GBM glioblastoma
GBS Guillain–Barré syndrome
GC granule cell
GCA giant cell (or temporal) arteritis
GCD granule cell dispersion
GCI global cerebral ischaemia; glial cytoplasmic inclusion
GCL granule cell layer
GCS Glasgow Coma Scale
GDAP1 ganglioside-induced differentiation-associated protein 1
GDNF glial cell-derived neurotrophic factor
GEMM genetically engineered mouse model
GFAP glial fibrillary acidic protein
GFP green fluorescent protein
GH growth hormone
GHR GH receptor
GI gastrointestinal
GIST gastrointestinal stromal tumour
GLAST glutamate/aspartate transporter
GLB1 galactosidase, beta 1
GLD globoid cell leukodystrophy
GLM glial limiting membrane
GM gliomesodermal tissue
GOM granular osmiophilic material
GP globus pallidus
GPI glycosylphosphatidylinositol
GROD granular osmiophilic deposit
GSC glioma stem cell
GSD glycogen storage disease
GSN gelsolin
Gsp G-protein oncogene
GSS Gerstmann-Sträussler-Scheinker disease
gTSE genetic transmissible spongiform encephalopathy
GU genitourinary
GWAS genome wide association studies
HAART highly active antiretroviral therapy
HACE high altitude cerebral oedema
HAD HIV-associated dementia
HAM HTLV-1-associated myelopathy
HAN hereditary neuralgic amyotrophy
HANAC hereditary angiopathy with nephropathy, aneurysms and muscle cramps
HAS high-altitude stupid
HAT human African trypanosomiasis
HB-EGF heparin-binding epidermal growth factor
HCG human chorionic gonadotropin
HCHWA-D hereditary cerebral haemorrhage with amyloid angiopathy of the Dutch
HCHWA-F hereditary cerebral haemorrhage with amyloid angiopathy of the Flemish
HCHWA-I hereditary cerebral haemorrhage with amyloid angiopathy of the Icelandic
HCMV human cytomegalovirus
HD Huntington's disease
HDL high density lipoprotein
HDL1 Huntington disease-like type 1
HDL2 Huntington disease-like type 2
HDL3 Huntington disease-like type 3
HE hepatic encephalopathy
H&E haematoxylin and eosin
HERNS hereditary endotheliopathy with retinopathy, nephropathy and stroke
HERV human endogenous retrovirus
HES hairy/enhancer of split
HES-1 hairy/enhancer of split 1
hGH human growth hormone
HH hypothalamic hamartoma
HHV-8 human herpesvirus 8
HIF hypoxia inducible factor

HIHRATL	hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy
HIMAL	hippocampal malrotation
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	helix-loop-helix
HMEG	hemimegalencephaly
HMERF	hereditary myopathy with early respiratory failure
HMG	high mobility group
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
H-MRS	proton magnetic resonance spectroscopy
HMSN	hereditary motor and sensory neuropathy
HNE	hydroxy-2-nonenal
HNPCC	hereditary nonpolyposis colorectal cancer
HNPP	hereditary neuropathy with liability to pressure palsy
H_2O_2	hydrogen peroxide
HPC	haemangiopericytoma
HPE	holoprosencephaly
HPF	high-power field
HPS	haematoxylin-phloxine-safranin
HPV	human papillomavirus
HRE	hypoxia response elements
HRP	horseradish peroxidase
HS	hippocampal sclerosis
HSA	hereditary systemic angiopathy
HSAN	hereditary sensory and autonomic neuropathy
HSP	heat-shock protein; hereditary spastic paraplegia
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine
hTERT	human telomerase reverse transcriptase
HTLV-I	human T-cell lymphotropic virus I
HVR	hereditary vascular retinopathy
IBM	inclusion body myositis
ICA	internal carotid artery; internal cerebral artery
ICAM-1	intercellular adhesion molecule-1
ICD	I-cell disease; intracellular domain
ICE	interleukin-converting enzyme
ICH	intracerebral haematoma
iCJD	iatrogenic Creutzfeldt-Jakob disease
ICP	intracranial pressure
IDH	intradural haemorrhage
IENF	intra-epidermal nerve fibre
IFS	isolated familial somatotropinoma
IGF	insulin-related growth factor
IgM	immunoglobulin M
IHC	immunohistochemistry
IHI	incomplete hippocampal inversion
IIM	idiopathic inflammatory myopathy
IL-1β	interleukin-1 beta
ILAE	International League Against Epilepsy
ILOCA	idiopathic late-onset cerebellar ataxia
ILS	isolated lissencephaly sequence
IMAM	inflammatory myopathy with abundant macrophages
IMD	inherited myoclonus-dystonia
IML	inner molecular layer
IMNM	immune-mediated necrotizing myopathy
IMT	inflammatory myofibroblastic tumour
INAD	infantile neuroaxonal dystrophy
INCL	infantile neuronal ceroid lipofuscinosis
iNOS	inducible nitric oxide synthase
ION	inferior olivary nucleus
IPI	initial precipitating injury
iPSC	induced pluripotent stem cell
IPSP	inhibitory postsynaptic potential
IRD	infantile Refsum's disease
IRES	internal ribosomal entry site
IRIS	immune reconstitution inflammatory syndrome
IRS	insulin receptor substrate
ISF	interstitial fluid
ISPD	isoprenoid synthase domain-containing
ISSD	infantile sialic acid storage disease
ITPR-1	inositol triphosphate receptor type 1
IUGR	intrauterine growth restriction
IVH	intraventricular haemorrhage
JAK/STAT	Janus kinase and downstream signal transducer and activator of transcription
JAM	junctional adhesion molecule
JME	juvenile myoclonic epilepsy
JNCL	juvenile neuronal ceroid lipofuscinosis
JXG	juvenile xanthogranuloma
kb	kilobase
KO	knockout
KPS	Karnofsky performance status
KRS	Kufor-Rakeb syndrome
KS	Korsakoff's syndrome
KSS	Kearns-Sayre syndrome
LA	lupus anticoagulant
LB	Lewy body
LCH	Langerhans cell histiocytosis
LCMV	lymphocytic choriomeningitis virus
LDD	Lhermitte-Duclos disease
LDL	low-density lipoprotein
LEAT	long-term epilepsy-associated tumour
LFB	Luxol fast blue
LFB-CV	Luxol fast blue-cresyl violet
LGI1	leucine-rich glioma-inactivated 1
LGMD	limb-girdle muscular dystrophy
LGN	lateral geniculate nucleus

LH luteinizing hormone
LIF leukaemia inhibitory factor
LINCL late infantile neuronal ceroid lipofuscinosis
LMNA lamin A/C
LNMP last normal menstrual period
LOH loss of heterozygosity
LPH lipotropin
LRPN lumbosacral radioplexus neuropathy
LSA lenticulostriate artery
L-SS Lewis-Sumner syndrome
LTD long-term depression
LTP long-term potentiation
MAG myelin-associated glycoprotein
MAGE-A melanoma-associated cancer-testis antigen
MAP microtubule-associated protein
MAPK mitogen-activated protein kinase
MATPase myofibrillar adenosine triphosphatase
MBD Marchiafava-Bignami disease
MBEN medulloblastoma with extensive nodularity
MBP myelin basic protein
MCA middle cerebral artery
MCB membranous cytoplasmic body
MCD malformation of cortical development
MCI mild cognitive impairment
MCM2 minichromosome maintenance 2
MCP-1 monocyte chemoattractant protein 1
MDC1A merosin-deficient CMD
MELAS mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
MEN multiple endocrine neoplasia
MEN2 multiple endocrine neoplasia type 2
MERRF myoclonic epilepsy with ragged-red fibres
MFN2 mitofusin 2
MFS Miller Fisher syndrome; mossy fibre spouting
MGUS monoclonal gammopathy of unknown significance
MHC myosin heavy chain
MHC-I major histocompatibility complex class I
MHV mouse hepatitis virus
MIBE measles inclusion body encephalitis
MJD Machado-Joseph disease
ML mucolipidosis
MLC myosin light chain
MLD metachromatic leukodystrophy
MLI mucolipidosis I
MM methionine homozygosity
MMN multifocal motor neuropathy
MMP matrix metalloproteinase
MMR mismatch repair; measles-mumps-rubella
MNCV motor nerve conduction velocity
MND motor neuron degeneration; mild neurocognitive disorder; motor neuron disease
MNGC multinucleated giant cell
MNGIE mitochondrial neuro-gastrointestinal encephalomyopathy
MnSOD manganese-containing superoxide dismutase
MNU methylnitrosourea
MOG myelin-oligodendrocyte protein
MPNST malignant peripheral nerve sheath tumour
MPO myeloperoxidase
MPS mucopolysaccharidosis
MPT mitochondrial permeability transition
MPTP N-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine
mPTS membrane peroxisomal targeting sequence
MPZ myelin protein zero
MR magnetic resonance
MRC Medical Research Council
MRI magnetic resonance imaging
mRNA messenger ribonucleic acid
MRS magnetic resonance spectroscopy
MRT malignant rhabdoid tumour
MS multiple sclerosis
MSA multiple system atrophy; myositis-specific autoantibody
MSA-C cerebellar form of multiple system atrophy
MSB Martius scarlet blue
MSD multiple sulphatase deficiency
MSH melanotropin
MSI microsatellite instability
mtDNA mitochondrial DNA
MTI magnetization transfer imaging
MTLE mesial temporal lobe epilepsy
MTMR2 myotubularin-related protein 2
mTOR mammalian target of rapamycin
MTR magnetization transfer ratio
MuSK muscle-specific kinase
MV valine heterozygous
MVE Murray Valley encephalitis
NAA *N*-acetylaspartate
NAD+ nicotinamide adenine dinucleotide
NADH-TR nicotinamide adenine dinucleotide-tetrazolium reductase
NAHI non-accidental head injury
NALD neonatal adreno-leukodystrophy
NAM necrotizing autoimmune myopathy
NARP neuropathy, ataxia and retinitis pigmentosa
NAT non-accidental trauma
NAWM normal-appearing white matter

NBCCS naevoid basal cell carcinoma syndrome
NBIA neurodegeneration with brain iron accumulation
NBIA1 neurodegeneration with brain iron accumulation, type 1
NBIA2 neurodegeneration with brain iron accumulation, type 2
NCAM neural cell adhesion molecule
NCI neuronal cytoplasmic inclusion
NCIPC National Center for Injury Prevention and Control
NCL neuronal ceroid lipofuscinosis
NCM neurocutaneous melanosis
NECD notch extracellular domain
NF neurofilament protein
NF1 neurofibromatosis type 1
NF2 neurofibromatosis type 2
NFL National Football League
NFP neurofilament protein
NFT neurofibrillary tangle
NGF nerve growth factor
NHNN National Hospital for Neurology and Neurosurgery
NIFID neuronal intermediate filament inclusion disease
NIID neuronal intranuclear inclusion disease
NINDS National Institute of Neurological Disorders and Stroke
NINDS-PSP National Institute of Neurological Disorders and Stroke and the Society for Progressive Supranuclear Palsy
NIRS near-infrared spectroscopy
NK natural killer
NMDA *N*-methyl-D-aspartate
NMDAR *N*-methyl-D-aspartate receptor
NMO neuromyelitis optica
nNOS neuronal nitric oxide synthase
NO nitric oxide
NOS not otherwise specified
NOTCH3 notch homolog 3
NPC Niemann-Pick disease type C
NPH normal pressure hydrocephalus
NPY neuropeptide Y
NSAID non-steroidal anti-inflammatory drug
NSC neural stem cell
NSE neuron specific enolase
NTD neural tube defect
NTE neuropathy target esterase
NTS nucleus of the solitary tract
OCT optimal cutting temperature; optical coherence tomography
OEF oxygen extraction fraction
O-FucT-1 O-fucosetransferase 1
OH hydroxyl radical
OMIM Online Mendelian Inheritance in Man
OML outer molecular layer
OPC oligdendrocyte precursor cell
OPCA olivopontocerebellar atrophy
OPIDPN organophosphate-induced delayed polyneuropathy
ORF open reading frame
PACNS primary angiitis of the central nervous system
PAFAH platelet activating factor acetyl hydrolase
PAMP pathogen-associated molecular pattern
PAN polyarteritis nodosa; perchloric acid naphthoquinone
p-ANCA perinuclear ANCA
PARK1 Parkinson's disease and alpha-synuclein
PAS periodic acid–Schiff
PB pineoblastoma
PBD peroxisome biogenesis disorder
PBH parenchymal brain haemorrhage
PBP progressive bulbar palsy
PC pineocytoma
PCD Purkinje cell degeneration
PCNA proliferating cell nuclear antigen
PCNSL primary central nervous system lymphoma
PCP planar cell polarity
PCR polymerase chain reaction
PCV packed cell volume
PD Parkinson's disease; pars distalis
PDC parkinsonism/dementia complex
PDCD programmed cell death
PDD Parkinson's disease dementia
PDGF platelet-derived growth factor
PDGFB platelet-derived growth factor beta
PDH pyruvate dehydrogenase
PECAM platelet-endothelial cell adhesion molecule
PEM protein-energy malnutrition
PEO progressive external ophthalmoplegia
PEP postencephalitic parkinsonism
PERM progressive encephalomyelitis with rigidity and myoclonus
PES pseudotumoural encephalic schistosomiasis
PET paraffin-embedded tissue; positron emission tomography
PGNT papillary glioneuronal tumour
PGP protein gene product
PHF paired helical filament
PHP pseudo-Hurler polydystrophy
PhyH phytanoyl-CoA hydroxylase
PI pars intermedia
PiB Pittsburgh compound B
PICA postero-inferior cerebellar artery
PKAN pantothenate kinase-associated neurodegeneration

PKC protein kinase C
PLA2G6 phospholipase A2, group VI
PLAN PLA2G6-associated neurodegeneration
PLP proteolipid protein
PLS primary lateral sclerosis
PMA pilomyxoid astrocytoma; progressive muscular atrophy
PMCA protein misfolding cyclic amplification
PMD Pelizaeus-Merzbacher disease
PME progressive myoclonic epilepsy
PML progressive multifocal leukoencephalopathy
PMNS post-malaria neurological syndrome
PMP peroxisomal membrane protein
PMP2 peripheral myelin protein 2
PMS psammomatous melanotic schwannoma
PN pars nervosa
PNDC progressive neuronal degeneration of childhood with liver disease
PNET primitive neuroectodermal tumour
PNMA paraneoplastic Ma antigen
PNS peripheral nervous system
pO_2 partial pressure of oxygen
POEMS polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes
POLG polymerase γ
POMC proopiomelanocortin
PPA primary progressive aphasia
PPB familial pleuropulmonary blastoma
PPCA protective protein with cathepsin A-like activity
ppm parts per million
pPNET peripheral primitive neuroectodermal tumour
PPS pentosan polysulphate; post-polio syndrome
PPT pineal parenchymal tumour
PPTID pineal parenchymal tumour of intermediate differentiation
PR progesterone receptor
PRBC parasitized red blood cell
PRES posterior reversible encephalopathy syndrome
PRL prolactin
PRNP PrP gene
PROMM proximal myotonic myopathy
PROP-1 prophet of Pit-1
ProtCa activated protein C
ProtS protein S
PrP prion protein
PrP-CAA PrP-cerebral amyloid angiopathy
PRR pattern recognition receptor
PSAP prosapson
PSD post-stroke dementia
PSIR phase-sensitive inversion recovery
PSP progressive supranuclear palsy
PSP-CA progressive supranuclear palsy with cerebellar ataxia
PSP-CST atypical progressive supranuclear palsy with corticospinal tract degeneration
PSP-P progressive supranuclear palsy with parkinsonism
PSP-PAGF pure akinesia with gait freezing with subsequent development of typical signs of progressive supranuclear palsy
pSS primary Sjögren's syndrome
PTAH phosphotungstic acid haematoxylin
PTC periodic triphasic complex
PTD primary (idiopathic) torsion dystonia
ptd-FGFR4 pituitary tumour-derived FGFR4
PTLD post-transplant lymphoproliferative disorder
PTPR papillary tumour of the pineal region
PTRF polymerase I and transcript release factor
PTS peroxisomal targeting signal
Ptx2 pituitary homeobox factor 2
PVH/IVH periventricular/intraventricular haemorrhage
PVL periventricular leukomalacia
PWI perfusion weighted imaging
PXA pleomorphic xanthoastrocytoma
QuIC quaking induced conversion
RALDH retinaldehyde dehydrogenase
RANO response assessment in neuro-oncology
RAR retinoic acid receptor
RARE retinoic acid response element
RC2 reaction centre type 2
RCA-1 *Ricinus communis* agglutinin 1
rCBF regional cerebral blood flow
rCBV regional cerebral blood volume; relative cerebral blood volume
RCC renal cell carcinoma
RCDP rhizomelic chondrodysplasia punctata
RDD Rosai-Dorfman disease
RDP rapid onset dystonia-parkinsonism
RE Rasmussen encephalitis
REM rapid eye movement
rhNGF recombinant human nerve growth factor
RIG radiation-induced glioma
RIM radiation-induced meningioma
RING Really Interesting New Gene
RIP1 receptor-interacting protein 1
RIS radiologically isolated syndrome
RNI reactive nitrogen intermediate
ROS reactive oxygen species
RPLS reversible posterior leukoencephalopathy syndrome
RPS rhabdoid predisposition syndrome
Rpx Rathke's pouch homeobox
RRF ragged-red fibre

RRMS	relapsing-remitting form of multiple sclerosis
RSMD1	rigid spine muscular dystrophy type 1
RSV	Rous sarcoma virus
RTA	road traffic accident
RTK	receptor tyrosine kinase
RVCL	retinal vasculopathy with cerebral leukodystrophy
RXR	retinoid X receptor
SAH	subarachnoid haemorrhage
SANDO	sensory ataxic neuropathy, dysarthria and ophthalmoparesis
SAP	serum amyloid P
Sap-A	sapsosin-A
Sap-B	sapsosin-B
Sap-C	sapsosin-C
SAR	specific absorption rate
SBF2	set binding factor 2
SBMA	spinal and bulbar muscular atrophy
SBP	systemic blood pressure
SBS	shaken baby syndrome
SCA	spinocerebellar ataxia
SCAR1	spinocerebellar ataxia recessive type 1
SCD	subacute combined degeneration
SCI	spinal cord injury
sCJD	sporadic Creutzfeldt-Jakob disease
SCLC	small cell lung cancer
SCMAS	subunit c of mitochondrial ATP synthase
SCO	subcommissural organ
SCS	spinal cord schistosomiasis
SDF-1	stromal cell-derived factor 1
SDH	subdural haematoma; succinate dehydrogenase
SDS	Shy-Drager syndrome
SE	spin echo; status epilepticus
SEER	Surveillance, Epidemiology and End Results
SEGA	subependymal giant cell astrocytoma
SF-1	steroidogenic factor-1
sFI	sporadic fatal insomnia
SFT	solitary fibrous tumour
SFV	Semliki forest virus
Shh	Sonic hedgehog
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIS	second impact syndrome
SKL	serine-lysine-leucine
SLD	sudanophilic (orthochromatic) leukodystrophy
SLE	systemic lupus erythematosus; St. Louis encephalitis
Sm	Smith
SMA	spinal muscular atrophy
SMARD	spinal muscular atrophy with respiratory distress
SMC	smooth muscle cell
SMN	survival motor neuron
SMNA	sensorimotor neuropathy with ataxia
SMTM	sulcus medianus telecephali medii
SN	substantia nigra
SNAP	sensory nerve action potential
SNARE	soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex
SND	striatonigral degeneration
SNP	single nucleotide polymorphism
SNPC	substantia nigra pars compacta
SNPR	substantia nigra pars reticulata
SO	slow-twitch oxidative
SOD	superoxide dismutase
SPECT	single photon emission computed tomography
SPLTLC1	serine-palmitoyltransferase 1
SPS	stiff-person syndrome
SRP	signal recognition protein
SSPE	subacute sclerosing pan-encephalitis
SUDEP	sudden unexpected death in epilepsy
SVD	small vessel disease
SVZ	subventricular zone
SWI	susceptibility-weighted imaging
SYN	synaptophysin
TACE	TNFα converting enzyme
TAI	traumatic axonal injury
TBI	traumatic brain injury
TBP	TATA box-binding protein
TCGA	The Cancer Genome Atlas
TCI	total contusion index
TCR	T-cell receptor
TEF	thyrotroph embryonic factor
TGA	transposition of the great arteries
TGF	transforming growth factor
TGM6	transglutaminase 6
THCA	trihydroxycholestanoic acid
TIA	transient ischaemic attack
TLE	temporal lobe epilepsy
TLR	Toll-like receptor
TME	transmissible mink encephalopathy
TMEV	Theiler's murine encephalomyelitis virus
TNF	tumour necrosis factor
TOCP	triorthocresylphosphate
Topo II alpha	topoisomerase II alpha
TPNH	triphosphopyridine nucleotide
TPP	thiamine pyrophosphate
TS	Tourette's syndrome; Turcot syndrome
tSAH	traumatic subarachnoid haemorrhage
TSC	tuberous sclerosis complex
TSE	transmissible spongiform encephalopathy
TSH	thyrotrophin

TSP tropical spastic paraparesis
TTF-1 thyroid transcription factor 1
TTP thrombotic thrombocytopenic purpura
TTR transthyretin
UBO unidentified bright object
UCH-L1 ubiquitin carboxy-terminal hydrolase
uPA urokinase plasminogen activator
UPDRS Unified Parkinson's Disease Rating Scale
UPR unfolded protein response
UPS ubiquitin-proteasome system
UV ultraviolet
VaD vascular dementia
VCAM-1 vascular cell adhesion molecule 1
VCI vascular cognitive impairment
vCJD variant Creutzfeldt-Jakob disease
VCP vasolin-containing protein
VEE Venezuelan equine encephalomyelitis
VEGF vascular endothelial growth factor
VEP visual evoked potential
VGKC voltage-gated potassium channel
VHL Von Hippel-Lindau
VLBW very low birth weight
VLCFA very-long-chain fatty acid
VLDL very low density lipoprotein
VLM visceral larva migrans
VM vacuolar myelopathy
VMB vascular malformation of the brain
VPF vascular permeability factor
VPSPr variably protease sensitive prionopathy
VSMC vascular smooth muscle cell
VV valine homozygous
vWF von Willebrand factor
VZ ventricular zone
WBC white blood cell
WE Wernicke's encephalopathy
WEE western equine encephalitis
WHO World Health Organization
WKS Wernicke-Korsakoff syndrome
Wlds wallerian degeneration slow
WM white matter
WNV West Nile virus
WSM widely spaced myelin
XMEA X-linked myopathy with excessive autophagy
YAC yeast artificial chromosome
ZASP Z-line alternatively spliced PDZ protein
ZPT zinc pyridinethione
ZS Zellweger syndrome

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CHAPTER 1

General Pathology of the Central Nervous System

Harry V Vinters and B K Kleinschmidt-DeMasters

Neurons....1
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NEURONS

The neuron is the excitable cell type responsible for the reception of stimuli and information, and conduction of electro-chemical impulses in the brain, spinal cord and ganglia. Neurons are 10–50 times less numerous than their supporting cells, the neuroglial astrocytes, oligodendrocytes and ependymal cells,[27] and are estimated to constitute only 5 per cent of the cells within the cerebral grey matter.[56] Yet they are responsible for the most critical and complex (arguably defining) cellular functions of the organ. They also undergo the greatest number of microscopic changes in response to acute and chronic cell injury and are the principal site of damage for several of the diseases associated with the highest morbidity and mortality in our society, i.e. cerebrovascular and neurodegenerative diseases.

The complex functions of the neuron are responsible for its high metabolic demand for glucose and oxygen/blood supply and are also reflected in its specialized morphological features. Neurons possess a nucleus, nucleolus, cytoplasm and many of the same cytoplasmic organelles found in other cells in the body. However, their extreme protein synthetic and energy requirements, the extraordinary length of their cell processes, and the need for a complex cytoskeletal architecture to support these long cell processes mandate the need for some of these subcellular structures to be better developed than in cells elsewhere in the body, or even in their neighbours, the neuroglial cells.

