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TEXTBOOK OF PATHOLOGY

病理学

Original Editors

Parakrama Chandrasoma
Clive R. Taylor

Chief Editors of Adaptation Edition

Zhou Gengyin（周庚寅）
Jiang Xucheng（姜叙诚）

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Preface for Adaptation Edition

Bilingual teaching, for example, in both Chinese and English, has been long promoted in China. However, we still lack a satisfactory textbook of pathology. Original editions of textbooks in English from abroad are not only too expensive for students but also somewhat unsuitable for teaching. Therefore there is a great demand for a suitable textbook. For this purpose, Science Press was authorized by McGraw-Hill Companies to have the copyright of ***Concise Pathology*** to be adapted for use in China.

The goal to adapt this textbook is to teach pathology according to the content, category and catalogue of textbook used in China based upon the style of the original book. The basic content of the book remains largely unchanged although the catalogue was rearranged to be consistent with pathologic textbook in China. Some chapters have been updated and largely rewritten.

Actually for Chinese authors to rewrite the original textbook of pathology in English is not easy because we have not yet had such experience before. We are deeply indebted to all the authors who have done their great endeavors to adapt and review the chapters in their areas of expertise. A lot of extra time with short notice was used to complete this edition accurately as well as quickly. We are especially grateful to the secretary for this book, Dr. Meng Bin, who organized this book so efficiently. We are particularly thankful to Professor Anders Zetterberg and his wife, from the Department of Oncology and Pathology, Karolinska Institute, Sweden, for helping in reviewing and correcting the English for some chapters during his academic visiting to the Department of Pathology, Shandong University School of Medicine.

There could be some errors in spelling or grammar in English, even in the basic knowledge of pathology. There is still room for improvement in future if it is republished. Hopefully the medical faculties and students will use this book and provide helpful suggestions and critiques in the future.

Zhou Gengyin, Jiang Xucheng
August, 2005

前　言

为使医学教育逐渐同世界接轨，双语教学在我们国家已倡导和推行多年，但至今仍然缺乏令人满意的病理学教科书。英语原版教材价格较高，且与中国目前的教学内容不甚吻合。基于对英语双语病理学教材的广泛需求，科学出版社获得了麦格劳-希尔公司《Concise Pathology》的合作改编权。其目的是在不改变原书风格和基本内容的前提下，通过改编使其内容及编排顺序比较符合中国的教学习惯。

由于缺乏经验和英语水平所限，虽是改编，实属不易。各位编委在担任繁重的医教研工作的同时，夜以继日、辛勤劳作，在较短的时间内完成了初稿和互审。本书编委会秘书孟斌博士在沟通信息和组织改编的过程中做了大量卓有成效的工作。在最后定稿期间，我们又特邀了瑞典卡罗琳斯卡医学院肿瘤病理科 Zetterberg 教授和他的夫人对某些章节的英语修辞和语法提出了建议和修改，在此表示衷心的感谢。

在改编过程中，对原书内容和目录进行了删节、调整和适当补充，个别章节有较大的更新和改动。在章节内容衔接上，尤其是英语语言的表达上，疏漏和错误之处在所难免。恳请同道和学生在实际使用过程中，不断提出意见，以期再版时进一步完善。

周庚寅　姜叙诚

2005 年 8 月

CONTENTS

Introduction The Discipline of Pathology

Cui Jin

WHAT IS PATHOLOGY?

Pathology is the study of disease. In its broadest sense, it is the study of how the organs and tissues of a healthy body - the basis of normal anatomy and physiology - change to those of a sick person. The study of pathology therefore provides an understanding of the disease processes encountered (*pathogenesis*), their causes (*etiology*), their structural and functional changes (*pathological change*), and their clinical effects (*clinical pathological correlation* and *prognosis*). In this way, pathology constitutes a logical and scientific basis of medicine. Pathology in this broad sense is what we aim to teach medical students.

