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TEXTBOOK OF PATHOLOGY

病　理　学

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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 oncise 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.

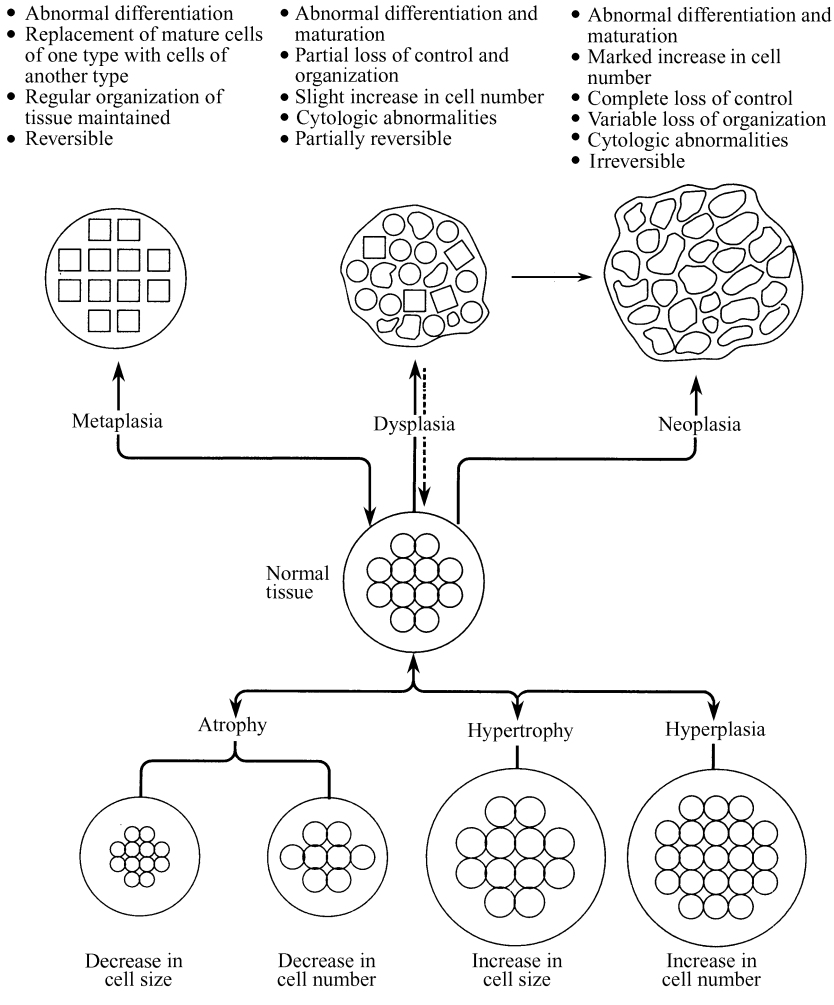

Figure 1-1 Adaptation and dysplasia of cell and tissue. Note that more than one abnormality may be present in a given case, e. g. the respiratory mucosa may show squamous metaplasia associated with dysplasia

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 re-established. 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.

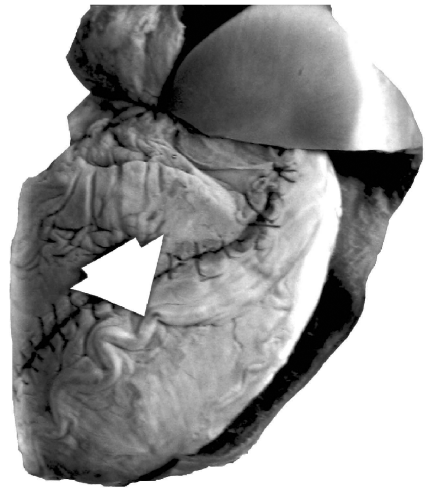

Figure 1-2 Atrophic heart, showing the decrease of size, and the coronary on the surface is tortuous (arrow)

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.