Under normal, non-injury conditions, usually only the nuclei and cell bodies of neurons are visible to the pathologist on routine histochemical stains used in daily practice, such as haematoxylin and eosin (H&E) or Luxol fast blue–H&E. Immunohistochemical stains commonly employed in routine neuropathology practice to identify proximal portions of neurons (the dendrites and/or soma) include primary antibodies to synaptophysin (a presynaptic vesicle protein), NeuN (a neuronal nuclear protein), microtubule-associated protein 2 (MAP-2), and some of the three polypeptide subunits of neurofilament, which constitutes the major cytoskeletal intermediate filament type for neurons. Low (NF-L, 68 kDa), medium (NF-M, 160kDa) and heavy (NF-H, 200 kDa) subunits exist within the neuron and selective antibodies have been developed over the past 20 years against each. Early work with antibodies directed against these various NF subunits showed no staining of neuronal perikarya and dendrites with antibodies directed against the heavy 200 kDa component.[47] It was subsequently recognized that the antibody directed against NF-L recognized a component in the central core of neurofilaments, and the NF-H antibody a component of the interneurofilamentous cross-bridges; because neurofilaments in mammalian axons were extensively cross-linked, it was not surprising that axons immunostained best with the antibody directed against NF-H.[97] Later work further showed that a lower ratio of NH-L to NH-M and NH-H was found in dendrites and that this proportion was essential for the shaping and growth of complex dendritic trees in motor neurons.[127] Antibodies were also raised to phosphorylated (SM131, NE14) and non-phosphorylated (SM132) NF subtypes. Phosphorylation of NFs was correlated with abundance of NFs and bundling and cross-linking between NF core filaments.[86] Anti-phosphorylated NF antibodies showed strongest immunostaining in axons where NFs are abundant and show this cross-linking, but not in dendrites

and perikarya where NFs are sparse and are present singly.[86]Although there are variations among cell types and the distribution of NFs changes in disease states, a general principle is that antibodies directed against non-phosphorylated subunits of NF best stain the dendrites and perikarya of neurons, whereas those against phosphorylated NFs are used to highlight axons. Neuron specific enolase (NSE), despite its name, is unfortunately not specific for neurons but does also highlight the neuronal cell body.[77] Among the many definitely non-neuronal entities that NSE stains, myeloma and lymphomas can be the most problematic for the diagnostic surgical neuropathologist.[168]

Specific subsets of neurons can be further identified by immunostaining for calretinin, galanin or any of the various specific neurotransmitters and neuromodulators that they produce (γ-aminobutyric acid (GABA), glutamine, dopamine, acetylcholine, neuropeptide Y, etc.), but these techniques are almost exclusively employed in research rather than routine daily practice.

Antibodies to markers of neuronal lineage have application both in the study of normal central nervous system (CNS) and peripheral nervous system (PNS) neurons and in assessing brain tumours of possible neuronal lineage/differentiation. Antibodies have been raised to α-synuclein, a presynaptic nerve terminal protein found in normal neurons, and immunostaining for this has found widest application in the study of inclusion bodies in neurodegenerative disorders. However, α-synuclein immunostaining has also been found in human brain tumours manifesting neuronal differentiation, such as ganglioglioma, medulloblastoma, neuroblastoma, primitive neuroectodermal tumours and central neurocytoma.[117] The proportion of tumours immunopositive for α-synuclein was reported to be lower than that labelled with more commonly used neuronal antibodies, including those to synaptophysin, MAP-2, NSE and tau, but higher than the proportion positive for neurofilament or chromogranin A.[117] Other neuronal markers such as TrkA, TrkB, TrkC, the α1 subunit of the GABA receptor, N-methyl-D-aspartate receptor subunit 1, glutamate decarboxylase and embryonal neural cell adhesion molecule have also occasionally been utilized to detect putative neuronal lineage in human brain tumours.[270]

The full extent of the cell processes of neurons, termed neurites, cannot be discerned on H&E staining and is only fully appreciable with special stains. The neurites responsible for receiving synaptic information from other neurons and for afferent conduction of electrochemical impulses towards the cell body (soma) are termed dendrites. The full arborization pattern of dendrites is best visualized using Golgi staining techniques (a time-consuming process not usually available in non-research settings). The single elongate process responsible for efferent conduction of impulses away from the cell soma is the axon. Axons can be visualized using staining techniques widely available in most diagnostic laboratories, including the modified Bielschowsky and Bodian silver histochemical stains or immunohistochemical methods that target phosphorylated neurofilaments.

The number, length and position on the neuronal cell body of the branching dendrites determine the shape and morphological classification of the neuron. Unipolar neurons possess a single cell process that divides a short distance from the cell body; an example is the dorsal root ganglion cell. Bipolar neurons have an elongate cell body with two cell processes emerging at either end of the cell soma; examples include retinal bipolar cells and cells of the sensory cochlear and vestibular ganglia. The vast majority of neurons are, however, multipolar, with large numbers of dendrites arranged in a radiating pattern around the entire cell body (motor neurons of the spinal cord), at the apex of a triangular cell body (pyramidal cell of cerebral cortex) or near the top of a flask-shaped cell (Purkinje cell neuron of cerebellum). Multipolar neurons can be further subdivided based on the length of their efferent axonal process. Golgi type II neurons, with a short axon that terminates near the cell body, greatly outnumber Golgi type I neurons. Golgi type I neurons possess a long axon that may be up to several feet in length in the case of some motor neurons, or less lengthy in the case of pyramidal cells of the cerebral cortex or Purkinje cells of the cerebellar cortex.[224]

The cross-sectional diameter of the neuronal cell body, by contrast, is largely determined by the length of the axon. The size of neuronal cell bodies varies greatly, from the small, 5 µm-diameter, granule cell neurons of the cerebellum to the large, 135 µm-diameter, anterior horn cells of the spinal cord.[224] The volume of the neuronal soma parallels the length of the axon for which it is responsible: the longer the axon, the larger the cell body must be – specifically, the larger the cytoplasmic volume and organelle machinery must be to sustain that axon. Hence, Golgi type I neurons have larger amounts of cell cytoplasm that are readily visible even on H&E preparations, whereas Golgi type II neurons have scant cytoplasm that may give the neuron a 'naked nucleus' appearance on routine stains. Examples of the latter include the 'lymphocyte-like' granule cell neurons of the cerebellar cortex, which have a densely basophilic nucleus but in routine preparations appear to possess no cytoplasm, or the small interneurons of the cerebral cortex, which because of the paucity of their cytoplasm may be difficult to distinguish from neuroglial cells in H&E-stained sections.

The neuronal nucleus is the repository for the chromosomes and in resting, non-mitotic conditions the chromatin is generally fairly evenly dispersed throughout the nucleus. The prominent large nucleolus seen especially in Golgi type I neurons is a reflection of the need for a high rate of protein synthesis to maintain the numerous proteins within the large cytoplasmic volume, determined largely by the length of axon. The nuclear membrane is well defined on routine H&E staining, but the double-layering of the membrane and the presence of fine nuclear pores, through which substances can diffuse into and out of the nucleus, is appreciable only on electron microscopy (EM). The nuclear pores are a conduit through which newly synthesized ribosomal subunits can pass from the nucleus into the cytoplasm. The cytoplasm contains both granular and non-granular endoplasmic reticulum. The granular, RNA-containing, endoplasmic reticulum extends throughout the cell body into the proximal parts of the dendrites; it is absent from the area of cytoplasm immediately adjacent to the axon, known as the axon hillock, and from the axon itself.

Subcellular organelles of the neuron can be variably appreciated on H&E staining. Components that contain appreciable amounts of DNA (nucleus) or RNA (nucleolus and abundant cytoplasmic rough endoplasmic reticulum arranged in parallel arrays known as Nissl substance) in the cell have affinity for the haematoxylin dye used in

routine histochemical staining. Therefore, the nucleus, nucleolus and Nissl substance of large neurons manifest a distinct blue-purple colouration and are readily visible on staining with H&E. The DNA- and RNA-containing structures within the neuron can be further highlighted by other histochemical staining techniques such as the modified Nissl method, which originally used aniline but has been modified to use toluidine blue, cresyl violet or others. The monochromatic Nissl staining method is often employed by investigators interested in morphometric analyses of neuronal populations in normal or diseased states. The Nissl stain is often used to highlight neuronal loss in chronic neurodegenerative disorders.

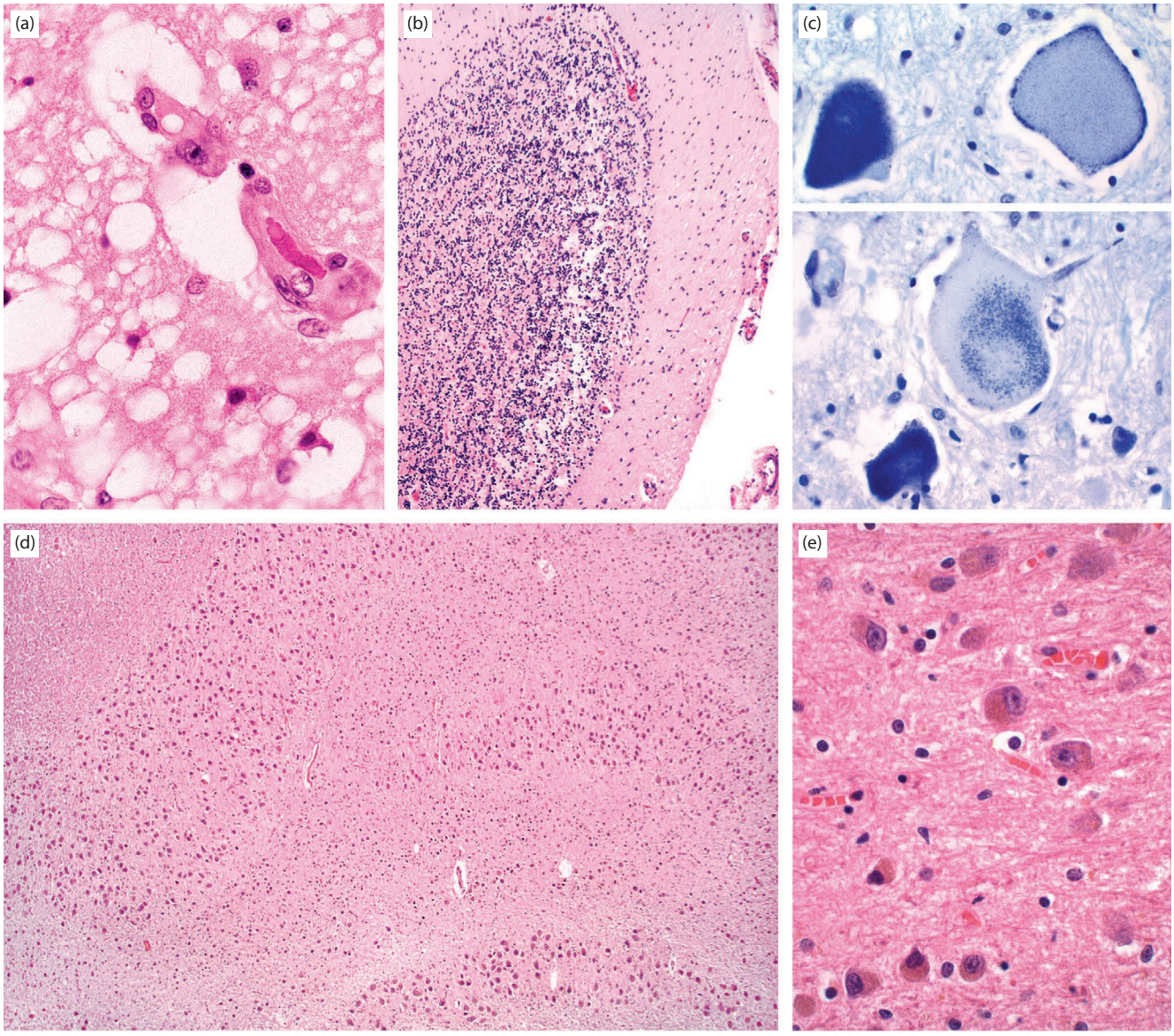
The remaining, non-DNA or RNA containing organelles in the neuron, such as the mitochondria, Golgi complex, lysosomes, neurofilaments, microtubules and microfilaments, are individually unresolvable by H&E at the light microscopic level under normal conditions. These neuronal organelles blend together within the eosinophilic, pink cytoplasm in H&E-stained normal cells and can be appreciated only on EM. The complexity of the synapse is also appreciable only by EM. A number of antibodies directed to synaptic vesicle proteins have, however, been developed that can highlight the synapse and give an indication as to its function or dysfunction. The more common of these include synaptophysin, synaptobrevin (vesicle associated membrane protein, VAMP), synaptotagmin I and synaptic vesicle protein 2 (SV2).

In order to function normally, neurons require complex membrane pumps to exclude toxic calcium ions and to maintain the correct balance between internal (intracellular) and external (microenvironmental) electrolyte concentrations of sodium and potassium in order to transmit electrical signals.[56] With microenvironmental damage to neuronal membranes or with energy deprivation, these pumps fail, calcium ions flood the neuron and irreparable cell damage – known as necrosis – occurs. Local oxygen deprivation, such as that seen in stroke, may result in transient (recoverable) or permanent (irreparable, necrotic) injury to the neuron (see Chapter 2, Vascular Disease, Hypoxia and Related Conditions). This oxygen deprivation can affect cell energy requirements, membrane integrity, and/or the immediate surrounding microenvironment.[56] Thus calcium-channel blocking 'neuroprotectant' agents used in the treatment of stroke may work not just at the level of the neuron alone but also on the microvessels and supportive glial cells around them, the so-called 'neurovascular unit'.[56]

At the light microscopic level, acute sustained deprivation of energy (oxygen/blood supply or glucose), however, is best appreciated in the neuron itself. The irreparable cell damage can be visualized as the brightly eosinophilic 'red (dead) neuron' (Figure 1.1a). This change, seen most often with ischaemia, is manifested by cell shrinkage, nuclear pyknosis, loss of nucleolar detail and loss of basophilic cytoplasmic staining as a result of dissolution of granular endoplasmic reticulum. These result in a smaller, triangular cell, condensed nuclear chromatin, loss of the nucleolus and eosinophilia of the cytoplasm (Figure 1.1a). It should be emphasized that neurons may succumb within several minutes at normal body temperature to severe deprivation of oxygen. However, when body temperature is lowered, metabolism is slowed and considerably longer time periods without oxygen may be endured by the human brain, with relatively lesser amounts of irretrievable neuronal loss. This explains the remarkable recovery of some people immersed for an hour or more at the bottom of a cold lake who, when retrieved and resuscitated, are able to survive in a relatively cognitively intact state! It should also be emphasized that at normal body temperature, neurons are actually irreparably damaged within minutes when subjected to complete lack of oxygen, but to fully appreciate the 'red cell change' in these same cells under the microscope, at least 8 hours and optimally 18–24 hours must elapse after the injury event before these changes can be confidently diagnosed. The corollary to this is that if a patient dies soon after a cardiac arrest and the family and treating physician of the deceased want to know exactly how widespread the ischaemic neuronal injury was in the patient's brain at autopsy, the pathologist reviewing the case will be unable to answer this question by using routine autopsy techniques. A spectrum of morphological changes ('necrophanerosis') evolves over variable time intervals prior to final ('definite') necrosis; these changes depend upon a variety of factors such as the rate and extent of blood (re-) perfusion, body temperature and others. Animal studies on ischaemic cell injury in neurons often avoid this problem by using rapid perfusion-fixation and EM to detect early, subtle organelle injury. During the acute phase, brain tissue surrounding a focus of ischaemic injury has an eosinophilic neuropil and exhibits significant vacuolation due to oedema (Figure 1.1a). This should not be mistaken for the spongiform change seen in transmissible spongiform encephalopathies. These changes are considered in detail in Chapter 2, Vascular Disease, Hypoxia and Related Conditions).

When neurons undergo cell death and necrosis, no effective neuronal mitosis or replenishment of neurons from stem cells is present within the adult human brain: neuron(s) and their function(s) are lost to the host. Irreversibly damaged neurons are removed over the next few days by phagocytosing microglial cells and macrophages. Astrocytes begin to proliferate in response to injury and may leave a distinctive, tell-tale indication of where the now-removed neurons formerly resided. The classic example of this is Bergmann astrocytosis in the layer of cerebellar cortex where the Purkinje cell neurons formerly resided (Figure 1.1b). Occasionally, morphological evidence of sublethal cell injury in neurons can be detected, best typified by peripheral (Figure 1.1c, bottom) and central (Figure 1.1c, top) chromatolysis. Chromatolysis refers to the response to injury usually seen in Golgi I motor neurons in the anterior horn of the spinal cord when their long axonal process is transected or severely injured. Chromatolysis can be thought of as reorganization by the cell soma and redistribution of Nissl substance in an attempt to reconstitute the axon; central and peripheral chromatolysis may be different phases of this process. If the axonal injury is too severe or the axonal transaction too proximate to the cell body, the efforts of the cell body and its chromatolytic response will be insufficient to produce a new healthy axon and the neuron will itself eventually disappear.

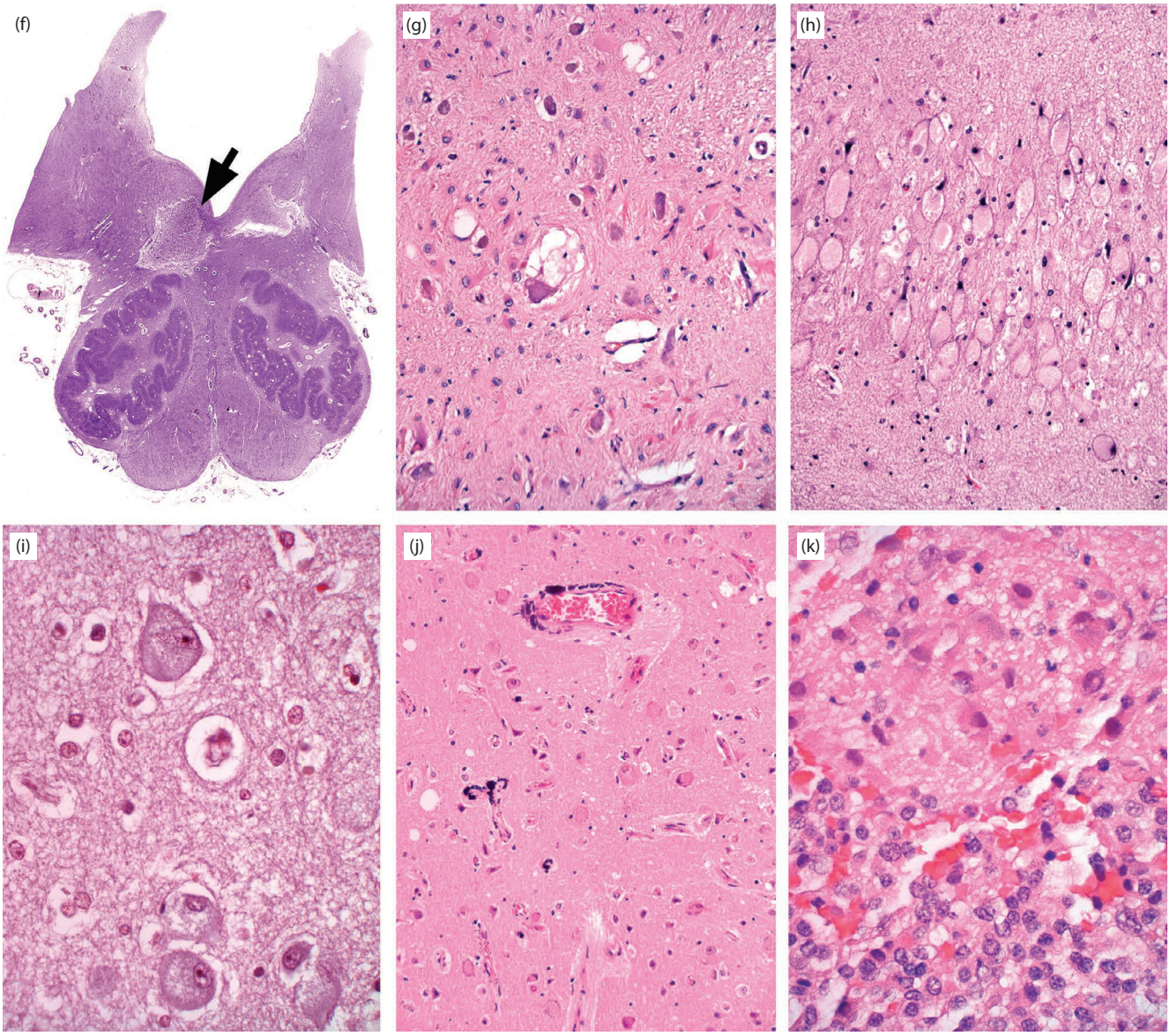
Sublethal injury to neurons may manifest not as eosinophilic change but by cell shrinkage and atrophy. This can occur in a variety of neurodegenerative disorders but is typified by neurons affected by trans-synaptic neuronal degeneration.



1.1 Neuronal abnormalities in diseases of the CNS. (a) Red, dead neurons with loss of nucleoli and Nissl substance after cerebral ischaemia. Note the vacuolated, oedematous background neuropil. **(b)** Absence of Purkinje cell neurons and gliosis, but good preservation of granule cell neurons as a result of chronic ischaemic cerebellar injury. **(c)** Central (bottom) and peripheral (top) chromatolysis. Nissl stain. **(d)** and **(e)** Trans-synaptic degeneration in lateral geniculate nuclei; see text for detailed description.

Trans-synaptic degeneration occurs when a neuron loses the major source of its axonal input from connecting (incoming) fibres, usually as a result of the loss of 'upstream' neurons that give rise to these axons. A good example of this process is seen following enucleation of one eye. Axons from retinal ganglion cells synapse on neurons in the lateral geniculate nuclei. The example of trans-synaptic degeneration illustrated in Figure 1.1d is from an autopsy performed on a female who underwent right eye removal for retinal melanoma 6 years prior to death, with subsequent wallerian degeneration of the ipsilateral optic nerve and trans-synaptic degeneration in the lateral geniculate nuclei. Because of the differing patterns of projection of axons from the ipsilateral and contralateral eye, the left lateral geniculate ganglion showed atrophy of neurons in layers 1, 4 and 6, whereas the right showed atrophy of neurons in layers 2, 3 and 5. Note the bands of preserved large cells alternating with the bands containing severely shrunken neurons, making them nearly invisible at low magnification (Figure 1.1d). The atrophic neurons (lower left) are readily seen at higher magnification (Figure 1.1e) and contrast with the adjacent normal neurons from preserved layers (upper left).

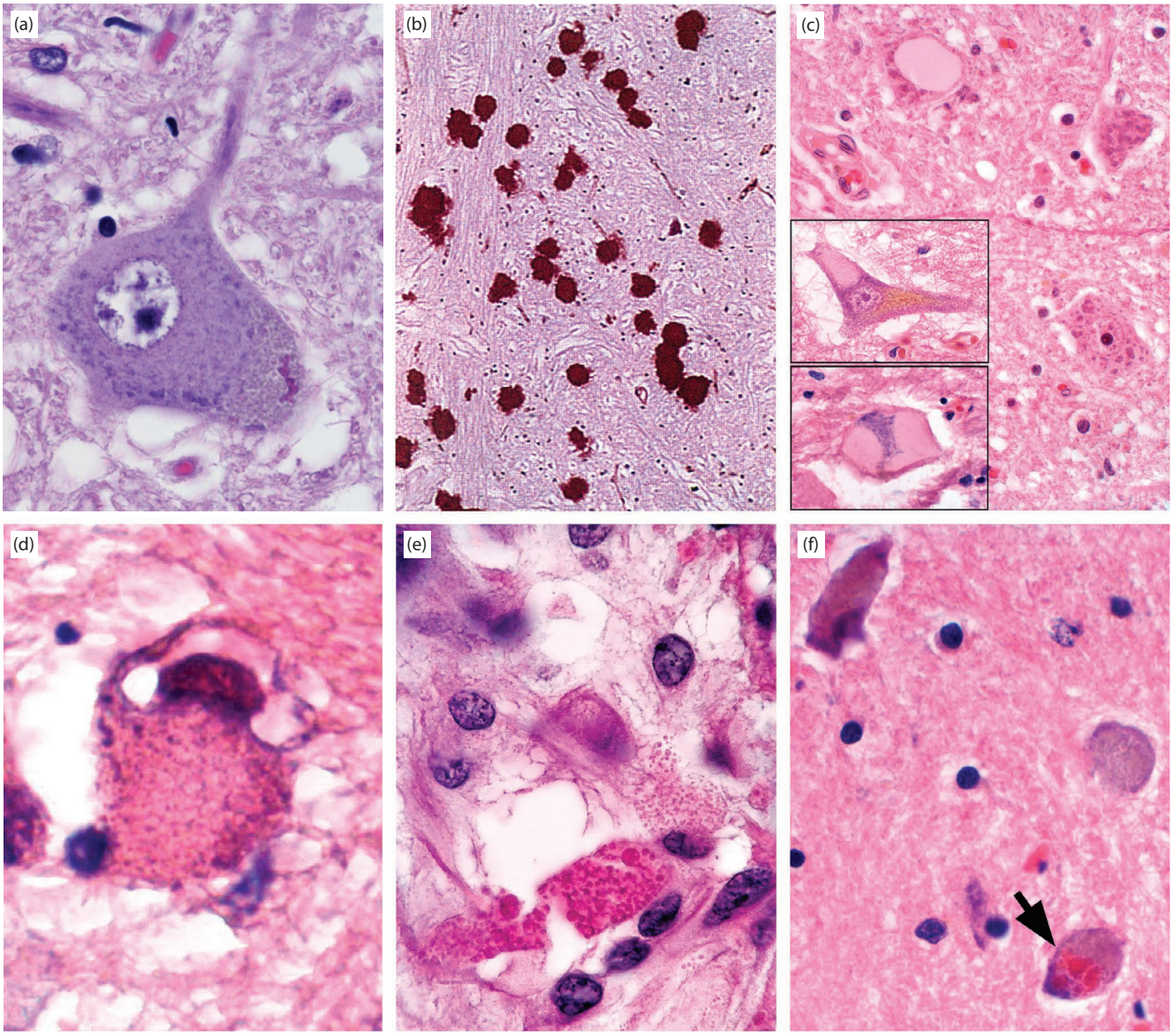
A special variant of trans-synaptic neuronal degeneration occurs when axons emanating from the inferior olivary nucleus (ION) are disrupted and their synaptic connections lost, or input to the ION is interrupted. Lesions in the ipsilateral central tegmental tract or the contralateral dentate nucleus result in unilateral olivary hypertrophy. In these instances, the neurons individually enlarge to the degree that they collectively produce hypertrophy of the entire nucleus, visible grossly or at low magnification (Figure 1.1f), and even on high resolution neuroimaging studies carried out while a patient is alive. The illustrated example originates from a man with multiple small cavitary



1.1 (*Continued*) Neuronal abnormalities in diseases of the CNS. (f) Bilateral olivary hypertrophy; this change on any given side is due to disruption of the ipsilateral tegmental tract or contralateral dentate nucleus. Note the area of remote infarction (arrow) in the medulla. Nissl stain. **(g)** Vacuolation/fenestration of neurons in inferior olivary nucleus in the example seen in panel **(f)**. **(h)** Neuronal storage diseases cause accumulation of abnormal cytoplasmic material, evidenced by cytoplasmic bloating. Tay–Sach's disease illustrated. **(i)** Neuronal alterations in some storage disorders manifest as fine vacuolation in the cytoplasm. Hunter's disease illustrated. **(j)** Neuronal enlargement and calcification of blood vessels may occur after cranial irradiation; the latter change is much more common than the former. **(k)** Rare pituitary adenomas (lower part of photomicrograph) manifest neuronal metaplasia (upper part), the so-called mixed pituitary adenoma-gangliocytoma.

