Synopsis of Pathophysiology in Nuclear Medicine

Abdelhamid H. Elgazzar

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To
My granddaughters Laila and Niveen

Preface

Nuclear medicine is a unique and dynamic field which requires diverse knowledge which includes many basic science components such as physics, chemistry, radiation biology, dosimetry, and others. Knowledge of the pathophysiological features of diseases is of crucial importance to the understanding and practice of nuclear medicine. This concept has an increasing importance since nuclear medicine has changed to study molecular changes of normal and diseased organs. This was behind the book on pathophysiological basis of nuclear medicine, and its third edition will appear soon. The idea of the synopsis came from the readers and colleagues who demanded a simplified text of the subject to help students, including technology students, technologists, residents, and practicing physicians, while the other text remains as a comprehensive reference with more details.

In this book, simple presentation of the basic understanding of the principles of pathophysiology, normal and abnormal cells, cell biology, and basis of radiopharmaceutical uptake and distribution in physiological and different pathological processes are included. Since clinical nuclear medicine is simply the application of such basic principle in the study of many conditions of virtually every organ in the body, the pathophysiological features of relevant disease processes are discussed in several chapters of organ systems along with essentials in imaging and its clinical significance.

This book starts by an introductory chapter defining and explaining basic pathophysiology, followed by a chapter on the features of different cells and tissues with biological features. The mechanisms of radiopharmaceutical uptake by different tissues and effects of pathophysiological changes on its distribution are included in a separate chapter. These basic parts are followed by several chapters for organ systems in addition to chapters on inflammation, oncology, and hematology. The pathophysiological basis of the therapeutic effects of radionuclides and applications in treating relevant diseases are included in one chapter, followed by a concluding short chapter on biologic effects of ionizing radiation.

The objective of this volume is to provide a brief, simple, readable, easy-to-use, yet comprehensive and informative enough text to help the readers, students, and professionals understand nuclear medicine in depth which will be reflected on practice and patient care.

Safat, Kuwait Abdelhamid H. Elgazzar, MD, FCAP, ABNM

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Pathophysiology: General Principles

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1.1 Introduction

Understanding the pathophysiology of disease is essential for all who study and work in any field of medicine. Since nuclear medicine deals with functional and molecular changes, it becomes crucial to understand the pathophysiological changes of relevant diseases and disease-like conditions to properly study and practice the field.

Pathophysiology has been changing and expanding with added new knowledge. Since the late 1970s, tremendous developments in molecular biology and genetics have provided medical science with an unprecedented chance to understand the molecular basis of disease. Disease can now be defined on the basis of abnormal deviation from normal regional biochemistry. Since pathophysiology is a bridge between pathology and physiology, it is imperative to understand the principles of both disciplines.

1.2 Pathology

Pathology is concerned with the study of the nature of disease, including its causes, development, and consequences with emphasis on the structural changes of diseases. Specifically, pathology describes the origin of disease, its etiologies, and how it progresses and manifests clinically in individuals in order to determine its treatment. Pathology plays a vital role across all

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facets of medicine throughout life, and currently it extends to the examination of molecules within organs, tissues, or body fluids.

1.3 Definition of Disease

The precise definition of disease is as complex as an exact definition of life. It may be relatively easier to define disease at a cellular and molecular level than at the level of an individual. Throughout the history of medicine, two main concepts of disease have predominated: ontological and physiological [1].

The ontological concept views a disease as an entity that is independent and self-sufficient and runs a regular course with a natural history of its own. The physiological concept, on the other hand, defines disease as a deviation from normal physiology or biochemistry; the disease is a statistically defined deviation of one or more functions from those of healthy people under circumstances as close as possible to those of a person of the same sex and age of the patient. Most diseases begin with cell injury, which occurs if the cell is unable to maintain homeostasis.