Pathology is a bridge between basic science and clinical medicine. Before beginning the study of pathology, the normal structure and function of the body have been provided by basic medical courses of anatomy, embryology, histology, cellular biology, physiology and biochemistry. The basic science of pathology is that branch of medicine which is concerned with the response of the host to injury through a series of mechanisms or processes. For the student, this knowledge of the processes of disease provides a foundation for clinical medicine; for the pathologist these processes provide an unlimited area for basic research. The second task of pathology is to introduce the student to clinical medicine, which is concerned with the diagnosis and treatment of the disease entities. It must be emphasized that the student, before undertaking the study of the diseases themselves, should have correlative knowledge of the chemical, physical, and biologic agents that produce injury and of the fundamental pathologic processes through which the host responds. On the other hand, the pathologic diagnosis, which is an authoritative diagnosis based on pathologic features of organs and tissues observed grossly and microscopy, is more objective and precise than other clinical diagnosis such as iconography.

Pathology is not only basic scientific medicine but also practical clinic medicine; it is also named *Diagnostic Pathology or Surgical Pathology*. According to the different entity studied, pathology can be divided into *Human Pathology* and *Experimental Pathology*.

Human Pathology

The principal aim of human pathology considers structural abnormalities of cells and tissues grossly and microscopically examined from the patient's tissues. The surgical pathology laboratory in a hospital includes subdivisions such as autopsy, biopsy and cytology.

Autopsy means "see for yourself", this is one of the basic pathologic methods. Autopsy is a special surgical operation, performed by specially-trained physicians (usually a pathologist), on a dead body. Its purpose is to identify the cause of death, but also has several other functions:

- Clarify the causes of death in cases without clinical diagnosis or in those in which the patient's death was unexpected. Learn the patient's health status while alive.
- Diagnosis and treatment quality control. Autopsy findings may reveal flaws in diagnosis, treatment and therapy prevent future errors.
- Recognizing of negligence. Autopsies can also be ordered in every state when there is suspicion of foul play.
- Recognition of new diseases and new disease patterns.
- Source of information for the Secretary of Health, statistical analysis of the most frequent diseases, influence health policies and State and Municipal districts.
- Provide material for the residents, students and staff education. The clinical-pathological correlation done during all stages of the autopsy is an excellent exercise in pathology.
- Material for scientific research.
- Recognition of treatment effectiveness.

Biopsy is the removal of a sample of tissue from the body for examination. The tissue will be examined under a microscope to assist in diagnosis. Therefore, only very small samples are needed. Sometimes, it is enough just to scrape over an area. This is the case with cell examinations of the cervix. During examination of the large intestine, a biopsy can be taken with forceps through a tube known as an endoscope. In other cases, for instance, a liver or kidney biopsy, the biopsy is taken using a large hypodermic needle.

Cytology is responsible for preparation, staining and microscopic examination of patient samples. The cytological samples may be used for screening (cervical-vaginal), diagnosis (FNA) and improving overall diagnostic accuracy (brushes, washes). Pathologists perform Fine Needle Aspiration Biopsy (FNAB) using cytology to diagnose palpable masses. The pathologists in conjunction with Radiologists perform FNA of non-palpable thoracic, abdominal and soft tissue masses.

Experimental Pathology

Experimental pathology researches cellular processes incorporate animal experiment and tissue and cell cultures. **Animal Experimentation** is a pathological method using animal model to study disease and effects of disease within the body. We can become knowledgeable about diseases on all levels, from the molecular to the cellular and more. Animals are very different from human being in genus, so we must be careful when apply the results of experiments to explain human disease. Tissue and Cell culture is another major method in academic research. A viable culture from a human or animal tissue sample is obtained and maintained in vitro for experimental, diagnostic or therapeutic purposes.

WHO IS A PATHOLOGIST?

In western countries, a pathologist may be a physician (MD) or a person with a doctorate (PhD) in pathology who has been trained in the proper performance and interpretation of laboratory procedures. Training as a physician pathologist takes many years. In the United States, a five-year pathology residency follows the MD degree and covers all aspects of clinical and anatomic pathology. In England, pathology training also lasts for five years, being general in the first two years and more specialized in the last three. Pathologists in small hospitals maintain a basic knowledge of all areas of pathology. In large academic medical centers, an individual pathologist may specialize in surgical pathology, hematopathology, chemical pathology, microbiology, immunology, and so forth. The PhD program in pathology provides training in the scientific methods of pathology. PhD pathologists play a vital role in basic scientific research and function in many hospital laboratories in their spheres of expertise. Pathologists serve as consultants to their clinical colleagues, make diagnoses on biopsy material, run laboratories and interpret tests. They serve as educators for the hospital staff and have been termed "the doctor's doctor".