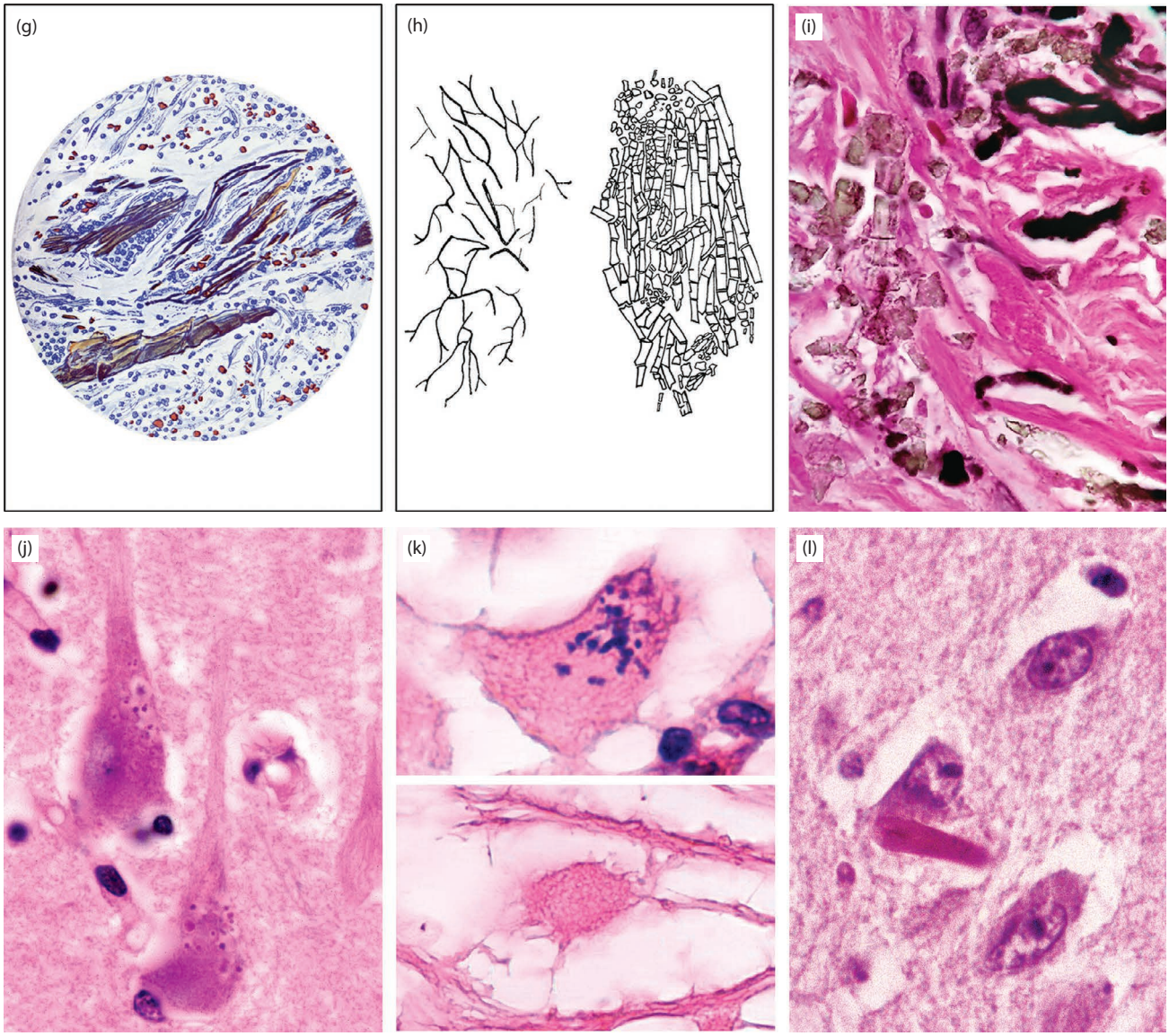
remote infarcts that were present in the medulla (arrow) and elsewhere in the brain stem and cerebellum and that disrupted these tracts on both sides. Note the bilateral inferior olivary nuclear enlargement (Figure 1.1f). Microscopically, neurons showed characteristic vacuolation ('fenestration') and enlargement, accompanied by considerable astrocytosis (Figure 1.1g). The reason for this special microscopic response to trans-synaptic degeneration in the inferior olivary nucleus is unknown but involves fragmentation within the Golgi apparatus and trans-Golgi network[234] and redistribution of presynaptic vesicles, as manifested by an altered pattern of synaptophysin immunoreactivity.[116]

Less common reactions of neurons to injury include the accumulation of abnormal cytoplasmic storage material, such as in inherited, autosomal recessive storage disease disorders seen in childhood (see Chapter 6, Lysosomal Diseases). Two illustrated examples depict the neuronal changes seen in Tay–Sachs disease (Figure 1.1h) and Hunter's disease (Figure 1.1i). Neuronal enlargement and gigantism may occur in the brain tissue adjacent to a tumour after cranial radiation therapy for a nearby neoplasm, and may be accompanied by other manifestations of tissue injury such as calcification (Figure 1.1j). Unlike many epithelial cell types, neurons rarely undergo metaplasia. In rare pituitary adenomas, most often of growth hormone-secreting type, adenoma cells (Figure 1.1k, lower portion) transform focally into neurons (Figure 1.1k, top);[81] these cells, phenotypically identical to other neurons, may also express small amounts of pituitary hormones.



1.2 Inclusion bodies and abnormal deposits I. (a) Bunina body in anterior horn cell in a patient with amyotrophic lateral sclerosis (motor neuron disease). The significance of these structures is discussed in detail elsewhere. **(b)** Buscaino bodies (mucocytes, metachromatic bodies) in white matter can occur secondary to poor tissue fixation and post-mortem degeneration of myelin. On H&E staining, these are barely visible as pale blue bodies or almost clear vacuoles; the periodic acid–Schiff stain, used here, demonstrates these bodies strikingly. **(c)** Colloid bodies (hyaline inclusions) are pale eosinophilic areas within the cytoplasm of neurons and correspond on electron microscopy to dilated cisternae of endoplasmic reticulum. Although usually seen in the hypoglossal nucleus (large picture), they may also be found in the anterior horn cells of the spinal cord (top inset) and very rarely in other neurons, such as the nuclei of Clarke's column (bottom inset, lowest left). They are of no known pathological significance and should not be mistaken for pathological accumulations of proteins or chromatolytic change. **(d)** Cowdry A inclusion bodies are seen in herpetic viral infections of the nervous system (herpes simplex type I and II, cytomegalovirus infection, and varicella-zoster virus infection but not infections with Epstein–Barr virus). On electron microscopy, it can be appreciated that they are due to accumulations of virions within the nucleus of the host cell. Note the clearing of the host cell nuclear chromatin centrally, with margination of chromatin at the edge of the nuclear membrane and the 'owl's eye' appearance of the viral inclusion. In this case of cytomegalovirus infection, the cell cytoplasm is also enlarged (cytomegaly) and distended by viral particles. **(e)** Eosinophilic granular bodies (EGBs) are dot-like, refractile, proteinaceous deposits most commonly encountered in the background neuropil in or adjacent to certain types of low grade brain tumours, as here in a pleomorphic xanthoastrocytoma. They can be further highlighted by periodic acid–Schiff staining. **(f)** Eosinophilic crystalline inclusions can occasionally be seen in the cytoplasm of neurons of the inferior olivary nucleus, especially in aged individuals and are of no known pathological significance.

Although necrosis is the type of neuronal cell death that predominates in acute energy-deprivation states, neuronal apoptosis plays a critical role during embryonic development. Apoptosis or programmed cell death refers to a controlled, coordinated biochemical process leading to the death of affected cells and is a physiological part of normal development. In a wide variety of disparate organisms, apoptosis involves the triggering of a series of biochemical events in which caspases (cysteine aspartases) play a key role.[170] Although the morphological manifestations of apoptosis



1.2 (*Continued*) Inclusion bodies and abnormal deposits I. (g) Gamna–Gandy bodies are foci containing linear, bamboo-like fibrous tissue and collagen fibres encrusted with iron pigments and calcium salts. They were originally described in the spleen in patients with congestive splenomegaly but can be seen around cavernous angiomas, cholesterol granulomas of temporal bone, pituitary adenomas, and a variety of other highly vascular primary and metastatic neoplasms and cysts in the nervous system that are subject to recurrent bouts of haemorrhage. However, when first described in the 1920s, the authors had to go to great lengths to exclude a fungal causation for these structures, which are illustrated in a colour drawing from a 1922 article. **(h)** Gamna–Gandy bodies, illustrated in black and white drawings of from a 1929 article by Hu *et al*.;[102] these authors showed that there was no morphological identity between the wavy encrusted fibres (left) or waxy septate, bamboo-like fibres (right) and true fungal mycelia. **(i)** Gamna–Gandy bodies in tissue from a region of recurrent brain haemorrhage. **(j)** Granulovacuolar degeneration (of Simchowicz, granulovacuolar bodies, GVBs) appear as tiny dots within clear vacuoles that can be seen particularly in the cytoplasm of pyramidal neurons of the hippocampal gyrus in normal ageing and, to a greater extent, in patients with Alzheimer's disease. These structures contain abnormal accumulations of several proteins including tubulin, neurofilament proteins and tau. **(k)** Granular mitoses (top) are clusters of chromatin often encountered in cells in highly mitotically active tissues. Although usually found, and illustrated, in the context of acute demyelinating lesions, this example comes from a case of cytomegalovirus ventriculitis and should not be mistaken for a micro-organism. Herring bodies (bottom) are spherical or ovoid eosinophilic structures with an apparent surrounding membrane that are normal findings in the posterior pituitary gland (neurohypophysis). They represent normal storage sites within axons for oxytocin and vasopressin. **(l)** Hirano bodies are elongate (when longitudinally sectioned) to oval (in cross-section), brightly eosinophilic neuronal inclusions that are encountered in pyramidal neurons of the hippocampal gyrus in normal ageing, and, to a greater extent, in patients with neurodegenerative diseases such as Alzheimer's disease. Although they often seem to be extraneuronal, by electron microscopy Hirano bodies can be seen to lie within the neuronal soma or cell processes. They are composed of actin and α-actinin.

(b) Reproduced with permission from Graeber MB, Blakemore WF, Kreutzberg GW. Cellular pathology of the central nervous system. In: Graham DI, Lantos PL (eds). Greenfield's Neuropathology, 7th edn. London: Arnold, 2002, pp. 123–192.
(h–j) From Kleinschmidt-Demasters, BK. Gamna–Gandy bodies in surgical neuropathology specimens: observations and a historical note. Journal of Neuropathology and Experimental Neurology 2004;63:106–12. Reproduced with permission from the Journal of Neuropathology and Experimental Neurology.

are classically described as 'cell shrinkage, membrane blebbing and nuclear DNA condensation and fragmentation',[146] these may not be seen in non-vertebrate systems.[216]

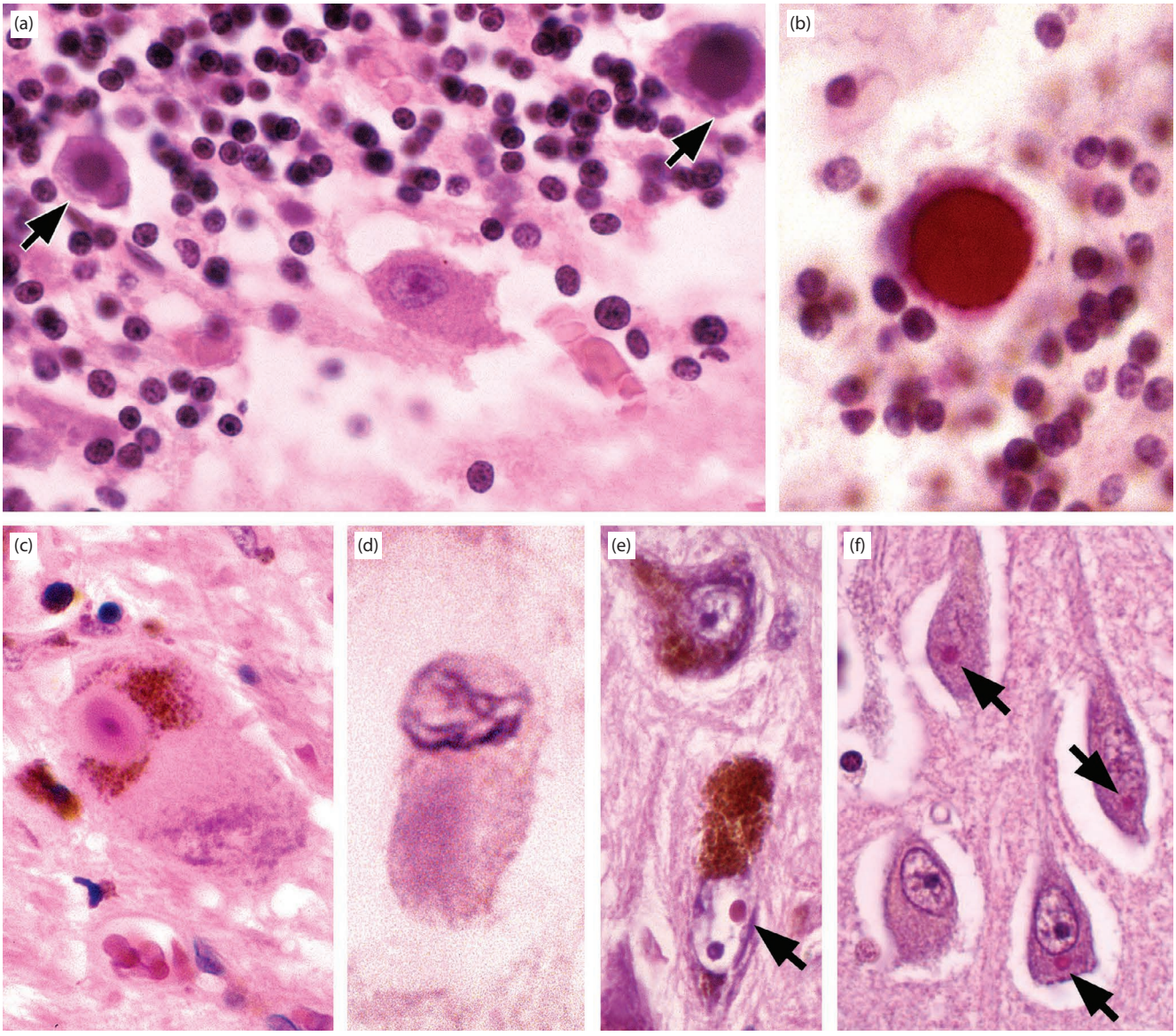
Neuronal apoptosis also occurs in pathological disease states and involves similar 'execution systems' and proteins.[170] At least 14 different mammalian caspases have been identified thus far, but these may have both death-related and death-unrelated functions in the cell.[170] Neuronal necrosis and apoptosis are not always mutually exclusive processes and the co-existence of both has been emphasized in some pathological conditions.[136] For instance, a shift from apoptotic to necrotic types of neuronal death may occur when energy levels are rapidly compromised.[136] The practical aspect of identifying a role for neuronal apoptosis in a disease process lies in the fact that small peptide caspase inhibitors have been developed and may have therapeutic utility. Caspase inhibitors may be useful in preserving sublethally injured neurons at the perimeter (penumbra) of an acute infarct that might be less severely affected by excitotoxic-ischaemic injury than is the necrotic core of the infarct.[170] They may also act to protect against the deleterious effects of oxygen radicals, cytokines and lipid peroxidation products that are generated in the necrotic core of the infarct and seep out to the penumbra.[139,146] Among human diseases, especially prominent neuronal apoptosis is seen in the (rare) perinatal disorder, pontosubicular necrosis. In neurodegenerative diseases, apoptosis may play differing roles at different time points during the disorder, explaining why caspase inhibitors may not be universally effective therapies. In addition, apoptosis can occur without involvement of the caspase system.[24] A further consideration is whether or not the preservation of neurons that would otherwise undergo apoptosis is desirable in neurodegenerative disorders such as Huntington's disease or Alzheimer's disease, especially if the preserved cells have aberrant function.[170] A role for neuronal apoptosis has been implicated in numerous disorders other than ischaemia and neurodegenerative disease; these include spinal cord trauma, head injury[194] and viral nervous system infections.[51] This complex topic has been the subject of several excellent reviews (e.g. Schulz and Nicotera,[215] Nicotera *et al.*,[170] Robertson *et al.*,[194] Paulson,[180] Mattson[146]).

Although individual cellular organelles in neurons are not distinguishable under normal, resting conditions on light microscopy using routine stains, in ageing or in disease processes, massive accumulations of some organelles can be discerned. These processes result in the development of 'inclusion bodies'.[27,76,77] Some of these have limited pathogenic implications (colloid bodies, Marinesco bodies), although others are almost exclusively seen in specific disease conditions (Lafora bodies). Yet more are seen in small numbers in 'normal' ageing but in significantly greater numbers in specific neurodegenerative disorders (neurofibrillary tangles, granulovacuolar degeneration/bodies, Pick bodies). Still other 'bodies' occur in the background tissues but are discussed here with neuronal inclusion bodies because their exact intracellular (Hirano bodies, Figure 1.2l) or extracellular (Gamna–Gandy bodies, Figure 1.2g,h) location may not be apparent in H&E-stained sections. A pictorial, alphabetically arranged chronology of these 'bodies' – most of which develop in neurons – is depicted in Figures 1.2 and 1.3. Most of these are fully identifiable on H&E staining, including Bunina bodies, colloid bodies (Figure 1.2c), granulovacuolar bodies (Figure 1.2j), Lewy bodies (Figure 1.3c and d), neuroaxonal swellings, neurofibrillary tangles, Pick bodies (Figure 1.3j, insert) and Lafora bodies (Figure 1.3a). Special silver histochemical and immunohistochemical staining, however, can further delineate these normal and abnormal accumulations. Modified Bielschowsky or Bodian histochemical silver stains generically identify neurofilament-containing inclusions or structures in various diseases, such as globose or flame-shaped neurofibrillary tangles (Figure 1.3h,j), Pick bodies (Figure 1.3j) and neuroaxonal swellings, also known as 'spheroids' (Figure 1.3g). Identification of inclusions specific for certain neurodegenerative disorders can be achieved with immunohistochemical methods that identify tau (including its isoforms), ubiquitin, huntingtin or α-synuclein. It is an unresolved issue as to whether neuronal inclusions play a role in direct neuronal injury or represent a mechanism by which neurons protect themselves by sequestering abnormal proteins (reviewed by Paulson[180]).

Neurons are post-mitotic, fully differentiated cells that have little or no capacity to regenerate effectively and reconstitute functions lost when the cell is lost. Neuronal plasticity plays an important role in development and early childhood in overcoming major areas of brain tissue damage but this ability is lost in the adult brain, in which neurons cannot be innately regrown or replaced, even by the small numbers of neural stem cells that are known to be present (discussed later).

