Similar types of tissue reaction result as a final common pathway from a wide array of different internal brain pathophysiological states and external insults. Since these cellular and tissue reactions are largely independent of the specific type of insults, they are, therefore, non-specific. The tissue reactions are to be differentiated according to their specific pathogenetic mechanisms, though these mechanisms as well as the phenomena are overlapping as demonstrated in Fig. 4.1; brain ischemia as a type of metabolic disturbance, edema, intracranial pressure, necrosis, herniation and inflammation are influencing themselves and are dependent on each other. Some will be mentioned again in later chapters as viewed from different forensic aspects; therefore, a certain redundancy is unavoidable. Immediately following, we offer a survey of the individual types of reaction and their fundamental pathophysiological principles and morphology.
PART I: Principles of Forensic Neuropathology

4.1 Increased Brain Volume – Edema

4.1.1 Definition

If brain volume increases, both blood and CSF are displaced until the intracranial pressure (ICP) increases. The consequent pressure of the brain against the inelastic dura mater (Fig. 4.2) and the skull can lead to a lethal series of complications in clinical neurology. The following remarks are based largely on Ironside and Pickard (2002).

Brain volume depends on the following factors:

1. Water content (cerebral hydration). The brain has a normal water content of about 75%. A disturbance of the blood–brain barrier (BBB) can lead to an increase in the fluid content, with a consequent increase in brain volume.

2. Intracranial blood volume (Hirai et al. 1986). This can be driven upward by a number of factors: arterial hypertension (Marshall et al. 1969); enhanced cerebral blood flow secondary to elevated cerebral perfusion pressure (Artru et al. 1976); a decline in the cerebrovascular resistance of arterioles, capillaries, and postcapillary vessels (Langfitt et al. 1965) due to hypercapnia, hypoxemia associated with severe elevation of arterial pressure (Marmarou et al. 1997), or due to obstruction of the venous outflow of the brain. Elevated cerebral blood volume, also known as “brain swelling,” is a congestive process.

3. Cerebrospinal fluid (CSF) pressure. The central nervous system (CNS) of the average adult contains a CSF volume of approximately 120–140 ml. Among the causes of a rise in CSF pressure is acute obstructive high pressure hydrocephalus (see pp. 54 f).

A number of additional factors may also influence brain volume. The congested brain expands particularly rapidly under high arterial pressure (Leech and Miller 1974). Nawashiro et al. (1995) used experimental closed brain injury in rats to demonstrate a rapid and widespread increase in regional cerebral blood flow and impaired cerebral autoregulation. In humans a variety of factors act in concert after the incidence of severe brain injury. Cerebral computed tomography (CCT) and magnetic resonance imaging (MRI) studies have shown that brain edema is the major fluid component of brain swelling (Marmarou et al. 1997, 2000). A reactive hyperemia is an additional factor and may be the mechanism underlying mechanical/ischemic brain injury (Seida et al. 1989). Moreover, regional cerebral ischemia additionally is attributed to a compromised, leaky microvasculature rather than to vasospasm of larger vessels (Schröder et al. 1998).

The conclusion that brain swelling is due primarily to edema and not congestion of blood appears to be valid also for children (see Chap. 20, pp. 415 f). Cerebral blood flow in children with severe head injuries is not substantially increased over that in uninjured children (Zwienenberg and Muizelaar 1999). This has also been demonstrated following experimental generation of brain trauma in newborn and juvenile pigs (Armstead and Kurth 1994). The experimental findings of Biagas and coworkers (1996), in contrast, demonstrated a delayed rise in cerebral blood flow following experimental contusion in young and adult, but not in elderly, rats.

4.1.2 Clinical Features

Normal adult ICP is less than 2 kPa (1 kPa=7.5 mm Hg=7.5 torr), mild elevations in pressure range from 2 kPa to 3 kPa, moderate elevations attain 4 kPa, while major intracranial hypertension exceeds 5 kPa (Miller and Ironside 1997). Normal CSF pressure in adults is 0–1.3 kPa, with an upper limit of 2 kPa. While a short-term rise in ICP pressure of up to 10 kPa may be tolerated so long as it does not cause distortion of the brain (Johnston and Paterson 1974), a MBI-induced rise of more than 8 kPa with distortion of the brain can result in herniation and brain death syndrome.

The classic symptoms associated with elevated ICP are vomiting, headache, papilledema, and coma.
Distortion or pressure on the floor of the fourth ventricle are most likely responsible for the vomiting, while stretching and distortion of the dura mater and major intracranial blood vessels, all sensitive to pain, probably account for the headache. The papilledema is not a direct result of the rise in water content, but the consequence of an accumulation of axoplasm in the optic papilla secondary to the blockade of axoplasmic flow from ganglion cells along the optic nerve. Papilledema is a common symptom of chronic intracranial hypertension. It is not, however, a common feature of MBI (Selhorst et al. 1985), and its absence does not necessarily mean that ICP is normal. A further increase of ICP leads to a loss of consciousness and coma.

Elevated ICP affects other organ systems as well. It often induces arterial hypertension and systolic blood pressure may climb to 40 kPa or more. The arterial hypertension is caused by an increase in sympathetic activity. Cases of raised ICP with myocardial involvement often exhibit pathological alterations consisting of subendocardial hemorrhage and widespread focal myocardial necrosis as well as electrocardiographic changes such as T-wave inver-

Fig. 4.2a–d. Macroscopic findings in brain swelling. a Tightened dura; b flattened gyri; c compressed ventricles and notches (arrows) which give evidence of a slight herniation; d compressed cerebellar tonsils
sion and elevation of the ST-segment, which point to myocardial ischemia (Connor 1968). Respiratory disturbances associated with elevated ICP often precede apnea. Central neurogenic hyperventilation is observed in connection with the midbrain lesion. In patients with raised ICP, neurogenic pulmonary edema can complicate the clinical course. The mucosa of the digestive and urogenital tracts can become hemorrhagic, eroded, and ulcerated, gastric erosions being particularly common in comatose patients with elevated ICP.

4.1.3 Pathogenesis

A fundamental distinction must be made between global and focal cerebral edema. The former follows acute systemic hypoxic events, e.g., transitory cardiac arrest or chronic hypoxia in respiratory diseases. Global cerebral edema may also be associated with metabolic diseases, intoxications, and inflammation. Focal cerebral edema results from focal tissue destruction or alteration of brain tissue that has undergone membrane failure in cells and vessels due to infarction or traumatic hemorrhage or tumor. The tissue surrounding the central lesion has passed only the upper threshold of electrical silence and thus retains the capacity to recover if perfusion is restored in time (Harding and Copp 1997). This zone resembles the penumbra surrounding the moon in full eclipse (Astrup et al. 1981). Because these tissue changes are partly reversible, they are of considerable therapeutic interest (see pp. 63 f).

Information on the incidence of intracranial hypertension has been gained mainly from survivors of MBI. Miller and his associates (1977) reported that ICP levels exceeded 2.7 kPa for 5 min or longer in 44% of 160 patients in one series and in 53% of another series of 215 patients (Miller et al. 1981). Raised ICP was found in more than 70% of cases in a more detailed prospective study of elevated ICP in victims with severe head injury by Marmarou and colleagues (1991). Jones and colleagues (1994) found elevated ICP in more than 80% of 74 brain injury patients (54 severe, 17 moderate and 3 minor) undergoing artificial ventilation with ICP monitoring. These findings indicate that intracranial hypertension is a common event, especially in comatose patients. Certain features detected by CCT are consistently associated with elevated ICP. Loss of the images of the third ventricle and perimesencephalic CSF cisterns, and dilatation of the lateral ventricle contralateral to a mass lesion, as well as the absence of these features are no guarantee that ICP will remain normal (Teasdale et al. 1984; O'Sullivan et al. 1994).

Elevated ICP is also common in patients who are comatose from causes other than brain injury (Chandler and Kindt 1976). Among the possible causes are liver failure (hepatic coma), intracranial hemorrhage (subarachnoid and intracerebral), post-hypoxic states (cardiorespiratory arrest, near drowning), infection (meningitis, abscess, and encephalitis), as well as various other types of inflammation and intoxication.

Adams and Graham (1976) published neuropathological criteria for determining at autopsy whether ICP in victims of brain injury was elevated during life. The same team (Graham et al. 1987) compared the nature of the brain damage in patients with and without elevated ICP after suffering a non-missile brain injury who had survived long enough to receive treatment in a neurosurgical unit. Pressure necrosis of the parahippocampal gyrus, an indicator of high supratentorial ICP and tentorial herniation, was present in two-thirds of the 434 patients in their most recent study. It was closely associated with skull fracture, brain swelling, diffuse axonal injury, hypoxic brain damage, and extensive supratentorial hematoma. The brain stem was damaged in 68% of victims with pressure necrosis, the anterior lobe of pituitary was necrotic in 45%, and there was hemorrhagic infarction in the distribution of the posterior cerebral artery in 36%.

4.1.4 Types of Brain Edema

Klatzo (1967) distinguishes two types of edema: vasogenic edema and cytotoxic edema (Table 4.1). This distinction continues to be of both theoretical and practical value (cf. Kimelberg 1995a, b; Mendelow et al. 2000).

4.1.4.1 Vasogenic Edema

Blood vessels in the CNS are uniquely restricted in their permeability. Many substances are exchanged between the blood and brain parenchyma at slower rates and the concentrations in CNS at steady state are lower than in other organs (Lee 1982). Dyes as well as proteins, drugs, and microorganisms introduced into the CSF enter the brain freely, while those introduced into the blood stream do not. This limited permeability is attributed to the BBB, a specialized feature of the CNS that restricts the entry of viruses and bacteria, emigration of immune cells, and diffusion in the CNS of drugs and soluble molecules from the systemic compartment.

Intravenously applied Evans blue will bind to serum albumin and permeate the BBB only under pathological conditions. This phenomenon is demonstrated after experimentally induced ischemia of one hemisphere by means of macroscopic observation (Fig. 4.3a) and by means of fluorescence micros-
### Table 4.1. Classification of the two types of edema: vasogenic edema and cytotoxic edema

| Vascogenic edema                                                                 | Cytotoxic edema                                                                 |
|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Intercellular accumulation of fluid associated with volumetric enlargement of the brain | Intracellular accumulation of fluid and (possibly) secondary increase of the brain volume |
| Perifocal edema (penumbra) surrounding hemorrhages, tumors, abscesses, etc.       | Ischemia (generalized or focal), intoxications, especially by triethyltin and cyanide, metabolic diseases, etc. |
| Injury of endothelial cells (tight junction)                                     | Injury of brain cell membranes in neurons by metabolic or electrophysiologic mechanisms |
| Increased vascular permeability with leakage of plasma including plasma proteins | Impairment of the cellular Na-K membrane pump                                     |
| Involvement of the white matter                                                 | Involvement of the gray (and white) matter                                        |
| Enlargement of the extracellular spaces                                          | Hydropic swelling of astrocytes and (mostly irreversibly injured) neurons          |
| Swelling of the perivascular astrocyte foot processes                            | Light-microscopic demonstration of potassium loss in astrocytes and neurons        |
| Light-microscopic demonstration of plasma proteins in the perivascular neuropil and astrocytes |                                                                                   |

**Fig. 4.3a–d.** Vasogenic and cytotoxic edema. Experimentally induced ischemia of the right hemisphere in gerbils results in a disruption of the blood−brain barrier (vasogenic edema: a, b) and a potassium loss (cytotoxic edema – see Oehmichen et al. 2000: c); d human brain expresses extravasated albumin (brown color) exclusively during the very early postmortem interval (see Oehmichen and Gencic 1980a) (a, b Evans blue fluorescence; magnification b ×100; c histochemical demonstration of potassium; d albumin reactivity, magnification ×300)
copy (Fig. 4.3b). The demonstration of albumin in human brain using immunohistochemistry will only succeed during the very early postmortem interval (Fig. 4.3d) — before a general diffusion of blood serum occurs within the brain parenchyma — as a morphological marker of the diffuse postmortem BBB disturbance. Under experimental conditions an accumulation of plasma proteins in Purkinje cells (Oehmichen and Gencic 1980a, Ikegaya et al. 2004) takes place.

Anatomically the BBB consists of a capillary endothelium containing intercellular tight junctions and specialized enzymes, such as transpeptidases, dehydrogenases, decarboxylases, and monoamine oxidases (Reese and Karnowsky 1967; Brightman and Reese 1969; Lee 1982). The intercellular junctions are most conspicuous near the luminal surface where the cell membranes fuse. A basement membrane in contact with astrocytic foot processes surrounds the endothelial cells. Pericytes are enclosed by an envelope of the perivascular basement membrane, which splits to enclose the pericyte. Brain capillaries are almost totally invested by astrocytic processes. Astrocytes exert inductive actions during development and are thereby largely responsible for the special attributes exhibited by endothelial cells, such as the presence of tight junctions between the cells (Abbott et al. 1992). Astrocytes and microglia both contribute to the formation of the BBB (Prat et al. 2001).

There is an inverse hemodynamic relation between ICP and cerebral blood flow (CBF): the higher the ICP, the lower the CBF. If cerebral circulation and circulatory autoregulation are normal, a drop in ICP will induce only a slight increase in CBF until a threshold level of about 8 kPa is attained. CBF is regulated by mechanisms such as compensatory dilatation of small arteries and arterioles.

Patients suffering from acute MBI, intracranial hemorrhage, or hypoxic brain injury need a mean arterial blood pressure above 8 kPa to maintain perfusion. The brain damage in such circumstances is associated with a rise in cerebrovascular resistance due to the vessels’ spastic reactivity. Baseline ICP levels may even need to be higher in order to drive sufficient blood through the brain tissue (Chan et al. 1992). Should CBF drop below 10 (ml/min)/100 g, potassium levels in the intercellular spaces rise, while intracellular sodium and calcium increase. Cellular edema causes the cells to swell and a calcium influx triggers a series of autodestructive processes.

The BBB can be compromised by the following three mechanisms (see Miller and Ironside 1997):
1. Enhanced vesicular transport and creation of transendothelial channels by perturbation of endothelial plasmalemma, increased pinocytic activity, the activity of free oxygen radicals, or an increase in superoxides. Subarachnoid application of hemoglobin and hemoglobin degradation are known to cause brain edema (Huang et al. 2002).
2. Disconnection of the interendothelial tight junctions, e.g., by substances of very high osmolarity.
3. Structural or biochemical modification of the endothelial membrane that intensifies its permeability.

It has also been known for a long time that the ability of certain substances to pass through the BBB depends on their specific properties:

- Their nature regarding the capacity of the BBB for active transport (Broman and Steinwall 1967)
- Their affinity for carrier molecules (Lajtha 1968).
- Their molecular radius (Thompson 1970).
- Their lipid solubility (Oldendorf 1977).

As shown in detail later, the permeability of the BBB also depends on age. A good example of this is bilirubin encephalopathy, which is caused by bilirubin crossing the BBB of certain nuclei during the perinatal period — a feat it is incapable of in later life — and inflicting damage on nerve cells and, to a lesser extent, on glial cells and the basal ganglia.
degree, on astrocytes (for further information see pp. 452 ff). Thus for bilirubin at least the BBB appears to be less efficient at birth than in children or adults (Haymaker et al. 1961). In MBI with intracerebral hemorrhages and associated elevation of the bilirubin level the perifocal edema can be marked by a green color demonstrating extravascular bilirubin as demonstrated in Fig. 4.4. In senile and mentally disturbed patients, the BBB has been found to have a lower rate of transport, a reduced uptake of glucose and other nutrients, plus a diminished outflow of metabolic wastes (Quadbeck 1967, 1968).

4.1.4.2 Cytotoxic Edema

The movement of water from the vascular compartment to intracellular or interstitial spaces is not regulated biochemically by the BBB since hydrostatic and more powerful osmotic gradients enable free water to diffuse passively across capillary membranes. The passage of ions and molecules of various sizes is controlled by lipid-soluble substances in the endothelial wall and by ionic channels and active pumps. The white matter of the brain is 68% water, the gray matter 80% (Adachi and Feigin 1966). A rise in brain water content entails an increase in brain volume, i.e., brain edema.