Training in clinical pathology includes learning the methodology of chemical, microbiologic, and immunologic procedures and learning how to operate the various instruments so as to produce accurate results. Training in anatomic pathology deals with microscopic diagnosis of disease by recognizing deviations from normal of cells and tissues by light and electron microscopic study.

The end product of a pathologic procedure is a **pathology report** that contains the result of the procedure. This may be a number (in chemical tests), the name of a microorganism (in microbiology), or a diagnosis based no the microscopic features of a tissue section (in surgical pathology). Interaction with the laboratory in terms of ordering the most appropriate laboratory procedures and being able to interpret the pathology report correctly is a vital part of the training of all physicians.

BASIC EXAMINATION METHOD FOR PATHOLOGY

The study methods of pathology include autopsy, biopsy, cytology, animal experiment, and tissue and cell culture as previous described. Main routine methods are:

A. Gross Examination

It is the basic method for pathologic examination. The morphological feature of a lesion – such as size, form, weight, color, circumscription, surface appearance, cut and position – can be observed by eye or assisted by using a ruler, steelyard, magnifying glass or other tools.

B. Histological and Cytological Examination

The specimens from patients are prepared as a section or smear, then stained, and examined by using microcopy. The diagnosis can be made via analysis the morphologic characteristics. The most common and basic stain method of a section is Haematoxylin and Eosin technique (H. E stain). However, other special stain methods or new techniques are necessary for assistance the diagnosis when it cannot be made by H. E stain. Special lesions on section must be examined grossly first noting density, color. Afterward, whole tissue can be examined carefully under low magnification, which is very important for making the diagnosis. High magnification examination is only used to observe cellular features.

C. Histochemistry and Cytochemistry Examination

Also called special stain method, some tissue structures and substances (e. g. protein, enzyme, nucleic acid, glycogen and lipid) are colored when a chemical group (e. g. carboxyl, phosphoric or aldehyde) reacts with the stain. For example, fat remains in the cytoplasm can be demonstrated by Sudan black B stains, and the glycogen in the cytoplasm, by PAS stains.

Other examination methods, such as *immunohistochemistry*, *electron microscopy*, *in situ hybridization*, *polymerase chain reaction* (*PCR*), chromosome analysis by fluorescence in situ hybridization (*FISH*), *flow cytometry* and *confocal laser scanning microscopy* are also now wildly used in clinical practice if necessary.

A BRIEF HISTORY OF PATHOLOGY

In 1761, **Dr. John Morgagni**, an Italian, wrote the great book "**The Seats and Causes of Disease, Investigated by Anatomy**" based on his series of 700 autopsies. This book summed up his lifetime's experience and is still a great read. Dr. Morgagni was among the most beloved people of his era. Thanks to his work, all disease was now recognized as **disease of organs** (***Organ Pathology***), and disease "sat" in different organs in different patients. Dr. Morgagni meticulously related his patients' symptoms to their diseased organs, making the first clinic-pathologic correlations. This was real progress, but Dr. Morgagni had no real idea of how disease in one organ caused malfunction in another organ, or even what disease is.

Dr. Rudolf Virchow (1821–1902), a German, is the greatest pathologist of all time. He liked to cut thin sections of diseased tissues with a razor, and look at them using the latest technology, the *microscope*. Dr. Virchow first achieved renown by discovering leukemia and myelin. In 1858, he wrote the famous book "**Cell Pathology**" which is the basis for all modern pathology. He established the principle that **all cells come from pre-existing cells** and he emphasized that **all disease is disease of cells** (***Cellular Pathology***). Dr. Virchow's ideas were introduced within months of two great unifying principles of today's science, the periodic table of the elements and the common origin of living things.

