Robbins & Cotran, Pathologic Basis of Disease

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CHAPTER 2

Cellular Responses to Stress and Toxic Insults: Adaptation, Injury, and Death

CHAPTER CONTENTS

Introduction to Pathology

Pathology is devoted to the study of the structural, biochemical, and functional changes in cells, tissues, and organs that underlie disease. By the use of molecular, microbiologic, immunologic, and morphologic techniques, pathology attempts to explain the whys and wherefores of the signs and symptoms manifested by patients while providing a rational basis for clinical care and therapy. It thus serves as the bridge between the basic sciences and clinical medicine, and is the scientific foundation for all of medicine. In chapter 1 we examined the cellular and molecular mechanisms that "define" healthy cells. In this chapter we will build upon that knowledge to discuss the fundamental mechanisms that underlie various forms of cell injury and death.

Traditionally the study of pathology is divided into general pathology and systemic pathology. General pathology is concerned with the common reactions of cells and tissues to injurious stimuli. Such reactions are often not tissue specific: thus acute inflammation in response to bacterial infections produces a very similar reaction in most tissues. On the other hand, systemic pathology examines

- *Cell death.* With continuing damage the injury becomes irreversible, at which time the cell cannot recover and it dies. *Historically, two principal types of cell death, necrosis and apoptosis, which differ in their morphology, mechanisms, and roles in physiology and disease,* have been recognized.
  - Necrosis has been considered an "accidental" and unregulated form of cell death resulting from damage to cell membranes and loss of ion homeostasis. When damage to membranes is severe, lysosomal enzymes enter the cytoplasm and digest the cell giving rise to a set of morphologic changes described as necrosis. Cellular contents also leak through the damaged plasma membrane into the extracellular space, where they elicit a host reaction (inflammation). Necrosis is the pathway of cell death in many commonly encountered injuries, such as those resulting from ischemia, exposure to toxins, various infections, and trauma.
  - In contrast to necrosis, when the cell's DNA or proteins are damaged beyond repair, the cell kills itself by *apoptosis*, a form of cell death that is characterized by nuclear dissolution, fragmentation of the cell without complete loss of membrane integrity, and rapid removal of the cellular debris. Because cellular contents do not leak out, unlike in necrosis, there is no inflammatory reaction. Mechanistically, apoptosis is known to be a highly regulated process driven by a series of genetic pathways. It is hence also sometimes called "programmed cell death."
  - *Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with cell injury.* Despite the distinctive morphologic manifestations of necrosis and apoptosis, it is now clear that the mechanistic distinction between necrosis and apoptosis is not as clear cut as previously imagined. In some cases necrosis is also regulated by a series of signaling pathways, albeit largely distinct from those that are involved in apoptosis. In other words, in some cases necrosis, like apoptosis, is also a form of programmed cell death. In recognition of this similarity, this form of necrosis has been called *necroptosis* as will be discussed later. Despite some potential overlap of mechanisms, it is still useful to discuss necrosis and apoptosis, the two principal pathways of cell death, separately because of the differing circumstances in which they develop.

The morphologic features, mechanisms, and significance of these death pathways are discussed in more detail later in the chapter. We will discuss first the causes of cell injury.

Causes of Cell Injury

The causes of cell injury range from the physical violence of an automobile accident to subtle cellular abnormalities, such as a mutation causing lack of a vital enzyme that impairs normal metabolic function. Most injurious stimuli can be grouped into the following broad categories.

Oxygen Deprivation. *Hypoxia* is a deficiency of oxygen, which causes cell injury by reducing aerobic oxidative respiration. Hypoxia is an extremely important and common cause of cell injury and cell death. *Causes of hypoxia* include reduced blood flow (*ischemia*), inadequate oxygenation of the blood due to cardiorespiratory failure, and decreased oxygen-carrying capacity of the blood, as in anemia or carbon monoxide poisoning (producing a stable carbon monoxyhemoglobin that blocks oxygen carriage) or after severe blood loss. Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die. For example, if an artery is narrowed, the tissue supplied by that vessel may initially shrink in size (atrophy), whereas more severe or sudden hypoxia induces injury and cell death.

Physical Agents. Physical agents capable of causing cell injury include mechanical trauma, extremes of temperature (burns and deep cold), sudden changes in atmospheric pressure, radiation, and electric shock (Chapter 9).

Chemical Agents and Drugs. The list of chemicals that may produce cell injury defies compilation. Simple chemicals such as glucose or salt in hypertonic concentrations may cause cell injury directly or by deranging electrolyte balance in cells. Even oxygen at high concentrations is toxic. Trace amounts of *poisons*, such as arsenic, cyanide, or mercuric salts, may damage sufficient numbers of cells within minutes or hours to cause death. Other potentially injurious substances are our daily companions: environmental and air pollutants, insecticides, and herbicides; industrial and occupational hazards, such as carbon monoxide and asbestos; recreational drugs such as alcohol; and the ever-increasing variety of therapeutic drugs. Many of these are discussed further in Chapter 9.

Infectious Agents. These agents range from the submicroscopic viruses to tapeworms several feet in length. In between are the rickettsiae, bacteria, fungi, and higher forms of parasites. The ways by which these biologic agents cause injury are diverse (Chapter 8).

Immunologic Reactions. The immune system serves an essential function in defense against infectious pathogens, but immune reactions may also cause cell injury. Injurious reactions to endogenous self antigens are responsible for several autoimmune diseases (Chapter 6). Immune reactions to many external agents, such as viruses and environmental substances, are also important causes of cell and tissue injury (Chapters 3 and 6).