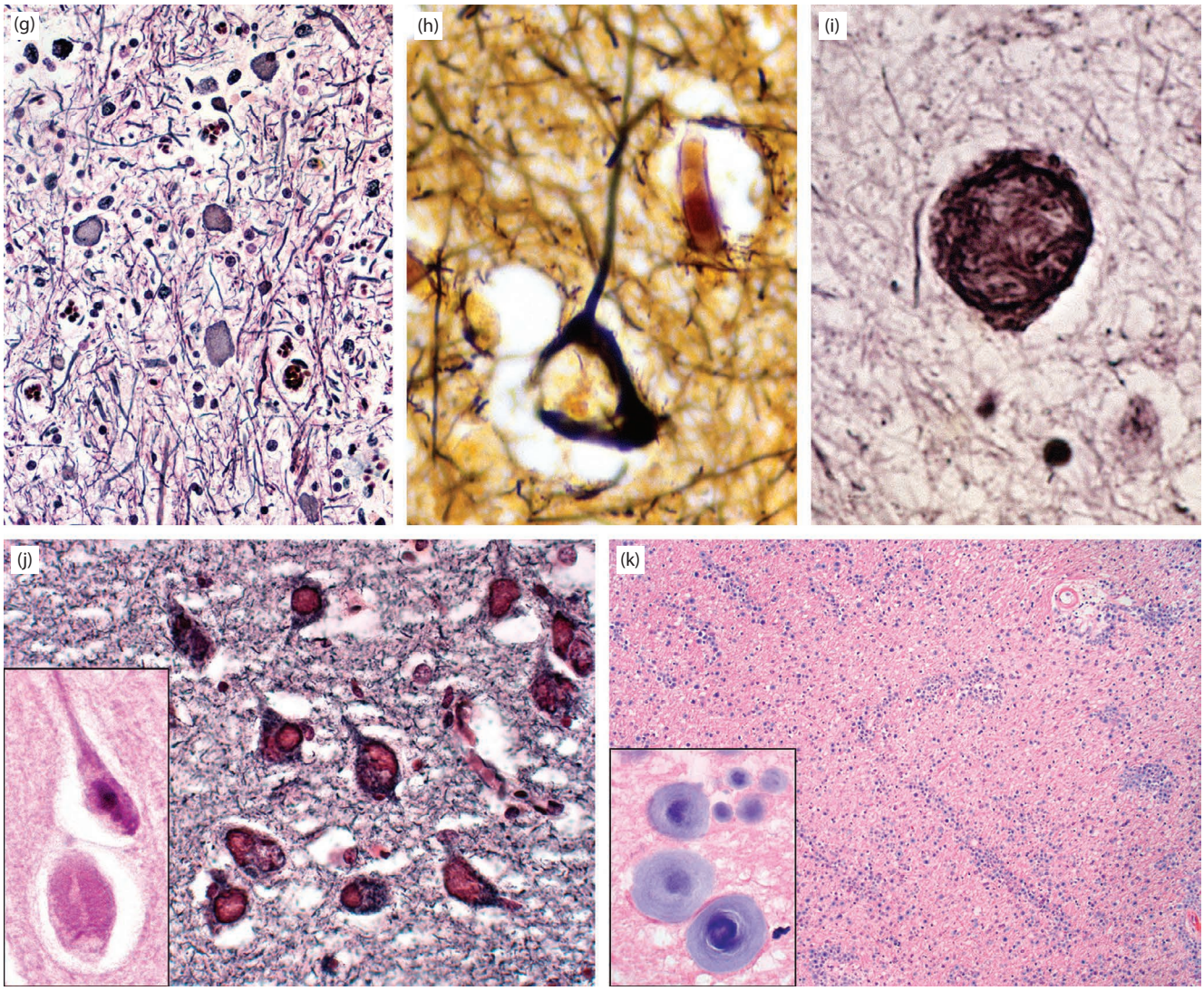
ASTROCYTES

Astrocytes are, together with oligodendrocytes/oligodendroglia, the two cell types in the nervous system often described as macroglia, to distinguish them from microglia (see later). These specialized glial cells outnumber neurons by over five-fold.[226] Generally considered to be, in part, the CNS counterpart of fibroblasts, with a significant role in producing scar tissue (described as 'astrocytic gliosis', 'astrogliosis' or simply 'gliosis') within the brain or spinal cord, astrocytes are now known to have myriad physiological and biochemical functions in both brain development and maintenance of homeostasis (especially with respect to the make-up of the interstitial fluid of the brain) and may even contribute to regeneration and repair after brain/spinal cord injury.[255] Many of these properties will be described in detail later. Based upon recent discoveries in molecular neurobiology, the function(s) of astrocytes within normal brain and their relationship to neurons are being so radically redefined that even the nomenclature defining these cells (in relation to neurons) has been called into question. Changes from astroglial to neuronal phenotype (in select cell populations) are now well documented, although brain parenchyma in some lesions (e.g. malformations of cortical development associated with epilepsy) contains cells that have features of both a neuronal and astrocytic phenotype.[254] As one expert in the field



1.3 Inclusion bodies and abnormal deposits II. (a,b) Lafora bodies are basophilic inclusions that are composed of polyglucosans and occur in Lafora's disease, a neurodegenerative storage disease of children. These inclusions occur in many different types of cell and tissue, including neurons, choroid plexus, sweat glands, peripheral nerves, cardiac and striated muscle, and liver and skin. They closely resemble corpora amylacea and, like corpora amylacea, stain intensely with periodic acid–Schiff, but are usually surrounded by a corona of radiating filaments or spicules and are not restricted to the sites of predilection for corpora amylacea. In addition, corpora amylacea are infrequent in children. These figures illustrate Lafora bodies in the cerebellum. **(c)** Lewy bodies (brain stem type) are intracyoplasmic inclusions that represent abnormal proteinaceous accumulations consisting predominantly of α-synuclein. Like many proteinaceous deposits, they are readily visualized in H&E-stained sections. They are easiest to identify in pigmented neurons, such as this one from the substantia nigra compacta, where they displace the normal intracytoplasmic, brown neuromelanin pigment. Note the targetoid appearance; however, most are not so eye-catching. Lewy bodies can be encountered in the substantia nigra compacta and especially in the locus coeruleus in normal ageing, but even in this instance may represent preclinical disease. They are more numerous and more widely distributed in patients with idiopathic Parkinson's disease and related disorders. **(d)** Lewy bodies (intracortical type), when located in small neurons of the cerebral cortex, are far less well-defined in H&E-stained sections but can be highlighted by immunostaining for α-synuclein or ubiquitin. Cortical Lewy bodies are usually associated with disease, not normal ageing. **(e)** Marinesco bodies, sometimes referred to as 'maraschino cherry bodies' by residents trying to remember the names of all of the various bodies for board examinations, are intranuclear eosinophilic bodies (arrow), about the same size as the nucleolus. They are largely confined to the pigmented, neuromelanin-containing neurons of the substantia nigra compacta and are usually found in aged individuals. They are proteinaceous inclusions of no known pathological significance, but are very similar to the intranuclear bodies seen in large numbers of neurons in patients with the childhood degenerative disorder, neuronal intranuclear inclusion disease. **(f)** Negri bodies are a pathognomonic finding in rabies viral infection (rabies viral encephalitis) of the central nervous system. These well-circumscribed intracytoplasmic, red cell-like bodies are easily overlooked, particularly when the virus fails to elicit an inflammatory host reaction.

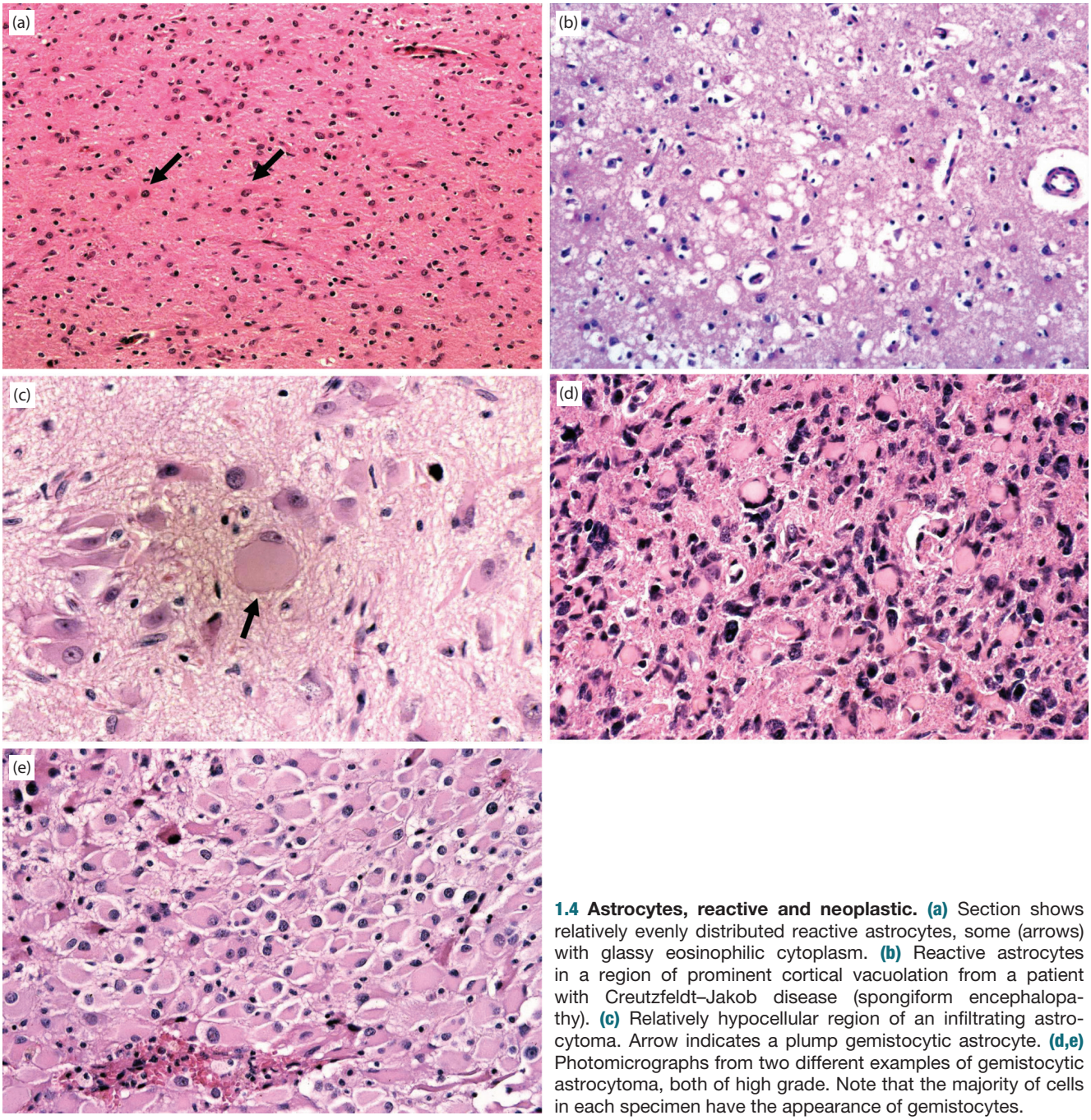
Continued



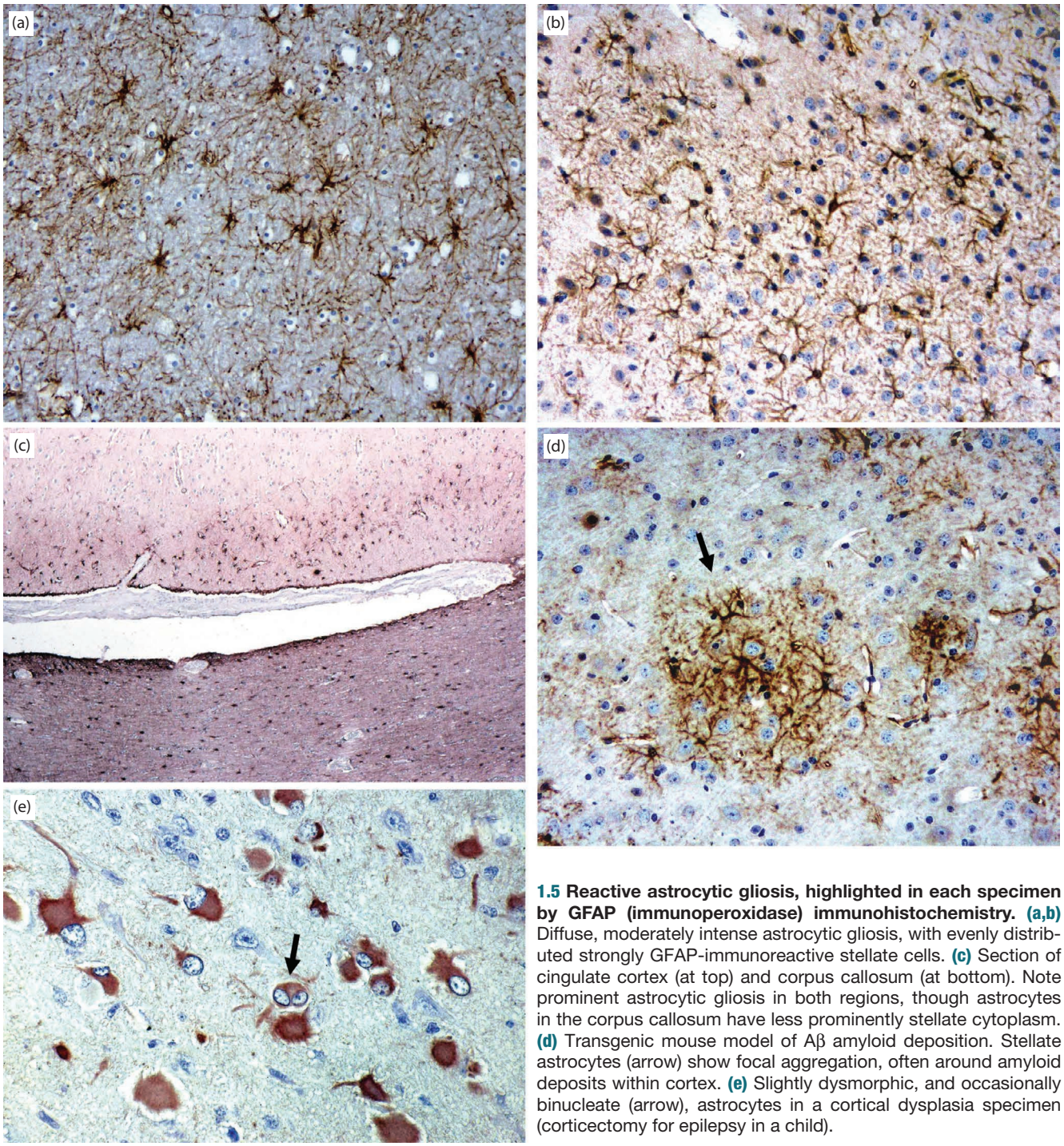
1.3 (*Continued*) Inclusion bodies and abnormal deposits II. (g) Neuroaxonal swellings (spheroids) are round or ovoid structures formed when transportation of intra-axonal neurofilaments is disrupted by axonal injury or transection. Although also discernible in sections stained with H&E they are better highlighted with silver stains, as here. They are illustrated here in the anterior horn of a patient with short-duration amyotrophic lateral sclerosis. **(h)** Neurofibrillary tangles (flame-shaped) are easily recognized by even novice pathologists by their flame-shaped profiles, demonstrated best with silver stains. The classical shape usually illustrated in textbooks is the one seen here in a pyramidal neuron of the cerebral cortex, and the intracytoplasmic location of the tangle, which loops around the (unstained) nucleus, is easily appreciated. Scattered tangles may be encountered in pyramidal neurons of the hippocampal gyrus in normal ageing, but they are seen in greater numbers and in a wider neocortical and brain stem distribution in patients with neurodegenerative diseases such as Alzheimer's disease. **(i)** Neurofibrillary tangles (globose) contain skein-like tangles of abnormal, hyperphosphorylated tau protein and may be seen in brain stem neurons in Alzheimer's disease or in progressive supranuclear palsy; the latter disease is illustrated here. The shape of the tangle is predicated on the shape of the neuronal cell body in which it resides. The coarse internal structure of the globose tangle distinguishes it from argentophilic Pick bodies seen in **(j)**. Pick body-like structure associated with neurodegenerative disease. Bodian silver stain. **(j)** Pick bodies are intracytoplasmic bodies found in the pyramidal neurons of the hippocampal gyrus, the granule cell neurons of the dentate gyrus, smaller cortical neurons especially in layer 2, and in brain stem neurons of patients with Pick's disease, a neurodegenerative disease associated with lobar atrophy of the frontal and temporal lobes. They have a relatively homogeneous appearance on both H&E (inset) and silver staining, in contrast to globose neurofibrillary tangles, but sometimes a degree of overlap exists. Unlike neurofibrillary tangles, Hirano bodies or granulovacuolar bodies (degeneration), Pick bodies are almost never encountered in normal aged individuals. **(k)** Polyglucosan bodies are histologically indistinguishable from the corpora amylacea but occur in very large numbers in individuals affected by adult polyglucosan body disease,[23] illustrated here in a section of white matter from a middle-aged patient with this disorder. The variably blue-grey bodies may have a concentric, targetoid appearance (inset). Corpora amylacea are a normal finding in aged individuals, but not in so great a number, and are usually more concentrated in (but not confined to) subpial, subependymal and perivascular locations and the spinal cord. In polyglucosan body disease, heart, skeletal muscle, liver, and dermal sweat glands in addition to peripheral nerves and brain may contain these bodies. They are composed largely of sulphated polysaccharides (polyglucosans) and stain deeply with haematoxylin, periodic acid–Schiff and methyl violet. By electron microscopy, polyglucosan bodies in the nervous system are seen to consist of densely packed 6–7 nm filaments that are not bounded by a unit membrane and lie within astrocytic processes, within axons and few within the neuropil, but not within the neuronal soma.

has boldly and bluntly stated, '… virtually every aspect of brain development and function involves a neuron–glial partnership. It is no longer tenable to consider glia as passive support cells'.[17]

By morphological criteria, astrocytes have been subclassified as protoplasmic (found mainly within the grey matter) or fibrous/fibrillary (located predominantly within the subcortical white matter).[226] The phenotype of astrocytes is defined by the location within their cytoplasm of the intermediate filament protein, glial fibrillary acidic protein (GFAP).[60,64,255] Though not all astrocytes express GFAP that is immunohistochemically detectable within the cytoplasm by light microscopy (and some non-CNS cells do), the presence of this protein essentially remains, in daily diagnostic work, a defining feature of the cell type. GFAP is especially abundant within the cytoplasm of reactive or hypertrophic (and often neoplastic) astrocytes, though unfortunately the extent and robustness of GFAP immunoreactivity do not correlate well with the specific type or duration of CNS insult to which the astrocytes have reacted (Figures 1.4 and 1.5). GFAP immunohistochemistry has become the standard way to assess astrocytic gliosis (both qualitatively and quantitatively) in both animal studies and human CNS disease tissue examined at biopsy or autopsy. It has superseded older classic cytochemical stains such as the Holzer and phosphotungstic acid haematoxylin



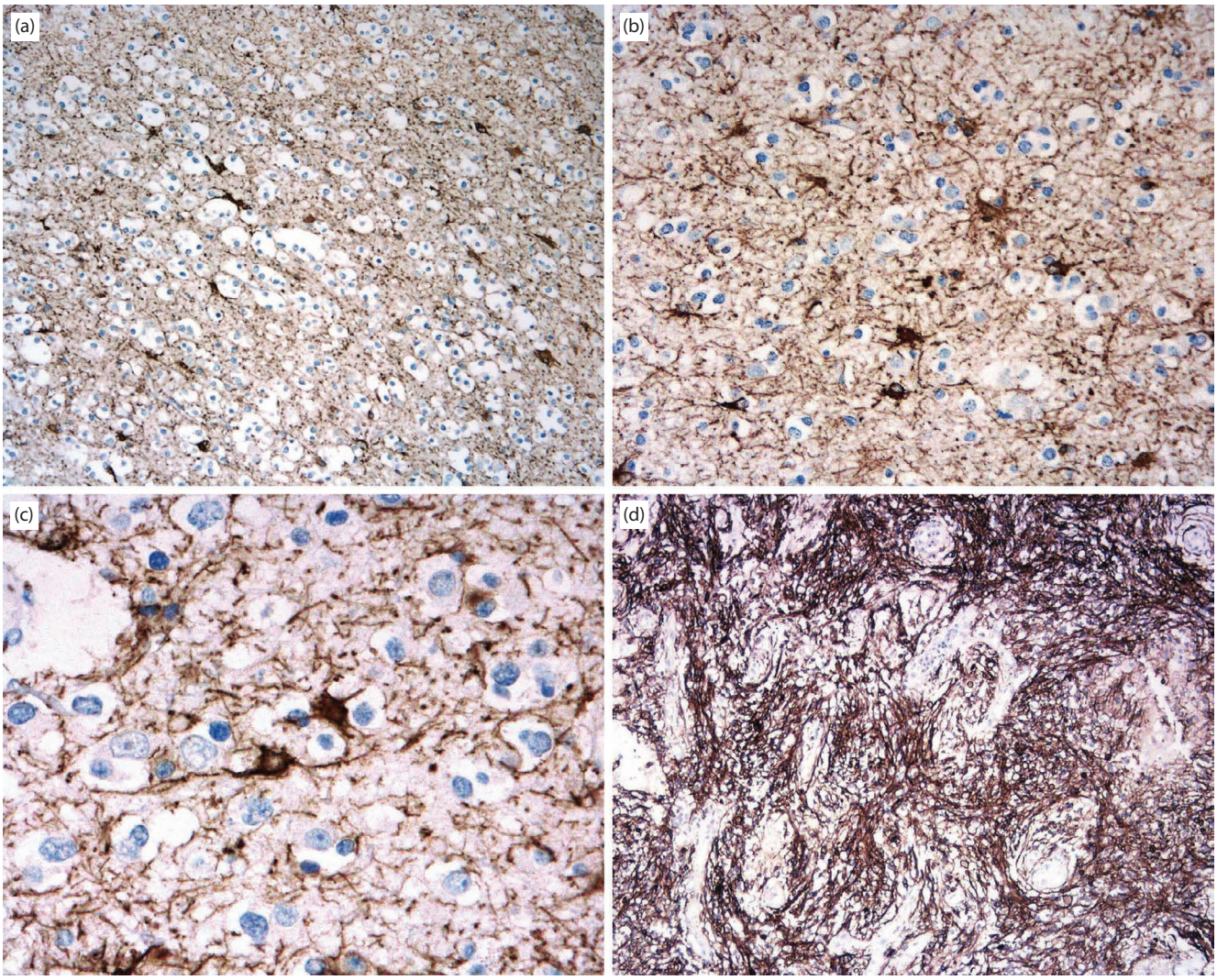
1.4 Astrocytes, reactive and neoplastic. (a) Section shows relatively evenly distributed reactive astrocytes, some (arrows) with glassy eosinophilic cytoplasm. **(b)** Reactive astrocytes in a region of prominent cortical vacuolation from a patient with Creutzfeldt–Jakob disease (spongiform encephalopathy). **(c)** Relatively hypocellular region of an infiltrating astrocytoma. Arrow indicates a plump gemistocytic astrocyte. **(d,e)** Photomicrographs from two different examples of gemistocytic astrocytoma, both of high grade. Note that the majority of cells in each specimen have the appearance of gemistocytes.



1.5 Reactive astrocytic gliosis, highlighted in each specimen by GFAP (immunoperoxidase) immunohistochemistry. (a,b) Diffuse, moderately intense astrocytic gliosis, with evenly distributed strongly GFAP-immunoreactive stellate cells. **(c)** Section of cingulate cortex (at top) and corpus callosum (at bottom). Note prominent astrocytic gliosis in both regions, though astrocytes in the corpus callosum have less prominently stellate cytoplasm. **(d)** Transgenic mouse model of Aβ amyloid deposition. Stellate astrocytes (arrow) show focal aggregation, often around amyloid deposits within cortex. **(e)** Slightly dysmorphic, and occasionally binucleate (arrow), astrocytes in a cortical dysplasia specimen (corticectomy for epilepsy in a child).

(PTAH) techniques, although the latter stains retain value in some settings. Vimentin and S100β are also prominent components of the astrocytic cytoplasm, though vimentin immunoreactivity in astroglial cells lacks specificity, as this epitope is expressed in many non-glial cell types. By electron microscopy, astrocytes contain abundant intermediate filaments, cytoplasmic dense bodies, gap junctions and multiple cellular processes.[64,255] Astrocytes may also express a variety of growth factor receptors, including those for epidermal growth factor and basic fibroblast growth factor.[60,93]

Prominent cytoplasmic GFAP immunoreactivity also characterizes neoplastic astrocytes within astrocytomas, especially gemistocytic astrocytomas, and other types of tumour-related astrocytes, e.g. the mini-gemistocytes commonly found in oligodendrogliomas (Figure 1.6) (see Chapter 26, Introduction to Tumours). The term 'gemistocyte/gemistocytic' used to describe an astrocyte does not, however, classify it as being malignant or reactive–gemistocytes are also common in brain tissue surrounding infarcts, vascular malformations, traumatic lesions, cerebritis/encephalitis and metastatic neoplasms, as well as in numerous other

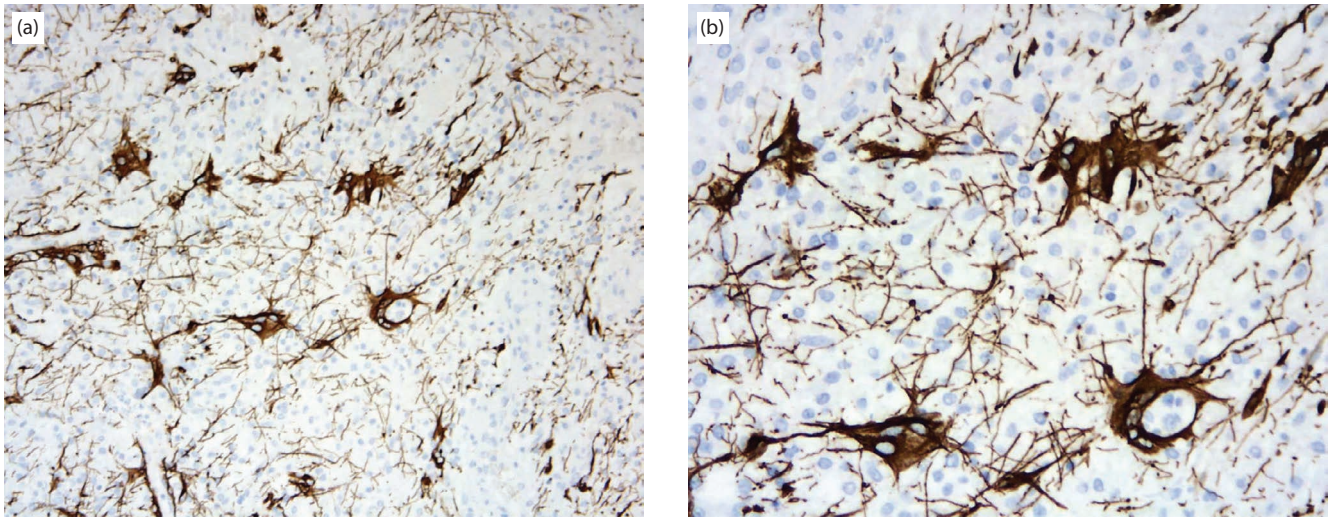


1.6 (a–c) A predominantly oligodendroglial neoplasm (oligodendroglioma; micrographs are at various magnifications) contains numerous GFAP-immunoreactive astrocytic cells, including mini-gemistocytes. Note the different morphology of tumour cells (round, regular nuclei with clear cytoplasm) and the more characteristically stellate appearance of the astrocytic element. By contrast, note the widespread GFAP-immunoreactivity of tumour cells and their processes **(d)** in a predominantly astrocytic tumour (astrocytoma).

reactive settings. GFAP immunoreactive cells may even be encountered within the interstices of a metastatic neoplasm (Figure 1.7), leading to diagnostic difficulty in distinguishing an anaplastic primary glioma from a poorly differentiated metastasis.

