高等医药院校双语教材

供临床医学、口腔医学、药学与制药工程专业用

病理学

PATHOLOGY

主 编 刘东璞 卢凤美 王 抒

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Preface

Bilingual teaching has long been promoted in China. The necessity of having a simple, systematized and complete English textbook on pathology has been a very important problem. More and more eagerly needed for such a book about pathology in Chinese medical colleges and universities becomes an urgent task. We have great pleasure in presenting one of those textbooks to readers.

In this book, much attention has been taken to ensure that the text provides all the information necessary for an intelligent understanding of essential pathologic features of various diseases. This textbook is an integration of basic and applied aspects of pathology, which is comprehensively written to meet the curriculum requirements of undergraduate courses in medical, dental, pharmacy, life sciences and other related categories which students are to learn pathology as one of the subjects. Furthermore, this book has been designed to develop in students' sustained interest and enthusiasm to learn the concepts of pathology in a logical and stepwise manner. For medical students, a sound knowledge of pathology is essential to have the rough understanding of health problems and diseases in human beings. This will help them for treatment of diseases effectively during their future medical practice.

Without my coauthors' cooperation and encouragement, this book could never been written. Thanks for all people who had helped me. I am very grateful to my teachers and friends, whose knowledge has been freely distributed to the preparation of this book.

Maybe there are some errors on spelling and grammar in English, even on the basic knowledge of pathology. The authors welcome comments and suggestions from the faculty, students and other readers, and this will help us make improvement in the next edition. Thank you!

Liu Dongpu
March 2008

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CONTENTS

INTRODUCTION TO PATHOLOGY \ 1

CHAPTER 1 CELL ADAPTATION AND INJURY \ 8

CHAPTER 2 REPAIR \ 37

CHAPTER 3 HEMODYNAMIC DERANGEMENT \ 56

CHAPTER 4 INFLAMMATION \ 82

CHAPTER 5 NEOPLASIA \ 108

CHAPTER 6 DISEASE OF CARDIOVASCULAR SYSTEM \ 166

CHAPTER 7 DISEASE OF RESPIRATORY SYSTEM \ 222

CHAPTER 8 ALIMENTARY SYSTEM DISEASES \ 261

CHAPTER 9 DISEASE OF HEMATOPOIETIC AND LYMPHOID SYSTEMS \ 300

CHAPTER 10 DISEASE OF URINARY SYSTEM \ 327

CHAPTER 11 DISEASE OF THE REPRODUCTIVE SYSTEM AND THE BREAST \ 360

CHAPTER 12 DISEASE OF THE ENDOCRINE SYSTEM \ 400

CHAPTER 13 DISEASE OF NERVOUS SYSTEM \ 422

CHAPTER 14 INFECTIOUS DISEASES \ 448

INTRODUCTION TO PATHOLOGY

Learning of Pathology / 1
Scope of Pathology / 2
Investigation of Pathology / 3
Development of Pathology / 5

Pathology is literally the study (logos) of disease (pathos). More specifically, it is a bridging discipline involving both basic science and clinical practice of medicine, and is devoted to the study of the structural and functional changes in cells, tissues, and organs that underlie disease. In clinical practice and medical education, pathology also has a wider meaning, which constitutes a large body of scientific knowledge, ideas and investigative methods, which are essential for the understanding and practicing of modern medicine.

The four aspects of the disease process that form the core of pathology are the underlying cause (etiology), the mechanism of development (pathogenesis), the structural alteration induced in the cells and organs of the body (morphologic change), and the functional consequence of the morphologic change as well as the signs and symptoms of the patient (clinical significance). The ultimate goal of pathology is the identification of disease, from the molecular level to the effect on the individual, a fundamental objective that leads to successful therapy and disease prevention.

The cause, mechanism and effect of a disease have influence upon the various organs and systems of the body. These two perspectives are complementary and inseparable. Pathology is the foundation of medical science and practice. Without pathology, the practice of medicine would be reduced to myths and folklore; and pathology would be meaningless if it is deprived of clinical implications.