As a result of energy failure (deprivation of oxygen and glucose), which disables the sodium-potassium membrane ATPase pump system, water accumulation within the cells follows an osmotically obliged response to an increase in intracellular sodium and loss of potassium (Fig. 4.3c). The influx of osmotically drawn water causes swelling of the cell. The energy failure is accompanied by an influx of sodium and chloride and an efflux of hydrogen ions, potassium, and bicarbonate. There is a parallel disturbance of the voltage- and ligand-gated mechanisms that regulate the entry of calcium into the cell that initiates a calcium-mediated destructive sequence. Cytotoxic edema is the result of the action of various cytotoxic agents, e.g., of cyanide or triethyl tin (also see Chaps. 16, 17).

Brain cells can also swell without a concomitant increase in brain volume if fluid shifts from an extracellular to an intracellular space. Although this does not produce an immediate rise in ICP, cellular edema ultimately draws water from the vasculature into the brain, increasing brain volume and precipitating a rise in ICP.

Ischemic edema is a cytotoxic edema whose clinical effects depend on how much and for how long cerebral blood flow is reduced (Bell et al. 1985). Klatzo (1967) showed that the initial cytotoxic edema following permanent occlusion of a major blood vessel causes irreversible ischemic cell damage, resulting in a secondary vasogenic edema when endothelial cells are damaged. Even temporary ischemia with subsequent reperfusion will induce reactive hyperemia and secondary endothelial damage that produces a secondary vasogenic edema (Greenwood 1991).

As a whole, the brain is resistant to pure hypoxia (diminished oxygen supply) (pp. 276 ff, see also Miyamoto and Auer 2000), which causes no or only partial breakdown of the BBB and which may be reversible after recovery (Bakay and Lee 1968; Auer 2000). Anoxia (complete lack of oxygen), by contrast, results in a rapid rise in BBB permeability that becomes irreversible after just a few minutes (pp. 280 ff). If anoxia acts in combination with complete ischemia secondary to ligation of both common carotid and subclavian arteries, the BBB can retain its impermeability for as long as 3 h (Broman 1949; Blank and Kirshner 1977). Incomplete ischemia, however, will rapidly and completely break down the BBB (Bakay and Lee 1965).

Kimmelberg and colleagues (1997) could demonstrate the potential toxic mechanisms of this type of edema on neurons. They describe a primary cytotoxic effect on astrocytes that induces astrocytic swelling. This swelling in turn leads to the release of excitatory amino acids such as glutamate, whose levels increase in extracellular spaces following the incidence of MBI (Kanthan and Shuaib 1995). A rise in extracellular glutamate levels causes cell death due to an influx of Ca++ via the neurons’ activated ionotropic glutamate receptors (Choi and Rothman 1990).

Other authors have offered a somewhat different explanation for the irreversible injury: it may be induced by simultaneously generated free radicals or extravasated plasma components that stimulate the activation of nitric oxide synthase (NOS) in reactive cells. Nitric oxide thus generated may contribute to diffuse degeneration of the white matter (Gotth et al. 1998). The accumulation of plasma proteins within neurons and microglia in combination with cytochrome-C release by astrocytes can lead to DNA fragmentation and cell death (Matz et al. 2001).

4.1.4.3 Conclusion

Klatzo’s (1967) classification of brain edema has proved to be a useful aid in distinguishing between various pathogenetic mechanisms and their sequelae. In experimental and clinical practice however it must be assumed that brain swelling is caused by a combination and/or a temporal overlapping of a number of processes, as described by Kimelberg et al. (1997).

Non-invasive diffusion-weighted (DW) MRI is able of calculating changes in the apparent diffusion coefficient (ADC) of water protons in the brain (Garcia et al. 1995; Chu et al. 2001). A decline in ADC has
been attributed mainly to a reduction of the extracellular space and a rise in intracellular volume, although other contributing factors are possible (Pierpaoli et al. 1996). In this manner cellular (cytotoxic) edema can be differentiated from extracellular (vasogenic) edema and a correlation made with the severity of injury and consequent deficit. Because DW-MRI (see also Mendelow et al. 2000) enables edema types to be determined intra vitam under clinical conditions, current classifications of edema types could be revised in light of new findings. However, we should remember that all edema ultimately arises from the blood. It is the size of the leak in the brain vasculature that gives rise to the artificial distinction between cytotoxic and vasogenic edema, cytotoxic edema being mainly water and vasogenic edema including proteins also derived from the blood.

**4.1.5 Neuropathology**

Brain swelling caused by edema, congestion or a rise in CSF pressure can obliterate the subarachnoid space, flatten the gyri, reduce ventricular size (Squier 1993, Fig. 4.2), and cause herniation (see pp. 51 ff). At autopsy the white matter seems softer in consistency and paler than normal. The normal, sharp demarcation between gray and white matter is lost, often with thinning of the cortex overlying the zone of white matter edema. The arcuate fibers are spared.

In rare cases of vasogenic edema associated with liver insufficiency combined with elevated bilirubin levels in serum the spread of edema may be characterized by a greenish-yellow color (Fig. 4.4). Under normal conditions bilirubin is not able to permeate the BBB, with one exception: the newborn (see pp. 452 ff).

**Cytotoxic edema**, which predominates in gray matter, is characterized by astrocytic swelling and the enlargement of perineuronal and perivascular spaces indicative of the swelling of astrocytic foot processes around neurons, capillaries, and arterioles (Fig. 4.5). The hallmarks of *vasogenic edema* include swelling of pericapillary astrocytic processes and of oligodendrocyte cytoplasm, plus the spread of exudate in the extracellular space of white matter (Fig. 4.6). Macroscopically vasogenic edema induces a slight green discoloration of the white matter.

Histologically, edema, vasogenic edema in particular, features extensive cytoplasmic vacuolation in the white matter with status spongiosus where a clear space surrounds small vessels and nuclei (Fig. 4.6). Ultrastructurally, few visible changes are evident in...
49

CHAPTER 4: Cell and Tissue Reactions

...the cerebral capillaries. The brain parenchyma, in contrast, exhibits swelling of glial processes or dendrites, splits in the myelin laminae and, less often, enlargement of the extracellular space. Vacuolation may be especially prominent in myelinated fiber bundles and constitute the earliest and most consistent elementary edema-induced change. Following immersion fixation, however, these phenomena can often be difficult to distinguish from (postmortem) artifacts.

These phenomena may be associated in the beginning with a leukocyte emigration (Fig. 4.7a) and in the last stage with astrocytic hyperplasia and hypertrophy (Fig. 4.7c, d). Astrocytes and macrophages also ingest extravasated plasma proteins. Myelin sheaths undergo increasing fragmentation and macrophages phagocytose lipid breakdown (Figs. 3.8f, 9.15b, 9.16). Oligodendrocytes are much less likely to partake in the alterations of edematous brain tissue. Most cases of brain edema exhibit a combination of cytotoxic and vasogenic edema. Inhibition of ion pumping or secondary retrograde reaction can cause swelling of neurons. The usual reaction is neuronal shrinkage, commonly combined with swelling of neighboring glial cells, especially of astrocytic processes. Irreversible changes in the myelin sheath are unequivocally manifested by the apposition of macrophage reaction in the form of compound granular cells. Involvement of the white matter by edema of this severe degree coincides with a so-called edematous necrosis (Jacob 1947). The final phase of terminal edema can be marked by cystic alteration or glial scaring.

4.1.6 Space-Occupying Effects

Brain swelling is one of a wide variety of neurological conditions, among them tumors, hemorrhages, and ischemia/hypoxia, that can induce an increase in ICP. A rise in ICP leads not only to compression of the brain, but to diminished CSF volume, shifting, and herniation, as well as to secondary complications such as ischemia and hemorrhage. If not treated, ICP can rapidly progress to death due to brain stem compression secondary to cerebellar or uncal herniation (Meyer 1920). Focal expanding mass lesions must be distinguished from diffuse space-occupying processes.

- **Diffuse brain lesions** such as inflammation, bilateral intracranial hemorrhage, total brain ischemia (cardiac arrest) or intoxication are macroscopically characterized (Fig. 4.2) by a tension of
PART I: Principles of Forensic Neuropathology

Distortion of the brain results from compressive forces exerted by adjacent structures, which leads to overall expansion of the hemispheres. The dura mater may become so tense as to compress the terminal branches of the cerebral arteries, with consequent ischemic or hemorrhagic necrosis of cortical structures (Lindenberg 1955) or impairment of perfusion (Janzer and Friede 1979) accompanied by perisulcal infarcts.

Continued expansion of the mass may provoke contralateral displacement of the midline structures (see Chap. 7 and Fig. 4.8a). If the contralateral foramen of Monro is obliterated, the contralateral lateral ventricle may become enlarged, triggering a further rise in ICP. A lesion that expands in the frontal lobe may displace the free margin of the anterior part of the falx cerebri (Fig. 4.8a, d). If a lesion expands in the temporal lobe, a disproportionately pronounced shift of the third ventricle will occur (Fig. 4.8a), with upward displacement of the Sylvian fissure and neighboring branches of the middle cerebral artery.

Focal intracranial processes such as abscess, tumor, infarction or subdural hemorrhage (Fig. 4.8a, b) are also capable of inducing a life-threatening homolateral rise in ICP. Because they allow time for intrinsic compensatory mechanisms to operate, particularly reduced CSF volume, slowly expanding focal lesions are less likely to cause an early increase in ICP and brain shift. However, the distortion and herniation of the brain in such cases can be considerable. Rapidly expanding focal lesions, by contrast, are more likely to produce an immediately elevated ICP. Brain death often supervenes in such cases before much distortion or herniation can occur.

Distortion of the brain results from compressive forces exerted by adjacent structures, which leads to overall expansion of the hemispheres. The dura mater may become so tense as to compress the terminal branches of the cerebral arteries, with consequent ischemic or hemorrhagic necrosis of cortical structures (Lindenberg 1955) or impairment of perfusion (Janzer and Friede 1979) accompanied by perisulcal infarcts.

Continued expansion of the mass may provoke contralateral displacement of the midline structures (see Chap. 7 and Fig. 4.8a). If the contralateral foramen of Monro is obliterated, the contralateral lateral ventricle may become enlarged, triggering a further rise in ICP. A lesion that expands in the frontal lobe may displace the free margin of the anterior part of the falx cerebri (Fig. 4.8a, d). If a lesion expands in the temporal lobe, a disproportionately pronounced shift of the third ventricle will occur (Fig. 4.8a), with upward displacement of the Sylvian fissure and neighboring branches of the middle cerebral artery.
CHAPTER 4: Cell and Tissue Reactions

4.1.7 Herniation

The ultimate result of the space-occupying process is development of lateral and then downward herniation, visible at several loci:

1. Falx cerebri (cingulate, or subfalcine herniation).
2. Tentorium cerebelli (lateral, or uncal herniation).
3. Thalamus/hypothalamus (central, or diencephalic herniation) which may result in downward displacement and hemorrhage in the midbrain and pontine tegmentum.
4. Foramen magnum (tonsillar herniation).

4.1.7.1 Uncal Herniation

A bilateral expanding supratentorial mass can cause herniation-induced notches as well as hemorrhages of the uncal area. This in turn exerts downward pressure on the medial part of the parahippocampal gyrus toward and through the tentorial incisura (Figs. 4.8b, 4.9). The clinical and morphological se-
The sequelae of uncal herniation depend on the magnitude of the supratentorial pressure and on anatomical variations in the size of the tentorial notch, position of the brain stem within the notch, position of the oculomotor or third nerve, and the inter-oculomotor nerve angle. They also depend on the structure and course of the posterior cerebral artery, known to play a role in herniation syndromes (Adler and Milhorat 2002).

Herniation of the parahippocampal gyrus (Fig. 4.9) creates narrowing of the midbrain along its transverse axis and compression of the aqueduct. This pushes – in the case of a unilateral expanding mass – the contralateral cerebral peduncle against the opposite free tentorial edge (Fig. 4.8b), pinning the ipsilateral oculomotor nerve between the petroclinoid ligament or free edge of the tentorium and the posterior cerebral artery. The lesion of the ipsilateral oculomotor nerve is associated clinically with ptosis and dilatation of the ipsilateral pupil, which becomes unresponsive to light.

The elevated ICP produces a wedge of hemorrhagic necrosis along the parahippocampal gyrus groove (so-called pressure necrosis, to be differentiated from “herniation contusion” – see Figs. 4.8b, 4.9b). Pressure necrosis can result from an ICP exceeding 5.4 kPa (see Adams and Graham 1976). It is analogous to necrosis due to brain retractor pressure in neurosurgery. Clinically, uncal herniation is accompanied by an abrupt worsening of the patient’s neurological status, with loss of consciousness and onset of decerebrate rigidity, both due to midbrain impairment caused by pressure coming from above.

Fig. 4.9a, b. Symmetrical (bilateral) supratentorial pressure causes bilateral uncal herniation as demonstrated by notches (a arrows); these notches may be marked by a hemorrhage and tissue necrosis (b arrows)

Fig. 4.10a, b. Supratentorial pressure induced compression of the basal arteries, especially of the posterior cerebral artery, which leads to a hemorrhagic infarct of the occipital lobe (arrows)
Compression of arteries can also cause secondary necrosis: if the anterior choroidal artery is occluded, the result can be infarction of the medial part of the globus pallidus; posterior cerebral artery occlusion can cause hemorrhagic infarction of the thalamus, of the medial and inferior surfaces of the cortex of the occipital lobe (Figs. 4.10, 9.24), and of the temporal lobe including the hippocampus.

4.1.7.2 Cingulate Herniation

Herniation of the ipsilateral cingulate gyrus under the free edge of the falx results from the unilateral growth of a mass in the frontal or parietal lobe and causes selective displacement of the pericallosal arteries away from the midline (Fig. 4.8a, d). Should this compromise circulation through the pericallosal arteries, the parietal parasagittal cortex can become infarcted, which is expressed clinically as weakness or sensory loss in one or both legs.

4.1.7.3 Central Transtentorial Herniation

A frontal or parietal mass lesion can induce downward axial displacement of the diencephalon (Fig. 4.8a) and rostral brain stem (Figs. 4.8c, 4.11a). The consequent symmetrical herniation of both parahippocampal gyri (Fig. 4.9a, b) may be manifested clinically by bilateral ptosis and failure of upward gaze. The final clinical result is loss of consciousness, decerebrate rigidity, and bilateral dilatation of the pupils with loss of the pupillary light reflex. The blood pressure rises due to increased sympathetic activity.
Hemorrhage or necrosis of the midbrain and/or pons are the possible sequelae of supratentorial space-occupying processes located adjacent to the midline (Figs. 4.8a, 4.11a, 9.23). These lesions are caused by caudal displacement and anterior-posterior elongation of the rostral brain stem and by side-to-side compression by the tentorial hernia, coupled with relative immobility of the basilar artery. Progressive displacement stretches and narrows the central perforating branches of the basilar artery which supply the rostral brain stem, causing spasm, infarction or hemorrhage.

An early complication of expanding masses in the posterior cranial fossa is displacement of the cerebellar tonsils through the foramen magnum (Figs. 4.2d, 4.11b, c). This may also be caused, however, by lesions occupying the supratentorial space. Morphologically, the tips of the tonsils display hemorrhagic necrosis and grooving of the ventral surface of the medulla where it impinges on the anterior border of the foramen magnum. Clinically these changes give rise to apnea, which can occur while the victim is still conscious. Among the other common neurological deficits are decerebrate rigidity and impairment of brain stem reflexes.

4.1.7.4

Upward Tentorial Displacement

Upward tentorial displacement (Fig. 4.8e) is produced by enlargement of an infratentorial mass in the posterior cranial fossa. Both the fourth ventricle and aqueduct become compressed and displaced contralaterally. There is upward herniation of the superior surface of the cerebellum, which is distinguished clinically by the abrupt manifestation of bilateral extensor rigidity and loss of pupillary light response.