The recent discovery of mutations in the active site of isocitrate dehydrogenase (IDH1) gene in >70 per cent of intermediate-grade diffuse gliomas, i.e. diffuse astrocytomas grade II, oligodendrogliomas grade II, mixed oligoastrocytomas grade II and anaplastic variants grade III,[15] and the finding that a high-fidelity antibody correlates well with a specific mutational (R132H) status[33,34] have provided the pathologist with a truly tumour-specific glial marker that can be used in daily diagnostic practice. Capper *et al.* demonstrated that the antibody can be used to distinguish diffuse glioma from non-neoplastic reactive gliosis associated with metastases, vascular malformations, abscesses, progressive multifocal leukoencephalopathy, and ischaemic or haemorrhagic lesions (Figure 1.8).[35] In addition, they showed that the IDH1 antibody was superior to p53 or Wilms Tumor 1 (WT1) antibodies in identifying neoplastic glial cells.[35]

Astrogliosis is sometimes subclassified (on purely morphologic grounds) as being isomorphic (when astrocytes arrange themselves along an anatomical structure such as a tract, e.g. the corticospinal tract, in association with wallerian degeneration) or anisomorphic (cells arranged more haphazardly, as at the edges of an infarct or cerebritis/abscess; see Figure 1.9).[64] Brisk reactive astrocytic gliosis can also be associated with the proliferation of Rosenthal fibres, which represent protein aggregates in astrocytic processes that also contain ubiquitin, αB-crystallin and heat shock protein HSP27 (Figure 1.10). Dominant missense mutations in the human GFAP gene are associated with a leukodystrophy (Alexander's disease) characterized by overwhelming proliferation of Rosenthal fibres within the diseased white matter.[137,159,245] The GFAP gene on chromosome 17 includes four α-helical segments within the central rod domain, joined by non-helical linkers. Of interest, GFAP-null mice show relatively subtle neuropathological abnormalities, although animals that overexpress GFAP 10–15-fold manifest a fatal encephalopathy associated with prominent astrocytic swelling.[159]



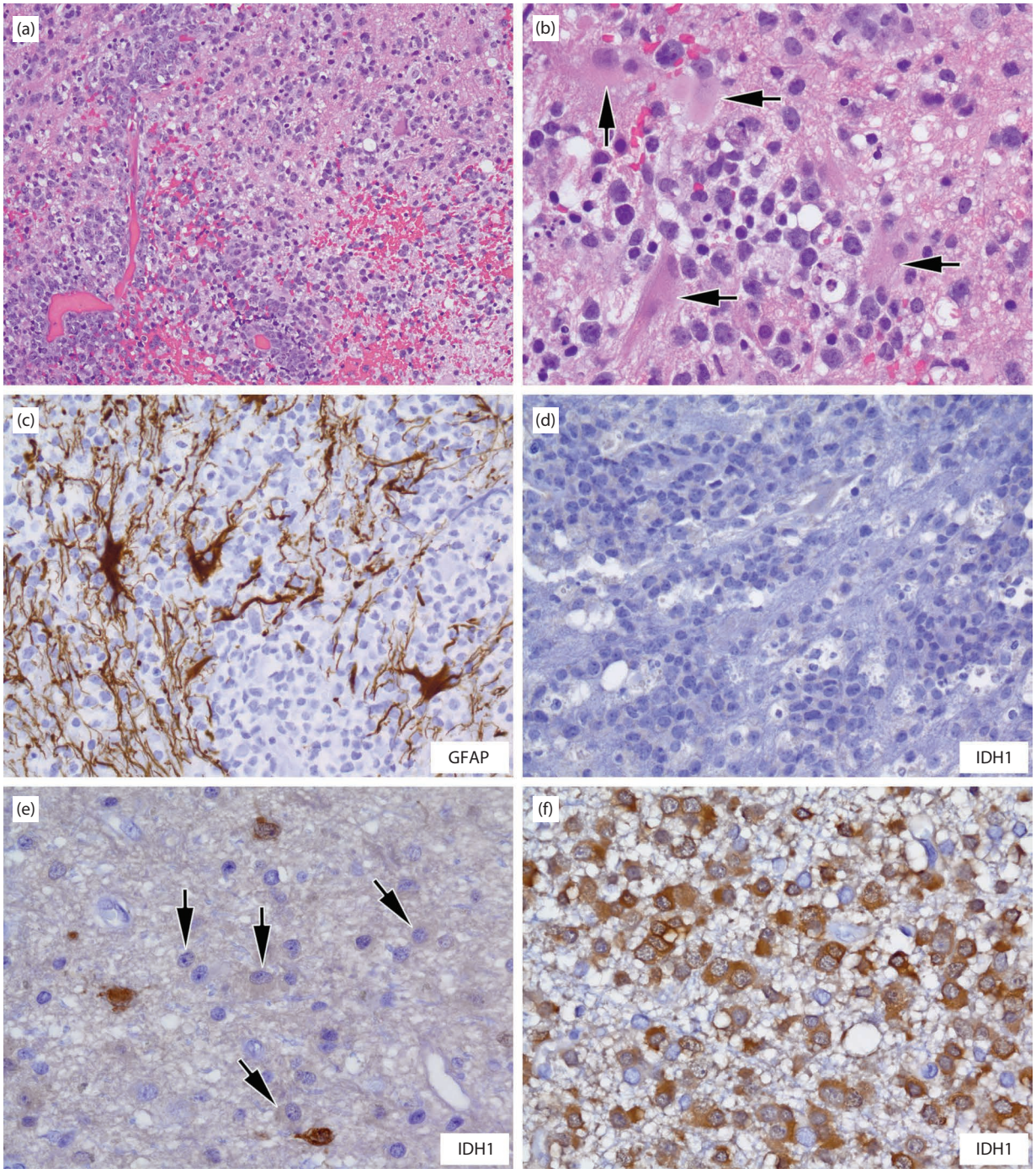
1.7 Both panels show GFAP-immunoreactive reactive astrocytes in an atypical teratoid rhabdoid tumour (AT/RT). Note ramified processes of the reactive astrocytes throughout the tumour.

Role of Astrocytes in CNS Development and Regeneration

Experimental evidence now suggests remarkable plasticity and regenerative potential for at least some populations of astrocytes and astrocyte precursors, a view that would have been somewhat heretical as recently as 20–30 years ago.[58] Since the late 1800s, radial glia have been recognized as key players in brain development. Their elongated fibres span the full width of the developing cerebral wall in most mammals. In the cerebellum, radial glia extend from the pia to the Purkinje cell layer, and are quite regularly and evenly spaced in the molecular layer (Figure 1.11). These cells, at least in the cerebrum, retain the capacity to divide. An increasingly complex understanding of their role in CNS development has coincided with more sophisticated ways to study this unique cell type.[187] In the late stages of cortical development, radial glia appear to divide asymmetrically in the ventricular zone to generate (more) radial glia and intermediate progenitor (IP) cells. IP cells then divide symmetrically in the subventricular zone to give rise to multiple neurons.[144] During development of the brain, radial glia (which provide the 'guidewires' by which neuroblasts in the germinal matrix find their way to the cerebral cortex) are thought to give rise to astrocytes.[211,257] Adult astrocytes may revert to their radial glial phenotype (in tissue culture) when exposed to embryonic brain extracts.[103] However, it is now clear that they can themselves also function as neural progenitor cells.[84] The molecular developmental and neurobiological events in this process are extraordinarily complex, and are well reviewed elsewhere.[8,89,129,158,162,226,241] Astrocytes, in addition to giving rise to new neurons in the adult hippocampus,[218] are now recognized as a major component of 'neurogenic niches', which have the potential to generate neuroepithelial cells from the subventricular zone during early brain development and possibly also at later time point.[8] Increased generation of neuronal progenitor cells after ischaemic stroke has even been demonstrated in human autopsy brain specimens originating from quite elderly individuals.[143] Astrocytes secrete molecules that may support neurogenesis (fibroblast growth factor/FGF, insulin-like growth factor-1, glutamate, etc.) or inhibit it (astrocyte-derived bone morphogenetic protein).

In the developing mammalian brain, the subventricular zone (SVZ), a germinal region of the brain, contains abundant astrocytes and astrocyte precursors, together with migrating neuroblasts, undifferentiated immature precursors and ependymal elements. In experimental animals, it has been shown that SVZ astrocytes can divide to generate neuroblasts and immature neuronal precursors, and that such astrocytes placed into tissue culture can grow into multipotent neurospheres.[58] Many astrocytes may have a latent neurogenic potential that is suppressed by various inhibitory signals, or expressed only in certain well-defined anatomic locations, e.g. the subventricular zone surrounding the lateral ventricles. Experiments utilizing transgenic targeted cell fate mapping strategies have also shown that morphologically distinct GFAP-positive progenitor cells may represent the major source of cells that are key to constitutive adult neurogenesis in the adult mouse forebrain; in experimental systems, astrocytes appear to have important neuroprotective functions.[80,225] Whereas astrocytic gliosis has historically been thought to inhibit axonal regeneration, experiments in rats have shown that reactive astrocytes may in fact act as a permissive substrate for axon outgrowth from neurons sensitive to (implanted) nerve growth factor (NGF) within the brain.[115]

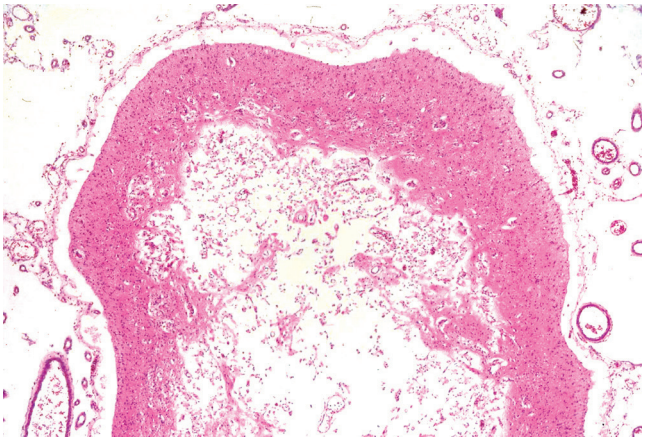
Sometimes contradictory experimental data continue to fuel the debate as to whether astrocytic scarring or some cellular components overexpressed during that process of scar formation inhibits CNS regeneration. Axonal sprouting in rats is increased in lesioned septohippocampal circuits in parallel with accentuated GFAP immunoreactivity, suggesting that astrocytes may produce trophic factors (e.g. nerve growth factor and related molecules) that facilitate this reparative response.[78] Yet in knockout mice that are rendered deficient in both GFAP and vimentin, improved anatomical regeneration, axonal plasticity and functional recovery have clearly been observed in lesioned spinal cords.[153] Organotypic slice culture experiments have demonstrated that astroglial-associated fibronectin may play a significant role in axonal regeneration within the white matter.[240]



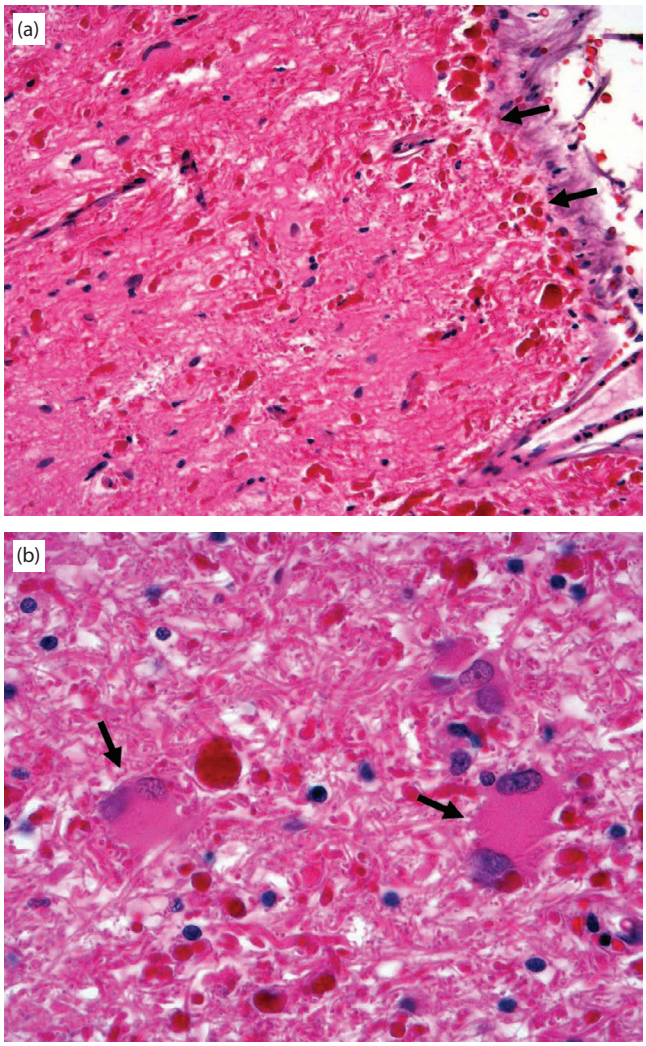
1.8 IDH1 immunohistochemistry is negative in the numerous non-neoplastic reactive astrocytes (arrows) intimately admixed with the neoplastic lymphocytes in this primary CNS lymphoma, as seen on H&E (a,b, high power), GFAP (c), and IDH1 immunohistochemistry (d). In contrast, IDH1 immunoreactivity distinguishes individually-infiltrating tumour cells **(e)** from reactive astrocytes (arrows) on the edge of a glial neoplasm, as well as large numbers of tumour cells in the centre of this anaplastic oligodendroglioma **(f)**.

Trophic Effects and Influence of Astrocytes on Vascular Structure, Integrity and Physiology

The physical proximity of astrocytes and their processes to CNS microvasculature (Figure 1.12), together with the obvious neuroanatomical observation that cerebral blood vessels are 'swimming in' a sea of astrocytes, intuitively suggests that astrocytes and molecules released by them influence microvascular structure and function. Astrocytes may be instrumental in subdividing brain segments into microdomains, thus defining the functional architecture of the CNS through 'gliovascular units'.[167] The observation of this intimate neuroanatomical association between glia and blood vessels was first noted by Golgi over 120 years ago.[222] A modular organization has even been proposed to define the association of cerebral microvessels, neurons and astrocytes, which are now described as forming



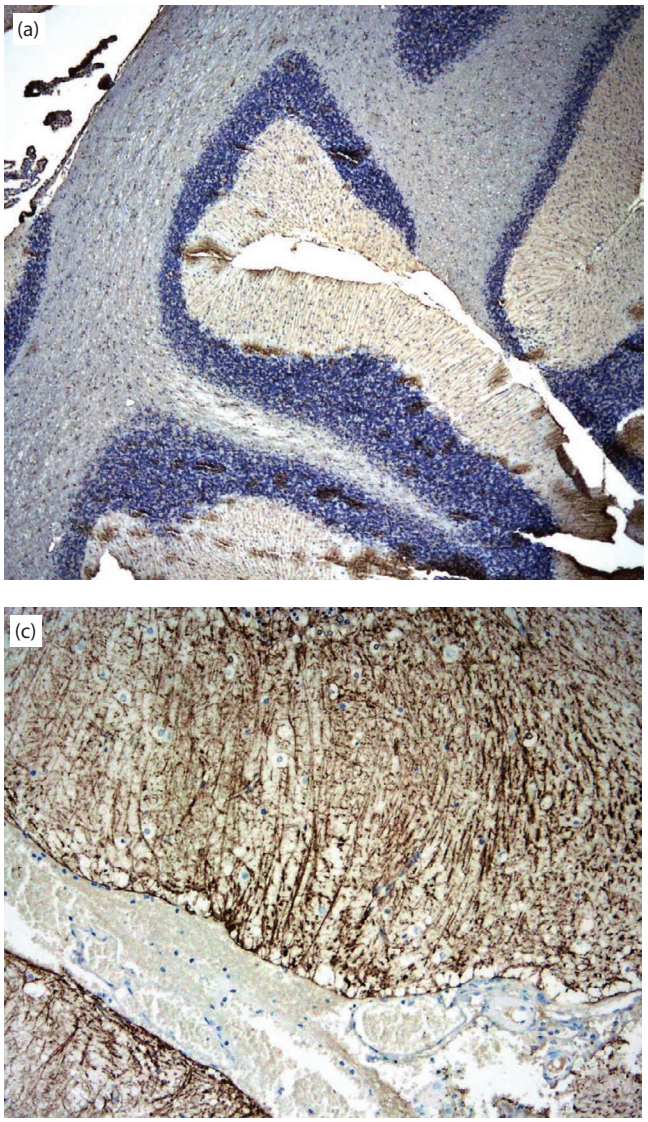
1.9 An example of anisomorphous/anisomorphic gliosis is seen in the lining of a cystic cavity that occupies most of this gyrus, sampled at necropsy from an infant with severe perinatal brain damage. The centre of the cavity contained irregular clumps of glial fibres admixed with numerous foamy macrophages.



1.10 Rosenthal fibres and astroglia. This is an unusual corticectomy specimen from a child with intractable epilepsy. **(a)** Note numerous hyaline rod-like Rosenthal fibres aggregated at the pial surface (arrows) and in the underlying cortex. **(b)** Two gemistocyte-like cells (arrows), including a binucleated astrocyte (at right) are seen amid numerous Rosenthal fibres.

functional 'neurovascular units' (NVUs).[3] Other elements of the NVU include pericytes (in the case of capillaries) and medial vascular smooth muscle cells (SMCs) in the case of arterioles. Astrocytes are a key link in these units, because they communicate with both synapses and blood vessels, as well as with other astrocytes (via gap junctions and through the release of ATP).[126] They appear to act as crucial intermediaries in intercellular signalling in this putative neurovascular unit. The role of astrocytes in mediating many physiological and biochemical functions of the cerebral capillary endothelium, site of the blood–brain barrier (BBB, see later), has been established by elegant tissue grafting and transplantation, as well as cell culture experiments (for reviews, see Pardridge;[174] Nag;[163] Ballabh *et al.*[13]). Co-culture studies (first carried out in the mid-1980s, when cerebral capillary isolation techniques became routine) have been performed in which brain-derived capillary endothelial cells[252] are seeded on one side of a porous mesh separating two fluid-filled chambers, another cell type (astrocytes, pericytes, etc.) on its other side. Such protocols were used extensively to demonstrate the inductive effect of astrocytes on both structural and physiologic properties of the BBB, e.g. its well-known 'polarity' for transport of certain molecules.[19,163,174]

Though the morphological site of the BBB is widely accepted as being cerebral capillary endothelium (see later), its physiologic functions and integrity are affected by both adjacent pericytes and astrocytes in the NVU.[3,13,163] The tight junction proteins that mediate many BBB functions (see also discussion later) are expressed very early in human CNS development within the germinal matrix, cerebral cortex and subcortical white matter.[14] Proteins known to be crucial for calcium signalling between cells (purinergic receptors and gap junctions Cx43) are expressed mainly by perivascular astrocyte end-feet that are an invariable finding on the abluminal aspects of CNS blood vessels, both capillaries and larger arteries. Brain slice experiments show that electrical field stimulations cause an increase in astrocytic calcium, which is transmitted to perivascular end-feet, resulting in arteriolar smooth muscle cell oscillations and dilatation of these vessels.[126] Molecules that may mediate communications between astrocytic end-feet and vascular smooth muscle cells include prostaglandins, epoxyeicosatrienoic acids (EETs), potassium ions and arachidonic acid. Astrocyte-mediated control of cerebral blood flow also occurs through the action of calcium transients in astrocytic end-feet.[161,235] Increased blood flow that is coupled to neuronal activity (and is thus used as an indirect measure of brain activity by techniques such as functional magnetic resonance imaging [fMRI]) is modulated in part by cyclooxygenase-2 metabolites, EETs, adenosine and NO derived from neurons. Neuronal activation that results in increased astrocytic calcium is partly mediated by activation of metabotropic glutamate receptors (mGluRs). In tissue culture systems, calcium signalling may be influenced by adenosine and EETs that are produced by astrocytes. Astrocytes are even able to transmit signals to brain surface (pial) arterioles to ensure their continuous adequate supply of blood to parenchymal arterioles.



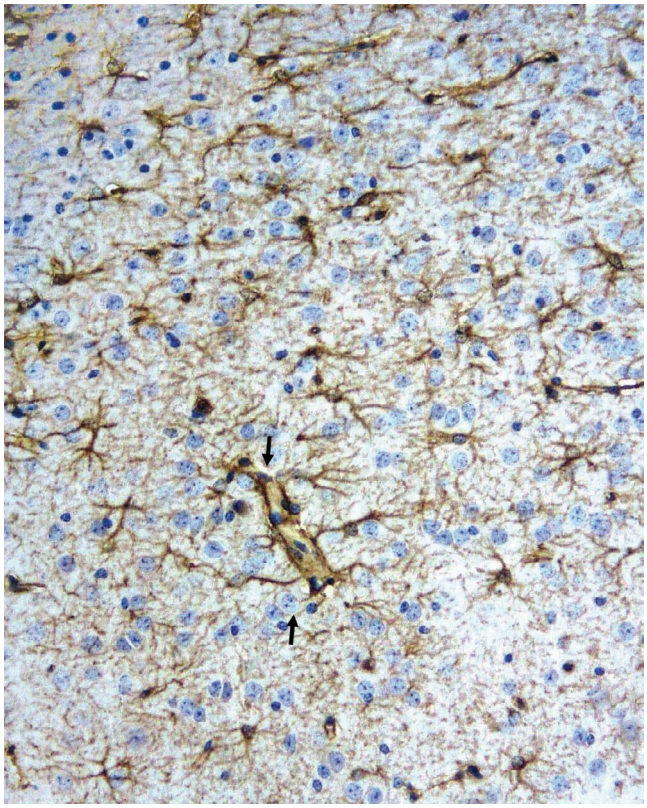
1.11 Radial glia in the cerebellum (all panels represent micrographs from GFAP-immunostained sections). (a,b) Rat cerebellum. Note GFAP-immunoreactive processes that extend from the Purkinje cell layer to the pial surface throughout the specimen, best seen at higher magnification in **(b)**. **(c)** Fragment of human cerebellum adjacent to a surgically resected lesion shows similar radial glia, though in a slightly more disorganized arrangement.

Astrocytes are also a key element in the regulation of water movement into and out of the brain through the BBB (also see later). An important molecule in this physiological regulation is aquaporin-4 (AQP4), the major water channel expressed within CNS perivascular astrocytic foot processes.[169] In normal circumstances, AQP4 activity is associated with osmotically induced water efflux, probably through functional linkage to ion/solute channels. In experimental animals with reduced AQP4, reduction of osmotic water efflux causes astrocytic foot processes to become swollen. In the setting of water influx to the CNS (with induced brain oedema), astrocytic foot processes swell more in wild-type animals than in AQP4-knockout (KO) mice.

Physiology, Metabolism and Neurochemistry of Astrocytes

Astrocytes play several roles in maintaining neurochemical homeostasis within the CNS.