Learning of Pathology

The study of pathology is divided into general pathology and systematic pathology. In this book, we will first cover the principles of general pathology and then proceed to specific disease processes as they affect particular organs or systems.

General pathology is the current principal understanding of causes, mechanisms and characteristics of the major categories of diseases. These processes are covered in chapter 1 to 5, including adaptation, injury and repair of the cells and tissues, local hemodynamic derangement, inflammation and neoplasm. The principle of general pathology must be understood before an attempt is made to study the systematic pathology of specific disease.

Systematic pathology is the description of specific diseases of individual organs or systems, and is covered in chapter 6 to chapter 15, dealing with the cause, etiology, pathogenesis and pathological changes of the individual diseases. Each specific disease can usually be attributed to the operation of one or more categories of causation and mechanisms featured in general pathology.

Like most branches of medical science, pathology has its own vocabulary of special terms. The student must not confuse the learning of the language with the learning of the mechanisms and their affects of diseases on individual organs and patients. A logical and orderly way of thinking about diseases and their characteristics must be cultured by learning pathology, because it is the first subject dealing with disease in a student's medical learning career. Although pathology and other disciplines are frequently taught as separate subjects in the curriculum, students must develop an integrated understanding of the disease. In this textbook, the pathologic basis of common clinical signs is frequently emphasized, so that students can develop an interface between their everyday clinical experience and their knowledge of pathology. The problem-oriented approach and the disease-oriented approach are the most successful ways of studying pathological knowledge.

Scope of Pathology

Scientific knowledge about disease is derived from observation of patients or from experimental studies of animal models and cell or tissue cultures. As a professional discipline, pathology has a key role in transitional research by facilitating the knowledge from the laboratory investigation into clinical practice.

Human Pathology

Human pathology is based on a longitudinal approach to a patient's illness by examination and investigation during his life or after his death. The greatest contribution comes from the detailed fields on human pathology as shown below.

1. Autopsy

The first opportunity for the study of disease comes from the internal examination of the body after death. Autopsies (necropsy or postmortem examination) are performed scientifically for medical or legal purposes. Autopsies reveal much information that helps to clarify the nature of many diseases. Autopsies are performed to determine the cause of death and to collect evidence that may be used in the prosecution of those alleged to be responsible for the death, and diagnostic discrepancies are revealed by autopsies in approximately 30% of hospitalized cases. Autopsies are also useful for gathering accurate statistics about disease incidence, for accuracy of clinical diagnosis and treatment response, and for research into the causes and mechanisms of disease.

2. Biopsy

In living patients, we often investigate and diagnose their illness by examination of tissue

biopsies. If there are clinical indications to do so, it may be possible to obtain a series of samples, from which the course of the disease can be monitored. A biopsy is performed to establish a precise diagnosis by the removal and examination, usually microscopically, of tissue from the living body. By using limited surgical resection, endoscopic and fine-needle aspiration techniques, a biopsy is usually the primary mode of diagnosis to distinguish tumors and inflammatory reactions; and it also gives prognostic information by grading and staging diseases of the patient.

3. Cytology

Cytology specimens consist of single cells or clumps of cells, which are dissociated from their surrounding tissues. Cytologic sampling is generally more convenient and less complicated than an open biopsy. For cytological examination, cell smears may be collected from epithelium shed of the body fluid or secretions such as sputum, urine and abdominal fluid, or scraped from a body surface, or collected by aspirating cells through a fine bore needled into a syringe. The samples are stained by an appropriate method, and examined by light microscopy. The main features used commonly in cytology are the pleomorphism of the nuclear size, the staining of DNA in the nucleus, and the ratio of nuclear area to cytoplasmic area. Since the cells are dissociated from their surrounding tissue, some features of cytology could be used in a histopathological examination.