In the twentieth century, as the new techniques and methods developed and a new branches pathology can into be: *Ultrastructural Pathology*–Electron microscopy (EM) has contributed extensively to the understanding of cell structure and function as well as provided insight into pathologic processes. *Immunopathology* utilizes immunohistochemical methods to detect cell or tissue antigens on tissue section based on immunoenzimatic reactions using antibodies (mono or polyclonal). *Molecular Pathology* and *Genetic Pathology* are the subspecialties in which the principles, theories, and technologies of molecular biology and molecular genetics are used to make or confirm clinical diagnosis in neoplasia, infectious disease, tissue typing/identity testing, Mendelian genetic disorders and non-Mendelian genetic diseases. *Quantitative Pathology* is a branch of pathology concerned with the application of morphometry and image analysis technique.

Today there is a new emphasis on disease as it involves gene, molecules, cells, organs, whole persons and groups of people. Pathology deals with abnormal gross and microscopic anatomy, abnormal biochemistry, and abnormal physiology.

ORGANIZATION AND APPROACH OF THIS BOOK

The study of pathology is traditionally divided into general and systemic pathology, and we preserve this distinction.

In the *general pathology* chapters, the pathologic changes occurring in a hypothetic tissue are consi-

dered. This idealized tissue is composed of parenchymal cells and interstitial connective tissue and is the prototype of every tissue in the body. General pathology explores and explains the development of basic pathologic mechanisms without detailing the additional specific changes occurring in different organs.

In the *systemic pathology* chapters, the pathologic mechanisms discussed in the general pathology section are related to the various organ systems. In each system, normal structure, function, and the symptoms and signs that arise from pathologic changes are discussed briefly first. The diseases in each organ system are then considered, with emphasis given to those that are more common, so that the student can become familiar with most of the important diseases encountered in clinical practice.

Part A General Pathology

Chapter 1 Adaptation and Injury of Cell and Tissue

Zhang Zongji

CHAPTER CONTENTS

The normal cell is a highly complex unit in which the various organelles 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 nonlethal (regeneration) or lethal (necrosis and apoptosis).

ADAPTATION OF CELL AND TISSUE

Within limits, most cells can adapt to environmental stresses by modifying their size/shape, pattern of growth, and/or metabolic activity. This process is referred to as *adaptation*. The adaptive changes in cell growth and differentiation that are particularly important in pathologic conditions include *atrophy*, *hypertrophy*, *hyperplasia* and *metaplasia* (see Figure 1-1).

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.

Atrophy is classified as two patterns: physiologic and pathologic atrophy.