One important way by which this occurs is through the regulation of glutamate levels in the extracellular fluid.[6] Astrocytes have been described as a 'ready source (for) glutamate on demand'.[147] Glutamate functions as the major CNS excitatory neurotransmitter and can also act as a potent neurotoxin – so much so that glutamate toxicity has been implicated (with varying degrees of supporting evidence) as a key pathogenetic factor in diseases as different as ischaemic stroke, amyotrophic lateral sclerosis (motor neuron disease) and epilepsy. Brain extracellular glutamate is normally present at a concentration of approximately 2 µM, whereas cytosolic concentrations are in the much higher range of 1–10 mM, depending upon the cell type. Glutamate can be transported by a variety of CNS cell types, including neurons, astrocytes and even endothelia, but uptake of this neurotransmitter by astrocytes is considered quantitatively the most important. Glutamate uptake into astrocytes is mediated by both Na+-dependent and Na+-independent systems, the latter characteristically chloride-dependent glutamate/cystine antiporters, sensitive to quisqualate inhibition. The Na+-dependent glutamate transporters are termed EAAT1 and EAAT2. Because of the huge concentration gradient against which glutamate moves to gain access to the cytosol, significant brain energy is expended in moving glutamate from extracellular fluid into cells – this is estimated to be



1.12 A close anatomic association frequently exists between astrocytes and capillaries. Arrows indicate a cerebral capillary that contains many astrocytic foot processes on its abluminal aspect. GFAP-immunostained section.

greater than 1 ATP per molecule of glutamate transported.[6] There is debate as to whether this ATP is generated by astrocytic glycolysis – tissue culture experiments suggest that this is not the case. When glutamate transporters analogous to EAAT1 and EAAT2 (GLAST and GLT-1) are 'knocked-out' *in vivo* (in rats) by use of antisense oligonucleotides, severe neurological abnormalities (e.g. paralysis) ensues in affected animals, probably the result of neurodegeneration related to excitotoxicity caused by glutamate.[198]

Intracellular (astrocytic) glutamate 'handling' may occur in several ways, though glutamine formation and its release into the extracellular space (where it may be taken up by neurons) or entry into the tricarboxylic acid cycle appear to be the most important of these. Glutamate uptake can be modulated by alterations in transporter activity and/or expression, and the transporter activity is in turn governed by both thermodynamic and kinetic factors, a detailed consideration of which is beyond the scope of this chapter. Glutamate uptake kinetics are influenced by signalling molecules (including other neurotransmitters).[82] Even amyloid precursor protein (APP), a molecule that is central to the pathogenesis of Alzheimer's disease[16] and often used as a marker of axonal injury,[10] can affect astrocytic glutamate levels. In tissue culture systems, APP increases glutamate uptake by a process that is sensitive to both protein kinase A and C inhibitors. Astrocytes may even participate in the determination of synaptic structure and function – synapses throughout the CNS show varying degrees of ensheathment by astrocytic processes. Astrocytic processes are more prominently distributed near synapses with a greater likelihood of showing 'glutamate escape'. Glutamate released by synapses follows one (or more) of three subsequent pathways: it can (1) diffuse further between synapses, (2) be cleared by neuronal glutamate receptors, or (3) be cleared by transporters on astrocytes or their processes. The importance of each of these mechanisms varies in different regions of the CNS, determined to some extent by the degree of synaptic ensheathment by astrocytes. It appears that astrocytes are much more important synaptic glutamate sinks than are neurons.[6]

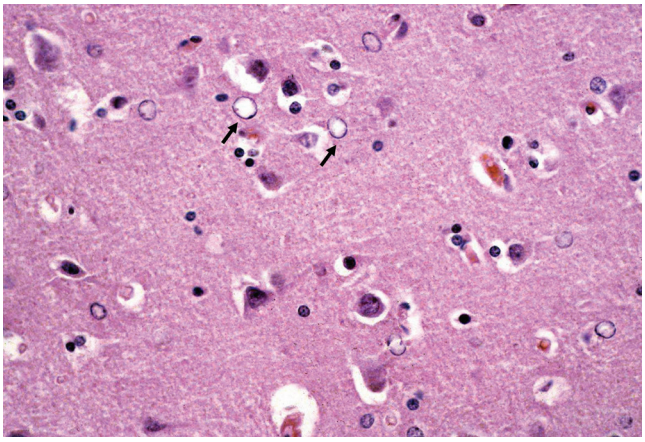
Of course, 'what comes into cells … may also go out'! Glutamate release from astrocytes occurs through the process of 'transport reversal', through anion channels activated by cell swelling or through gap junction hemichannels.[271] In the adverse circumstance of ATP depletion (e.g. during irreversible, severe cerebral ischaemia), the key membrane gradients keeping glutamate within astrocytes disappear, causing 'flooding' of the extracellular (including synaptic) spaces by this potentially neurotoxic molecule. Glutamate efflux may also occur in less dire circumstances, e.g. in response to certain signalling mediators and processes. Calcium-dependent glutamate release can occur in response to bradykinin, some prostaglandins and even extracellular ATP.[6] Glutamate release may also take place as a consequence of cytoplasmic swelling; the astrocyte responds to this by the 'expulsion' of chloride and glutamate (among other molecules) through volume-sensitive organic osmolyte-anion channels (VSOACs). The delicate balance of astrocytic modulation of glutamate levels has practical implications in our understanding of, for example, the neurobiology of traumatic brain injury (TBI). Glutamate neurotoxicity can greatly exacerbate the secondary CNS damage that occurs after TBI. Unfortunately, one of the consequences of TBI may be downregulation of the very receptors (EAAT1, EAAT2) that can potentially ameliorate glutamate-mediated injury. Clinical intervention (to minimize secondary injury after TBI) using glutamate receptor antagonists has also been largely unsuccessful as a preventative strategy.[272]

Tissue co-culture experiments utilizing retinal ganglion cells and neuroglia (including astrocytes) suggest that developing neurons *in vitro* form inefficient, largely inactive synapses that only become fully and vigorously functional when exposed to glial signals.[183] Glia may even control the number of mature synapses.[243] Neuronal stimulation may trigger electrophysiological and/or calcium responses in cultured astrocytes or experimental brain slices. In addition to glutamatergic pathways already described, NO-mediated signalling may also occur. Neuron-to-astrocyte signalling can activate subcellular compartments, the entire cell, or it can activate a multicellular astrocytic response in the form of a 'calcium wave' – a phenomenon that may also occur, somewhat surprisingly, in pure cultures of astrocytes.[20,210]

Water and ion homeostasis by astrocytes is achieved partly through hormonal mechanisms, viz. the varying effects of vasopressin (AVP), atrial natriuretic peptide (atriopeptin), angiotensinogen (AGT) and angiotensin (Ang) II on astroglial water and chloride uptake, which in turn is linked to their intrinsic osmoregulation.[221] Astrocytic swelling of a pronounced degree appears to be a key element in the cerebral oedema seen in patients who experience fulminant hepatic failure. This 'cellular

oedema' has numerous negative consequences for the CNS, including a failure of astrocytes to take up neurotransmitters, reduction in size of the extracellular space leading to abnormally elevated extracellular ion concentrations, and even vascular compromise through compression of the microvasculature. A neuropathologic correlate of hepatic encephalopathy is the presence of characteristic Alzheimer type II astrocytes, identified predominantly within cortical grey matter and deep central grey structures (Figure 1.13).[64,171] This condition may be potentially severe enough to cause fatal internal herniation of brain tissue and results in severe metabolic encephalopathy.[172] Its proximate cause appears to be hyperammonaemia. Various lines of evidence suggest that the pathogenesis of ammonia-induced astrocytic swelling involves oxidative stress, induction of the mitochondrial permeability transition (MPT, associated with a sudden increase in permeability of the inner mitochondrial membrane to small molecules), and intracellular accumulation of glutamine, which then act as an intracellular osmolyte. It has been hypothesized that glutamine induces both oxidative stress and the MPT.

Further metabolic linkage between neurons and astrocytes may result from their utilization of specific energy substrates. Astrocytes have a prominent capacity for aerobic glycolysis and production of lactate even in the presence of normal oxygen levels. Glucose is the major energy substrate within adult CNS, but lactate and ketone bodies may serve as alternative energy substrates in prolonged starvation, diabetes mellitus or during hypoglycaemia.[181] In the course of normal brain function, approximately 90–95 per cent of brain energy consumption is attributed to neurons, only 5–10 per cent to glia (especially astrocytes). Recent data suggest that glial cells may function as 'nursing partners' for neurons, releasing a metabolic intermediate from glucose that can be taken up and oxidized by neurons. It has also been claimed that astrocytes 'sense' synaptic activity at glutamatergic synapses (see earlier) and metabolize glucose into lactate that can be passed to neurons. Energy transfer from astrocytes to axons may also occur (during aglycaemic conditions) through the degradation of astrocytic glycogen to lactate, the latter molecule then being used by neurons as a supplementary energy source.[28] High-resolution imaging methods (e.g. two-photon fluorescence imaging of nicotinamide adenine dinucleotide) can now be used to study metabolic interactions between neurons and astrocytes at the single cell level.[112] For a thorough discussion of the physiological and biophysical aspects of neuronal and astrocytic metabolism in the course of afferent and efferent neural activity in the brain, see Gjedde *et al*.[82]



1.13 Alzheimer type II astrocytes. These are easily appreciated in H&E-stained sections, as in this section through the basal ganglia. Arrows indicate two such cells, characterized by enlarged clear nuclei, often with tiny eccentric nucleoli.

Pathological Reactions and Role in Neurologic Disease

Neurons and astrocytes (the latter vastly outnumbering the former),[226] once thought to act independently in CNS development and response to injury, are now known to be tightly linked in both processes, with well-defined cell-to-cell contacts between the two cellular elements in many regions of the CNS. Until the early 1990s, there was a widespread tendency to view reactive astroglia as generic cells with uniform biological properties regardless of their location within the CNS. This approach has been largely superseded by an appreciation of their significant functional and regional heterogeneity throughout the brain and spinal cord.[93] A second assumption was that, in the face of CNS injury, supportive astroglial cells become transformed into elements that actively inhibit axonal regrowth–the classic 'glial scar' that poses a major barrier to CNS regeneration after brain or spinal cord injury. A third major assumption about astrocytes was that brain or spinal cord injury led directly to glial proliferation ('astrocytic gliosis') and associated scarring. All of these assumptions have recently been questioned or re-evaluated. In experimental models, CNS injury of only certain types (e.g. that caused by physical tearing or laceration, as often occurs in traumatic brain and spinal cord injury) reliably induces gliosis. As well, the gliosis may be regionally accentuated; furthermore, there may be an increase in the GFAP content of individual astrocytes (astroglial hypertrophy) without an actual increase in their number (hyperplasia). Neurons may substantially regulate astroglial proliferation and differentiation. Experiments using cultured cerebellar granule cells (admittedly a highly specialized type of neuron but one fairly easy to maintain *in vitro*) and astroglia further highlight potential neuronal–glial interactions in the response to injury. When postnatal astroglia were grown in the absence of neurons, they expressed low levels of GFAP and grew rapidly. When granule cell neurons were added to the cultures (especially at a ratio of at least 4:1), DNA synthesis (in the astrocytes) decreased substantially and GFAP protein expression increased.[93] GFAP appears to be necessary but not sufficient for the formation of astroglial processes in the presence of neurons. As indicated earlier, astrocytes may support axonal growth; their degree of differentiation (rather than chronological age) may be a key determinant of glial support of axonal growth. Astroglia are also capable of expressing extracellular matrix molecules (such as laminin, heparan sulphate) and cell adhesion receptor systems–these and other molecules may play a role in axonal guidance following injury.

The function (and malfunction) of both microglia (see later) and astrocytes is inextricably linked to an understanding of cytokines, low molecular weight (MW) glycoproteins that may be secreted or function as membrane-bound

complexes.[110,171] These molecules exert their actions in a paracrine or autocrine fashion. They interact with specific cell-surface receptors, most cytokines having the capability of acting as ligands for several different receptors. The biological properties of a given cytokine are determined by the receptor that is activated, more than the cytokine itself. Astrocytes both produce cytokines and are, under a variety of physiological and pathophysiological circumstances, highly responsive to them. Properties of cytokines and their receptors have been elucidated through the use of elegant (usually transgenic) animal models and tissue culture experiments. In these studies, genes specific for cytokines and/or their receptors are deleted or overexpressed, often in specific cell types or anatomically defined populations, allowing for a detailed dissection of their myriad effects on the CNS (for a detailed review, see John *et al.*[110]). Although many of these experimental studies looking at the effects of cytokines on neural cells are illuminating from the perspectives of cellular neurobiology, their relevance for understanding complex neurologic diseases is not always clear.

Reactive gliosis, a non-specific but highly characteristic response to almost any type of CNS injury, can be thought of as resulting from astrocytic proliferation (hyperplasia) and enlargement (hypertrophy), both associated with distinctive patterns of gene expression. As indicated earlier, reactive gliosis can be either a positive process that results in neuroglial survival or a negative one causing diminution in neuroglial growth, migration or both processes. Targeted ablation of reactive astrocytes can cause both increased neuronal degeneration and, simultaneously, an increase in neuritic outgrowth, together with accentuated chronic inflammation and a delay in post-injury re-establishment of BBB integrity.[32] Interleukin-1β (IL-1β), tumour necrosis factor-α (TNFα), IFNγ and transforming growth factor-β1 (TGFβ1) have all been implicated as players in the initiation or modulation of reactive gliosis. Furthermore, astrocytes possess receptors for all four of these cytokines, each apparently having a different role in the astrocytic response to injury, and each response in turn is mediated by specific gene expression patterns. IL-1β, especially, appears to have a pro-inflammatory role in CNS disease, but may also be involved in CNS regeneration,[110] some of these effects being modulated through ciliary neurotrophic factor (CNTF) or nerve growth factor (NGF). *In vitro* experiments suggest that IL-1β induces genes that are key elements in the acute or subacute immune response and include other cytokines, chemokines and several adhesion molecules. By contrast with IL-1β, IFNγ (produced in abundance by activated lymphocytes) appears to potentiate (rather than initiate) astrocytic gliosis, possibly through the induction of MHC class I and II molecules and chemokines, and the potentiation of IL-1β-induced expression of TNFα and nitric oxide synthase (NOS) (inducible NOS type II can be expressed by astrocytes). Complex interactions among infiltrating lymphocytes, microglia and astrocytes determine the microenvironment in which the CNS functions or malfunctions. NOS II may be downregulated in astrocytes via a complex cascade that involves both microglia and IL-4 (produced by TH2 lymphocytes) acting upon TH1 lymphocytes to modify their synthesis of IFNγ. Both IL-1β and IFNγ may thus be of importance in, for example, the pathogenesis and progression of multiple sclerosis (and its experimental animal model, experimental allergic encephalomyelitis, EAE), in which lymphocytic infiltration into spinal cord or brain is an integral part of the neuropathologic picture.[64,255]

TGFβ1, expressed in both astrocytes and microglia in the context of brain trauma, infarction or inflammation, is itself an apparent stimulant of astrocytic gliosis. Inhibiting TGFβ1 activity prevents formation of a glial membrane at the site of CNS injury and downregulates production of extracellular matrix molecules, e.g. fibronectin and laminin. Other effects of TGFβ1 include inhibition of astrocytic expression of MHC class II molecules, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) and TNFα, as well as the induction of numerous molecules important in CNS wound healing (fibronectin, tenascin, collagen, laminin, actin and actin depolymerizing factor among many others). TNFα itself is synthesized by astrocytes, may stimulate astrocytic gliosis but may also have a part to play in CNS repair after injury. It can also be cytotoxic to both oligodendroglia and neurons. These somewhat paradoxical effects are probably affected via the distinctive signalling pathways mediated by two TNF receptors, TNFRI/p55 and TNFRII/p75; the former appears to be linked to cell death, the latter to cell viability and growth. IL-6 activates many signalling cascades, and houses the signalling receptor gp130, which is activated through the Jak/Stat pathway. In the CNS, IL-6 promotes neuronal survival and neurite outgrowth, may impact cell-fate decisions (e.g. progression of stem cells to neurogenesis *versus* gliogenesis), and has an immunomodulatory function in the highly complex glial cytokine network–abnormalities of which may result (under some circumstances) in CNS inflammation and neurodegeneration. Complex and potentially confusing as all of these interactions may appear to be, they appear to become even more so with every passing week! Summaries of the interactions among microglial and astrocyte-secreted factors are to be found in recent reviews of these cell types.[226,268] Immune responses mediated through cytokines, chemokines and lymphokines, especially involving cell surface receptors, are especially important in understanding the evolution of viral infections of the CNS, especially those that impact on neurons.[39]

Astrocytic gliosis plays a part in virtually all neurological diseases and neuroanatomical lesions–whether they be degenerative, traumatic, metabolic, neoplastic, inflammatory or of any other aetiology. Astrocytes are commonly found in microscopic lesions as disparate as the neuritic plaques of Alzheimer disease,[205] the demyelinating plaques of multiple sclerosis, and foci of viral encephalitis that have little to do with plaques! Recently, it has been suggested that astrocytes play a major role in the generation of epileptic seizures through their modulation of glutamate and calcium signalling.[238] The potential roles of astrocytes in specific entities are further considered in the chapters dealing with these diseases. The molecular and cellular basis of astrogliosis itself has been the topic of substantial debate.[60] Reactive gliosis appears to vary quantitatively and qualitatively–the nature of the glial response being determined by both the nature of the lesion/injury and the microenvironment in which it occurs.[193] Astrogliosis is recognized by the apparent proliferation and hypertrophy of GFAP-expressing astrocytes. However, by definition this excludes a consideration (within a given lesion) of any reactive astrocytes that fail to express

GFAP. Furthermore, because of their apparently minimal proliferative and migratory potential, it has been suggested that reactive astrocytes (in regions of acute/subacute neural injury) may simply represent a change in the phenotype of locally residing astrocytes. The transition of resting astrocytes to activated cells is associated with the expression of new molecules not normally expressed (in the resting state), as well as the upregulation of molecules that are expressed at low levels in the resting state (for a catalogue of these molecules, see Eddleston and Mucke;[60] Ridet *et al*.[193]).

One of the myths to be banished in recent years is that astrocytic processes (in glial scars) are a major impediment to axonal regeneration, e.g. after traumatic spinal cord injury or stroke.[93] Axons appear to grow quite happily on astrocytic scars; it has therefore been postulated that, because scars are in fact a complex admixture of various cell types, extracellular matrix components and other elements, some combination of non-astrocytic components may actually impede axonal growth after a spinal cord injury or cerebral infarct. Despite this, strategies aimed at re-establishing spinal cord function are frequently aimed at bypassing the scarred and gliotic site of cord injury, which is still perceived by many investigators as a significant barrier to axonal regeneration.[30,220] Nevertheless, one strategy in the treatment of experimental spinal cord contusional or transection injury is to acutely transplant glial-restricted precursor cells (which have the potential to differentiate into oligodendroglia and astrocytes) into the lesion.[50,96] When reactive astrocytes were selectively ablated from a region of spinal cord injury in a novel transgenic mouse model, the absence of astrocytes caused failure of BBB repair, leukocyte infiltration, severe demyelination with local tissue disruption, and oligodendroglial/neuronal death, resulting in pronounced neurologic deficits in experimental animals.[67,225] One obvious conclusion from this work was that reactive astrocytes have important neuroprotective functions that could be harnessed in post-injury repair of neural tissue.

Given the central role of astrocytes in brain energetics, water and ion homeostasis, vascular regulation, and genesis of the neurovascular unit, discussed elsewhere in this chapter, astrocytes would appear to be an attractive cell population to target in new therapeutic approaches in neuroprotection (for review, see Nedergaard and Dirnagl[166]). As one example, sustained astrocytic expression of the glycoprotein clusterin significantly improved brain remodelling after ischaemia in mice.[106] Genetically modified astrocytes may be a way to deliver therapeutic factors into lesioned (whether artificially or by nature) portions of brain or spinal cord.[182] A comprehensive review of the complex biological and pathological features of astrocytes has recently been published.[226]

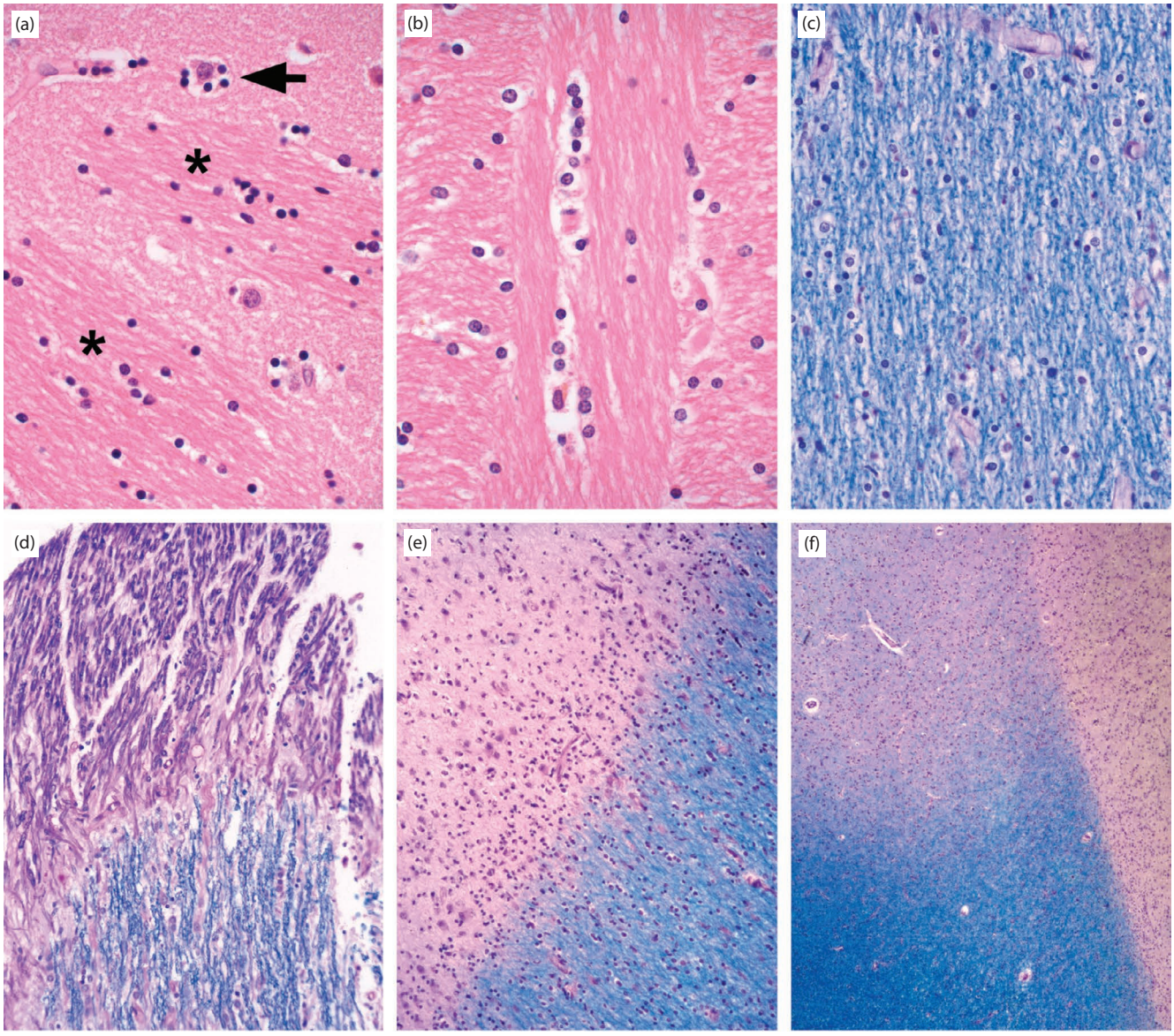
OLIGODENDROCYTES

Oligodendrocytes are neuroglial cells with small cell bodies, few (Greek: *oligos*, little, few) short cell processes, and no cytoplasmic filaments. They are found in grey matter, where they cluster around neuronal cell bodies (Figure 1.14a, arrow) and are seen in the pencil fibres of white matter that course through the putamen (Figure 1.14a, asterisks). In compact regions of white matter they are often arranged in rows between myelinated fibres (Figure 1.14b), and in cortex often lie adjacent to neurons. The functions of oligodendrocytes are likely to be different in the grey and white matter. In the grey matter, the standard explanation for the role of oligodendrocytes that encircle neurons is that they play sustentative roles for neurons, analogous to the role of satellite or capsular Schwann cells in dorsal or peripheral sensory ganglia, or that they represent progenitor cells.[27]

In central nervous system white matter, oligodendrocytes are the cell type responsible for myelin formation and are thus analogous to Schwann cells in the peripheral nervous system. Oligodendrocytes must undergo a series of complex series of steps, from proliferation, migration, differentiation, to myelination before they finally are capable of producing an ensheathment of axons.[26] Oligodendrocytes are among the most vulnerable cells to injury in the CNS.[26] A large recent review addresses the development of oligodendrocytes, particularly in rodents[26] and several of these discoveries in rodents are likely analogous in human oligodendroglial development as well. New insights into oligodendroglial development include the fact that: (1) there appears to be a common progenitor cell origin for neurons and oligodendrocytes; (2) a ventral-to-dorsal progression occurs in oligodendroglial development; (3) there are multiple origins for oligodendrocytes and (4) there is an interrelationship between axonal signalling and myelination (reviewed in Bradl and Lassmann[26]).

Both CNS and PNS myelin can be histochemically stained with a number of different stains, the most commonly used of which is the Luxol fast blue (LFB) stain with which CNS myelin appears in paraffin sections as a slightly vacuolated robin's egg-blue substance surrounding the axon (Figure 1.14c). In autopsy tissues, LFB may be suboptimal or yield patchy, variably intense staining; therefore, immunohistochemistry incorporating primary antibodies to, for example, myelin basic protein may better demonstrate myelinated fibres. The tinctorial properties differ slightly for PNS myelin, which appears darker blue than CNS myelin on being stained with Luxol fast blue-periodic acid Schiff (LFB-PAS). This can be easily seen at a transition zone between oligodendrocyte-mediated CNS myelin and Schwann cell-mediated PNS myelin where cranial nerves or spinal nerves exit the CNS (Figure 1.14d, 5th cranial nerve illustrated). Additional differences exist between oligodendrocytes and Schwann cells. Schwann cells are surrounded by basement membrane and have a single cell process responsible for ensheathing only a single myelin segment lying between two nodes of Ranvier, whereas the oligodendrocyte is devoid of basement membrane and its several cell processes can each form several internodal segments of myelin. Schwann cells have a more limited responsibility, with one cell responsible for one internodal segment on one axon, which they spirally enwrap to produce myelin. Oligodendrocytes, in contrast, may form as many as 60 internodal segments.[224] In both the CNS and PNS, myelin serves similar functions, allowing increased speed of conduction of impulses, which propagate by saltation from node to node along myelinated axons; on loss of myelin, conduction slows or ceases.