4.1.8

Forensic Implications

A number of clinical complications associated with brain swelling, brain edema, and BBB can arise during diagnostic and therapeutic interventions in the CNS carried out by physicians or nursing personnel. Since the sequelae are foreseeable — and in most cases avoidable — these complications will be dealt with briefly in the following.

- In patients with elevated ICP, a lumbar puncture of the CSF can give rise to herniation. Papilledema, though not always associated with ICP, must be excluded before every CSF puncture. Should other clinical signs of high ICP be present, a CT examination must be carried out prior to puncture.

- Pharmacotherapy must not be performed without knowing whether the agent can permeate the BBB and affect the CNS. This is especially true of substances such as antibiotics or cytostatics that are intended to reach and act upon the CNS. Other substances are not intended to reach the CNS because they are toxic there; thus, the contraindication for intrathecal application of vincristine (see p. 359).

- If CNS edema already exists, the BBB may be (pathologically) permeable to substances not intended to reach the CNS, some of which can then have a toxic effect. A MBI-induced perifocal edema, for example that arises in the context of polytrauma-induced shock, can produce greenish discoloration of the perifocal edema as a consequence of an accompanying hepatic insufficiency, which can have an additional neurotoxicologic effect on the neurons.

- The status of the BBB may well be age dependent, its postnatal status differing from that of adults. Blood group incompatibility between mother and child during pregnancy or after birth can cause bilirubin encephalopathy (see pp. 452 ff). The BBB appears to be less permeable in the elderly.

- A cytotoxic effect can be mediated by alcohol in MBIs with consequent loss of neurons. Alcohol lowers cerebral perfusion pressure (CBF) and depresses ventilation. It diminishes respiratory drive in response to elevated PaCO₂ levels. Ethanol-induced respiratory depression and hypotension can increase the morbidity and mortality associated with brain injury. The theoretical considerations of Kimelberg et al. (1997) appear to contradict these empirical findings, arguing rather that alcohol inhibits both the excitotoxin receptor function of neurons (Simson et al. 1991) and the influx of Ca²⁺ via NMDA receptor ion channels.

4.2

Hydrocephalus

4.2.1

Classification and Pathogenesis

Hydrocephalus is characterized by abnormal accumulation of fluid within CSF spaces, i.e., within the cerebral ventricles and subarachnoid space. By this time, there is atrophy of the brain parenchyma and additional ventricular enlargement. CSF is formed by the choroid plexus at a rate that remains unchanged within a wide range of ICP values: 15–25 ml/h will avert a long-lasting imbalance between its formation and absorption. Elevated CSF pressure is associated
only with acute or obstructive hydrocephalus (see below).

The subarachnoid space and ventricular system are connected via the foramina of Luschka and Magendie in the basal cisterns. CSF is absorbed by the arachnoid villi, which do not fully develop until adolescence or young adulthood (Grassman and Potts 1974). In fetuses and infants, CSF is absorbed mainly through nerve roots and periventricular and arachnoid veins.

External hydrocephalus ex vacuo involves diffuse loss of gray matter that gives rise to external atrophy, with dilatation of the subarachnoid space (Fig. 31.6a, b). Diffuse loss of white matter can cause expansion of the ventricular system, the so-called internal hydrocephalus ex vacuo (Fig. 31.6c). The causes of the gray and white tissue damage may vary, but CSF kinetics and anatomic pathways are important considerations (see also pp. 482 f).

A distinction is made between normal pressure hydrocephalus of still unknown etiology (Adams et al. 1965; Hurley et al. 1999), low pressure hydrocephalus, and high pressure hydrocephalus. The latter is caused by accumulation of fluid secondary to elevated CSF production (hypersecretory hydrocephalus) or insufficient resorption (malabsorptive hydrocephalus or communicating hydrocephalus). Distension of the ventricles results from pressure-induced fluid build up in the cerebral ventricles (reversible) or from pressure-induced (irreversible) atrophy as a result of parenchymal loss. Fluid may also enter the periventricular tissue (trans-ependymal resorption of CSF seen on neuroimaging). Normal pressure hydrocephalus can feature repeated brief episodes of elevated ICP, possibly in the form of an intermittent pressure or occult hydrocephalus.

Normal pressure hydrocephalus can also result from a hydrocephalus ex vacuo, which is associated with primary ventricular system enlargement and white matter destruction. It is often found in victims of severe brain injury, in alcoholics, and vascular disease patients with multi-infarct dementia or other types of progressive degenerative brain disorders, especially age-dependent dementia (Miller and Ironside 1997). Hydrocephalus ex vacuo can also be caused by long-lasting generalized brain edema with high ICP.

The causes of obstructive hydrocephalus are MBI, subarachnoid hemorrhage, meningitis and arachnoid fibrosis, Arnold-Chiari malformation, aqueductal stenosis (for complete list see Table 4.2, for review see Garton and Piatt 2004). The latter can be either congenital due to atresia or acquired due to inflammation, compression or reactive gliosis, hemorrhages or tumor. The responsible congenital abnormalities consist in most cases of replacement of the aqueduct lumen by numerous random, narrow channels or ependymal nests.

### 4.2.2 Neuropathology

External hydrocephalus, whatever the causes are, exhibits dilation of the subarachnoid space, with no increase in collagenous fibers or cellular elements, but an increase in CSF. The causative encephaloclastic disease may be diagnosed on the basis of other phenomena, such as liver cirrhosis in alcoholics, or loss of neurons in the presence of plaques and tangles in senile dementia or Alzheimer’s disease.

Typical macroscopic features of internal hydrocephalus include an enlarged ventricular system (Fig. 4.12a, b) (Weller and Shulman 1972), interstitial edema, disruption of the ependymal cells lining the ventricle, and axonal and myelin destruction in the periventricular white matter (Del Bigio 2004). Secondary changes in neurons reflect compensation to the stress or ultimately the disconnection. Proliferating astrocytes and/or gliosis (Fig. 4.12c) replace in part the interrupted ependymal cell line. These glial nodules appear granular or like small tumors (Fig. 4.12c) upon macroscopic inspection of the inner surface of the ventricles (Fig. 4.12b). There is also a partial reestablishment of flattened ependymal

### Table 4.2. Causes of obstructive hydrocephalus.

Source: Garton and Piatt 2004

| Condition                                |
|------------------------------------------|
| Prematurity (posthemorrhagic hydrocephalus) |
| Myelomeningocele                          |
| Other congenital or developmental conditions affecting the brain |
| Dandy–Walker malformation                |
| Arachnoid cysts                           |
| Interhemispheric cysts                    |
| Aqueductal stenosis                       |
| Encephalocele                             |
| Brain tumor                               |
| Subarachnoid hemorrhage                   |
| Mechanical brain injury                   |
| Aneurysmal subarachnoid hemorrhage        |
| Congenital or developmental conditions affecting the skull |
| Crouzon’s and Pfeiffer’s syndromes         |
| Achondroplasia                            |
| Meningitis                                |
PART I: Principles of Forensic Neuropathology

4.2.3 Clinical Features

In adults, the clinical symptoms of hydrocephalus are non-specific; in infants and children they may be specific (see Chap. 21 – pp. 482 f) and depend on the causes and the time course of the hydrocephalus. The salient symptoms comprise psychopathological alterations such as dementia, memory disturbances, and loss of orientation, culminating in the most severe cases in loss of consciousness.

The first step in diagnosing hydrocephalus involves the use of imaging techniques, MRI and CCT, to establish its presence. The second step seeks to determine the underlying cause, and again employs as its methods of choice MRI and CCT, in combination with clinico-chemical (Fishman 1980) and cytological analysis of the CSF itself (Oehmichen 1976a).

4.3 Cell and Tissue Decay

“Necrosis” (for review see Lindenberg 1982) is commonly used to designate the death of tissue components, including that of cells and their processes in a defined area of blood and oxygen supply. After a severe episode of ischemia, MBI or epilepsy, it is typical to find necrotic cell death within the injury core. In addition, a substantial number of neurons in regions surrounding the injury core have been observed to die via the programmed cell death pathways due to secondary effects derived from the various types of insults (Liou et al. 2003). “Apoptosis” (for review see Vermes et al. 1998) is applied to the selective (programmed) death of one or more individual cells. Apoptosis is the more active and physiological form of cell death. In necrotic cell death, a stimulus such as ischemia, hemorrhage, mechanical or chemical damage alters cell homeostasis thus causing cell death, whereas in apoptosis an internal death stimulus triggers the innate cellular suicide program, the latter (not the stimulus itself) mediating the cellular demise (Beal 1995). In the following, the various pathogeneses and mechanisms of these types of cell death will be described, along with their different morphologies and underlying molecular factors.

4.3.1 Injury-Induced Cell Death: Necrosis

The most common cause of necrosis is ischemia. Other causes include mechanical injury (contusion...
necrosis), toxic agents (formic acid in methyl alcohol), heat (thermocoagulation), freezing (cryosurgery), infections (poliovirus), and overexposure to ultrasound. Each case, however, involves the action of additional factors independent of the type of primary traumatic event. Chief among these factors are free radicals and nitric oxide (NO). Reaction products of NO and O\textsubscript{2}, including potent oxidizing molecules such as peroxynitrite and nitrogen dioxide, can be more toxic than NO itself.

The type of brain necrosis depends in large part on the duration of local circulatory arrest:
1. Transient ischemia only destroys neurons and oligodendrocytes, inducing \textit{incomplete necrosis} or selective neuronal necrosis (Scholz 1953).
2. Prolonged ischemia, termed “infarction,” gives rise to complete necrosis of all tissue components.

\subsection{Incomplete Necrosis}

\textit{Morphologically} cell necrosis, especially neuronal necrosis, features irreversible changes of the cytoplasm (condensation, hydropic swelling, intense eosinophilia, loss of structure, homogenization) (Fig. 4.14) and of the nucleus (pyknosis, karyolysis, karyorrhexis) (Majno and Joris 1995).

\textbf{Time Course.} The data vary on how soon after the onset of ischemia the first microscopic neuronal changes become evident. Some authors report an interval of 30 min (Jacob and Pyrkosch 1951), others 14/15 h (Müller 1930). The data may differ in part due to prolongation of the necrotic process for as long after death as brain temperature remains favorable (Lindenberg 1982).
PART I: Principles of Forensic Neuropathology

Inflammation. Necrotic tissue and cells always attract neutrophils, macrophages, and sometimes lymphocytes. The tissue can activate the scavenger function of resting microglia for elimination of myelin as well as cell debris. Hsu et al. (1995) have published an overview of the association between cell-mediated injury and cellular reactions. Lipid inflammatory mediators are crucial for cellular interactions in sterile inflammation. Among the mediators involved in inflammatory processes as a reaction to cell necrosis are thromboxane A₂, leukotrienes, and prostaglandins, collectively termed eicosanoids (Hsu et al. 1995).

4.3.1.2 Tissue Necrosis: Infarction

Prolonged ischemia-induced tissue necrosis is termed “infarction” or liquefactive necrosis. The infarcted area displays macroscopically evident pallor on H&E, Nissl, and myelin preparations within 3–5 h as an indication of acidosis. A narrow halo of even greater pallor surrounds the necrotic area (Fig. 4.20a). Around the necrotic area, vessels are distended and release fluid into the infarcted tissue and surrounding tissue by way of a vascular network (perifocal edema).

Neurons become thorny and severely shrunken within 12–36 h, with darkly staining incrustation of their pericellular structures. A survival time of 12 h leads to homogenization of the cytoplasm and nuclear and cytoplasmic pallor. Between 36 h and 48 h, the neurons disappear except for the nuclei (see Fig. 4.14c).

Within 1–2 h the necrotic tissue is characterized by an emigration of neutrophil leukocytes (Fig. 4.15a, b). Within 18 h the necrotic area exhibits proliferation and extensive activation of microglial cells (Fig. 4.15c–f). Along the infarct margin, macrophage numbers increase. Hypertrophic astrocytes appear along the border zone within the brain parenchyma after 4–6 days (Fig. 4.16). The infarct liquefies at its center and macrophages phagocytose the debris. The final stage of cortical liquefactive necrosis is termed “laminar necrosis” (Fig. 4.17a–c) associated with intense gliosis during the final phase (Fig. 4.17d). The final stage of ischemic involvement of the basal ganglia and the thalamic nuclei is a cystic necrosis (Fig. 4.18). Ischemic damage of the hippocampal area is characterized by a segmental loss of neurons in the hippocampal cortex (Fig. 4.19a, b) associated
CHAPTER 4: Cell and Tissue Reactions

with compensatory (early) microglial activation (Fig. 4.19c) and secondary gliosis (Fig. 4.19d).

Another type of brain tissue necrosis is the rare phenomenon “persistent coagulative necrosis” first described by Spielmeyer (1922) (Fig. 4.20), which affects cell tissue elements. Within gray matter the outlines of dead neurons are recognizable, their cytoplasm is intensely eosinophilic and usually contains numerous, often large, vacuoles, and the nucleus stains poorly with hematoxylin. This picture, which is recognizable within the first 4–6 h, is followed by decreasing stainability of nucleus and cytoplasm until a barely recognizable ghost cell is all that remains. Acute and enduring deprivation of blood supply causes necrosis of cells and tissue components, the lesion remaining in a state of “coagulation” for a prolonged period. The cells appear only as shadows and the necrotic tissue persists within the brain as a foreign body and sometimes becomes encapsulated in mesenchymal tissue. The pathogenesis of this rare type of necrosis is still unknown (Escolá and Hager 1963; Cervos-Navarro and Ferszt 1977).

Fig. 4.15a–f. Cytologic sequelae of regional necrosis. a, b An early leukocyte reaction is demonstrated by means of N-AS-DCIAE; c–e CD68 reactive macrophages in the cortex as well as (f) in the white matter increase (magnification c ×100; a, b, d, f ×500, e ×1,000)
4.3.2  
Gene-Regulated Cell Death: Apoptosis

Apoptosis can be differentiated from necrosis based on differences in their pathogenesis, cell reactions, and morphologic features. Apoptosis is the programmed death of a cell as regulated by specific death genes (for review see Clarke 1998). It initiates a delayed secondary death of neurons in response to environmental changes, deficient metabolic and trophic supply, and changed gene transcription. During apoptosis, the integrity of mitochondria is compromised and various pro-apoptotic proteins are released into the cytoplasm. This results in activation of caspases, proteases that orchestrate the death of the cell (Waterhouse 2003). Apoptosis requires active protein synthesis (McIntosh et al. 1998; Raghupathi et al. 2000). A single cell can undergo a switch between the two types of cell death based on several pathways (McConkey 1998; Fiskum et al. 1999; see also Leist et al. 1990) (for further informations, see p. 620).

The characteristic morphology of apoptosis exhibits cleavage of the internucleosomal chromatin that can be identified in situ using the terminal

---

**Fig. 4.16a, b.** Activated astrocytes along the border zone of necrosis. a Astrocytic reaction in the cortex and (b) in the white matter (GFAP reactivity; magnification a ×1,000, b ×500)

**Fig. 4.17a−d.** Cortical necrosis, i.e., laminated necrosis. a Macroscopic view of long-time survival of cortical necrosis which is associated with a complete cortical (cystic) necrosis (b) while in the cerebellum the necrosis (c) is totally replaced (d) by a distinct gliosis (b−d H&E; magnification b, c ×100; d ×200)
CHAPTER 4: Cell and Tissue Reactions

Fig. 4.18a–d. Global ischemia leads to cystic necrosis of the basal ganglia. Two cases are demonstrated: (a, c) and (b, d) with a long survival time after cardiac arrest demonstrating necrosis of the pallidum (a, b: MRI)

Fig. 4.19a–d. Neuronal loss in the hippocampal area (CA1 sector) and glial reaction (see also Fig. 14.14, p. 309). a The Ammon’s horn CA1 sector is characterized by a distinct loss of nerve cells; b by high magnification of the marked sector (see a) intact neurons are seen in the center as well as a bilateral loss of neurons; c the lost neurons are replaced by CD68 reactive microglia and d in cases of longer survival time, by astrocytes (a, b MAP2 reactivity; c CD68 reactivity; d GFAP reactivity; magnification a ×50; b, c, d ×500)
deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) method (Gavrieli et al. 1992). Apoptosis causes pyknosis of the nucleus and condensation and shrinkage of the cell body. As it progresses, budding and karyorrhexis occur, and ultimately a breakup into clusters of apoptotic bodies (Majno and Joris 1995).