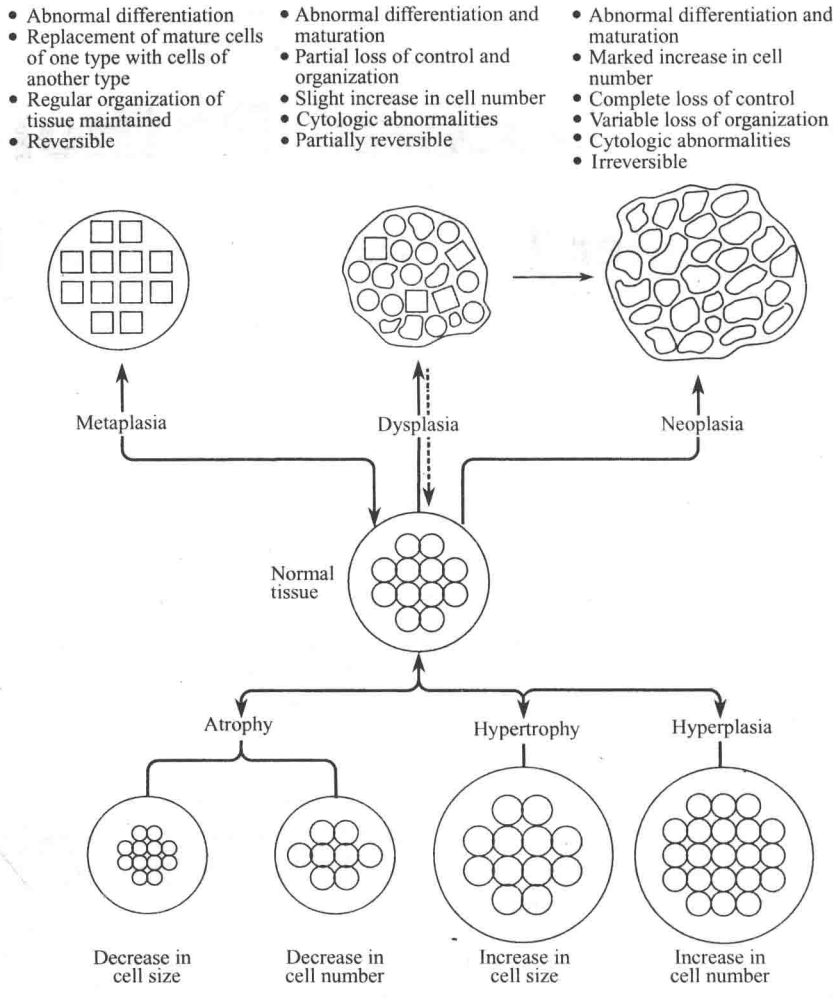

Figure 1-1 Adaptation and dysplasia of cell and tissue. Note that more than one abnormality may be present in a given case, e. g. the respiratory mucosa may show squamous metaplasia associated with dysplasia

Physiologic Atrophy

Physiologic atrophy is often seen when structures that are well developed and required at certain stages of development, later wither. A good example is that of endometrium, vaginal epithelium, and breast which occurs with menopause and the loss of estrogen stimulation. In the aging process, atrophy can be a normal morphologic change. It is most apparent in tissues populated by permanent cells, e. g. the brain and heart.

Pathologic Atrophy

A. Atrophy of Disuse

Atrophy of disuse occurs in immobilized skeletal muscle and bone, as when a fractured limb is put in a cast or when a patient is restricted to complete bed rest. Skeletal muscle atrophies rapidly with disuse. Initially, there is a rapid decrease in cell size that is readily reversible when activity is resumed. With more prolonged immobilization, muscle fibers decrease in number as well as in size. Because skeletal muscle can regenerate only to a very limited extent, restoration of muscle size after loss of muscle fibers can only occur through compensatory hypertrophy of the surviving fibers, which often requires a long rehabilitation period . Bone atrophy results when bone resorption occurs more rapidly than bone formation; it is characterized by decreased size of the trabeculae (decreased mass), leading to osteoporosis of disuse.

B. Denervation Atrophy

Skeletal muscle is dependent on its nerve supply for normal function and structure. Damage to the lower motor neuron at any point between the cell body in the spinal cord and the motor end plate leads to rapid atrophy of the muscle fibers supplied by that nerve. When denervation is temporary, physical therapy and electrical stimulation of the muscle are important to prevent muscle fiber loss and ensure that normal function can be restored when nerve function is reestablished. Many primary muscle diseases (e.g. the genetically determined **dystrophies**) also show irregular atrophy of muscle fibers.

C. Atrophy Due to Loss of Trophic Hormones

Many endocrine glands are dependent on trophic hormones for normal cellular growth, and withdrawal of these hormones leads to atrophy. Pituitary disease associated with decreased secretion of pituitary trophic hormones results in atrophy of the thyroid, adrenals, and gonads. High-dose adrenal corticosteroid therapy, which is sometimes used for immunosuppression, causes atrophy of the adrenal glands because it suppresses pituitary corticotrophin (ACTH) secretion. Such patients soon lose the ability to secrete cortisol and become dependent on exogenous steroids. Withdrawal of steroid therapy in such patients must be gradual enough to permit regeneration of the atrophied adrenal.

D. Atrophy Due to Lack of Nutrients

Severe protein-calorie malnutrition (marasmus) results in the utilization of body tissues such as skeletal muscle as a source of energy and protein after other sources such as adipose stores have been exhausted. Marked muscle atrophy is seen in marasmus.

A decrease in blood supply (ischemia) to a tissue as a result of arterial disease result in atrophy of the tissue due to progressive cell loses. Cerebrovascular disease, for example, is associated with cerebral atrophy, including neuronal loss.