1.3.1 Homeostasis

The term homeostasis is used by physiologists to mean maintenance of static, or constant, conditions in the internal environment by means of positive and negative feedback of information. About 56 % of the adult human body is fluid. Most of the fluid is intracellular, and about one third is extracellular fluid that is in constant motion throughout the body and contains the ions (sodium, chloride, and bicarbonate) and nutrients (oxygen, glucose, fatty acids, and amino acids) needed by the cells to maintain life. Extracellular fluid was described as the internal environment of the body and hypothesized that the same biological processes that make life possible are also involved in disease [1]. As long as all the organs and tissues of the body perform functions that help to maintain homeostasis, the cells of the body continue to live and function properly [1].

1.3.2 The Genome

At birth, molecular blueprints collectively make up a person's genome or genotype that will be translated into cellular structure and function. A single gene defect can lead to biochemical abnormalities that produce many different clinical manifestations of disease, or phenotypes, a process called pleiotropism. Many different gene abnormalities can result in the same clinical manifestations of disease—a process called genetic heterogeneity. Thus, diseases can be defined as abnormal processes as well as abnormalities in molecular concentrations of different biological markers, signaling molecules, and receptors.

1.4 Physiology

Physiology is the study of normal, healthy bodily function. It is concerned with the science of the mechanical, physical, bioelectrical, and biochemical functions of humans in good health, their organs, and the cells of which they are composed. It is a broad science which aims to understand the mechanisms of living, from the molecular basis of cell function to the integrated behavior of the whole body.

1.5 Pathophysiology

Pathophysiology is a convergence of pathology and physiology. It deals with the disruption of normal mechanical, physical, and biochemical functions, either caused by a disease or resulting from a disease or abnormal syndrome or condition that may not qualify to be called a disease and now includes the molecular mechanisms of disease. In the year 1839, Theodor Schwann discovered that all living organisms are made up of discrete cells [2]. In 1858, Rudolph Virchow observed that a disease could not be understood unless it were

realized that the ultimate abnormality must lie in the cell. He correlated disease with cellular abnormalities as revealed by chemical stains, thereby founding the field of cellular pathology. He defined pathology as physiology with obstacles [2].

Since the time of Virchow, gross pathology and histopathology have been a foundation of the diagnostic process and the classification of disease. Traditionally, the four aspects of a disease process that form the core of pathology are etiology, pathogenesis, morphological changes, and clinical significance [3]. The altered cellular and tissue biology and all forms of loss of function of tissues and organs are ultimately the result of cell injury and cell death. Therefore, knowledge of the structural and functional reactions of cells and tissues to injurious agents, including genetic defects, is the key to understanding the disease process. Currently, diseases are defined and interpreted in molecular terms and not just as general descriptions of altered structure. Accordingly, pathology is evolving into a bridging discipline that involves both basic science and clinical practice and is devoted to the study of the structural and functional changes in cells, tissues, and organs that underlie disease [3]. The use of molecular, genetic, microbiological, immunological, and morphological techniques is helping us to understand both ontological and physiological causes of disease.

1.6 Basic Major Principles of Pathophysiology

1.6.1 Cell Injury

Cellular injury occurs if the cell is unable to maintain homeostasis. The causes of cellular injury may be hypoxia (oxygen deprivation), infection, or exposure to toxic chemicals. In addition, immunological reactions, genetic derangements, and nutritional imbalances may also cause cellular injury (Table 1.1). In hypoxia, glycolytic energy production may continue, but ischemia (loss of blood supply) compromises the availability of metabolic substrates and may injure tissues faster than hypoxia. Various types of cellular injury and their responses are summarized in v.

Table 1.1 Mechanisms of cellular injury

Hypoxic: most common
Chemical
Structural trauma
Infectious
Immunological/inflammatory
Genetic derangement
Nutritional imbalance

1.6.1.1 Biochemical Cell Injury Mechanisms

Regardless of the nature of injurious agents, there are a number of common biochemical themes or mechanisms responsible for cell injury [4]:

1. ATP depletion: Depletion of ATP is one of the most common consequences of ischemic and toxic injury. ATP depletion induces cell swelling, decreases protein synthesis, decreases membrane transport, and increases membrane permeability.
2. Oxygen and oxygen-derived free radicals: Ischemia causes cell injury by reducing blood supply and cellular oxygen. Radiation, chemicals, and inflammation generate oxygen-free radicals that cause destruction of the cell membrane and cell structure.
3. Loss of calcium homeostasis: Most intracellular calcium is in the mitochondria and endoplasmic reticulum. Ischemia and certain toxins increase the concentration of Ca2+ in cytoplasm, which activates a number of enzymes and causes intracellular damage and increases membrane permeability.
4. Mitochondrial dysfunction: A variety of stimuli (free Ca2+ levels in cytosol, oxidative stress) cause mitochondrial permeability transition (MPT) in the inner mitochondrial membrane, resulting in the leakage of cytochrome *c* into the cytoplasm.
5. Defects in membrane permeability: All forms of cell injury and many bacterial toxins and viral proteins damage the plasma membrane. The result is an early loss of selective membrane permeability.

Table 1.2 General response to injury

Cellular adaptation
Atrophy
Hypertrophy
Hyperplasia
Metaplasia
Dysplasia
Cell death
Apoptosis
Necrosis

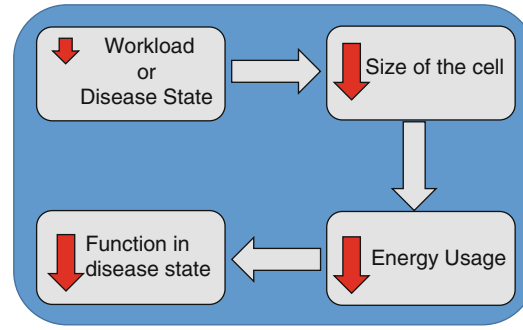

Fig. 1.1 Atrophy

1.6.1.2 Intracellular Accumulations

Normal cells generally accumulate certain substances such as electrolytes, lipids, glycogen, proteins, calcium, uric acid, and bilirubin that are involved in normal metabolic processes. As a manifestation of injury and metabolic derangements in cells, abnormal amounts of various substances, either normal cellular constituents or exogenous substances, may accumulate within the cytoplasm or in the nucleus, either transiently or permanently. One of the major consequences of failure of transport mechanisms is cell swelling due to excess intracellular fluid. Abnormal accumulations of organic substances such as triglycerides, cholesterol and cholesterol esters, glycogen, proteins, pigments, and melanin may be caused by disorders in which the cellular capacity exceeds the synthesis or catabolism of these substances. Dystrophic calcification occurs mainly in injured or dead cells, while metastatic calcification may occur in normal tissues due to hypercalcemia that may be a consequence of increased parathyroid hormone, destruction of bone tissue, renal failure, and vitamin D-related disorders.

All these accumulations harm cells by "crowding" the organelles and by causing excessive and harmful metabolites that may be retained within the cell or expelled into extracellular fluid and circulation.

1.6.2 Cell and Tissue Response to Injury

The normal cell is able to handle normal physiological and functional demands, so-called normal homeostasis. However, physiological and morphological cellular adaptations normally occur in response to excessive physiological conditions or to some adverse or pathological stimuli [3]. The cells adapt in order to escape and protect themselves from injury. An adapted cell is neither normal nor injured but has an altered steady state, and its viability is preserved. If a cell cannot adapt to severe stress or pathological stimuli, the consequence may be cellular injury that disrupts cell structures or deprives the cell of oxygen and nutrients. Cell injury is reversible up to a certain point, but irreversible (lethal) cell injury ultimately leads to cell death, generally known as necrosis. By contrast, an internally controlled suicide program, resulting in cell death, is called apoptosis (Table 1.2).