The time course of apoptosis following a traumatic event is as follows: about 4 h after a traumatic event, apoptosis begins, and remains demonstrable for about 3 days (Yakovlev and Faden 1997).

Three major factors are known to participate in the apoptotic cascade of “delayed” neuronal death (for review Kermer et al. 1999; see also Huppertz et al. 1999):
1. Immediate early gene transcription factors (c-jun, jun-B, jun-D, c-fos, AP-1, ATF, NF-kB)
2. Proteases (calpains, caspases)
3. Glutamate-mediated toxicity (free radicals, protein-kinases, Ca^{2+} homeostasis, second messenger systems)

The death-inducing activity of the Bax, Bad, Bid, Bcl-x family members is thought by Raghupathi et al. (2000) to be in dynamic equilibrium with their survival-promoting cognates Bcl-2, Bcl-xL. Shifts in the protective intracellular Bcl-2-family-protein levels can tilt the balance toward cell death by activating the death-inducing cysteine proteases, caspases (Thornberry and Lazebnik 1998).

The death of single cells releases insufficient quantities of chemoattractants to allow effective concentrations of molecular species to reach the vascular endothelium. For this reason a genuine cell reaction does not occur. Neighboring cells that are not professional phagocytes cannibalize the cell debris in a process specific to apoptosis (Majno and Joris 1995). In inflammatory diseases, an essential factor in the resolution of the inflammatory attack is the clearance of apoptotic leukocytes by tissue-specific phagocytes (Platt et al. 1998). This process has been termed the “safe, phagocytic clearance of dying, yet intact leukocytes undergoing apoptosis” involving rapid recognition, uptake, and degradation.

Microglial cells were recently shown to be capable of protecting neurons, cerebellar granule neurons in particular, from apoptosis (Polazzi et al. 2001): molecules are released by apoptotic neurons that enable the anti-apoptotic activity of microglia. In vitro, normal microglia release molecules capable of rescuing neurons from apoptotic death.

4.3.3 Necrosis Versus Apoptosis

Microglia, astrocytes, and oligodendroglia may participate in apoptotic or necrotic processes. The reaction of neurons highly sensitive to injuries such as ischemia, hypoglycemia, infection, and mechanical trauma are described above and classified systematically in Table 4.3. A review by Rosenblum (1997) includes a comparison of various hypotheses regarding the underlying causes of “delayed” neuronal death, among them excitotoxicity, calcium, and apoptosis. Rubin (1997) and Abe (1999) review the phenomenon of neuronal apoptosis as it appears in various neurological diseases.
4.3.4 Penumbra

Astrup et al. (1981) first defined the ischemic penumbra as brain tissue perfused at a level within the thresholds of functional impairment and morphologic integrity, which has the capacity to recover if perfusion is improved. Because tolerance of tissue to ischemic damage is dependent on residual flow and duration of flow disturbance (Heiss and Rosner 1983), the ischemic penumbra is a dynamic process;

Table 4.3. Different pathophysiological and phenomenological features of necrosis and apoptosis. Sources: Granville et al. 1998; Abe 1999; König and Rosenberg 2000; Jellinger and Stadelmann 2000

| Features                  | Necrosis                                                                 | Apoptosis                                                                 |
|---------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Causes                    | Toxic influences                                                         | Developmental/programmed degenerative changes                               |
|                           | Massive ischemia                                                          | Growth factor deprivation                                                  |
|                           | Radiation (high dose)                                                     | Mild ischemia, radiation, etc.                                             |
| Cellular processes        | Non-coordinated events                                                   | Programmed cascade                                                         |
|                           | Cell membrane rupture                                                     | Membrane phospholipid asymmetry                                            |
|                           | Mitochondrial swelling                                                   | Organelles preserved/shrunk                                                |
|                           | Energy independence                                                       | Energy (ATP) dependence                                                    |
|                           | No protein synthesis                                                      | Requires protein synthesis                                                 |
|                           | No RNA synthesis                                                          | Requires new RNA transcription                                             |
| Molecular events          | ATP depletion                                                             | Mitochondrial permeability transition                                      |
|                           | Enzymatic digestion                                                       | Mitochondrial cytochrome c release                                        |
|                           | Protein denaturation                                                      | Caspase activations                                                        |
|                           | Diffuse DNA digestion                                                     | Internucleosomal endonucleases                                             |
| Tissue distribution       | Group of cells                                                            | Transglutaminase activation                                                |
|                           |                                                                           | Poly(ADP-ribose) polymerase cleavage                                       |
| Tissue reaction           | Lysis and release of cellular contents resulting in inflammation of      | Phagocytosis of membrane-enclosed vesicles by macrophages or neighboring   |
|                           | surrounding tissues                                                      | cells; little or no inflammation                                           |
| Morphology                |                                                                          |                                                                           |
| Cell                      | Swelling                                                                  | Cell shrinkage, loss of membrane contact with neighboring cells           |
|                           | Loss of integrity, enhanced permeability                                 | Blebbing formation of apoptotic bodies                                    |
| Plasma membrane           |                                                                           |                                                                           |
| Organelles                | Damaged                                                                   | Intact                                                                    |
| Nucleus                   | Disintegrated                                                            | Condensed and fragmented                                                  |
| Lysosomes                 | Ruptured                                                                  |                                                                           |
| Mitochondria              | Defective, ATP-depleted, swollen, ruptured                               | Swelling, permeability transition, may rupture                            |
| Biochemistry              |                                                                          |                                                                           |
| DNA                       | Non-specific degradation                                                  | Internucleosomal DNA cleavage                                             |
| Protein                   | Non-specific degradation                                                  | Activation of caspases, calpains                                           |
| Substrates                | Non-specific hydrolysis                                                   | Specific substrates                                                       |
| Anti-death molecules      | Bcl-2 (in some cases) (Kane et al. 1995)                                  | Bcl-2 family, IAPs, FLIPs, crmA, caspase inhibitors                       |
| Adenosine triphosphate    | No                                                                        | Yes                                                                       |
| requirement               |                                                                          |                                                                           |

---

Astrup et al. (1981) first defined the ischemic penumbra as brain tissue perfused at a level within the thresholds of functional impairment and morphologic integrity, which has the capacity to recover if perfusion is improved. Because tolerance of tissue to ischemic damage is dependent on residual flow and duration of flow disturbance (Heiss and Rosner 1983), the ischemic penumbra is a dynamic process;
Focal ischemia results in necrosis at the infarct core and activation of complex signal pathways for cell death and cell survival in the penumbra. Increased expression of caspase-1, -3, -8, and -9, and of cleaved caspase-8 has been observed in the penumbra (for details, see Ferrer and Planas 2003). But for a limited time interval, penumbral tissue has the potential for recovery and, therefore, is the target for interventional therapy in acute ischemic stroke (time window, Heiss 2000).

4.3.5 Dendritic Injury

Relatively little is known about the effects of injury of the dendritic processes of neurons. Axotomy of a motor neuron induces loss of some presynaptic terminals and the retraction of processes (Blinzinger and Kreutzberg 1968; Summer and Watson 1971). Abnormalities in dendritic spines have been report-
ed during the perinatal period in cases of developmental retardation (Purpura 1975, 1976).

Li et al. (1997) showed that expression of microtubule-associated protein 2 (MAP2) in perikaryons and dendrites is a sensitive marker of dendritic lesions in spinal cord trauma (Fig. 3.2b; see also Chap. 10 − pp. 226 f). As early as 4 h after moderate or severe compression of the spinal cord, loss of MAP2 immunoreactivity in dendrites and nerve cell bodies became evident in the injured segment. This phenomenon continued for the duration of the 9-day experimental period. How much MAP2 immunoreactivity is lost depends on how hard the cord is impacted (Li et al. 1995). The loss of immunoreactivity may result from an (impact-induced) influx of calcium, activating calcium-dependent proteolytic enzymes capable of degrading MAP2 (Inuzuka et al. 1990). The same phenomena may be observed as a result of hypoxic lesions in the hippocampal area (Fig. 4.21a, b).

4.3.6 Axonal Injury

Axonal injury is characterized by an interruption of axonal fibers (Fig. 3.2b) as demonstrable − for example − as a result of a gunshot: the axons will be fragmented (Figs. 8.13b, 9.19). Moreover, axonal injury induces an anterograde (Wallerian) and retrograde degeneration of the injured axons. The terms “anterograde” and “retrograde” refer to the directions of conduction of the nerve impulse along the axon, i.e., the degeneration following focal damage proceeds in a centrifugal or centripetal direction (for review see Brodal 1982).

An interrupted anterograde flow of proteins along the axon can cause the phenomenon of axonal injury. This phenomenon was once demonstrated by H&E stain and by silver staining techniques within 16–24 h after a traumatic event (Strich 1956; Adams et al. 1982). But since the injured axon is selectively characterized by expression of β-amyloid precursor protein (β-APP) (Fig. 4.21d–f; cf. Gentleman et al. 1993; Sherriff et al. 1994), it is now routinely confirmed in 105–180 min (Blumbergs et al. 1995; Oehmichen et al. 1999), in adult brains as well as in infant brains (Reichard et al. 2003). β-APP expression is seen even if the axonal injury is moderate or the axotomy delayed or incomplete (Povlishock 1992). Although axonal injury was long thought to be a morphological correlate of MBI, it is now known to be a non-specific phenomenon also associated with acute intoxication (Nies et al. 2002) or hypoxia/ischemia (Oehmichen et al. 1999).

In a recent study Graham et al. (2004) evaluated the pattern of β-APP immunoreactivity. The authors identified three different types:

1. A diffuse − multifocal type − in MBI, CO poisoning and hypoglycemia;
2. A type corresponding to the outlines of an infarct or hematoma with evidence of raised intracranial pressure;
3. A mixture of (1) and (2) which was seen in severe MBI.

It is still unclear which events trigger axonal degeneration within the CNS and PNS. Kapoor et al. (2003) suggest a link between nitric oxide (NO) and subsequent molecular events that previously have been indicated as contributors to reversible and irrevers-
nable axonal injury. Waxman (2003) demonstrates the axonal death cascade induced by hypoxia, ischemia, mechanical trauma, inflammation or NO. The molecular events involving sodium channels and the Na+/Ca2+ exchanger lead to an increase in intracellular calcium, which can provoke axonal degeneration.

Axonal injury of myelinated axons is always accompanied by a demyelinating process, i.e., a loss of myelin, which will be eliminated by mononuclear phagocytes (see: Fig. 9.15b). The sequelae will be a glial scar lacking myelin as demonstrable by Luxol fast blue stain (Fig. 4.22a) or by immunohistochemistry using an antibody against myelin basic protein (Fig. 4.22b, c).

### 4.3.6.1 Anterograde (Wallerian) Degeneration

Interrupted axons or injured neurons exhibit disintegration of the distal stump. Breakdown of the distal axonal stump is known as “Wallerian degeneration” and begins several days after a traumatic event. Its salient morphological features are lysis of axons and myelin, Schwann cell proliferation, and phagocytosis by invading macrophages. Axonal and myelin degeneration follow a time course described in detail by Brodal (1982) (see also p. 242).

### 4.3.6.2 Retrograde Degeneration

Axotomy induces a characteristic centripetally directed morphological change of the neuron termed retrograde axonal degeneration. This retrograde alteration is characterized by rounding of the neuronal contours, swelling of the neuronal cytoplasm, and a decline in the number of Nissl bodies at the center of the cytoplasm (central chromatolysis – see Fig. 3.1c). The nucleus becomes slightly deformed and is displaced to the periphery of the perikaryon. These changes correspond to the changed or increased neuronal gene expression after axotomy (Graeber et al. 2002). Axotomy is followed in hours by rapid upregulation of the immediate early genes, such as c-fos, c-jun, jun-B (Haas et al. 1993), in association with the upregulation of heat shock proteins (Kalmar et al. 2002). The one constant change associated with acute retrograde changes may be chromatolysis. These changes are sometimes accompanied by local proliferation of satellite glial cells whose time course has also been described by Brodal (1982) (see also pp. 242 and 304 f).

### 4.3.7 Regenerative Capacity

It is accepted as common knowledge that plasticity-associated molecular and structural events occur in the injured brain. These are at least partly responsible for functional recovery. Increases in dendritic arborization, spine density, and synaptogenesis in both peri-injury and intact cortical areas are the potential morphological strategies that enable the brain to reorganize its neuronal circuits (Keyvani and Schallert 2002).

On the other hand we have to consider that the scarring process is an ineffective regenerative process which is associated with cell proliferation. The cell proliferation will be – especially within the first 48 h after the traumatic event – non cell-specific, as immunostaining with markers for immature and mature astrocytes, activated microglia, neural precursors, and mature neurons will be negative (Chiru and Schallert 2002). Nevertheless, it is also accepted that both retrograde degeneration and the axonal injury-induced bulbs and swelling of the proximal axonal stump are markers of a regeneration process. Although the CNS has little innate capacity for repair, this capacity does exist for the peripheral nervous system. It is not known why axons in the adult CNS are not capable of better regeneration; it is known that they do in fact regenerate, as was recently confirmed by von Euler et al. (2002).

The observations of Schwab and Caroni (1988; Schwab 1993) are of major importance. They show that proteins released by oligodendrocytes inhibit axonal elongation. This inhibitory protein has since been identified and cloned (Chen et al. 2000; Grand-Prey et al. 2000; Prinjha et al. 2000). These authors also identified the protein (Nogo) of a previously unknown gene that encodes the inhibitory myelin protein in rats and humans. The myelin-derived axon outgrowth inhibitor Nogo protein binds to an axonal Nogo-66 receptor and at least accounts for the lack of CNS repair (Li and Strittmatter 2003; McGee and Strittmatter 2003). It remains unclear, however, what effect other factors may have, whether negative (e.g., the release by neurons of large quantities of glutamate following the incidence of spinal cord injury), or positive (e.g., release of tissue growth factors (Ramer et al. 2000) and cytokines, or induction of the macrophage scavenger function (see also Schwab 2000)).

It is now thought that neurons are renewed throughout life from endogenous stem cells and added to the dentate gyrus. Adult neurogenesis could be demonstrated in the subgranular and subventricular zones of the hippocampus (Kempermann et al. 1998; Cameron and McKay 1999) and the olfactory bulb (Craig et al. 1999). These are the only zones where differentiation of neural stem cells into neurons is
4.4 Inflammation

4.4.1 Principles of Neuroimmunology

The CNS was once described as an “immunologically privileged site” (Medawar 1948). This hypothesis was based mainly on the existence of the BBB (Pachter et al. 2003), which restricts diffusion of soluble molecules and the migration of immune cells out of the systemic circulation into the CNS (Oehmichen 1983). Pericytes, endothelial cells, microglia and astrocytes, by contributing to BBB function (see above), participate in CNS immune regulation (Prat et al. 2001). Meanwhile a number of basic processes are known (Bauer et al. 2001) that explain how the CNS responds to inflammatory attack by regulating local antigen presentation, by the different cell types, and by its special cytokine environment. It also eliminates inflammation via emigrating macrophages (Oehmichen et al. 1979 – for review Oehmichen 1982; Cserr and Knopf 1997) and destruction of apoptotic T-cells. In vitro and in vivo studies have elucidated the mechanisms underlying immune-mediated (via cytokines, macrophage/microglial toxins, and antibodies) tissue damage, featuring many different potential pathways.