E. Pressure Atrophy

Prolonged compression of tissue causes atrophy. A large, encapsulated benign neoplasm in the spinal canal may produce atrophy in both the spinal cord it compresses and the surrounding vertebrae. It is likely that such atrophy results from compression of small blood vessels, resulting in ischemia, and not from the direct effect of pressure on cells.

Morphology

In atrophic organs, there is a decreasing size and weight, the color is always darker than normal, consistency becomes hard or firm, and the margins of the organs is shrunken. On the surface of organs the arteries may be tortuous (Figure 1-2). Histologically, the size and/or the number of the parenchyma cells are decreased. Pigment deposition can be seen in the atrophic cytoplasm. At the same time, the interstitial connective tissue and the adipose tissue can proliferate. Under electron microscopy, decrease in the size of a cell results from a reduction in the amount of cytoplasm and the number of cytoplasmic organelles; it is usually associated with diminished metabolism. Degenerating organelles are taken up in lysosomal vacuoles for enzymatic degradation (autophagy). Residual organelle membranes often accumulate in the cytoplasm as brown lipofuscin pigment.

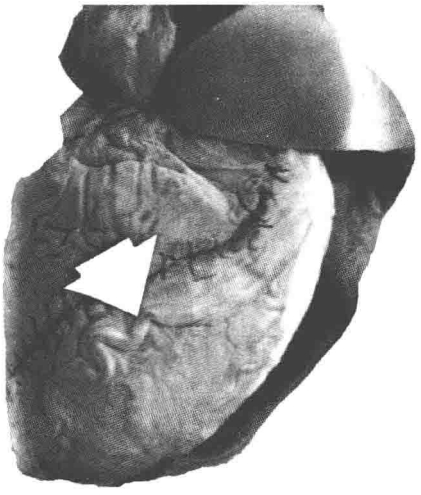

Figure 1-2 Atrophic heart, showing the decrease of size, and the coronary on the surface is tortuous (arrow)

HYPERTROPHY AND HYPERPLASIA

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 ac-

tivity cannot be met through cell multiplication.

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.

Table 1-1 Hypertrophy and hyperplasia of organs

Tissue	Cause of Increased Demand
Skeletal muscle hypertrophy	Physical activity, weight lifting
Cardiac muscle hypertrophy	Increased pressure load (high blood pressure, valve stenosis) or increased volume load (valve incompetence causing regurgitation of blood)
Smooth muscle (wall of intestine, urinary bladder) hypertrophy	Obstructive lesions
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)

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

Causes of Hypertrophy and Hyperplasia

Hypertrophy results from increased amounts of cytoplasm and cytoplasmic organelles in cells. In secretory cells, the synthetic apparatus - including the endoplasmic reticulum, ribosome, and the Golgi zone - becomes prominent. In contractile cells such as muscle fibers, there is an increase in size of cytoplasmic myofibrils. Hyperplasia results when cells of a tissue are stimulated to undergo mitotic division, thereby increasing the number of cells.

A. Physiologic Hypertrophy and Hyperplasia

Hypertrophy and hyperplasia may occur as an adaptation to increased demand (Table 1-1, Figures 1-3, and 1-4). Hypertrophy and hyperplasia are controlled responses reflecting increased demand; if the demand is removed, the tissues revert toward normal.

B. Pathologic Hypertrophy and Hyperplasia

Abnormal hypertrophy and hyperplasia occur in an appropriate stimulus of increased functional demand.

Myocardial hypertrophy, if it occurs without recognizable cause (e. g. in the absence of hypertension or valvular or congenital heart disease), is considered an example of pathologic hypertrophy. Such hypertrophy is frequently associated with abnormal cardiac function producing **cardiomyopathy.**

Endometrial hyperplasia is an important result of increased estrogen stimulation, particularly when estrogens are not opposed by progesterone secretion, as typically occurs near menopause. It is associated with irregular, often excessive uterine bleeding. The presence of excessive trophic hormones causes hyperplasia of the target organs, e. g. excessive secretion of ACTH causes bilateral adrenal hyperplasia. The hyperplasic target organs frequently show increased function. In the case of the adrenal gland, there is increased cortisol secretion (Cushing's syndrome).