1.6.2.1 Cell Adaptation

Some of the most significant physiological and pathological adaptations of cells involve changes in cellular size, growth, or differentiation [3, 4]. These include (a) atrophy, a decrease in size and function of the cell (Fig. 1.1); (b) hypertrophy, an increase in cell size (Fig. 1.2); (c) hyperplasia, an increase in cell number (Fig. 1.3); (d) metaplasia, an alteration of cell differentiation (Fig. 1.4); and dysplasia, an abnormal growth or development of cells (Fig. 1.5). The adaptive response may also include the intracellular accumulation of normal endogenous substances (lipids, protein, glycogen, bilirubin, and pigments) or abnormal exogenous products. Cellular adaptations are a common and central part of many disease states. The molecular mechanisms leading to cellular adaptation may

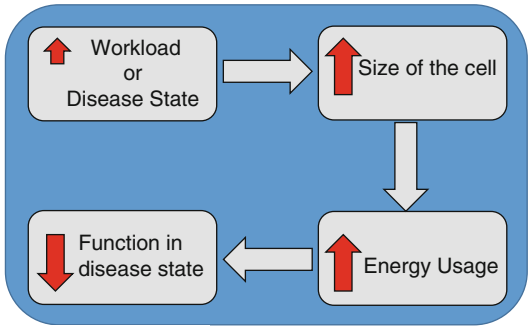

Fig. 1.2 Hypertrophy

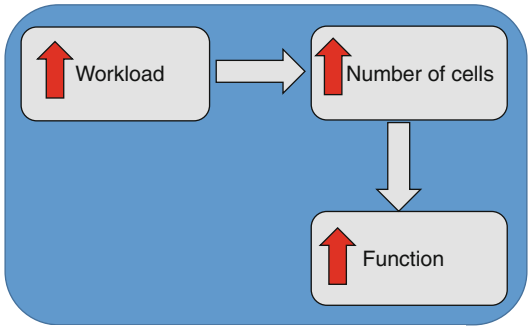

Fig. 1.3 Hyperplasia

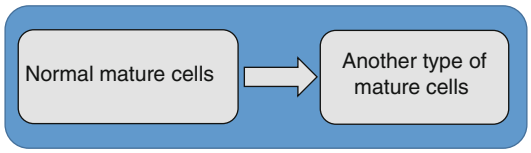

Fig. 1.4 Metaplasia

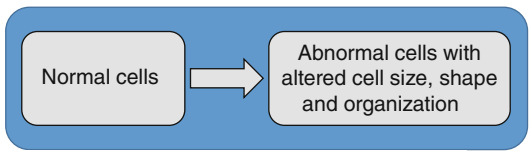

Fig. 1.5 Dysplasia

involve a wide variety of stimuli and various steps in cellular metabolism. Increased production of cell signaling molecules, alterations in the expression of cell surface receptors, and overexpression of intracellular proteins are typical examples.

1.6.2.1.1 Atrophy

Atrophy is a decrease in size of cells which may lead to decrease in the size of a body part, organ, or tissue which was normal in size for the individual, considering age and circumstance, prior to the diminution. Examples include muscle atrophy from lack of use (most common) or disease.

1.6.2.1.2 Hypertrophy

Hypertrophy is a non-tumorous enlargement of a tissue or organ as a result of an increase in the size rather than the number of constituent cells. Examples include myocardial muscle hypertrophy due to prolonged strain secondary to hypertension.

1.6.2.1.3 Hyperplasia

Hyperplasia is the abnormal multiplication or increase in the number of normal cells in a normal arrangement in an organ or a tissue. Typical hyperplasia is a physiological response to a specific stimulus, and the cells of a hyperplastic growth remain subject to normal regulatory control mechanisms. Examples include endometrial hyperplasia resulting from high levels of estrogen.

1.6.2.1.4 Metaplasia

Metaplasia is the transformation of one mature differentiated cell type into another mature differentiated cell type, as an adaptive response to some insult or injury. By this change in differentiation (and hence patterns of gene expression), the cells should be more resistant to the effects of the insult. It is usually a reversible phenomenon. Examples include transformation of columnar epithelial cells of salivary gland ducts to squamous epithelial cells when stones are present. Development of glandular epithelium (glandular metaplasia) in the esophagus in patients with gastric acid reflux is another example (Barrett's esophagus).