The normal CNS has limited expression of major histocompatibility complex (MHC) class I antigens, primarily on the endothelium and glial cells, and no expression of MHC-II and the various immunoactive adhesion molecules. Fontana et al. (1982) were the first to point out that cytokines such as interferon-γ (IFN-γ) are able to stimulate astrocytes to express MHC class II to secrete cytokines (IL-1, IL-3, TNF-α), and to present antigens such as myelin basic protein (MBP) to specific T-cell lines (Fontana et al. 1982, 1984; Massa et al. 1987). Frei et al. (1987) focused on microglia and found that they too could respond to IFN-γ by upregulating MHC-II. If IFN-γ or IFN-γ and TNF-α are introduced directly into the CNS, there is independent, progressive upregulation of both MHC classes and of adhesion molecules, such as the intercellular adhesion molecule-1 (ICAM-1), which are expressed first by perivascular macrophages (Hickey and Kimura 1988), subsequently by microglia and macrophages throughout the CNS, and finally by astrocytes (Massa et al. 1986). Experimental induction of autoimmune encephalitis (EAE) revealed that perivascular macrophages are the chief presenters of CNS antigens to circulating T-cells (Hickey and Kimura 1988).

The role of the endothelium in antigen presentation within the CNS is ambiguous. Astrocytes too are thought (Waksman 1997) to play an ambiguous role. When presenting antigen to specific T-cells in vitro, they are lysed. It is not known whether T-cells are induced to proliferate or to release inflammatory cytokines, or possibly both, or whether they shut down for lack of suitable co-stimulatory signals (so-called clonal anergy).

The duality of the inflammatory response is crucial to host repair and defense. It may also however cause loss or impairment of function, i.e., although otherwise beneficial, inflammation may impair neuronal function (Perry et al. 1999).

4.4.2 Inflammatory Cells

Instead of the BBB being a limiting factor of the CNS immune response as once believed, today it is thought that the brain itself is an immune system organ (Fabry et al. 1994; Chao et al. 1997). This conclusion is based on the numerous cytological and immunological findings of the past two decades showing that the targets to be protected are neurons, axons, and myelin. In the absence of protection these can become necrotic or succumb to apoptosis, be phagocytosed and disappear. Ultimately all signs of degenerative alteration can be demonstrated. There is no direct correlation however between leukocyte emigration and parenchymal cell death in vivo (Schmid-Schönbein et al. 1999).

Glial cells outnumber neurons in the cortex, where there are eight glial cells for every neuron. Among glial cells in the cortex, astrocytes comprise 80%, microglia 15%, and oligodendroglia 5% (Chao et al. 1997). These cells possess many immunological features marking them as important immunoregulatory cells. Hallmarks of CNS inflammation in particular are activated microglia and astrocytes. Inflammation undoubtedly serves primarily as a host...
defense mechanism in peripheral tissue, facilitating essential repair processes by altering local blood flow in the injured tissue, with accumulation of fluid and specialized cells. The brain possesses cellular host defense mechanisms since activated T-cells are capable of crossing the BBB (Hickey et al. 1991).

Cellular mediators of CNS inflammation in the brain have been shown to differ with regard to type and number from those of the periphery (see below). These differences are mainly due to the brain’s tight regulatory environment and the balance between inflammation-induced tissue damage and tissue repair (Parsons and Hunter 1999).

The specificity of the immune response appears to be controlled largely by CNS antigen presentation (Sedgwick and Hickey 1997), though the precise nature of the control remains unresolved. CNS antigen presentation according to Hart and Fabry (1995) occurs outside and inside the CNS, with the BBB playing a major role in the regulation of CNS immune function. Parsons and Hunter (1999) showed that the early events leading to T-cell activation by antigen-presenting cells result from MHC binding. Co-stimulatory molecules then bind to the antigen, presenting cell–T-cell complexes for further development of the cascade. MHC is expressed not only on astrocytes and microglia, but under certain conditions also on neurons and oligodendrocytes (Sedgwick and Hickey 1997). MHC II antigens are also expressed under normal conditions in a population of macrophages inhibiting the perivascular space, subarachnoid space, and choroid plexus. This expression may indicate that these cells perform a modulatory function at the blood/CSF interface (Matyszak et al. 1992). Under highly specific circumstances, physiological response mechanisms resembling those at the periphery also appear to take place in the brain.

Under pathological conditions, hematogenous cells that are absent or extremely rare under normal circumstances appear to accumulate in the brain, i.e., platelets (Fig. 4.23a), neutrophilic leukocytes (Fig. 4.23b,c), lymphocytes (Fig. 4.23d), and macrophages. The number and type of inflammatory cells in the CNS vary widely depending on the attracting stimulus or on their inherent ability to attack a CNS antigen.
4.4.2.1 Polymorphonuclear Leukocytes

The intravascular cells, especially the leukocytes, interact with vessel walls as determined by integrins (Hynes 1992), selectins (Bevilaqua 1993), and immunoglobulins of the supergene family (Springer 1990). Among the heterogeneous supergene family are MHC molecules, T-cell receptors, and ICAM-1. During emigration, i.e., extravasation, leukocytes initially come into loose contact with the walls of vessels of the microcirculation via selectin molecules or lectins, producing a rolling motion along the vessel wall (McEver 1994). They are then expressed on the endothelium. The selectin molecules are E-selectin (ELAM-1), L-selectin (LAM-1, LECCAM-1), and P-selectin (CD62). P-selectin plays a role in recruitment of neutrophils to the brain parenchyma (Bernardes-Silva et al. 2001), while E-selectin is thought to participate in both neutrophil and CD4+ T-cell adhesion (Harlan and Liu 1992). Endothelial selectins can be rapidly upregulated following wounding, P-selectin within minutes (<2 h − Zoppo 1997), and E-selectin within a few hours (Granger and Kubes 1994; McEver 1994). Among the stimuli for expression of endothelial cell adhesion receptors are TNF-α and IL-1.

Adhesion of leukocytes to endothelial cells is mediated by adhesion molecules such as Mac-1, the intracellular adhesion molecules (ICAMs), lymphocyte function-associated antigen-1 (LFA-1), and vascular cell adhesion molecule-1 (VCAM-1), all of which, as already mentioned, are upregulated in endothelial cells. In the CNS, ICAM-1 and VCAM-1 (Baron et al. 1993) are constitutively expressed on perivascular cells and some astrocytes. In areas of CNS inflammation they are readily upregulated on endothelial cells and astrocytes (Sobel et al. 1990), which stimulates recruitment of neutrophils to the site of injury. Such neutrophil emigration can be experimentally induced by extravasal injection of cytokines such as IL-1β (Bernardes-Silva et al. 2001) or TNF-α (Schmid-Schönbein et al. 1999).

Neutrophils are the first circulating leukocytes to reach the site of injury. Increase in vascular permeability is caused by the release of free radicals and lysosomal enzymes, giving rise to edema (Weiss 1989). Despite mechanisms evolved to restrict entry of neutrophils into the brain parenchyma, neutrophil recruitment is clearly a feature of acute brain injury, such as that caused by stroke or mechanical trauma. Numerous studies employing a transient or permanent model of focal ischemia in rats and mice have demonstrated that cerebral tissue injury is lessened by neutrophil depletion (Jean et al. 1998). A correlation between the development of cerebral edema and neutrophil recruitment has also been shown in models of MBI (Schoettle et al. 1990). This deleterious effect of neutrophil recruitment contrasts with their beneficial function and phagocytic ability as scavenger cells in cases of bacterial inflammation and of particular importance in cases of sterile inflammation.

4.4.2.2 Lymphocytes

The aforementioned recruitment of T-lymphocytes to the site of injury clearly depends on an accumulation of adhesion molecules, especially of VCAM-1, in the endothelial wall. When activated, T-cells express LFA-1 and can bind ICAM-1 on endothelium (van Kooyk et al. 1993), thus facilitating entry of T-cells into the CNS (Baron et al. 1993).

Few data have been published on the migratory requirements of B-cells. It is thought, however, that B-cells in their fully mature form as plasma cells have no or only limited migratory potential. Immunization of rats with a foreign, non-pathogenic antigen behind the BBB was found to result in the presence of B-cells and plasma cells specific for that antigen in the CNS (Knopf et al. 1994). This finding appears to indicate that, after entering, B-cells remain in the CNS at least in part because they have found their specific antigen (Hickey et al. 1997).

After entering the CNS, the function of T- and B-cells is to recognize their antigen. Among the potential antigen-presenting cells of the CNS are endothelial cells and astrocytes. Under inflammatory conditions, microglial and perivascular cells (members of the mononuclear phagocyte family residing in the CNS) constitute the chief antigen-presenting cells.

4.4.2.3 Microglia and Brain Macrophages

As already mentioned (pp. 27 f), a distinction must be made between activated and resident microglia, and leptomeningeal, perivascular, and choroidal macrophages. All of these cells represent different functional stages of blood monocytes (Oehmichen and Huber 1976; Oehmichen 1976a, b, 1978, 1983; cf. also Perry and Gordon 1997).

Microglia residing in the white matter do not express the MHC I antigen, and only a few express MHC class II (Hart and Fabre 1981). Leptomeningeal, perivascular, and choroidal macrophages, in contrast, do express MHC class II. The resident microglia also feature a downregulation of other antigens, the leukocyte common antigen (LCA), and ED-1 or CD4.

Monocytes emigrate under pathological conditions into the brain parenchyma, where their morphology and antigenic characterization both change. They now participate in the immunological process as macrophages and express MHC class II antigens. They also scavenge cell debris and myelin fragments left over from damaged tissue.
Astrocytes are among the first local cells to respond to CNS injury. The main responses are reactive gliosis and swelling of reactive (hypertrophic) astrocytes upregulating GFAP. Reactive astrocytes express acute phase reactive protein (Koo et al. 1991), MHC class Ia (Frank et al. 1986) and MHC class II antigens (Fierz et al. 1985), IL-1 (Griffin et al. 1989), plus multiple other factors (for review see Norenberg 1997). Astrocytes are known to act in conjunction with cells of the immune system and to be involved in immune/inflammatory processes. They are immunocompetent cells capable of augmenting, amplifying, and sometimes even of regulating an immune response. They produce many immune mediators and can in return be affected by them. By helping to eliminate infectious or foreign agents, astrocytes may contribute to a beneficial response.

**4.4.2.5 Endothelial Cells and Collagen Fibers**

Given their direct contact with leukocytes in the blood, endothelial cells constitute the ideal site for antigen recognition in the CNS (Sedgwick and Hickey 1997). The scarcity of T-cells in the CNS may be an indication that endothelial cells are the sole site capable of adequate T-cell antigen–MHC interaction. The finding that activated T-cells can enter the CNS through an intact BBB (Hickey et al. 1991), however, is a clear sign that antigen recognition at the endothelial cell surface need not occur.

Endothelial cells are thus regarded as major players in the inflammatory and immune response (Sternberger et al. 1989) and simultaneously guarantee the BBB. They also enable alterations in the form of receptor-mediated events (Dietrich 1999), i.e., an inflammatory response (for details, especially on the expression of adhesion receptors, see above).

Endothelial cells proliferate at the site of brain wounds (Fig. 4.24a). Therefore, the number of capillaries increases and – in a final phase – decreases near hemorrhages or infarcts (Fig. 4.24b, c) in association with an increase in collagen fibers, especially collagen type IV (Fig. 4.24c). This process leads to a network of collagen fibers and glial fibers, which is the last stage in the formation of a brain scar.
4.4.3 Inflammatory Mediators

Among the inflammatory mediators are cytokines and their subgroups, chemokines, in the sense of adhesion molecules. Other mediators of inflammation include effector molecules such as NO, NOS, reactive oxygen species (ROS), and free radicals.

4.4.3.1 Cytokines

Cytokines mediate the initiation, propagation, regulation, and suppression of immune and inflammatory responses (Benveniste 1999). They are proteins with low molecular weight and are synthesized during effector phase immunity. They are secreted by cells and are also expressed on their surfaces. Many different cell types are capable of producing the individual cytokines, which for their part can have a variety of effects on different cell types. Usually acting locally, cytokines begin to act on target cells by binding to specific cell-surface receptors, which generally have a high affinity for their ligands. It takes only minute amounts of a cytokine to evoke a biological response.

In multiple sclerosis or experimental allergic encephalitis, IFN-γ and IL-2 are known to be products of activated T-cells. TNF-α and IL-1 derive from activated astrocytes and macrophages. Astrocytes can be activated by IFN-γ and/or TNF-α, produce IL-1 and IL-3, TNF-α, transforming growth factor β (TGF-β), granulocyte-macrophage colony-stimulating factor (GM-CSF), and other types of molecules such as prostaglandin E2 (PGE2) (for review see Waksman 1997).

In human brains, TNF-α, IL-1, and IL-6 in particular can be induced by MBI or cerebral ischemia. Brain ischemia triggers rapid production of TNF-α mRNA, which peaks 6–12 h after ischemia and subsides 1–2 days later. It remains above baseline, however, for up to 5 days (Barone 1999). Neuronal cells in and around the ischemic tissue acutely express TNF-α in a so-called penumbra, but it also turns up several days later in macrophages in the infarcted tissue. TNF-α triggers adhesion molecule expression on activated glial cells and the endothelium, in this manner regulating gliosis, tissue remodeling, and scar formation. IL-1 levels rise before and during glial activation and neuronal damage (Rothwell et al. 1999).

4.4.3.2 Chemokines

Chemokines are chemoattractant cytokines. During inflammation they mediate leukocyte entry into the CNS. Among their known functions is the interaction of leukocytes with the endothelial surface, a multistep and sequential process mediated by selectin molecules by which the leukocyte rolls on the endothelium. The end result is firm adhesion. The entire process is mediated by interaction of ICAM-1 and VCAM-1 expressed by endothelial cells and their leukocyte-associated ligands. Moderate levels of ICAM-1 and very low levels of VCAM-1, two molecules responsible for the adhesive properties of granulocytes and of T-cells, are expressed by brain endothelial cells.

Chemokines constitute a subgroup of small cytokines (8–10 kDa) that attract certain inflammatory cell populations, among them lymphocytes, neutrophils and monocytes, to the target tissue (Meeusen et al. 1996; Bonecchi et al. 1998). The number of known chemokines and chemokine receptors continues to expand rapidly (for review see Prat et al. 2001). Three classes of chemokines are known, as defined by the arrangement in the mature protein of conserved cysteine (C) residues, CXC or α-chemokines, CC or β-chemokines, and of CC or γ-chemokines. Astrocytes, endothelial cells (Zach et al. 1997; Weiss et al. 1998), perivascular cells, and macrophages (Simpson et al. 1998) produce and release chemokines.

4.4.3.3 Effector Molecules

ROS and NO are generated in astrocytes and activated macrophages (Hartung et al. 1988). ROS, NO, and other free radicals are effector molecules that contribute to the inflammatory cascade and tissue damage. What role complement plays in CNS damage is not clear (Morgan 1999).

The enzyme NO synthase (NOS) synthesizes NO. Inducible NOS (iNOS) is an isoform of NOS that is induced transcriptionally by immunological stimuli. iNOS, which synthesizes large quantities of NO, participates in inflammation-induced cytotoxicity. In the brain, iNOS message, proteins, and enzymatic activity are induced de novo by cerebral ischemia (Iadecola 1999). iNOS is expressed by neutrophils in permanent ischemia and in vascular cells in transient ischemia. High levels of NO are synthesized by human astrocytes upon stimulation with IFN-γ, TNF-α, IL-1 and potentiate IL-1.

Dalkara et al. (1999) showed that NO plays a detrimental role in experimentally induced cerebral infarction in neuronal NOS knockout mice. The NOS knockout infarcts 24 h after permanent vessel occlusion were 38% smaller than those of wild type. These findings seem to indicate that expression of iNOS is a factor contributing to ischemic brain damage.

An apoptotic pathway mediates NO-induced neuronal cell death and an NMDA receptor antagonist blocks NO-mediated neurotoxicity. Neuronal cell...
death was shown by Chao et al. (1997) to be initiated by the release of IL-1 by the microglial cell, this in turn inducing the generation of astrocytes. Neurons are destroyed by NO via NMDA receptor-linked apoptosis.

Cerebral trauma, ischemia, and reperfusion are known to generate hydrogen peroxide and superoxide radicals, which then produce ROS and hydroxyl radicals (Chan 1999). Under normal conditions and following reperfusion injury, mitochondrial respiration creates ROS. Microglia and astrocytes that have been activated by cytokines produce vast quantities of neurotoxic free radicals. An intramitochondrial antioxidant enzyme, manganese superoxide dismutase (MnSOD), scavenges superoxide radicals and thus constitutes the first line of antioxidant defense.