Experimental Pathology

Experimental pathology is the observation of the effect of manipulations on experimental system, such as the animal model of disease and cell culture. Cell and tissue cultures are widely used in research and diagnosis of pathology, and they are an attractive medium for medical training, because of the ease, with which the cellular environment can be modified and the responses to it monitored. Although advances in cell culture have reduced the usage of laboratory animals in medical research, it is extremely difficult to mimic in experimental pathology the physiological milieu which prevails in the intact human body.

Investigation of Pathology

The general principles of pathological investigative methods are given in this chapter, and these are then related to the specific roles of gross pathology, histopathology, cellular pathology, immunohistochemistry, electron microscopy, and biomolecular techniques.

Gross Investigation

Before microscopy was applied to medical problems, gross investigation was confined to those made with the unaided eye, and thus from this accumulated much of our knowledge of diseases. Gross or macroscopic pathology is the nomenclature for this approach to the study of disease; and it is still an important investigative method at modern time. Gross observations deal with the size, shape, colour, weight, and morphologic features of the tissues or organs. Gross pathology of many diseases is so characteristic, when interpreted by the experienced pathologist,

that a fairly confident diagnosis can often be given before further investigation, for example by light microscopy.

Histopathological and Cytopathological Investigation

Both histopathology and cytopathology involve the microscopic examination of tissue or cell samples with light microscopy. Most diagnostic histopathology and cytopathology are performed on haematoxylin and eosin-stained sections or smears, removed by surgical excision or biopsy, and then embedded by paraffin wax for histopathologic examination. A special type of frozen section sometimes is made for a very urgent diagnosis and histochemistry. The sections and smears are stained to help distinguishment between different components of the tissue (e.g., nuclei, cytoplasm, collagen, et al.). Histopathology and cytopathology are valuable in documenting the diagnosis of infection, inflammation, neoplasm and so on, and they are the fundamental technologies for pathologic study morphologically. It is usually the primary mode of diagnosis for tumors that gives prognostic information by typing, grading and staging surgical resection and by giving comments on the surrounding tissue.

Histochemical and Immunohistochemical Investigation

Histochemistry is the study of the chemistry of tissues, usually by microscopy of tissue sections after treated with specific reagents, so that the chemical features of individual cells can be visualized. An increasingly commonly used technique is immunohistochemistry. In this method specific antibodies are used, which have been raised artificially to bind to specific interested substances by antigen-antibody complexes, if they are present in the tissue sections or cell preparations. The bound antibody is then visualized, using another antibody and a dye complex such as diaminobenzidine. This technique allows investigation of the functional aspect and histogenesis of diseases, presence of antigens in a tissue and differential diagnosis to tumors. Immunohistochemistry provides a bridge between the morphological and functional understandings of the lesion since it permits examination in situ.

Electron Microscopic Investigation

Electron microscopy has extended the range of pathology to the study of disorders at an organelle level, by which electron microscopy may be used to visualize subcellular details in tissue or cell samples. By means of both transmission and scanning electron microscopes, studying tissues or cells at the ultrastructural level allows a better understanding of disease processes and functional derangements. This technique is used for detecting features of differentiation of tumors, classification of diseases (such as glomerulonephritis), acute cellular injury, and special cell structures or microorganisms within a cell.

Morphometry and Image Analysis

The development of laser technology and histochemistry or immunohistochemistry

has enabled more detailed information about the form and structure of cells and tissues by morphometry and image analysis. Morphometry is an analytical technique, which can identify and characterize minute amounts of a substance by detection and measurement of the charateristic wavelength. The information about size, shape, density, numbers and staining specificities of the nucleus, organelles, cells and tissues is subjected to a computer, and then is calculated by a quantitative measurement automatically. Image analysis is a technique in which histological or cytological prepared cells are imaged using a scanning technique that divides the whole image into many smaller elements and aspects, which can then be analyzed by a computer and compared between many different cells or tissues in a series.