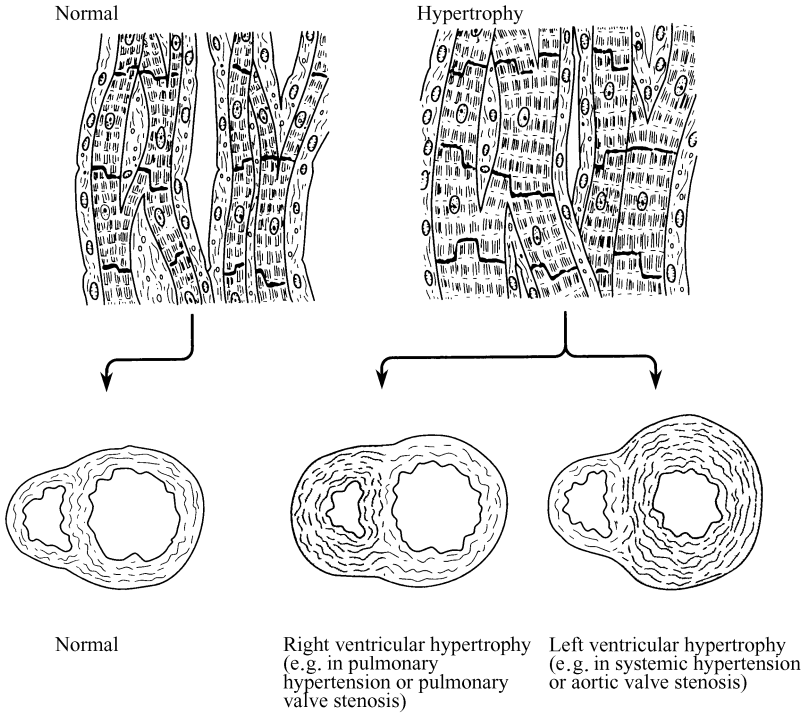

Figure 1-3 Cardiac muscle hypertrophy, showing the increase in size of cardiac muscle fibers. Hypertrophy may involve any of the cardiac chambers if they are subjected to an increased pressure or volume load (right and left ventricular hypertrophy and a few of their common causes are shown)

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).

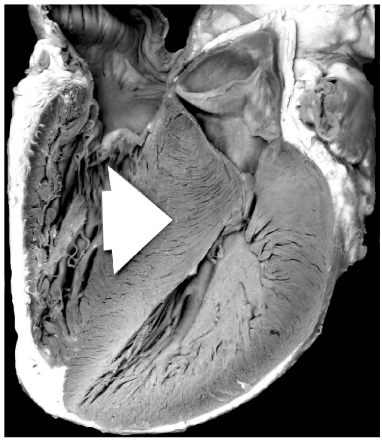

Figure 1-4 Hypertrophic heart, showing the size of the heart is as large as a normal heart, but the weight is increased. On the cut surface, the musculature of the left ventricle and septum is clearly enlarged, and the papillary muscles and trabeculae carneae are thickened. Without dilatation of the left ventricle, concentric hypertrophy results

Metaplasia most commonly involves epithelium. As the germinative stem cells multiply to replace cells shed at the surface , they differentiate in a manner that is abnormal for that location, resulting in epithelium of a type different from that usually present. Epithelial metaplasia is thus a manifestation of the varied potential for differentiation in stem cells and typically occurs following chronic physical or chemical irritation.

In **squamous metaplasia** – the most common type of epithelial metaplasia – nonsquamous pseudostratified columnar or cuboidal epithelium is replaced by a normal-appearing stratified squamous epithelium. Squamous metaplasia is common in the endocervix and the bronchial mucosa (Figure 1-5), it occurs less frequently in the endometrium and urinary bladder.

Glandular metaplasia occurs in the esophagus, where the normal squamous epithelium is replaced by glandular, mucus-secreting epithelium (either gastric or intestinal in type), usually as a result of acid reflux into the esophagus (see Barrett's esophagus). Metaplasia may also occur in the stomach and intestine, where the mucosa of one part is replaced by that of another, e.g. replacement of gastric mucosa with intestinal mucosa (intestinal metaplasia) or vice versa (gastric metaplasia). It may also affect the germinal epithelium of the ovary, as in the formation of serous and mucinous cysts.