4.4.4 Types of Inflammation

As already pointed out, inflammatory responses are based on an inflammatory cascade, whose details have become increasingly clear in recent years. Three basic types of inflammatory response are known: sterile inflammation, cell-mediated inflammation, and antibody-mediated inflammation. These types of response are mutually exclusive, but characterized by occasional overlapping.

4.4.4.1 Sterile Inflammation

In cases of mechanical violence, spontaneous intracerebral hemorrhage or stroke, sterile inflammation features an initial phase of infiltrating neutrophils and a second phase of infiltrating mononuclear phagocytes (bone marrow-derived monocytes, i.e., activated microglia and macrophages). Macrophages and neutrophils produce cytotoxic cytokines such as TNF-α, proteolytic enzymes (Anthony et al. 1997), reactive oxygen intermediates (Cross et al. 1998), cell death-inducing surface molecules such as Fas ligands (D'Souza et al. 1996), or even excitotoxins (Lipton 1998). The macrophages in particular take up the scavenger function and eliminate tissue and cellular debris. They also release mediators that promote the scarring process, i.e., induce fibroblasts to produce collagenous fibers and stimulate astrocytes to proliferation and produce fibrils, aiding healing by the production of a fibrillary glial-collagenous scar.

4.4.4.2 Cell-Mediated Inflammation

Multiple sclerosis (MS) is the classic model of T-cell-mediated inflammation whose inflammatory infiltrates are chiefly comprised of T-lymphocytes, fewer B-lymphocytes, as well as activated microglial cells and macrophages (Brück et al. 1995; Gay et al. 1997). MS features local expression and/or upregulation of markers of T-lymphocyte and macrophage activation (Brück et al. 1995), of class I and class II MHC antigens (Traugott 1987), of chemokines and adhesion molecules in addition to their receptors (Lassmann 1998), and of co-stimulatory molecules (Windhagen et al. 1995).

Diseases with an autoimmune background such as MS or virus-induced inflammatory diseases exhibit a uniform cellular and mediator profile. Unlike MS, lesions associated with viral inflammation of the brain display considerable differences in topography and in their patterns of structural damage. They also vary with regard to the nature of the immune response and its associated cellular tropism. In lesions of virus encephalitis CD8α-lymphocytes abound; in MS lesions both active and inactive CD8α-cells usually outnumber CD4α-cells (Gay et al. 1997).

Virus-infected cells generally evoke a cell-mediated immune response, although humoral mechanisms play a role as well (for review see Esiri and Kennedy 1997). Phagocytosis of infected cells by macrophages can also be promoted by antibodies. Antibody-dependent cell-mediated cytotoxicity (ADCC) is a process in which lymphocytes bearing Fc receptors for IgG lyse virus-infected cells bearing relatively small amounts of surface-bound antibody. The immunological specificity of the reaction derives from the antibody not the lymphocytes, which are not specific and have been designated killer cells. An important cell-mediated specific mechanism for killing infected target cells is provided by virus-specific cytotoxic T-cells. The cytotoxic effect is seen even if an antibody is lacking and is restricted by MHC class I antigens. Viral antigens on the surface of infected host T-cells are recognized by virus-induced cytotoxic T-cells in association with class I MHC antigens. The infected target T-cells are then killed by these T-cells only if they share the same MHC antigens, i.e., the T-cell killing is restricted by MHC (Zinkernagel and Doherty 1974).

Viral infection induces secretion of cytokines within the CNS, either by lymphomononuclear cell infiltrates or infected brain cells. Cytokines play an important role in the induction of MHC molecules. They stimulate humoral and cell-mediated immune responses by acting on immune system cells and neighboring brain cells, evoking the expression of surface recognition molecules such as MHC antigens and antiviral proteins such as Mx (Campbell 1991). Viral infections can provoke or amplify MHC class II expression on the surface of astrocytes and microglial cells, which is important in light of the significance of these antigen-presenting cells in the CNS. This process can occur as a direct effect of the
infection even in the absence of IFN-γ, as shown for measles virus-infected astrocytes and the murine coronavirus J. Howard Mueller virus (Massa et al. 1987).

### 4.4.4.3 Antibody-Mediated Inflammation

In viral and bacterial inflammation, both the cell-mediated immune response and the humoral response are highly important, the latter also usually dominating. Blood-borne dissemination of virus from the primary infection site to other organs is restricted by circulating antibodies, IgG or IgM. Antibodies in tissue spaces can stop the spread of infection from one cell to another by neutralizing extracellular viruses. However, viruses able to fuse cell membranes, such as measles or herpes viruses, can elude this mechanism without ever being exposed to antibody. Viruses can be inactivated by antibodies in a variety of ways. Antibodies can assist phagocytosis by coating the surface of the virion, or they may thwart attachment of the virus to specific receptors on vulnerable cells, or in the case of enveloped viruses they may promote viral lysis via attachment and activation of complement. In the absence of antibody, direct viral lysis can also be produced by complement alone.

### 4.4.5 Inflammation-Induced Ischemia

Edema can produce an increase in tissue pressure that disturbs the microcirculation of portions of the CNS that are anatomically prevented from swelling by bone or tight meningeal constraints. It is thought that this mechanism contributes to the formation of necrotic lesions in transverse myelitis. The inflammatory process often has a vasculitic component (Gray 1997) that causes occlusion of small veins and venules and is commonly associated with massive tissue damage. Ischemia can contribute to the development of structural damage and functional deficits in inflammatory CNS lesions.

Involvement of arteries and veins is rare in bacterial inflammation but the exudate is frequently accompanied by strands of fibrin. The edematous cortex exhibits large artificial perineuronal spaces and a spongiform neuropil. The cytoplasm of neurons often reveals ischemic cell necrosis and is acidophilic. If the course is subacute, fibrinoid necrosis and thrombosis may appear in a few blood vessels in the exudate, resulting in small foci of cortical necrosis.

### 4.5 Misinterpretable Findings

In the field of neuropathology both gross and microscopic changes can be misinterpreted. Only a few aspects will be discussed here, each involving routine immersion fixation with 10% buffered formalin, dehydration and embedding in paraffin (see above). A detailed overview of the problems associated with postmortem changes, artifacts, and misinterpretation has been provided by Lindenberg (1982).

#### 4.5.1 Gross Findings

**Autolysis**, a process involving self-digestion of tissue, can cause slides of the adult brain to be discolored or poorly staining. The morphology of the changes associated with autolysis are identical with those of respirator brain (brain death). They arise if fixation is done too late, i.e., if the interval between intracranial circulatory arrest and autopsy or brain fixation is too long. Depending on the ambient conditions, the brain will liquefy after a certain postmortem interval without fixation.

The brain emits a foul odor if it has undergone microorganism-induced putrefaction, and the central parts of brain slides display a faint pink coloration. Variably large bullous cavities (Fig. 4.25a, b) give an appearance of Swiss cheese to large sections of the brain. Such cavities are created by the activation of gas-producing microorganisms due to poor quality formalin.

Macroscopic necrosis of the cerebellar granular layer was interpreted by Ikuta et al. (1963) as a postmortem phenomenon, whereas Lindenberg (1982) thought that the necrotic process precedes or accompanies the onset of sublethal hypoxemia, i.e., shortly before death.

Neurons in the substantia nigra and locus coeruleus of the brains of infants and children up to 5 years of age normally possess no melanin pigment. This finding is neither an artifact nor pathological.

The spinal cord is especially sensitive to postmortem mechanical injury in an unfixed state. In this manner the so-called toothpaste-artifact can occur (Hughes 1978). If the tissue in a segment of the spinal cord is artificially constricted, proximal portions of the cord are squeezed upward, distal portions downward, thus appearing in histological sections at the wrong level.
PART I: Principles of Forensic Neuropathology

4.5.2 Microscopic Findings

Any tissue processing produces artifacts that have to be interpreted: fixation procedures as well as staining techniques. The artifacts are dependent on the time periods between death and fixation, the duration of the fixation process, the temperatures, etc. For example the freezing process of (brain) tissue leads to crystalline vacuoles within the tissue sections (Fig. 4.26a, b).

Additionally, the forensic neuropathologist fundamentally needs to be able to reliably distinguish between vital and postmortem changes (cf. Oehmichen 1995). This requires among other things the testing and use of novel histochemical and immunohistochemical staining techniques that can help to establish the length of the postmortem interval.

So-called dark neurons (Fig. 4.26c) can appear among otherwise normal neurons. Dark neurons are irregularly contoured, shrunken neurons that are created by excessive pressure on unfixed postmortem tissue (Scharrer 1938; Cammermeyer 1961, 1975). Apical dendrites also have a dark coloration, sometimes in combination with a corkscrew-like appearance. There is a danger of confusing dark neurons with ischemic cell necrosis. In our own investigations (Oehmichen and Gencic 1980a) we could observe that most, but not all dark neurons have a potent albumin uptake, an indication that they represent lesions of neuronal metabolism (and/or membrane).

Animal experiments demonstrate that the following three types of altered neurons appear at different postmortem intervals in rats (Oehmichen and Gencic 1980b):

1. Shrunken, hyperchromatic neurons, whose number declines as the postmortem interval proceeds.
2. Swollen and autolytic neurons, with a pale perikaryon and nucleoplasm, and an absence of Nissl bodies. The nucleus can no longer be differentiated from the vacuolated and autolyzing cytoplasm. The cells themselves have lost their contours and appear swollen and spherical. The swelling in particular represents the most fundamental postmortem change (whose differential diagnosis is retrograde degeneration).
3. Pericellular spaces surrounding neurons may be caused by postmortem autolytic processes that mimic edema, especially in the gray matter.

Children two years old and younger almost invariably exhibit periventricular and perivenous accumulation of cytoplasm-poor, lymphocyte-like mononuclear cells which suggest an encephalitis (so-called pseudoencephalitis). Those cell aggregations consist of neuroblasts as an indication of development, not of an inflammatory process. This age group also regularly shows a superficial granule layer of the cerebellar cortex composed of germinal cells (matrix cells). These usually disappear some time between the second and fourth years of life.

In cases of sudden death with brief agony or if tissues have been poorly fixed (Hirano 1981), extensive acute swelling of oligodendroglia is common. In addition, a generalized swelling and clasmatodendrosis of astrocytes is often seen. These changes are rather slight compared to the neuronal changes. They must also be regarded as non-specific and do not constitute markers of edema.

Lindenberg (1982) points out that the state of the brain before circulatory arrest also plays a role. If the agony was brief (healthy person who died within minutes), neurons and glial cells may show marked postmortem ischemic cell injury (vacuolation, homogenization, acute shrinkage associated with nuclear changes). Agony of long duration results in a largely unchanged cytology.

Not only does the architecture of the cells change, but their functional state and/or stainability with various reagents changes as well. Postmortem function and staining are influenced by many factors in addition to fixation procedures (time, temperature,
and type of procedure). It is further known that the enzyme activity of cells and tissue depends in large part on the length of the postmortem interval (for a survey of findings prior to 1980 see Oehmichen 1980).

Numerous variables are known to affect the immunoreactivity of cells and tissue in the antigen–antibody reaction for immunohistological demonstration of epitopes (Grizzle et al. 2001). Among these variables are the interval between cellular death and fixation as well as the duration of fixation, the method of tissue processing, the preparation of paraffin blocks, the method of attaching tissue sections to microscopic slides, the interval between cutting tissue sections and immunostaining. To summarize, once findings are obtained by performing the relevant investigations, their proper interpretation requires long experience in the routine practice of neuropathology.

**Bibliography**

Ironside JW, Pickard JO (2002) Raised intracranial pressure, oedema and hydrocephalus. In: Graham DI, Lantos PL (eds) Greenfield’s neuropathology, 7th edn, vol 1. Arnold, London, pp 193–231

Keane RW, Hickey WF (eds) (1997) Immunology of the nervous system. Oxford University Press, New York

Lee JC (1982) Anatomy of the blood–brain barrier under normal and pathological conditions In: Haymaker W, Adams RD (eds) Histology and histopathology of the nervous system, vol 1. CC Thomas, Springfield, Ill., pp 798–870

Lindenberg R (1982) Tissue reactions in the gray matter of the central nervous system. In: Haymaker W, Adams RD (eds) Histology and histopathology of the nervous system. CC Thomas, Springfield, Ill., vol 1, pp 973–1275

---

**Fig. 4.26a–c.** Mininterpretable findings. a, c Crystalline vacuoles as seen within tissue sections after freezing of native brain tissue; b dark neurons as a postmortem phenomenon (a–c H&E; magnification a ×50, b ×300, c ×500)
References

Abbott NJ, Revest PA, Romero IA (1992) Astrocyte-endothelial interaction: physiology and pathology. Neuropathol Appl Neurobiol 18:424–433

Abe K (1999) Neurons. Necrotic vs apoptotic changes. In: Walz W (ed) Cerebral ischemia: molecular and cellular pathophysiology. Humana, Totowa, N.J., pp 217–232

Adachi M, Feigin I (1966) Cerebral oedema and the water content of normal white matter. J Neurol Neurosurg Psychiatry 29:446–450

Adams JH, Graham DI (1976) The relationship between ventricular fluid pressure and the neuropathology of raised intracranial pressure. Neuropathol Appl Neurobiol 2:323–332

Adams JH, Graham DI, Muray LS, Scott G (1982) Diffuse axonal injury due to non-missile head injury in humans: an analysis of 45 cases. Ann Neurol 12:557–563

Adams RD, Fisher CM, Hakim S et al. (1965) Symptomatic occult hydrocephalus with “normal” cerebrospinal-fluid pressure: a treatable syndrome. N Engl J Med 273:117–126

Adler DE, Milhorat TH (2002) The tentorial notch: anatomical variation, morphometric analysis, and classification in 100 human autopsy cases. J Neurosurg 96:1103–1112

Anthony DC, Ferguson B, Matyszak MK et al. (1997) Different matrix and metalloproteinase expression in cases of multiple sclerosis and stroke. Neuropathol Appl Neurobiol 23:406–415

Armstead WM, Kurth CD (1994) Different cerebral hemodynamic responses following fluid percussion brain injury in the newborn and juvenile pig. J Neurotrauma 11:487–497

Artru F, Philippin B, Berger M, Deleuze R (1976) Cerebral blood flow, cerebral metabolism and cerebrospinal fluid biochemistry in brain-injured patients after exposure to hyperbaric oxygen. Eur Neurol 14:351–364

Astrup J, Siesjö BK, Symon L (1981) Thresholds in cerebral ischemia – the ischemic penumbra. Stroke 12:723–725

Auer RN (2000) Pure hypoxic and ischemic insults. In: Research in legal medicine, vol 24. Schmidt-Römhild, Lübeck, pp 27–39

Bakay L, Lee JC (1965) Cerebral edema. Thomas, Springfield, Ill.