1.6.2.1.5 Dysplasia

Dysplasia is an abnormality of the growth or development resulting in alteration in size, shape, and organization of adult cells or organs. It is characterized by a decreased amount of mature cells and an increased amount of immature cells, leading to an abnormal arrangement of tissue. Such cells could return to proper formation, but in some cases the cells worsen and become

carcinogens. In dysplasia, cell maturation and differentiation are delayed, in contrast to metaplasia, in which cells of one mature, differentiated type are replaced by cells of another mature cell [5].

1.6.2.2 Cell Death

Cell death is extremely important in the maintenance of tissue homeostasis, embryonic development, immune self-tolerance, and regulation of cell viability by hormones and growth factors.

1.6.2.2.1 Necrosis (Non Regulated, Inflammatory Accidental Cell Death)

Necrosis is cellular death resulting from the progressive derivative action of enzymes on the lethally injured cells, ultimately leading to the processes of cellular swelling, dissolution, and rupture. Cell membranes swell and become permeable. Lytic enzymes destroy the cellular contents, which then leak out into the intercellular space, leading to the mounting of an inflammatory response (Fig. 1.6a).The morphological appearance of necrosis is the result of denaturation of proteins and enzymatic digestion (autolysis or heterolysis) of the cell. Different types of necrosis occur in different organs or tissues. The most common type is coagulative necrosis, resulting from hypoxia and ischemia. It is characterized by denaturation of cytoplasmic proteins, breakdown of organelles, and cell swelling (Fig. 1.7), and it occurs primarily in the kidneys, heart, and adrenal glands. Liquefactive necrosis may result from ischemia or bacterial infections. The cells are digested by hydrolases and the tissue becomes soft and liquefies. As a result of ischemia, the brain tissue liquefies and forms cysts. In infected tissue, hydrolases are released from the lysosomes of neutrophils; they kill bacterial cells and the surrounding tissue cells, resulting in the accumulation of pus. Caseous necrosis, present in the foci of tuberculous infection, is a combination of coagulative and liquefactive necrosis. In fat necrosis, the lipase enzymes break down triglycerides and form opaque, chalky necrotic tissue as a result of saponification of free fatty acids with alkali metal ions. The necrotic tissue and the debris usually disappear by a combined process of enzymatic digestion and fragmentation or they become calcified.

1.6.2.2.2 Apoptosis (Regulated, Non Inflammatory Cell Death)

Apoptosis, a type of cell death implicated in both normal and pathological tissue, is designed to eliminate unwanted host cells in an active process of cellular self-destruction effected by a dedicated set of gene products. Apoptosis occurs during normal embryonic development and is a homeostatic mechanism to maintain cell populations in tissues. It also occurs as a defense mechanism in immune reactions and during cell damage by disease or noxious agents. Various kinds of stimuli may activate apoptosis. These include injurious agents (radiation, toxins, free radicals), specific death signals (TNF and Fas ligands), and withdrawal of growth factors and hormones. Within the cytoplasm a number of protein regulators (Bcl-2 family of proteins) either promote or inhibit cell death. In the final phase, the execution caspases activate the proteolytic cascade that eventually leads to intracellular degradation, fragmentation of nuclear chromatin, and breakdown of cytoskeleton.

The most important morphological characteristics are cell shrinkage, chromatin condensation, and the formation of cytoplasmic blebs and apoptotic bodies (Fig. 1.8) that are subsequently phagocytosed by adjacent healthy cells and macrophages. Unlike necrosis, apoptosis is characterized by nuclear and cytoplasmic shrinkage and affects scattered single cells. Two major apoptotic pathways have been defined in mammalian cells: the death-receptor pathway and the mitochondrial pathway (see Chap. 10 for details).

Cells undergo programmed death in response to both internal surveillance mechanisms and signals sent by other cells (Fig. 1.6b). Thus, some cells effectively volunteer to die, whereas other cells are nominated for death by others [6, 7].