Molecular Investigation

Many important advances are now coming from the revealing defects in the chemical structures and molecules, arising from errors in the sequence of genome bases that direct amino acid synthesis. Using in situ hybridization (ISH), it is possible to render the presence of specific genes or their messenger RNA (mRNA) visible in tissue sections or cell preparations. Minute quantities of nucleic acids can be amplified by the polymerase chain reaction (PCR), and by using oligonucleotide primers specific for the studied genes. Many other biomolecular techniques, such as northern blot, western blot and DNA sequencing are also widely used in modern pathology. The change of a single nucleotide in genomic DNA results in synthesis of defective production that may be the fundamental lesion in a particular disease.

Development of Pathology

The evolution of concept about the cause and nature of human disease reflects the prevailing ideas about the explanation for all worldly events and the techniques available for investigation. Thus, the early dominance of animism resulted in the attribution of disease to immaterial or supernatural forces. When the clinical signs and postmortem findings were established early in the long history of medicine, the nature of the underlying disease was thought to be due to an excess or deficiency of the various humors-phlegm, black bile, and so on. During the 19th century, medical science was advanced by Rokitansky and his colleagues, who meticulously performed and documented many thousands of autopsies. They correlated their findings with the clinical signs and symptoms of patients, and with the natural history of a wide variety of diseases. Rudolf Virchow, a German pathologist and the father of modern pathology, recognized that the cell was the smallest viable constituent unit of the body. He contrived a new and lasting set of ideas about diseases, both clinical pathology and experience pathology remain rooted in Virchow's cellular pathology, although it does not mean that Virchow's pathology is immutable. Indeed after that time, current advances have been achieved in biochemistry, electron microscopy, cellular and molecular biology that are revolutionizing our understanding of pathological alterations, explaining more reasonably the clinical manifestations of diseases.

Pathology is a continually subject to change, revision and expansion, with the application

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of new scientific methods. Pathology attempts to explain the whys and wherefores of the signs and symptoms manifested by patients, providing a sound foundation for rational clinical care and therapy. Major new subdivisions in modem pathology are ultrastructural pathology, immunopathology, molecular pathology, genetic pathology, quantitative pathology and so on. These subdivisions are more important professionally than educationally. These subjects must be taught and learnt in an integrated manner, for the body and its disease make no distinction between these conventional subdivisions.

SUMMARY

Pathology is the scientific study on disease including etiology, pathogenesis, pathological changes, clinical pathological correlation and prognosis. This textbook consists of two parts, general and systematic pathology. The general pathology is our current understanding of the causation, mechanisms and characteristics of the major categories of disease. These processes are covered in chapter 2 to 5 of this textbook and many specific diseases mentioned by way of illustration. The principles of general pathology must be understood before an attempt is made to study systematic pathology. It is the foundation of knowledge that has to be laid down before one can begin to study the systematic pathology of specific diseases. The systematic pathology is our current knowledge of specific diseases as they affect individual organs or systems. Each specific disease can usually be attributed to the operation of one or more categories of causation and mechanism featuring in general pathology. Systematic pathology is covered in chapter 6 to 14.

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(Yao Haitao)

Chapter 1

Cell Adaptation and Injury

CELL ADAPTATION / 8
Atrophy / 9
Hypertrophy and Hyperplasia / 11
Metaplasia / 13
CELL INJURY / 14
Causes and Mechanisms of Cell Injury / 15
Patterns and Morphological Changes of Injury / 17
APOPTOSIS / 28
Morphology and Biochemistry of Apoptosis / 28
Mechanisms of Apoptosis / 30
CELLULAR AGING / 32
Structural and Biochemical Changes with Cellular Aging / 32
Accumulation of Metabolic and Genetic Damage / 33

The normal cell is a highly complex unit in which the various organellae and enzyme systems continuously carry out the metabolic activities that maintain cell viability and support its normal functions.

Normal function is dependent on (1) the immediate environment of the cell; (2) a continuous supply of nutrients such as oxygen, glucose, and amino acids; and (3) constant removal of the products of metabolism, including CO_2 When cells encounter physiologic stress or pathologic stimuli, they can alter their structure and/or biochemical processes in order to achieve a new "steady state" and maintain near-normal physiologic functions; this is referred to as adaptation.