Bakay L, Lee JC (1965) Effect of hypoxia on the ultrastructure of the central nervous system. Brain 91:697–702

Baron JL, Madri JA, Ruddle NH et al. (1993) Surface expression of α4 integrin by CD4 T-cells is required for their entry into brain parenchyma. J Exp Med 177:57–68

Barone FC (1999) Tumor necrosis factor α in stroke and neurotrauma. In: Ruffolo RR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 327–348

Bauer J, Rauschka H, Lassmann H (2001) Inflammation in the nervous system: the human perspective. Glia 36:235–243

Benedetta Silva M, Anthony DC, Issekutz AC, Perry VH (2001) Recruitment of neutrophils across the blood–brain barrier: the role of E- and P-selectins. J Cereb Blood Flow Metab 21:1115–1124

Beilinaqua MP (1993) Endothelial-leukocyte adhesion molecules. Annu Rev Immunol 11:767–804

Bieniek SK, Grundl PD, Kochanek PM et al. (1996) Posttraumatic hyperemia in immature, mature, and aged rats: autoradiographic determination of cerebral blood flow. J Neurotrauma 13:189–200

Blank WF, Kirshner HS (1977) The kinetics of extracellular potassium changes during hypoxia and anoxia in the cat cerebral cortex. Brain Res 123:113–124

Blinzinger K, Kreutzberg G (1968) Displacement of synaptic terminals from regenerating motor neurons by microglial cells. Z Zellforsch Mikrosk Anat 85:145–157

Blumbergs PC, Scott G, Manavis J et al. (1995) Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. J Neurotrauma 12:565–571

Bonecchi R, Bianchi G, Bordignon PP et al. (1998) Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. J Exp Med 187:129–134

Brightman MW, Reese TS (1969) Junctions between intimately apposed membranes in the vertebrate brain. J Cell Biol 40:648–677

Brodal P (1982) The central nervous system. Oxford University Press, New York

Broman T (1949) The permeability of the cerebral vessels in normal and pathological conditions. Munksgaard, Copenhagen

Broman T, Steinwall O (1967) Model of the blood–brain barrier system. In: Klatzo I, Seitel-Berger F (eds) Brain edema. Springer, Berlin Heidelberg New York, pp 360–384

Brück W, Porada P, Poser S et al. (1995) Monocyte/macrophage differentiation in early multiple sclerosis lesions. Ann Neurol 38:788–796

Cameron HA, McKay RD (1999) Restoring production of hippocampal neurons in old age. Nat Neurosci 2:894–897

Cammermeyer J (1961) Histochemical phospholipid reaction in nerve tissue: a method application for comparison of nerve tissue ultrastructure. J Neurocytol 20:1–12

Cammermeyer J (1975) The importance of avoiding “dark” neurons. Acta Neuropathol 38:788–796

Cameron HA, McKay RD (1999) Restoring production of hippocampal neurons in old age. Nat Neurosci 2:894–897

Cammermeyer J (1961) The importance of avoiding “dark” neurons in experimental neuropathology. Acta Neuropathol 1:345–352

Cammermeyer J (1975) Histochemical phospholipid reaction in ischemic neurons as an indication of exposure to postmortem trauma. Exp Neurol 49:252–272

Campbell IL (1991) Cytokines in viral diseases. Curr Opin Immunol 3:486–491

Cervós-Navarro J, Ferszt R (1977) Beitrag zur Ätiopathogenese der Koagulationsnekrose im Gehirn. In: Schneider V (ed) Festschrift Walter Krauland zum 65. Geburtstag. Universitäts-druckerei, Berlin, pp 129–139

Chan KH, Miller JD, Dearden NM (1992) Intracranial blood flow velocity after head injury: relationship to severity of injury, time, neurological status and outcome. J Neurol Neurosurg Psychiatry 55:787–791

Chan PH (1999) The role of superoxide radicals in the pathogenesis of cerebral ischemic cell death. In: Ruffolo RR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells...
Graham DJ, Lawrence AE, Adams JH et al. (1987) Brain damage in non-missile head secondary to high intracranial pressure. Neuropathol Appl Neurobiol 13:209–217

Graham DJ, Smith C, Reichard R et al. (2004) Trials and tribulations using β-amyloid precursor protein immunohistochemistry to evaluate traumatic brain injury in adults. Forensic Sci Int 146:89–96

GrandPré T, Nakamura F, Vartanian T, Strittmatter SM (2000) Identification of the Nogo inhibitor of axon regeneration as a Reelin protein. Nature 403:439–444

Granger DN, Kubies P (1994) The microcirculation and inflammation: modulation of leukocyte-endothelial cell adhesion. J Leukoc Biol 55:662–675

Granville DJ, Carthy CM, Hunt DW, McManus BM (1998) Biology of disease. Apoptosis: molecular aspects of cell death and disease. Lab Invest 78:893–913

Grassmann CB, Potts DG (1974) Arachnoid granulations, radiology and anatomy. Radiology 113:95–100

Gray F (1997) Lesions of the central nervous system in the early stages of human immunodeficiency virus infection. Rev Neurol Paris 153:629–640

Greenwood J (1991) Mechanisms of blood–brain barrier breakdown. Neuroradiology 33:95–100

Griffin WS, Stanley LC, Ling C et al. (1989) Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. Proc Natl Acad Sci USA 86:7611–7615

Grizzle WE, Stockard CR, Billings PE (2001) The effects of tissue processing variables other than fixation on histochemical staining and immunohistochemical detection of antigens. J Histotechnol 24:213

Haas CA, Donath C, Kreutzberg GW (1993) Differential expression of immediate early genes after transection of the facial nerve. Neuroscience 53:91–99

Harding B, Copp AJ (1997) Malformations. In: Graham DJ, Lantos PL (eds) Greenfield’s neuropathology, 6th edn, vol 1. Arnold, London, pp 397–533

Harlan JM, Liu DY (1992) Adhesion: its role in inflammatory disease. WH Freeman, New York

Hart DNU, Fabre JW (1981) Demonstration and characterization of la-positive dendritic cells in the interstitial connective tissues of rat heart and other tissues, but not brain. J Exp Med 153:347–361

Hart MN, Fabry Z (1995) CNS antigen presentation. Trends Neurosci 18:475–481

Hartung HP, Heininger K, Schäfer B et al. (1988) Immune mechanisms in inflammatory polyneuropathy. Ann NY Acad Sci 540:122–161

Haymaker W, Margoles C, Pentschew A et al. (1961) Pathology of kernicterus and posticteric encephalopathy: presentation of 87 cases, with a consideration of pathogenesis and etiology. In: Swinyard CA (ed) Kernicterus and its importance in cerebral palsy. CC Thomas, Springfield, Ill., pp 21–52

Heiss WD (2000) Ischemic penumbra: evidence from functional imaging in man. J Cereb Blood Flow Metab 20:1276–1293

Heiss WD, Rosner G (1983) Functional recovery of cortical neurons as related to degree and duration of ischemia. Ann Neurol 14:294–301

Hickey WF, Kimura H (1988) Perivascular microglial cells of the CNS are bone marrow-derived and present antigen in vivo. Science 239:290–292

Hickey WF, Hsu BL, Kimura H (1991) T-lymphocyte entry into the central nervous system. J Neurosci Res 28:254–260

Hickey WF, Lassmann H, Cross AH (1997) Lymphocyte entry and the initiation of inflammation in the central nervous system. In: Keane RW, Hickey WF (eds) Immunology of the nervous system. Oxford University Press, New York, pp 200–225

Hirai O, Handa H, Ishikawa M (1986) Cerebral blood volume as another cause of intracranial hypertension following cold-induced edema. In: Miller JD, Teasdale GM, Rowan JO, Galbraith SL, Mendelow AD (eds) Intracranial pressure VI. Springer, Berlin Heidelberg New York, pp 146–150

Hirano A (1981) A guide to neuropathology. Igaku-Schoin, Tokyo

Hsu CY, Hu ZY, Doster SK (1995) Cell-mediated injury. In: Narayan RK, Wilberger JE, Povlishock JT (eds) Neurotrauma. McGraw-Hill, New York, pp 1433–1444

Huang F-P, Guohua XI, keep RF et al. (2002) Brain edema after experimental intracerebral hemorrhage: role of hemoglobin degradation products. J Neurosurg 96:287–293

Hughes JT (1978) Pathology of the spinal cord. Lloyd Luke, London, pp 181–190

Huppertz B, Frank H-G, Kaufmann P (1999) The apoptosis cascade – morphological and immunohistochemical methods for its visualization. Anat Embryol 200:1–18

Hurley RA, Bradley WG Jr, Latifi HT, Taber KH (1999) Normal pressure hydrocephalus: significance of MRI in a potentially treatable dementia. J Neuropsychiatry Clin Neurosci 11:297–300

Hynes RO (1992) Integrins: versatility, modulation, and signaling of cell adhesion. Cell 69:11–25

Iadecola C (1999) Inducible nitric oxide synthase gene expression and ischemic brain damage. In: Ruffolo RR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 113–136

Ikegaya H, Heino J, Laaksonen H et al. (2004) Accumulation of plasma proteins in Purkinje cells as an indicator of blood-brain barrier breakdown. Forensic Sci Int 146:121–124

Ikuta F, Hirano A, Zimmerman HM (1963) An experimental study of postmortem alterations in the granular layer of the cerebellar cortex. J Neuropath Exp Neurol 22:581–590

Inuzuka T, Tamura A, Sato S et al. (1990) Changes in the concentration of plasma proteins in Purkinje cells as an indicator of blood-brain barrier breakdown. Forensic Sci Int 146:121–124

Iwamoto K, Hirano A, Zimmerman HM (1963) An experimental study of postmortem alterations in the granular layer of the cerebellar cortex. J Neuropath Exp Neurol 22:581–590

Inuzuka T, Tamura A, Sato S et al. (1990) Changes in the concentration of plasma proteins in Purkinje cells as an indicator of blood-brain barrier breakdown. Forensic Sci Int 146:121–124

Jacob H (1947) Zur histopathologischen Diagnose des akuten und chronisch rezidivierenden Hirnödems. Arch Psychiatr Z Neurol 187:177–186

Jackson R, Friede RL (1979) Perisulcal infarcts: lesions caused by hypotension during increased intracranial pressure. Ann Neurol 6:339–404

Jean WC, Spellman SR, Nussbaum ES, Low WC (1998) Reperfusion injury after focal cerebral ischemia: the role of inflammation and the therapeutic horizon. Neurosurgery 43:1382–1397

Jellinger KA, Stadelmann C (2002) Problems of programmed cell death in neurodegenerative disorders. In: Oehmichen M,
Ritz-Timse S, Meissner C (eds) Aging. Morphological, biochemical, molecular and social aspects. In: Research in legal medicine, vol 27. Schmidt-Römhild, Lübeck, pp 123−144

Johnston I, Paterson A (1974) Benign intracranial hypertension II. CSF pressure and circulation. Brain 97:301−312

Jones PA, Andrews PJD, Midgley S et al (1994) Measuring the burden of secondary insults in head injured patients during intensive care. J Neurosurg Anesthesiol 6:4−14

Kalmr B, Burnstock G, Vrbova G et al (2002) Upregulation of heat shock proteins rescues motor neurons from axotomy-induced cell death in neonatal rats. Exp Neurol 176:87−97

Kanthis R, Shuaib A (1995) Clinical evaluation of extracellular amino acids in severe head trauma by intracerebral in vivo microdialysis. J Neurol Neurosurg Psychiatry 59:326−327

Kapoor R, Davies M, Blaker PA et al (2003) Blockers of sodium and calcium entry protect axons from nitric oxide-mediated degeneration. Ann Neurol 53:174−180

Kempermann G, Kuhn HG, Gage FH (1998) Experience-induced neurogenesis in the senescent dentate gyrus. J Neurosci 18:3206−3212

Kempermann G, Gast D, Gage FH (2002) Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. Ann Neurol 52:135−143

Kermer P, Klöcker N, Bähr M (1999) Neuronal death after brain injury. Models, mechanisms, and therapeutic strategies in vivo. Cell Tissue Res 298:383−395

Keyvani K, Schallert T (2002) Plasticity-associated molecular and structural events in the injured brain. J Neuropath Exp Neurol 61:831−840

Kimelberg HK (1995a) Brain edema. In: Kettenmann H, Ransoom BR (eds) Neuroglia. Oxford University Press, New York, pp 919−935

Kimelberg HK (1995b) Current concepts of brain edema. J Neurosurg 83:1051−1059

Kimelberg HK, Rutledge E, Feustel PJ (1997) Cell swelling and effects of alcohol in experimental neural trauma. In: Oehmichen M, König HG (eds) Neurotraumatology — biomechanic aspects, cytologic and molecular mechanisms. Schmidt-Römhild, Lübeck, pp 295−315

Klatzo I (1967) Neuropathological aspects of brain edema. J Neuropathol Exp Neurol 26:1−14

Knopf PM, Bass D, Sirulnick E et al. (1994) B cell traffic and intra-thecal antibody synthesis in normal brain. FASEB J 8:A248

Koo EH, Abraham CR, Potter H et al. (1991) Developmental expression of α-anti-chymotrypsin in brain may be related to astrogliosis. Neurobiol Aging 12:495−501

Kooy K, van, Wiel-van Kemenade E van de, Weder P et al. (1993) Lymphocyte function-associated antigen 1 dominates very late antigen 4 in binding of activated T-cells to endothelium. J Exp Med 177:185−190

Lajtha A (1968) Transport as control mechanism of cerebral metabolite levels. In: Lajtha A, Ford DH (eds) Brain barrier system. Elsevier, Amsterdam, pp 201−232

Langfitt TW, Weinstein JD, Kassell NF (1965) Cerebral vasomotor paralysis produced by intracranial hypertension. Neurology 15:632−641

Lassman H (1998) Pathology of multiple sclerosis. In: Compston A (ed) McAlpine’s multiple sclerosis, 3rd edn. Churchill Livingstone, London, pp 323−356

Leech PJ, Miller JD (1974) Intracranial volume/pressure relationships during experimental brain compression in primates. II. Effect of induced changes in arterial pressure. J Neurol Neurosurg Psychiatry 37:1099−1104

Leist M, Single B, Naumann H, Fava E et al (1990) Inhibition of mitochondrial ATP generation by nitric oxide switches apoptosis to necrosis. Exp Cell Res 249:396−403

Li GL, Ahlgren S, Farooque M et al. (1997) Lesions of axons and dendrites in spinal cord trauma. In: Oehmichen M, König HG (eds) Neurotraumatology — biomechanic aspects, cytologic and molecular mechanisms. In: Research in legal medicine, vol 17. Schmidt-Römhild, Lübeck, pp 187−201

Li GL, Farooque M, Holtz A, Olsson Y (1995) Microtubule-associated protein 2 as a sensitive marker for dendritic lesion after spinal cord trauma: an immunohistochemical study in the rat. Restor Neurol Neurosci 8:189−197

Li S, Strittmatter SM (2003) Delayed systemic nogo-66 receptor antagonist promotes recovery from spinal cord injury. J Neurosci 23:4219−4227

Lindenberg R (1955) Compression of brain arteries as a pathogenic factor for tissue necrosis and their areas of predilection. J Neuropathol Exp Neurol 14:233−243

Lindenberg R (1982) Tissue reactions in the gray matter of the central nervous system. In: Haymaker W, Adams RD (eds) Histology and histopathology of the nervous system, vol 1. CC Thomas, Springfield, Ill., pp 973−1275

Liou AK, Clark RS, Henschall DC et al. (2003) To die or not to die for neurons in ischemia, traumatic brain injury and epilepsy: a review on the stress-activated signaling pathways and apoptotic pathways. Prog Neurobiol 69:103−142

Lipton SA (1998) Neuronal injury associated with HIV-1: approaches and treatment. Annu Rev Pharmacol Toxicol 38:159−177

Majno G, Joris I (1995) Apoptosis, oncrosis, and necrosis. An overview of cell death. Am J Pathol 146:3−15

Marmarou A, Anderson RL, Ward JD et al (1991) NINCDS Traumatic coma data bank. Intracranial pressure monitoring methodology. J Neurosurg 75:521−527

Marmarou A, Barzo P, Fatouros P et al (1997) Traumatic brain swelling in head injured patients: brain edema or vascular engorgement? Acta Neurochir (Wien) 70:68−70

Marmarou A, Fatouros PP, Barzò P et al (2000) Contribution of edema and cerebral blood volume to traumatic brain swelling in head-injured patients. J Neurosurg 93:183−193

Marshall WJS, Jackson JLF, Langfitt TW (1969) Brain swelling caused by trauma and arterial hypertension. Arch Neurol 21:545−553

Massa PT, Schimpl A, Wecker E, Meulen V ter (1987) Tumor necrosis factor amplifies measles virus-mediated induction on astrocytes. Nature 320:543−546

Massa PT, Schimpfl A, Wecker E, Meulen V ter (1987) Tumor necrosis factor amplifies measles virus-mediated induction on astrocytes. Proc Natl Acad Sci USA 84:7242−7245