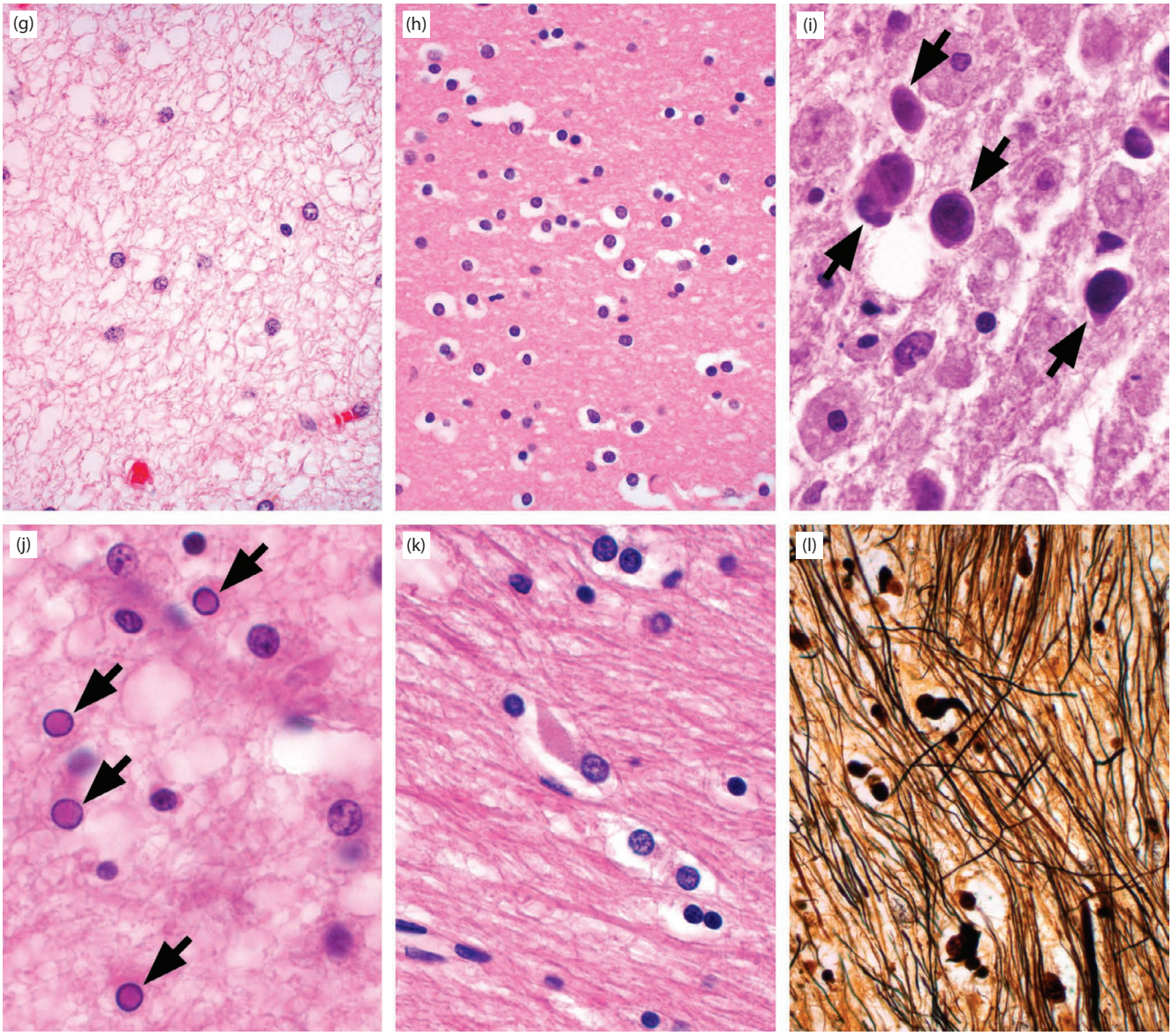
Myelin integrity requires both its formation and subsequent maintenance. Myelin formation begins at about the 16th week of intrauterine life[224] and continues throughout childhood. Although myelin formation is most rapid during



1.14 (a) Normal oligodendrocytes in the putamen, where they cluster around neuronal cell bodies (arrow) and are also seen in the white matter pencil fibres (asterisks). **(b)** In white matter, oligodendrocytes are arranged in rows between myelinated fibres. **(c)** Luxol fast blue-periodic acid Schiff (LFB-PAS) stain for myelin in normal white matter. **(d)** As demonstrated using the same histochemical LFB-PAS stain, the tinctoral properties differ for peripheral nervous system (PNS) myelin. PNS myelin appears darker blue, as seen in the illustrated transition zone between oligodendrocyte-mediated CNS myelin and Schwann cell-mediated PNS myelin, in the 5th cranial nerve root entry zone. **(e)** Edge of an active demyelinating plaque in multiple sclerosis (MS) shows oligodendrocyte proliferation, evidenced as a band of hypercellularity between the severely demyelinated zone (upper left) and less demyelinated edge of plaque (lower right). LFB-PAS. **(f)** Shadow plaque (upper left) represents an area of partial remyelination. LFB-PAS.

the first 2 years of life, diffusion tensor imaging studies suggest that myelination occurs well into the second decade.[123] Maintenance of myelin demands integrity of the oligodendrocyte cell body, high energy expenditure by the cell and, should the myelin be lost, effective remyelination by oligodendrocyte precursors. Loss of, or damage to, the cell body of the oligodendrocyte almost inevitably leads to loss of the myelin produced and supported by that cell's processes. Damage to axons in myelinated fibres leads to breakdown of the surrounding myelin sheath. Conversely, the oligodendrocyte is also important for axonal support and maintenance.[61]

In H&E-stained sections, the oligodendrocyte is seen as a round nucleus with evenly dispersed, dark chromatin, no nucleolus, and no visible cytoplasm (Figure 1.14a and b). In poorly-fixed tissues, most oligodendrocytes manifest an artefactual perinuclear clearing around the nucleus, the so-called 'perinuclear halo', leading to a 'fried-egg' appearance (Figure 1.14b). These perinuclear haloes are often not apparent in well-fixed small surgical biopsy specimens; hence identification of an oligodendrocyte–normal or neoplastic–cannot rest solely on the presence or absence of the 'halo'. The processes and cytoplasm of the oligodendrocyte cannot be discerned without special histochemical stains or EM. A number of antibodies have been used immunohistochemically to identify oligodendrocytes, such as Leu-7 (CD57), anti-myelin associated glycoprotein (MAG),



1.14 (*Continued*) (g) Centre of old, inactive MS plaque is hypocellular and contains almost no myelin or oligodendrocytes. **(h)** Photomicrograph illustrates normal myelin and axon content for comparison with panel **(g)**. **(i)** Oligodendrocyte nuclei with characteristic glassy, violaceous inclusion bodies in progressive multifocal leukoencephalopathy. **(j)** Oligodendrocyte nuclei bearing viral inclusion bodies, in subacute sclerosing panencephalitis. **(k)** Oligodendrocytes in multiple system atrophy contain cytoplasmic, linear, pointed, densely eosinophilic, glial inclusions, in affected regions of brain. **(l)** The glial cytoplasmic inclusions in multiple system atrophy are better highlighted by modified Bielschowsky silver impregnation (note that this also stains the axons).

anti-myelin oligodendrocyte protein (MOG), anti-CD44 (a cell surface glycoprotein)[25] and anti-OLIG1 transcription factor.[11] Several of these markers have now been recognized to be present in oligodendrocytes in differing stages of development, as reviewed by Bradl and Lassmann.[26] On paraformaldehyde-fixed brain tissue, differentiated oligodendrocytes express carbonic anhydrase II, 2′:3′-cyclic nucleotide 3′-phosphodiesterase (CNP), galactosylceramide (GalC), Kir4.1 (inwardly rectifying K+ channel subunit), myelin basic protein (MBP), MAG, MOG and proteolipid protein (PLP), although myelinating oligodendrocytes express RIP and TPPP/p25 and oligodendrocyte precursor cells (OPC) express CNP, OLIG2, NG2 and O4.[26] Although OLIG2 especially is being used in daily practice, it is not specific for gliomas of oligodendroglial lineage, and other markers are not part of the standard armamentarium of surgical neuropathologists. Hence the question, 'What is an oligodendrocyte?' or the corollary, 'What is an oligodendroglioma?'[31] remains a vexing one when we do not have a universally accepted immunohistochemical marker for these cells.

Compounding the problem have been *in vivo* studies that suggest neuron-like physiological properties in cells cultured from human oligodendroglial tumours,[178] as well as immunohistochemical studies demonstrating staining of oligodendroglial tumour cells for markers traditionally associated only with neurons, such as NF-H,[52] N-methyl-D-aspartate receptor subunit 1 or embryonal neural cell adhesion molecule.[270]

The repertoire of responses to injury available to the oligodendrocyte is limited. Proliferation of oligodendrocyte precursor cells has been documented in a number of

different disease processes including radiation injury,[10] vanishing white matter disease[246] and multiple sclerosis (MS) but, at least in the first two conditions, may be counterbalanced by neuronal apoptosis.

Oligodendrocyte proliferation from precursor cells is most confidently identified by the pathologist at the edge of an active demyelinating plaque in multiple sclerosis (MS), as a band of hypercellularity (Figure 1.14e). This precursor cell proliferation may produce a region of partially effective remyelination, known as the 'shadow plaque'. This appears as an area of partial, hazy myelin staining (reflecting inadequately thin sheaths) that is intermediate in intensity between normal-appearing white matter with its intense robin's-egg blue colour on Luxol fast blue stain for myelin, and the unstained, totally demyelinated parts of a plaque (Figure 1.14f). Unfortunately, remyelination seems to be transient, because it disappears in older lesions.[74] Although remyelination initially occurs as a result of recruitment of oligodendrocyte precursor cells, these may progressively become depleted,[145] may become quiescent or may respond to axonal inhibitory signals and cease the myelination process.[142] Whether or not oligodendrocyte apoptosis occurs in MS is still debated.[16,74] In any case, the centre of an old, inactive MS plaque does not evince effective remyelination, is quite hypocellular and contains naked axons and chronic gliosis but virtually no myelin or oligodendrocyte nuclei (Figure 1.14g). The extent of this hypocellularity and oligodendrocyte loss can be best appreciated when the centre of the plaque is compared side by side with the oligodendrocyte content of normal subgyral white matter (Figure 1.14h).

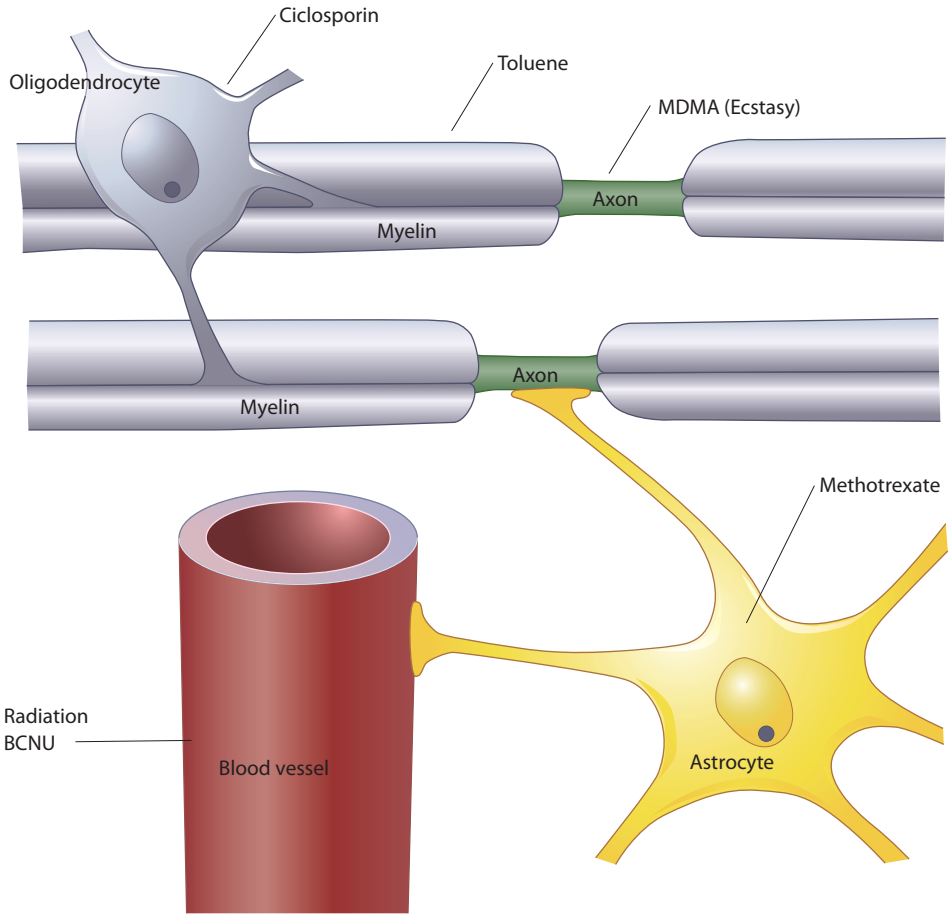
In many other diseases in which oligodendrocytes and myelin are lost in the CNS, no phase of oligodendrocyte proliferation has been confidently identified. In these situations, oligodendrocytes are simply injured and destroyed. A number of different viruses can infect oligodendrocytes and cause lytic infections, with loss of cell bodies and their dependent myelin sheaths. Prior to cell lysis, if sufficiently large clusters of viral particles accumulate, they may be seen in the cell nucleus as viral inclusion bodies, even on routine H&E staining. The associated margination of the normal nuclear chromatin underlines the fact that the nuclear machinery has been 'commandeered' by the virus for its own purposes. The characteristic glassy, violaceous inclusion bodies in progressive multifocal leukoencephalopathy (Figure 1.14i) are composed of myriad virions that fill the entire nucleus; much less frequently these form a condensed, 'owl's eye' viral inclusion. Subacute sclerosing panencephalitis similarly produces relatively homogeneous viral inclusions that fill the nucleus and are associated with a margination of nuclear chromatin (Figure 1.14j).

Less dramatic oligodendrocyte changes accompany almost all other disorders that damage myelin. Indeed, by the time these disorders, termed 'leukoencephalopathies', are encountered by the pathologist, hypocellularity, and a reduction in the number of oligodendrocyte nuclei and amount of myelin with a corresponding increase in the white matter water-to-myelin ratio, are the non-specific findings. Leukoencephalopathy is the term usually applied to non-inherited white matter damage (usually maximal in cerebral hemispheric white matter) that is a result of toxic, metabolic or ischaemic processes, with the alternate term 'leukoaraiosis' also applied to chronic ischaemic white matter injury. Examples of toxic substances that cause oligodendrocyte and myelin loss include: chronic substance usage (ethyl alcohol, 'ecstasy', and toluene, i.e. 'glue sniffing'), ciclosporin (US spelling cyclosporine), therapeutic radiation, and chemotherapeutic agents (carmustine and methotrexate) (Figure 1.15).[70] The latter two categories of agents also affect blood vessels and produce white matter damage via ischaemic mechanisms.

Oligodendrocytes are the second most vulnerable cell, after neurons, to anoxic-ischaemic central nervous system injury. In any acute deprivation of regional blood supply to grey and white matter, i.e. stroke, oligodendrocytes are lost, along with the neurons and virtually any other tissue components in the epicentre of the lesion. Significant, widespread, acute or chronic damage specifically to white matter may also occur, because of the vulnerability of oligodendrocytes to ischaemic injury. Deprivation of oxygen/blood supply to the white matter is especially likely to affect the cerebral hemispheres. Acute hypoxic-ischaemic injury to white matter may be accompanied by a haemorrhagic component and is known as hypoxic-ischaemic leukoencephalopathy. Chronic hypoxic-ischaemic injury to white matter is often maximal in boundary zones (watershed territories) of arterial distribution in the cerebral white matter between the middle and posterior cerebral arteries and the middle and anterior cerebral arteries. It tends also to be maximal in the regions of white matter midway between the ventricular and pial surfaces, not in periventricular regions. Chronic hypoxic-ischaemic injury to white matter may result from either severe arteriolosclerosis of deep white matter blood vessels and hypoperfusion (leukoaraiosis, causing Binswanger's disease in the most severe form) or an inherited, autosomal dominant disorder, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). This ischaemic injury to oligodendrocytes has usually been considered to be predominantly necrotic. However, recent studies of mild hypoxic/ischaemic insults occurring in the perinatal time period have suggested that O4+ oligodendrocyte precursor cells are particularly vulnerable to injury and die by apoptotic rather than necrotic mechanisms.[199] Ischaemic injury to the white matter is considered in more detail elsewhere in this text.

Inherited, usually autosomal recessive, storage diseases may cause oligodendrocyte injury and loss as a result of the accumulation of abnormal storage material within the cell cytoplasm. This type of white matter injury is designated a leukodystrophy (to reflect the intrinsic dysfunction in oligodendrocyte biology in these disorders, as opposed to the acquired injury to previously normal oligodendrocytes in leukoencephalopathies), and includes a number of rare disorders, the most well known of which are metachromatic leukodystrophy, Krabbe's disease, and adrenoleukodystrophy.

Finally, oligodendrocytes contain an extensive microtubular network and express tau, which is a microtubule-associated protein.[192] In neurodegenerative disorders, tau-positive inclusion bodies may form within oligodendrocytes, usually as 'coiled' bodies. These inclusion bodies can also be immunostained with antibodies against ubiquitin and heat shock proteins such as αB-crystallin.[192]



1.15 Examples of toxic substances that cause oligodendrocyte and myelin loss include: chronic substance usage (ethyl alcohol, 'ecstasy', and toluene, i.e. 'glue-sniffing'), ciclosporin (US spelling cyclosporine), therapeutic radiation, and chemotherapeutic agents (carmustine and methotrexate). The latter two categories of agents also affect blood vessels and produce white matter damage by ischaemic mechanisms.

Other inclusions are illustrated here in a case of multiple system atrophy, in which the cytoplasmic inclusions appear as linear, pointed, densely eosinophilic structures immediately adjacent to oligodendrocyte nuclei in select anatomic areas of the brain (Figure 1.14k). Although visible on careful inspection of H&E sections, they are better highlighted with silver stains as 'Papp–Lantos bodies' (Figure 1.14l) or by immunostaining for ubiquitin, alpha-synuclein or αB-crystallin. Ubiquitination is common to many very different types of neuronal and glial inclusions and makes antibodies to ubiquitin and p62 valuable and effective generic immunostains to have available in laboratories that study neurodegenerative disorders.

Reactions of the oligodendrocyte at the level of the myelin sheath include intramyelinic oedema, resulting in vacuolation of the neuropil, and myelin degeneration, resulting in myelin digestion by macrophages. Wallerian degeneration is the process that best illustrates the co-dependency of myelin sheaths and their axons. When axons are transected or otherwise severely injured, the axon distal to the transection will start to undergo dissolution. Following this, the myelin sheaths surrounding the axon start to break down into a string of myelin ovoids, separated by the oligodendrocytes that formed the myelin. These myelin debris-containing ovoids are quickly surrounded by astrocytic cell processes and are then phagocytosed by microglia and macrophages. Entire tracts may undergo wallerian degeneration, such as the descending corticospinal tracts in the spinal cord when a severe injury has occurred at a more proximal point in the tract (e.g. the internal capsule). Extensive wallerian degeneration is appreciable on both pre-mortem neuroimaging studies and, should the patient succumb, on gross brain examination.

In the PNS, one of the more striking responses at the level of the myelin sheath of Schwann cells to injury follows chronic, repetitive myelin loss caused by various types of peripheral neuropathies. This results in exuberant proliferation of Schwann cells, usually seen as multiple concentric layers of cells around a thinly myelinated axon, evidence that the process is not fully successful. Although an analogous reaction does not affect oligodendrocytes in the CNS, in severe proximal peripheral nerve injury, onion bulb formation by Schwann cells may extend into spinal cord parenchyma.[186,214]

EPENDYMA

Ependymal cells constitute the lining of the ventricular system, including the aqueduct of Sylvius and foramina that connect the different ventricles. Highly specialized

ependymal cells play a key role in fluid homeostasis between brain parenchyma and the cerebrospinal fluid, and ependymal cells are rich in the membrane water channel protein aquaporin-4.[173] This role in fluid homeostasis is relevant to both normal physiological conditions and disease states, especially ones that affect the ventricular lining (intraventricular haemorrhage, hydrocephalus, CNS infections resulting in ependymitis or ventriculitis). Ependymal cells have electrophysiological properties similar to those of astroglia.[203,204] They are also seen in the spinal cord 'central canal', even when the canal becomes vestigial and is identified only as a somewhat disorganized collection of cells that retain their phenotype. Ependymal cells resemble the relatively monotonous cuboidal and columnar epithelia that line the gastrointestinal and respiratory tracts (Figure 1.16), but do not have a well-defined basement membrane and are immunopositive for GFAP (see later). They show prominent cilia. Interspersed among the ependymal cells are tanycytes, which have radially directed basal processes that extend into the periventricular neuropil and enwrap blood vessels, or terminate on neurons, glia or the external glia limitans.[94] The innate immune response of ependymal cells may involve signalling through several pattern recognition receptors (PRRs) (see later under Identifying Microglia and Quantifying Microgliosis).

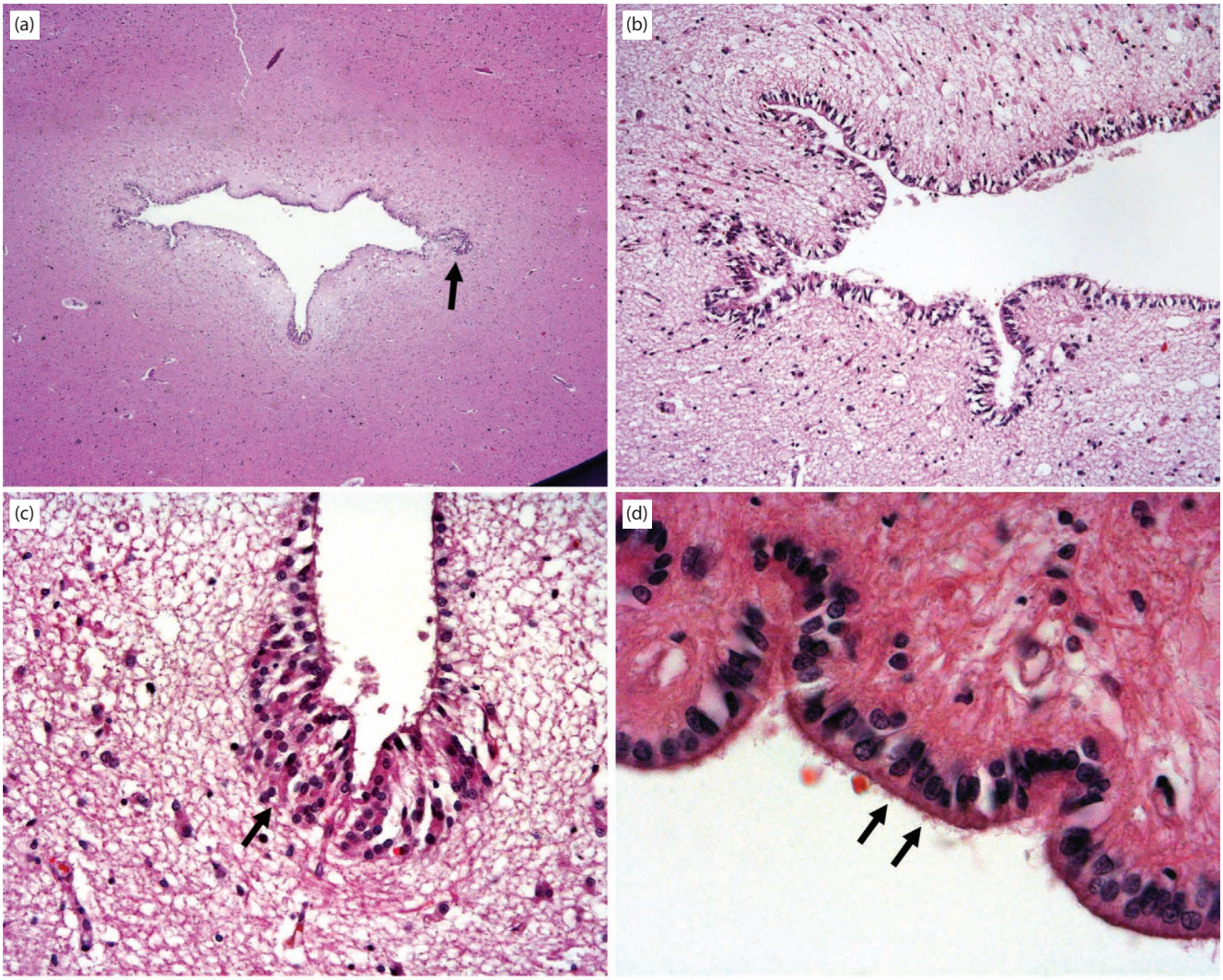
Ependymal cells arise from epithelium of the neural plate and the neural tube, which develops from the neural plate. Regions in the CNS destined to show an ependymal lining later in life, demonstrate (at 6 weeks of intrauterine development) only densely cellular pseudostratified columnar epithelium that is quite mitotically active. This mitotic activity essentially ends when the ventricular lining is fully developed, never to resume. However, the pseudostratified appearance of ependyma may occasionally be found in the ventricular lining of older patients, even adults (Figure 1.16). Immunohistochemical studies of human fetal ependyma show variably strong vimentin immunopositivity as early as 8 weeks into development in most ependymal regions (including spinal cord, the lining of all ventricles and cerebral aqueduct), though this diminishes (but does not disappear entirely) by 40 weeks of gestation.[203] Cytokeratin (CK-904) immunoreactivity is maximal in most regions, though surprisingly absent from the lining of the third ventricle, from 8 to 14 weeks of gestation but disappears thereafter. GFAP and S-100 antibodies show patterns of ependymal immunoreactivity that appear to be highly dependent on the precise locus within a given neuroanatomic structure being examined: as one example, GFAP immunoreactivity is prominent in the roof plate of the developing spinal cord but absent from its floor plate, although the opposite pattern of immunoreactivity is noted in the fourth ventricle and cerebral aqueduct.[203] By full term, fairly consistent and robust GFAP and S-100 immunoreactivity are noted only in the ependymal lining of the lateral and third ventricles and parts of the fourth ventricle.