Genetic Derangements. As described in Chapter 5, genetic abnormalities as obvious as an extra chromosome, as in Down syndrome, or as subtle as a single base pair substitution leading to an amino acid substitution, as in sickle cell anemia, may produce highly characteristic clinical phenotypes ranging from congenital malformations to anemias. Genetic defects may cause cell injury because of deficiency of functional proteins, such as enzyme defects in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins, both of which trigger cell death when they are beyond repair. DNA sequence variants that are common in human populations (polymorphisms) can also influence the susceptibility of cells to injury by chemicals and other environmental insults.

may harbor viral inclusions in progressive multifocal leukoencephalopathy. *Glial cytoplasmic inclusions*, primarily composed of α-synuclein, are found in oligodendrocytes in multiple system atrophy (MSA).

Ependymal cells, the ciliated columnar epithelial cells lining the ventricles, do not have specific patterns of reaction. When there is inflammation or marked dilation of the ventricular system, disruption of the ependymal lining is paired with proliferation of subependymal astrocytes to produce small irregularities on the ventricular surfaces *(ependymal granulations)*. Certain infectious agents, particularly CMV, may produce extensive ependymal injury, with viral inclusions in ependymal cells. However, neither oligodendrocytes nor ependymal cells mediate significant responses to most forms of injury in the CNS.

KEY CONCEPTS

Cellular Pathology of the Central Nervous System

- Each cellular component of the nervous system has a distinct set of patterns of response to injury.
- Neuronal injury commonly results in cell death, either by apoptosis or necrosis. Loss of neurons that is difficult to detect without formal quantification may still contribute to dysfunction.
- Astrocytes show morphologic changes including hypertrophy of the cytoplasm, accumulation of intermediate filament protein (GFAP), and hyperplasia.
- Microglia, the resident monocyte-lineage population of the CNS, proliferate and accumulate in response to injury.

Cerebral Edema, Hydrocephalus, and Raised Intracranial Pressure and Herniation

The brain and the spinal cord are encased and protected by the rigid skull and the bony spinal canal. The pressure within the cranial cavity may rise in one of three commonly observed clinical settings: generalized brain edema, increased CSF volume (hydrocephalus), and focally expanding mass lesions. Depending on the degree and rapidity of the pressure increase and the nature of the underlying lesion, the consequences range from subtle neurologic deficits to death.

Cerebral Edema

Cerebral edema (more precisely, brain parenchymal edema) is the result of increased fluid leakage from blood vessels or injury to various cells of the CNS. There are two main pathways of edema formation in the brain.

- *Vasogenic edema* is an increase in extracellular fluid caused by blood-brain barrier disruption and increased vascular permeability, allowing fluid to shift from the intravascular compartment to the intercellular spaces of the brain. The paucity of lymphatics greatly impairs the resorption of excess extracellular fluid. Vasogenic edema may be either localized (e.g., adjacent to inflammation or neoplasms) or generalized, as can follow ischemic injury.
- *Cytotoxic edema* is an increase in intracellular fluid secondary to neuronal, glial, or endothelial cell membrane injury, as might be encountered in someone with a generalized hypoxic/ischemic insult or with a metabolic derangement that prevents maintenance of the normal membrane ionic gradient.

In practice, conditions associated with generalized edema often have elements of both vasogenic and cytotoxic edema. In generalized edema, the gyri are flattened, the intervening sulci are narrowed, and the ventricular cavities are compressed. As the brain expands, herniation may occur.

Interstitial edema (hydrocephalic edema) occurs especially around the lateral ventricles when an increase in intravascular pressure causes an abnormal flow of fluid from the intraventricular CSF across the ependymal lining to the periventricular white matter.

Hydrocephalus

Hydrocephalus is the accumulation of excessive CSF within the ventricular system (Fig. 28-2). The choroid plexus within the ventricular system produces CSF, which normally circulates through the ventricular system and enters the cisterna magna at the base of the brain stem through the foramina of Luschka and Magendie. Subarachnoid CSF bathes the superior cerebral convexities and is absorbed by the arachnoid granulations. Most cases of hydrocephalus are a consequence of impaired flow and resorption of CSF; overproduction is a rare cause that can accompany tumors of the choroid plexus. An increased volume of CSF within the ventricles expands them and can elevate the intracranial pressure.

When hydrocephalus develops in infancy before closure of the cranial sutures, there is enlargement of the head,

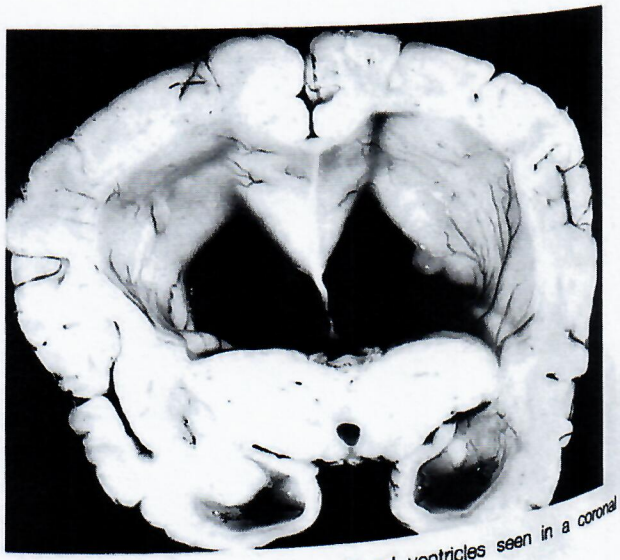

Figure 28-2 Hydrocephalus. Dilated lateral ventricles seen in a coronal section through the midthalamus.