Matyszak MK, Lawson LJ, Perry VH, Gordon S (1992) Stromal macrophages of the choroid plexus situated at an interface between the brain and peripheral immune system consti-
tutively express major histocompatibility class II antigens. J Neuroimmunol 40:173−181
Matz PG, Lewen A, Chan PH (2001) Neuronal, but not microglial, accumulation of extravasated serum proteins after intracerebral hemolysate exposure is accompanied by cytochrome C release and DNA fragmentation. J Cereb Blood Flow Metab 21:921−928
McConkey DJ (1998) Biochemical determinants of apoptosis and necrosis. Toxicol Lett 3:157−168
McEver RP (1994) Selectins. Curr Opin Immunol 6:75−84
McGee AW, Strittmatter SM (2003) The Nogo-66 receptor: focusing myelin inhibition of axon regeneration. Trends Neurosci 26:193−198
McIntosh TK, Saatman KE, Raghupathi R et al. (1998) The molecular and cellular sequelae of experimental traumatic brain injury: pathogenetic mechanisms. Neuropathol Appl Neurobiol 24:251−268
McKhan GM (2002) New neurons for aging brains. Ann Neurol 52:133−134
Medawar PB (1948) Immunity of homologous grafted skin. Ill. The fate of skin monograms transplanted to the brain, to subcutaneous tissue and to the anterior chamber of the eye. Br J Exp Pathol 29:58−69
Meeussen EN, Premier RR, Brandon MR (1996) Tissue-specific migration of lymphocytes: a key role for Th1 and Th2 cells? Immunol Today 17:421−424
Mendelow AD, Baethmann A, Czernicki Z et al. (2000) A summary of the XIth International Brain Edema Symposium held in Newcastle-upon-Tyne, England in June 1999. In: Mendelow AD, Baethmann A, Czernicki Z et al (eds) Brain edema XI. Proceedings of the 11th International Symposium, Newcastle-upon-Tyne, UK, 6−10 June 1999, pp 9−10
Meyer A (1920) Herniation of the brain. Arch Neurol Psychiatry 4:387−400
Miller JD, Ironside JW (1997) Raised intracranial pressure, oedema and hydrocephalus. In: Graham DJ, Lantos PL (eds) Greenfield’s neuropathology. Arnold, London, pp 157−195
Miller JD, Becker DP, Ward JD et al. (1977) Significance of intracranial hypertension in severe head injury. J Neurosurg 47:503−516
Miller JD, Butterworth JF, Gudeman SK et al. (1981) Further experience in the management of severe head injury. J Neurosurg 54:289−299
Miyamoto O, Auer RN (2000) Hypoxia, hyperoxia, ischemia and brain necrosis. Neurology 54:362−371
Morgan BP (1999) Complement in brain inflammation and injury. In: Ruffolo RR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 283−296
Müller G (1930) Zur Frage der Altersbestimmung histologischer Veränderungen im menschlichen Gehirn unter Berücksichtigung der örtlichen Verteilung. Z Neuroch Psychiat 124:1−112
Nawashiro H, Shima K, Chigasaki H (1995) Immediate cerebrovascular responses to closed head injury in the rat. J Neurotrauma 11:189−197
Niess C, Grauel U, Toennes SW, Bratzke H (2002) Incidence of axonal injury in human brain tissue. Acta Neuropathol (Berl) 104:79−84
Norenberg MD (1997) Astrocytes: normal aspects and response to CNS injury. In: Keane RW, Hickey WF (eds) Immunology of the nervous system. Oxford University Press, New York, pp 173−199
Oehmichen M (1976a) Cerebrospinal fluid cytology. An introduction and atlas. WB Saunders, Philadelphia, Pa.
Oehmichen M (1976b) Characterization of mononuclear phagocytes of human CSF using membrane markers. Acta Cytol 20:548−552
Oehmichen M (1978) Mononuclear phagocytes in the central nervous system. Springer, Berlin Heidelberg New York
Oehmichen M (1980) Enzyme alterations in brain tissue during the early postmortem interval with reference to the histomorphology: review of the literature. Z Rechtsmed 85:81−95
Oehmichen M (1982) Functional properties of microglia. In: Smith WT, Cavanagh JB (eds) Recent advances in neuropathology, vol 2. Churchill Livingstone, Edinburgh, pp 83−107
Oehmichen M (1983) Inflammatory cells in the central nervous system. Current state of basic research in immunology, pathology and forensic medicine. In: Zimmermann HM (ed) Progress in neuropathology, vol 5. Raven, New York, pp 227−335
Oehmichen M (1995) Estimating wound age and distinguishing intravital from postmortem processes in forensic medicine – introductory remarks. In: Oehmichen M, Kirchner H (eds) Research in legal medicine, vol 13, The wound healing process: forensic pathological aspects. Schmidt-Römhild, Lübeck, pp 15−21
Oehmichen M, Gencic M (1980a) Postmortal diffusion of plasma albumin in rat brain. Z Rechtsmed 84:113−123
Oehmichen M, Gencic M (1980b) Postmortal histomorphologic and histozymatic alterations in rats brain. Pathol Res Pract 169:72−83
Oehmichen M, Huber H (1976) Reactive microglia with membrane features of mononuclear phagocytes. J Neuropathol Exp Neurol 35:30−39
Oehmichen M, Grüninger H, Wiethöltner H, Gencic M (1979) Lymphatic efflux of intracerebrally injected cells. Acta Neuropathol (Berl) 45:61−65
Oehmichen M, Meissner C, Schmidt V et al. (1999) Pontine axonal injury after brain trauma and nontraumatic hypoxic-ischemic brain damage. Int J Leg Med 112:261−267
Oehmichen M, Ochs U, Meissner C (2000) Histochemical characterization of cytotoxic brain edema. Exp Pathol Toxicol 52:348−352
Oldendorf WH (1977) The blood–brain barrier. Exp Eye Res [Suppl] 25:177
O’Sullivan MG, Statham PF, Jones PA et al. (1994) Role of intracranial pressure monitoring in severely head injured patients without signs of intracranial hypertension on initial computed tomography. J Neurosurg 80:46−50
Pachtet JS, Cries HE de, Fabry Z (2003) The blood–brain barrier and its role in immune privilege in the central nervous system. J Neuropathol Exp Neurol 62:593−604
Parsons AA, Hunter AJ (1999) Perspectives in neuroinjury and disease. In: Ruffolo RR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 1−19
Rothwell N, Toulmond S, Allan S et al. (1999) Cytokines in acute brain injury and stroke. In: Ruffolo RR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 21–38

Pierpaoli C, Alger JR, Righini A et al. (1996) High temporal resolution diffusion MRI of global cerebral ischemia and reperfusion. J Cereb Blood Flow Metab 16:892–905

Platt N, Silva RP da, Gordon S (1998) Recognizing death: the phagocytosis of apoptotic cells. Trends Cell Biol 8:365–372

Polazzi E, Gianni T, Contestabile A (2001) Microglial cells protect cerebellar granule neurons from apoptosis: evidence for reciprocal signaling. Glia 36:271–280

Povlishock JT (1992) Traumatically induced axonal injury: pathogenesis and pathobiological implications. Brain Pathol 2:1–12

Prat A, Biernacki K, Wosik K, Antel JP (2001) Glial cell influence on cerebellar granule neurons from apoptosis: evidence for reciprocal signaling. Glia 36:145–155

Prinjha R, Moore SE, Vinson M et al (2000) Inhibitor of neurite outgrowth in humans. Nature 403:383–384

Purpura DP (1975) Morphogenesis of visual cortex in preterm infants. In: Brazier MAB (ed) Growth and development of the brain: nutrition, genetic and environmental factors. Raven, New York, pp 33–45

Purpura DP (1976) Structure dysfunction relations in the visual cortex of preterm infants. In: Brazier MAP, Coceani F (eds) Dysfunction in infantile febrile convulsions. Raven, New York, pp 223–236

Quadbeck G (1967) Physiologische und Pathologie der Blut-Hirnschanke. Hippokrates 38:45–53

Quadbeck G (1968) Clinical importance of alterations in barrier. In: Lajtha A, Ford DH (eds) Brain barrier systems. Elsevier, Amsterdam, pp 343–361

Raghupathi R, Graham DI, McIntosh TK (2000) Apoptosis after traumatic brain injury. J Neurotrauma 17:927–938

Ramsey MA, Priestley JV, McMahon SB (2000) Functional regeneration of sensory axons into the adult spinal cord. Nature 403:312–316

Reese TS, Karnowsky MJ (1967) Fine structural localization of a blood-brain barrier to exogenous peroxidase. J Cell Biol 34:207–217

Reichard RR, White CL, Hladik CL, Dolinak D (2003) Beta-amyloid precursor protein staining. I. Nonhomicidal pediatric medicoegal autopsies. J Neuropathol Exp Neurol 62:237–247

Reilly CE (2002) Astrocytes instruct stem cells to differentiate into neurons. J Neuro 249:950–952

Rosenblum WI (1997) Histopathologic clues to the pathways of neuronal death following ischemia/hypoxia. J Neurotrauma 14:313–326

Rothwell N, Toulmond S, Allan S et al. (1999) Cytokines in acute brain injury and stroke. In: Ruffolo RR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 471–482

Rubin LL (1997) Neuronal cell death: when, why and how. Br Med Bull 53:617–631

Scharer E (1938) On dark and light – cells in the brain and liver. Anat Rec 72:53–65

Schmid-Schönbein GW, DeLano FA, Costa J, Harris AG (1999) Parenchymal cell death and leukocyte-endothelial cell interaction in acute experimental inflammation. In: Ruffolo RR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 39–52

Schoettle RJ, Kochanek PM, Magargee MJ et al. (1990) Early polymorphonuclear leukocyte accumulation correlates with the development of postraumatic cerebral edema in rats. J Neurotrauma 7:207–272

Scholz W (1953) Selective neuronal necrosis and its topistic pattern in hypoxemia and oligemia. J Neuropath Exp Neurol 12:249

Schröder ML, Muizelaar JP, Fatouros PP et al. (1998) Regional cerebral blood volume after severe head injury in patients with regional cerebral ischemia. Neurosurgery 42:1276–1280

Schwab ME (1993) Experimental aspects of spinal cord regeneration. Curr Opin Neurol Neurosurg 6:549–553

Schwab ME (2000) Finding the lost target. Nature 403:257–260

Schwab ME, Caroni P (1988) Oligodendrocytes and CNS myelin are nonpermissive substrates for neurite growth and fibroblast spreading in vitro. J Neurosci 8:2381–2393

Sedgwick JD, Hickey WF (1997) Antigen presentation in the central nervous system. In: Keane RW, Hickey WF (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 364–418

Seida M, Vass K, Tomida S, Wagner HG, Klatzo I (1989) Observations on cerebral ischaemia in cats at injury threshold levels. Neurol Res 11:205–212

Selhorst JB, Gudeman SK, Butterworth JF et al (1985) Papilledema after acute head injury. Neurosurgery 16:357–363

Sherriff FE, Bridges LR, Sivaloganatham S (1994) Early detection of axonal injury after human head trauma using immunocytochemistry for β-amyloid precursor protein. Acta Neuropathol (Berl) 87:55–62

Simpson JE, Newcombe J, Cuzner ML, Woodroofe MN (1998) Expression of monocyte chemoattractant protein-1 and other beta-chemokines by resident glia and inflammatory cells in multiple sclerosis lesions. J Neuroimmunol 84:238–249

Simpson PE, Criswell HE, Johnson KB (1991) Ethanol inhibits NMDA-evoked electrophysiological activity in vivo. J Pharmacol Exp Ther 257:225–231

Sobel RA, Mitchell ME, Fondren G (1990) Intercellular adhesion molecule-1 (ICAM-1) in cellular immune reactions in the human central nervous system. Am J Pathol 136:1309–1316

Song H, Stevens CF, Gage FH (2002) Astroglia induce neurogenesis from adult neural stem cells. Nature 417:39–44

Spielmeyer W (1922) Histopathologie des Nervensystems. Springer, Berlin Heidelberg New York

Springer TA (1990) Adhesion receptors of the immune system. Nature 346:425–434

Squier MV (1993) Acquired diseases of the nervous system. In: Keeling JW (ed) Fetal and neonatal pathology. Springer, Berlin Heidelberg New York, pp 571–593
Sternberger NH, Sternberger LA, Kies MW, Shear CR (1989) Cell surface endothelial proteins altered in experimental allergic encephalomyelitis. J Neuroimmunol 21:241–248
Sternberger NH, Sternberger LA, Kies MW, Shear CR (1989) Cell surface endothelial proteins altered in experimental allergic encephalomyelitis. J Neuroimmunol 21:241–248
Strich SJ (1956) Diffuse degeneration of the cerebral white matter in severe dementia following head injury. J Neurol Neurosurg Psychiatry 19:163–185
Summer BE, Watson WE (1971) Retraction and expansion of the dendritic tree of motor neurones of adult rats induced in vivo. Nature 233:273–275
Swendsen CN (2002) The amazing astrocyte. Nature 417:29–32
Teasdale E, Cardos E, Galbraith S, Teasdale G (1984) CT scan in severe diffuse head injury: physiological and clinical correlations. J Neurol Neurosurg Psychiatry 47:600–603
Thompson AM (1970) Hyperosmotic effects on brain uptake of non-electrolytes. In: Crone CC, Lassen N (eds) Capillary permeability. Alfred Benzon Symposium II. Munksgaard, Copenhagen, pp 459–472
Thornberry NA, Lazebnik Y (1998) Caspases: enemies within. Science 281:1312–1316
Traugott U (1987) Multiple sclerosis: relevance of class I and class II MHC-expressing cells to lesion development. J Neuroimmunol 16:283–302
Vermes I, Haanen C, Reutelingsperger CPM (1998) Molecular biology of apoptosis and programmed cell death. In: Aruoma OI, Halliwell B (eds) Molecular biology of free radicals in human diseases. OICA International, London, pp 225–286
Waksman BH (1997) A brief history of neuroimmunology. In: Keane RW, Hickey WF (eds) Immunology of the nervous system. Oxford University Press, New York
Waterhouse NJ (2003) The cellular energy crisis: mitochondria and cell death. Med Sci Sports Exerc 35:105–110
Waxman SG (2003) Nitric oxide and the axonal death cascade. Ann Neurol 53:150–153
Weiss JM, Downie SA, Lyman WD, Berman JW (1998) Astrocyte-derived monocyte-chemotactant protein-1 directs the transmigration of leukocytes across a model of the human blood-brain barrier. J Immunol 161:6896–6903
Weiss SJ (1989) Tissue destruction by neutrophils. N Engl J Med 320:365–376
Weller RO, Shulman K (1972) Infantile hydrocephalus: clinical, histological and ultrastructural study of brain damage. J Neurosurg 36:255–265
Windhagen A, Newcombe J, Dangond F et al. (1995) Expression of costimulatory molecules B7-1 (CD80), B7-2 (CD86), and interleukin 12 cytokine in multiple sclerosis lesions. J Exp Med 182:1985–1986
Yakovlev AG, Faden AL (1997) Traumatic brain injury regulates expression of ced-related genes modulating neuronal apoptosis. In: Oehmichen M, König HG (eds) Neurotraumatology – biomechanic aspects, cytologic and molecular mechanisms. Schmidt-Römhild, Lübeck, pp 107–120
Zach O, Bauer HC, Richter K et al. (1997) Expression of a chemotactic cytokine (MCP-1) in cerebral capillary endothelial cells in vitro. Endothelium 5:143–153
Zinkernagel RM, Doherty PC (1974) Immunological surveillance against altered self components by sensitized T-lymphocytes in lymphocytic choriomeningitis. Nature (Lond) 251:547–548
Zoppo GJ del (1997) Selectins, ICAMs, and integrins in CNS injury. In: Ruffolo PR, Feuerstein GZ, Hunter AJ, Poste G, Metcalf BW (eds) Inflammatory cells and mediators in CNS diseases. Harwood Academic, New York, pp 395–412
Zwienenberg M, Muizelaar JP (1999) Severe pediatric head injury: the role of hyperemia revisited. J Neurotrauma 11:937–943

82 PART I: Principles of Forensic Neuropathology