Ependymal cells are connected to each other by gap junctions. Proteins known as connexins (Cx) are present at these junctions and contribute to 'intercellular communication, ion homeostasis, volume control and adherent connections between neighbouring cells'.[55] Connexin proteins Cx26, Cx30, Cx43, and Cx45 are mainly expressed at the apices of ependymal cells.[55] Aquaporins (AQPs) are well known to be expressed in the end feet of astrocytes, but the AQP4 channel that controls water movement in brain is also expressed in basal-lateral areas of ependymal cells, as are other members of the AQP family.[55]

Ependymal cells have apical cilia that beat in a coordinated fashion and this organized beating may, in part, be due to the gap junctions. Del Bigio notes that ependymal cilia 'may help to create concentration gradients of guidance molecules in cerebrospinal fluid that serve to direct neuroblast migration from the lateral ventricle wall into the olfactory bulb'.[55] Damage to ependymal cilia has, in rare human instances, been shown to produce hydrocephalus (or may indeed result from severe and/or prolonged hydrocephalus), although there are numerous examples of mice with mutations in ciliary proteins that have been proven to develop hydrocephalus, with or without occlusion of the cerebral aqueduct.[55]

Ependymal cells have a relatively circumscribed repertoire of responses to injury, and only limited regenerative capacity at all ages. However, subependymal zone (SEZ) cells in a thin layer surrounding the lateral ventricle have been found to show properties of neural stem cells.[206] In experimental models, injury to the cerebral cortex modestly increases metabolic activity in the SEZ (as measured by cytochrome oxidase activity), as well as its proliferative capacity. Cells in the SEZ may have the potential to repopulate lost neurons in the olfactory bulb and even regions of the cerebral cortex. Although spared in most degenerative and genetic diseases that afflict the nervous system, the ependyma is highly vulnerable in many other conditions, by virtue of its unique 'barrier' position and vulnerability to increases in ventricular size. It can undergo injury when stretched during the evolution of ventriculomegaly associated with hydrocephalus, a hematoma or infarct that involves the ventricular wall (e.g. germinal matrix haemorrhages that commonly extend into the ventricular cavities in distressed premature infants), and in infections or inflammatory processes that extend directly from the brain parenchyma or subarachnoid space.[204] Hydrocephalus in humans is often accompanied by neuroimaging abnormalities that include a subventricular band of 'transependymal oedema', which may be transient and has poorly characterized neuropathological correlates. In experimental models of hydrocephalus, discontinuities and gaps in the ependymal lining are filled by the processes of subependymal astrocytes, but residual ependymal cells do not become proliferative. Neither do subependymal cells undergo metaplasia to repopulate the ependymal ventricular lining.

The range of ependymal reactions to injury has been well summarized by Sarnat.[204] Atrophic ependymal cells, usually a response to ventriculomegaly, are characterized by flattening and loss of their cytoplasm. Ventricular enlargement, especially when rapidly evolving and progressive, can cause stretching and tearing of the ventricular lining. Sites of rupture are more likely to occur over the smooth ventricular surface than at the ventricular angles. Subventricular astrogliosis is characterized by glial cells that proliferate, often extending into the ventricular cavity. This phenomenon, thought to occur within 1–2 weeks subsequent to the ependymal injury, is often described (somewhat inaccurately, because true inflammation is almost never a histopathological feature) as 'granular ependymitis', and the protrusions of glial tissue as 'ependymal granulations'. The process is very patchy and multifocal throughout the ventricular



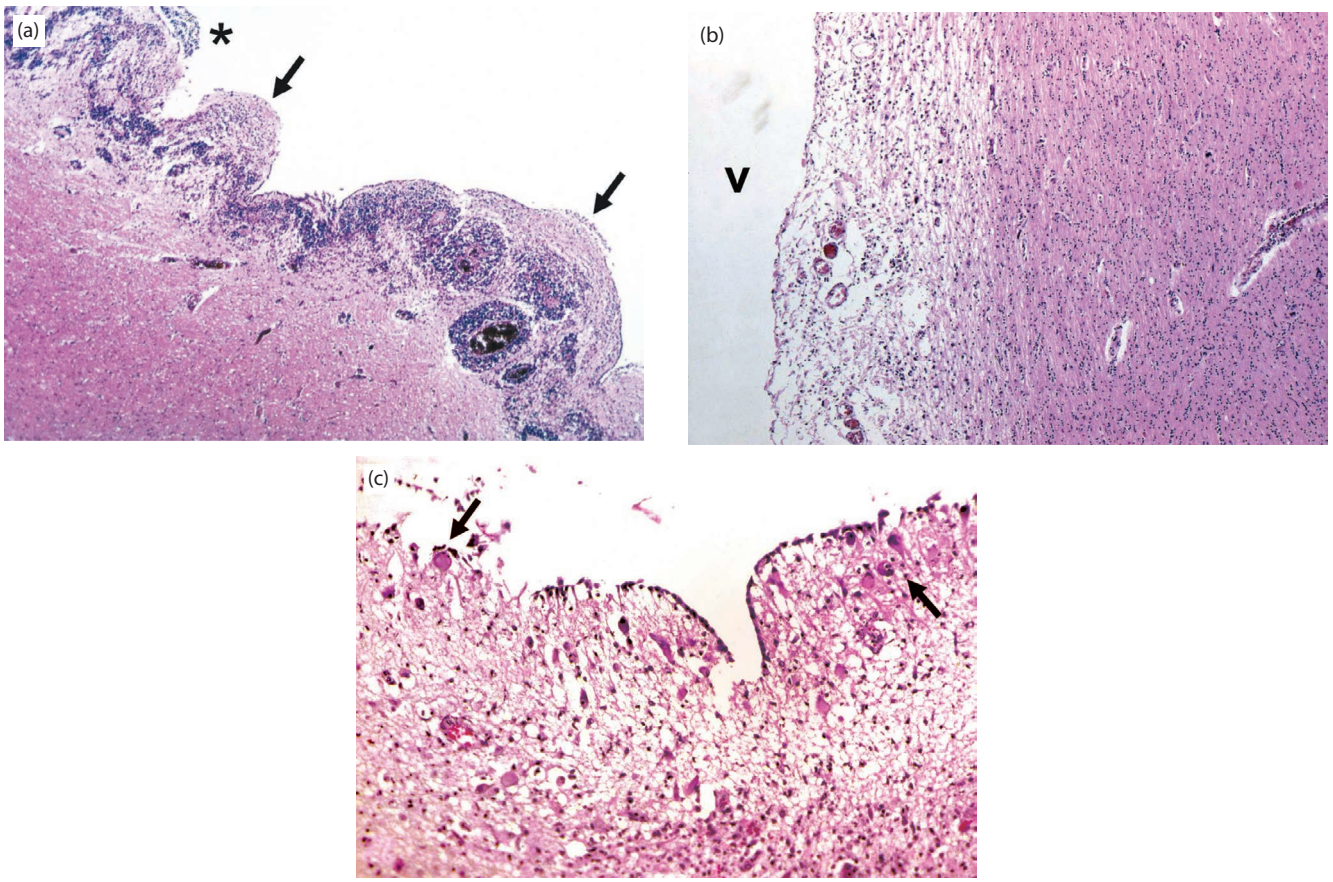
1.16 Histological features of normal ependyma. **(a)** Low-magnification view of the junction of the cerebral aqueduct (of Sylvius) with the fourth ventricle. Note small ependyma-lined 'outpouchings' (arrow), which are very common in any ependyma-lined structure. **(b,c)** Magnified views of the ependyma show a 'picket fence'-like structure with a slight tendency to stratification of ependymal cells in a few foci (arrow, [c]). **(d)** Relatively uniform ependymal nuclei, absence of a basement membrane deep to the ependyma, and wispy cilia on the ependymal surface (arrows). **(e)** Occasionally, as in this image from the wall of the third ventricle, the ependyma is arrayed in 'udder-like' folds – a finding of no pathological significance.

lining. These subventricular glial nodules may also represent the sequelae of a fairly indolent viral infection of the CNS (see later) and are commonly seen in the CNS of patients with acquired immunodeficiency syndrome (AIDS),[251] but are also commonly encountered as an incidental necropsy finding in individuals with no history of neurological disease.[204] When the ependyma has been injured by intraventricular haemorrhage (e.g. extending from a large germinal matrix bleed in a premature infant), macrophages, including siderophages or hemosiderin-laden macrophages, may be seen at or near the locus of injury. Ependymal rosettes, characterized by tiny 'tubules' of ependymal cells in the periventricular region (and sometimes forming hemi-rosettes rather than complete rosettes) may represent abortive attempts at recapitulating the formation of the embryonic neural tube; they may also be the result of ependymal residua within brain parenchyma, in which luminal/ periventricular astrocytic overgrowth has occurred. Similar rosettes are seen,

of course, in a variety of CNS tumours, most prominently ependymomas.

True ependymitis (to be distinguished from granular ependymitis, see earlier) may be suppurative/purulent, e.g. when encountered in association with a bacterial or fungal meningitis or brain abscess, polymorphonuclear leukocytes will then be present in abundance within and adjacent to the ependymal lining. Such an ependymitis may evolve into a ventriculitis; in its extreme form (for instance, when untreated) this can lead to filling of the ventricular cavity by pus and ventricular abscess formation.[204] Ependymitis may become so severe that it leads to fragments of ependyma being shed into the ventricular cavity and cerebrospinal fluid (CSF) pathways, rarely such cells are identified in samples obtained by lumbar puncture for evaluation of CSF cytology. Several viruses have a propensity to colonize ependyma and periventricular tissues. In the era of AIDS, this is most dramatically manifest with cytomegalovirus (CMV) infection, which can cause such a severe ependymitis/ventriculitis that a thick icing-like layer of exudative material is noted in cut sections through the fixed brain[251,253] (Figure 1.17c). This ependymal infection by CMV then commonly spreads in a 'ventriculofugal' direction, into the brain parenchyma. Much less commonly, adenovirus has been identified as causing a more subtle ependymitis/ventriculitis (Figure 1.17 b).[5] Mumps ependymitis, often with minimal inflammation, can lead to aqueductal stenosis, an important (though rare) cause of acquired hydrocephalus.[204] Ventriculomegaly becomes apparent weeks to months after a clinically apparent mumps virus infection, e.g. manifest as parotitis. Aqueductal stenosis has also been described after influenza and parainfluenza 2 infections. The only 'footprint' of many of these viral infections is the presence of microglial nodules in close proximity to the ependyma, and immunocytochemical evidence of viral infection within ependymal cells. In experimental animals, human respiratory syncytial virus (RSV) infection can also lead to viral antigen within ependymal cells and, eventually, aqueductal stenosis with hydrocephalus. Primary CNS neoplasms may extend to the ependymal lining (Figure 1.17a) and sometimes breach this barrier to gain access to the ventricular cavity, facilitating spread of such a tumour through the CSF pathways.

It is hardly surprising that the ependyma is vulnerable to infection by numerous pathogens, especially viruses, given its anatomically critical locus at the interface between CSF and brain parenchyma. Viruses may use specific receptors (e.g. CAR, JAM, CD46 and CD55) to target the ependymal and subependymal microenvironment. Choroid plexus



1.17 Ventricular/ependymal lining involved by neuropathologic lesions. (a) Widely infiltrating malignant primary brain tumour extends to the ependymal lining of the lateral ventricle. In one area, tumour appears (asterisk) to extend into the ventricular cavity. Other regions of the ependyma (arrows) show disruption. **(b)** Adenovirus encephalitis and ependymitis in a child with AIDS. Ventricular cavity is indicated by the 'V' (at left). Note almost complete loss of the ependyma, with spongy change and oedema in the periventricular region. **(c)** Cytomegalovirus ependymitis/ventriculitis affecting the fourth ventricle in a human immunodeficiency (HIV)-infected patient with AIDS. Note patchy denudation of the ependymal lining, with scattered cytomegalic cells (arrows) in or immediately adjacent to the ependyma. Sparse inflammatory cells are present in the periventricular neuropil.

epithelium, with anatomic similarities to ependyma, contains some cells that express pattern recognition receptors (PRRs) that in turn bind to pathogens opsonized with C3.[94] Thus both ependyma and choroid plexus epithelium, functionally linked by having crucial functions in maintaining ionic and fluid homeostasis in the brain, also play a direct role in preventing its colonization by micro-organisms, and maintaining the CSF in a sterile condition.

CHOROID PLEXUS

Choroid plexus is a villous, frond-like, convoluted structure located within ventricles and composed of epithelial cells, fenestrated blood vessels, and stroma; it is involved in the production of cerebrospinal fluid.[269] Four separate areas of brain contain choroid plexus: each lateral ventricle, the third ventricle, and the fourth ventricle. Choroid plexus cells are epithelial cells derived from neuroectoderm and thus constitute a subtype of macroglia. In early development, the epithelial cells are tall and pseudostratified, at intermediate stages of development they contain cytoplasmic glycogen, but by later stages of development they become cuboidal and lose glycogen.[269] Unlike ependymal cells that carry cilia, choroid plexus epithelial cells have frequent microvilli and cilia are rarely found. At their basal aspect, choroid plexus epithelial cells lie on a basal lamina and adjacent to highly fenestrated blood vessels that allow the choroid plexus (CP) to produce CSF from the blood. Wholesale diffusion of blood-borne substances, however, does not occur between the blood and CSF because of the presence of tight junctions between the CP epithelial cells. Tight junctions in CP cells contain the proteins occludin, claudin-3, claudin-5, and endothelial selective adhesion molecule (ESAM).[269]

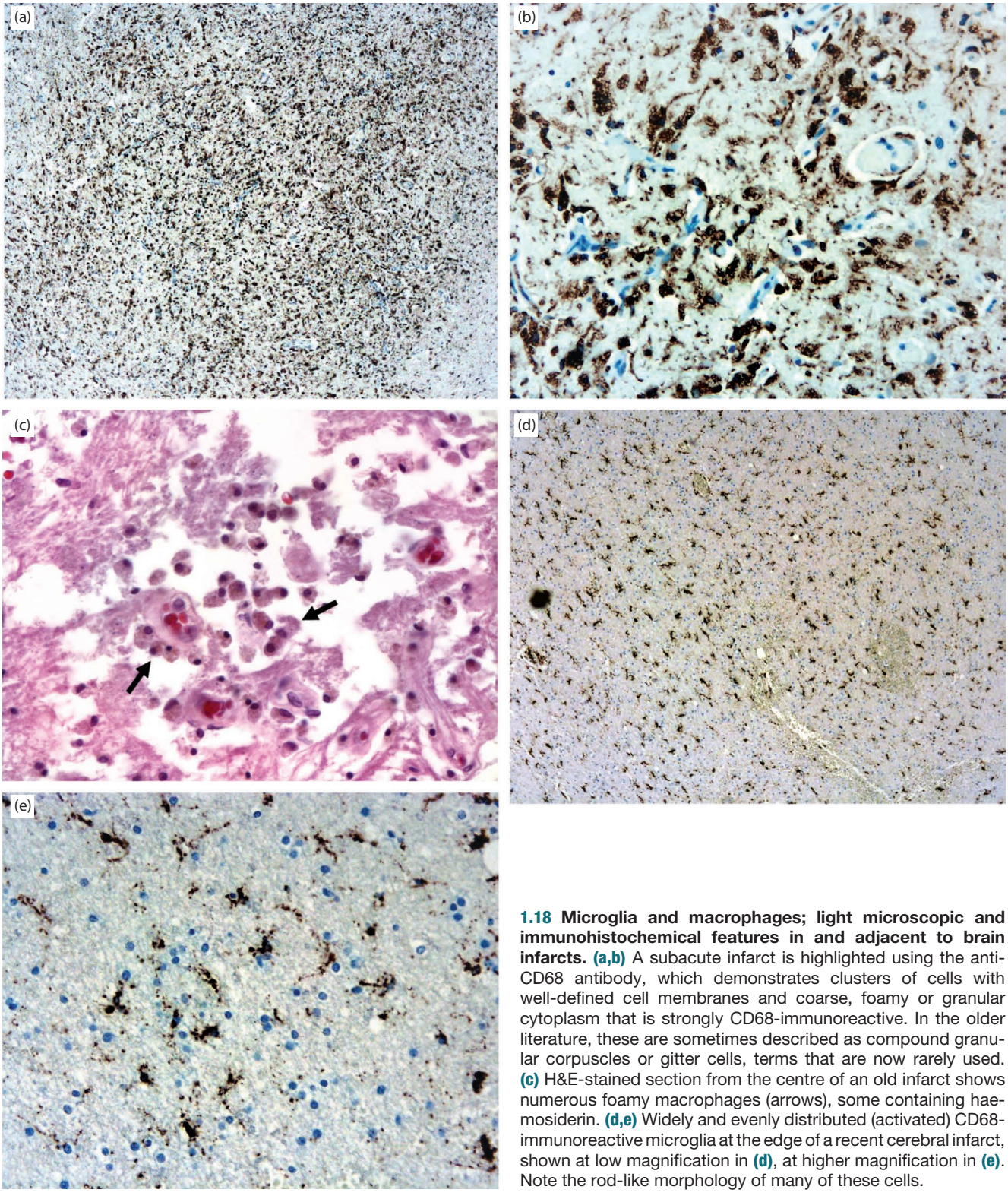
A comprehensive review of the functions of choroid plexus in health and different disease states has recently been published.[269] Abnormalities in CP cells are few in number, although progressive calcification of the stroma of the choroid plexus occurs with ageing. Aβ amyloid and Biondi ring tangles accumulate in CP epithelial cells in Alzheimer's disease, with the latter also seen to accumulate as part of normal ageing.[269] The amyloid source for Aβ amyloid accumulation in CP cells has been suggested to be uptake from CSF. Biondi rings are biochemically and ultrastructurally different from either neurofibrillary tangles or Aβ amyloid, and the exact nature of these structures is still being explored. Interestingly, some workers have suggested that Biondi ring tangles are among the earliest manifestations of Alzheimer disease.[155]

MICROGLIA AND MACROPHAGES

Microglial cells have historically been considered the cells within the CNS that respond to invasion of the parenchyma by viral agents, have important phagocytic functions and constitute the neural component of the reticuloendothelial system. A variety of observations, many of them originating in neuropathological specimens from patients, have led to a reformulation of the putative role of microglia in various diseases and responses of brain and spinal cord to injury.[121,247] It has become frustratingly clear that some ailments in which microglial proliferation is a key element, e.g. Rasmussen encephalitis associated with intractable partial epilepsy and cerebral hemiatrophy in children, do not have an obvious viral aetiology and may in fact be autoimmune disorders.[1,18,66] Microglia may also play a significant role in the progression of lesions seen in diseases of the CNS that are not primarily inflammatory, e.g. Alzheimer's disease, and under some circumstances may even have trophic/nutritive functions.[121] Thus, our understanding of microglial function and potential has greatly expanded in recent years. Much of this has also come about as a consequence of the AIDS pandemic. It became manifestly clear early in the worldwide epidemic of infection by the human immunodeficiency virus (HIV) that understanding the CNS consequences of direct HIV infection of the brain required a sophisticated understanding of the role of its microglial cells, the major cell type that harbours this retrovirus and is productively infected by it.[49,185] For these and other reasons, the 'rediscovery' of the importance of microglia has been reflected (as pointed out in a recent mini-symposium on this cell type) by a massive increase in the literature pertinent to their biology–between 2001 and 2005, almost 3600 articles had been published on microglia, more than in the prior 15 years![57]

Identifying Microglia and Quantifying Microgliosis

For decades, the origin of microglia/macrophages in the CNS has been controversial–the question has been formulated, somewhat simplistically, as 'Do they originate in the brain or the bone marrow or in both sites?' The current view is that blood-derived monocytes move into the brain during early embryonic development, then differentiate into microglia that share many surface markers or antigens with their blood-borne and visceral counterparts, monocytes and macrophages.[121] Under normal circumstances, microglia are inconspicuous bystanders in the scaffolding of the brain and spinal cord. Unlike neurons or ependymal cells, they are not identifiable by their striking and distinctive morphological characteristics or anatomical location. They are estimated to comprise as many as 15 per cent of cells in some parts of the CNS.[94] Though cells with characteristic microglial morphology had been recognized previously–probably even by Nissl in the late 1800s–their discovery and confirmation as a distinctive cell type is widely attributed to the work of del Rio Hortega and Penfield in 1927. They and other investigators seeking to study microglial biology in the early to mid-1900s utilized the silver carbonate method to demonstrate their presence in histological specimens. These methods have been largely supplanted by immunohistochemical stains of microglia/macrophages with primary antibodies directed against macrophage/microglial epitopes and surface antigens or receptors involved with immune system activation, including integrins and the ligands for ICAM-1. Frequently used markers are CD45 (relatively non-specific), CD68 (Figure 1.18), HAM (human alveolar macrophage)-56, CD11b (Mac1), CD11c (LeuM5), CD64 (an immunoglobulin receptor), MHC Class I antigen, MHC Class II antigen (HLA-DR), *Ricinus communis* agglutinin I lectin (RCA),[121] and a newer marker of great utility, Iba1.[268] Some microglia express both MHC class I and II antigens and may interact biologically with both T-helper (T4) and T-cytotoxic



1.18 Microglia and macrophages; light microscopic and immunohistochemical features in and adjacent to brain infarcts. (a,b) A subacute infarct is highlighted using the anti-CD68 antibody, which demonstrates clusters of cells with well-defined cell membranes and coarse, foamy or granular cytoplasm that is strongly CD68-immunoreactive. In the older literature, these are sometimes described as compound granular corpuscles or gitter cells, terms that are now rarely used. **(c)** H&E-stained section from the centre of an old infarct shows numerous foamy macrophages (arrows), some containing haemosiderin. **(d,e)** Widely and evenly distributed (activated) CD68-immunoreactive microglia at the edge of a recent cerebral infarct, shown at low magnification in **(d)**, at higher magnification in **(e)**. Note the rod-like morphology of many of these cells.

(T8) lymphocytes at the same time. Microglia are also demonstrated histochemically (in the mouse) by staining for nucleotide diphosphatase (NDPase).[267] Quantitative estimates of microglial number in the mouse fascia dentata have been provided through the use of unbiased stereological cell counting techniques; estimated numbers of microglia in this structure were on the order of 12 000.[266]

Microglial Types

Microglia were subclassified using the older silver carbonate technique as being amoeboid, ramified or of intermediate form.[121] They are now more commonly described as resting, activated or amoeboid phagocytic microglia, but are known to modify their structure and repertoire of expressed