If stressed cells cannot adequately adapt, critical cell functions may be impaired and the cell is said to be injured. Injury is defined as an alteration in cell structure or function resulting from some stress that exceeds the ability of the cell to compensate through normal physiologic adaptive mechanisms. Injury to a cell may be no lethal (regeneration) or lethal (necrosis and apoptosis).

SECTION 1 CELL ADAPTATION

Adaptation is a non-injurious reaction of cells, tissues and organs to exogenous or endogenous

harmful stimuli, and in fact, is a state between the normal and injury, as a result of adjudgement to the cell's development and differentiation. Adaptation involves all steps of cellular metabolism in expression and regulation of function genes, protein receptor binding, signal transduction, transcription and translation of protein production, and regulation of protein synthesis such as the processes of packaging and releasing. The major adaptive responses are atrophy, hypertrophy, hyperplasia and metaplasia.

Atrophy

Atrophy is a decrease in the size of a tissue or organ, resulting from a decrease either in the size of individual cells or in the number of cells composing the tissue. Note that atrophy, which is a decrease in size of a normally formed organ, is distinct from agenesis, aplasia, and hypoplasia, which are abnormalities of organ development.

In many situations, atrophy under microscopy is accompanied by membrane bound vacuoles within the cell that contain fragments of cell components (residual bodies, lipofuscin granules). Atrophy can be physiologic or pathologic. Physiologic atrophy is commonly seen, for example, in an ovary, breast or in the endometrium, caused by low estrogen levels following menopause. The process of atrophy also contributes to the physiological involution of organs such as the thymus gland in early adult life. Pathologic atrophy occurs under a variety of conditions outlined below.

1. Insufficient Nutrition

Starvation or inadequate protein-calorie nutrition is associated with chronic diseases which lead to cell atrophy, particularly after other reserves such as adipose stores have been depleted. This results in marked muscle wasting. In late adult life, the brain undergoes progressive atrophy, presumably as atherosclerosis narrows its blood supply. By bringing into balance the cell volume and low level of blood supply, nutrition or trophic stimulation, a new equilibrium is achieved. Apoptosis may be induced by the same signals that cause atrophy and thus may contribute to the loss of organ mass.

2. Pressure

Tissue compression for any length of time can cause atrophy. An enlarging benign tumor can cause atrophy in the surrounding compressed tissues, and the shrinkage of renal parenchyma in hydronephrosis represents pressure atrophy, after obstruction of upper urinary tracts.

3. Disuse

When a broken limb is immobilized in a plaster cast or when a patient is restricted to complete bed rest, skeletal muscle atrophy rapidly ensues, owing to a decreased workload. In both circumstances, a major factor is actually local tissue hypoxia. With resumption of normal activity, common size and function are restored.

4. Enervation

The normal function of skeletal muscle is dependent on its nerve supply. Damage to the nerves lead to rapid atrophy of the muscle fibers supplied by those nerves, because of the loss

of neuromuscular transmission, such as the loss of anterior horn cells of the spinal cord in poliomyelitis.

5. Loss of Endocrine Stimulation

Many endocrine glands are dependent on endocrine stimulation for normal function. The demands placed on the cell by the action of hormones can be eliminated by removing the source of the signal, for instance, the loss of ACTH stimulation after the pituitary ischemia and necrosis results in atrophy of the adrenal cortex.

6. Aging

Cell aging is a process independent of disease. The hallmark of aging, particularly in nonreplicative cells such as those of the brain and heart, is cell atrophy, also known as senile atrophy.