Thyroid hyperplasia (goiter; Graves' disease) results from increased TSH stimulation of the thyroid or from the action of autoantibodies that are able to bind to TSH receptors in thyroid cell membranes.

Hyperplasia of the prostate gland is common in older men and is due to hyperplasia of the glandular and the stromal elements. The cause is not known, although it is believed that waning androgen levels may be responsible.

METAPLASIA

Metaplasia is an abnormality of cellular differentiation in which one type of mature cell is replaced by a different type of mature cell — and the latter is not normal for the tissue involved (Table 1-2). Metaplasia results from abnormal differentiation of stem cells (Figures 1-1, 1-5, and 1-6). The new, metaplastic tissue is structurally normal, however, so the regular cellular organization is maintained. Metaplasia is reversible.

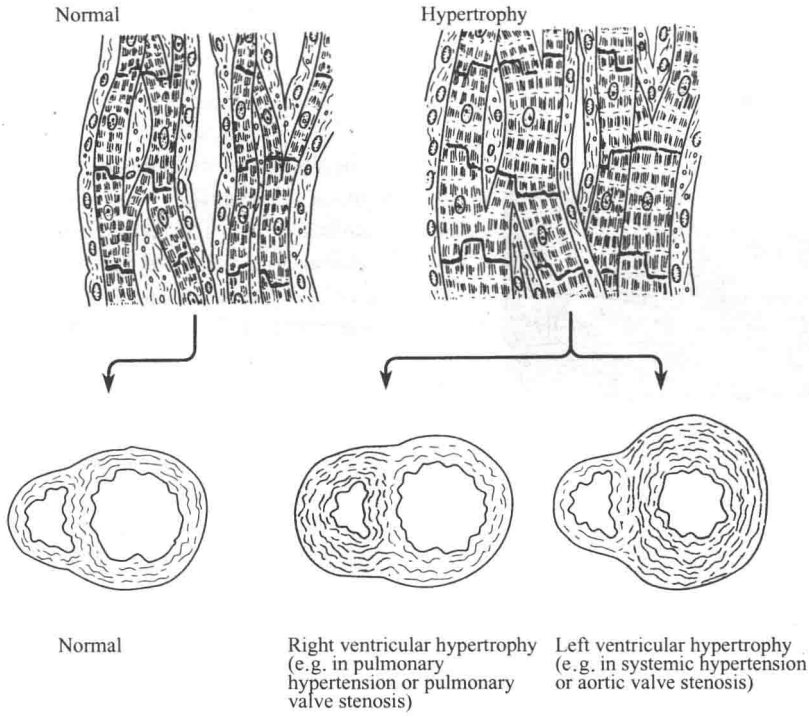

Figure 1-3 Cardiac muscle hypertrophy, showing the increase in size of cardiac muscle fibers. Hypertrophy may involve any of the cardiac chambers if they are subjected to an increased pressure or volume load (right and left ventricular hypertrophy and a few of their common causes are shown)

Table 1-2 Metaplasia[1]

Type of Metaplasia	Site	Causative Factors
Epithelial metaplasia		
Squamous metaplasia	Multiple sites Bronchus Endocervix Urinary bladder	Vitamin A deficiency Cigarette smoking, chronic inflammation Chronic inflammation Chronic inflammation, schistosomiasis
Intestinal metaplasia	Esophagus Stomach	Acid reflux Alkaline reflux, chronic inflammation
Gastric metaplasia	Esophagus Intestine	Acid reflux Unknown
Serous or mucinous metaplasia	Germinal epithelium of ovary	Trauma of multiple ovulation
Mesenchymal metaplasia		
Osseous metaplasia	Fibrous scars Areas of calcification	Unknown Unknown
Myeloid metaplasia[2]	Spleen, liver	Unknown

[1] See test for details of cell types involved.

[2] Myeloid metaplasia is the appearance of myeloid (bone marrow) elements outside the bone marrow and is not metaplasia in the strict sense because it is usually the result of extreme hyperplasia of bone marrow with extension of hematopoiesis into extramedullary sites such as the spleen and liver. (The last-named sites are normal sites of hematopoiesis in the fetus).