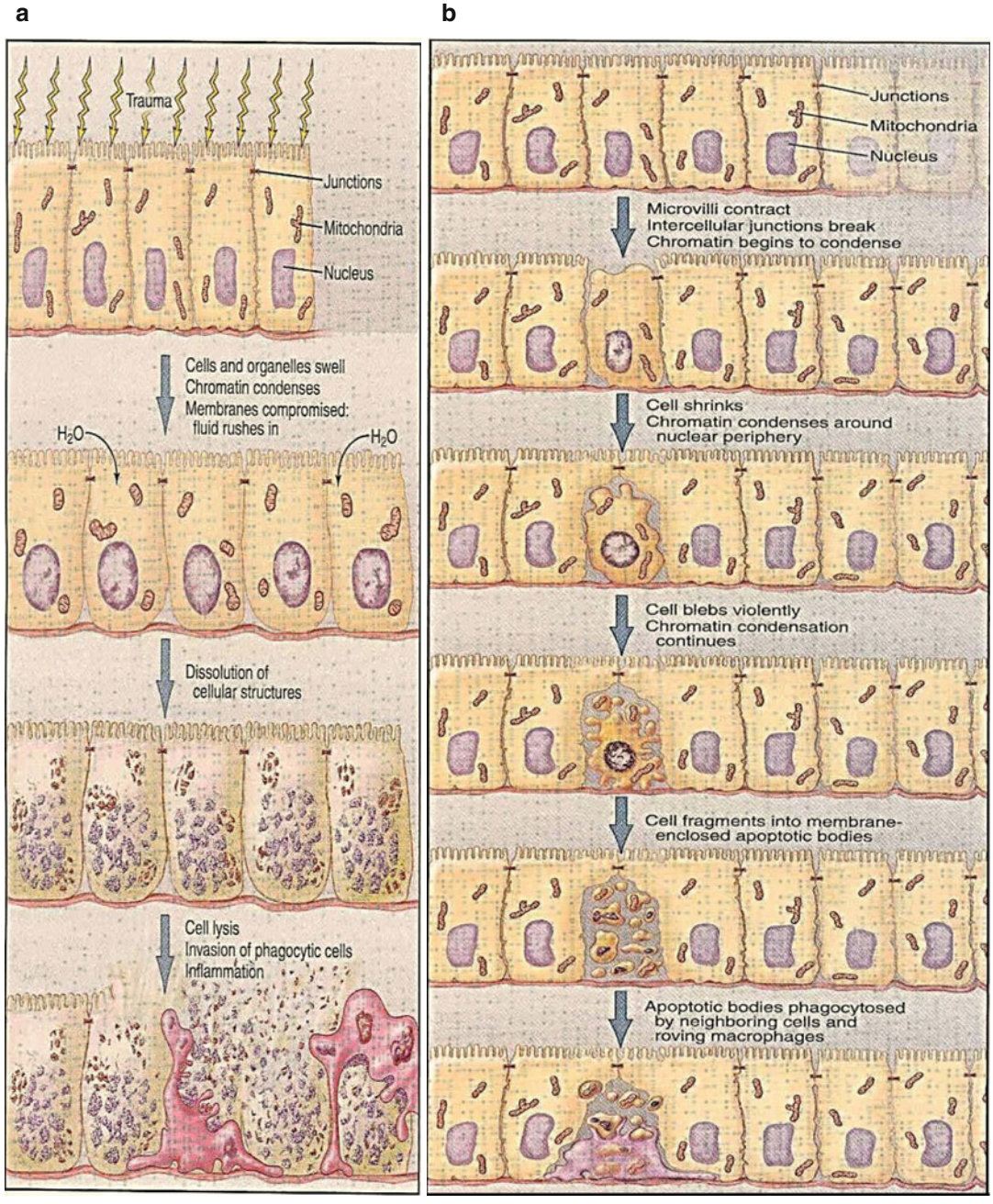

Fig. 1.6 (**a**, **b**) Diagram illustrating cell death. Accidental cell death (**a**) where necrosis occurs as a result of injury to cells. Typically, groups of cells are affected. In most cases, necrotic cell death leads to an inflammatory response (red "angry" macrophages). (**b**) Illustrates apoptosis or active cell suicide which typically affects single cells. Neighboring cells remain healthy. Apoptotic cell death does not lead to an inflammatory response (From Pollard and Earnshaw [6] with permission)