The fundamental cellular changes associated with atrophy are identical in all of these settings, representing a retreat by the cells to a smaller size at which survival is still possible. Atrophy results from a reduction in the structural components of the cell. In atrophic muscle, the cells contain fewer mitochondria and myofilaments and a reduced amount of endoplasmic reticulum. By bringing into balance cell volume and lower levels of blood supply, nutrition, or trophic stimulation, a new equilibrium is achieved. Although atrophic cells may have diminished function, they are not dead. However, atrophy may progress to the point at which cells are injured and deal. In ischemic tissues, if the blood supply is inadequate even to maintain the life of shrunken cells, injury and cell death may supervene. Furthermore, apoptosis may be induced by the same signals that cause atrophy and thus may contribute to loss of organ mass. For example, apoptosis contributes to the regression of endocrine organs after hormone withdrawal.

Mechanisms of Atrophy: The biochemical mechanisms responsible for atrophy are incompletely understood but are likely to affect the balance between protein synthesis and degradation. Increased protein degradation probably plays a key role in atrophy. Mammalian cells contain multiple proteolytic systems that serve distinct functions. Lysosomes contain acid hydrolases (e.g., cathepsins) and other enzymes that degrade endocytosed proteins from the extracellular environment and the cell surface as well as some cellular components. The ubiquitin-proteasome pathway is responsible for the degradation of many cytosolic and nuclear proteins. Proteins to be degraded by this process are first conjugated to ubiquitin and then degraded within a large cytoplasmic proteolytic organelle called the proteasome. This pathway is thought to be responsible for the accelerated proteolysis seen in a variety of catabolic conditions, including cancer cachexia. Hormones, particularly glucocorticoid and thyroid hormone, stimulate proteasome-mediated protein degradation; insulin opposes these actions. Additionally, cytokines, such as tumor necrosis factor (TNF), are capable of increasing muscle proteolysis by way of this mechanism.

In many situations, atrophy is also accompanied by marked increases in the number of autophagic vacuoles. These are membrane-bound vacuoles within the cell that contain fragments

of cell components (e.g., mitochondria, endoplasmic reticulum) that are destined for destruction and into which the lysosomes discharge their hydrolytic contents. The cellular components are then digested. Some of the cell debris within the autophagic vacuole may resist digestion and persist as membrane-bound residual bodies that may remain as a sarcophagus in the cytoplasm.

Hypertrophy and Hyperplasia

Hypertrophy

Hypertrophy is an increase in the size of a tissue due to increased size of individual cells (Table 1-1). It occurs in tissues made up of permanent cells, in which a demand for increased metabolic activity cannot be met through cell multiplication.

Table 1-1 Hypertrophy and hyperplasia of organs

Tissue	Cause of Increased Demand
Skeletal muscle hypertrophy	Physical activity, weight lifting
Cardiac muscle hypertrophy	Increase pressure load or increased volume load
Smooth muscle (wall of intestine, urinary) hypertrophy	Obstructive lesion
Renal hypertrophy	Unilateral disease of one kidney; removal of one kidney
Uterine myometrial hypertrophy	Pregnancy(hormone-induced)
Bone marrow hyperplasia erythroid hyperplasia	Increased destruction of erythrocytes (hemolytic process): prolonged hypoxia (living at high altitudes)
Megakaryocytic hyperplasia	Increased destruction of platelets in the periphery
Myeloid hyperplasia	Increased demand for neutrophils (as in inflammation)
Lymph node hyperplasia	Antigenic stimulation (proliferative immune response)
Breast hyperplasia	Pregnancy and lactation(hormone-induced)

Hyperplasia

Hyperplasia is an increase in the size of a tissue as a result of increased numbers of component cells (Table 1-1). It is the principal mechanism accounting for increased size in tissues composed of labile and stable cells.

Not uncommonly, increased size of a tissue is due to a combination of hypertrophy and hyperplasia.

Causes of Hypertrophy and Hyperplasia

Hypertrophy refers to an increase in the size of cells, often accompanied by an augmented function capacity. Hypertrophy results from increased amounts of cytoplasm and cytoplasmic organelles in cells, the synthetic apparatus including the endoplasmic reticulum, ribosome, and the Golgizone-becomes prominent. In contractile cells such as muscle fibers, there is an increase

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