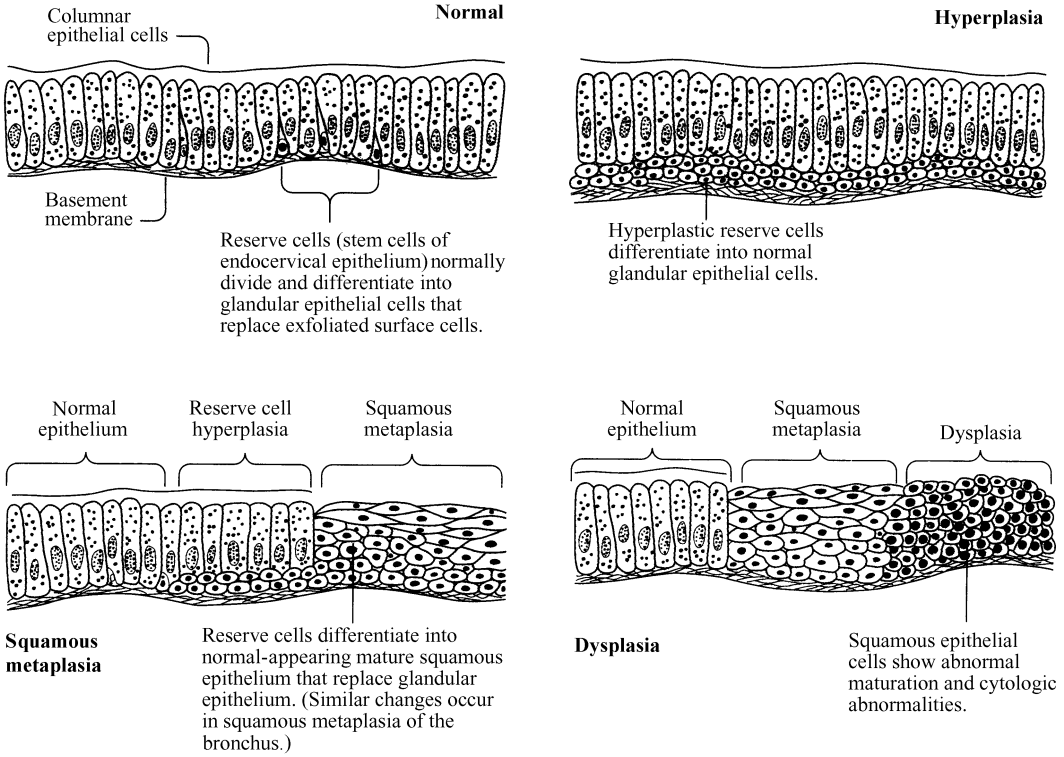

Figure 1-5 Hyperplasia, squamous metaplasia, and dysplasia occurring in the uterine endocervical epithelium. Similar changes may occur in the bronchial epithelium

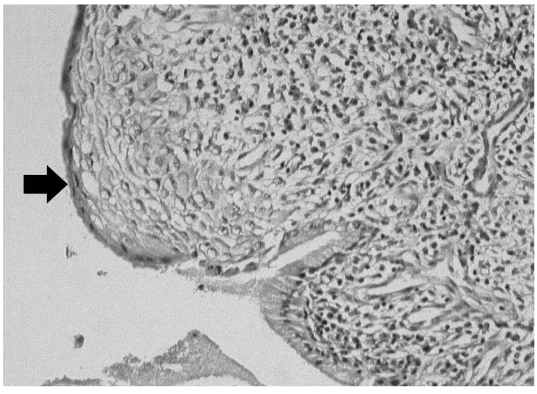

Figure 1-6 Endocervix, showing squamous metaplasia. The normal columnar epithelium (below) has been replaced by a squamous epithelium (arrow)

Metaplasia can occurs in mesenchymal tissue and is best exemplified by osseous metaplasia in scars and other fibroblastic proliferations. Metaplasia in mesenchymal tissue is the same as epithelial metaplasia in representing the potential for diverse differentiation of mesenchymal stem cells.

Most metaplasia is of little clinical significance, although important functional deficits may result in some areas; loss of cilia and of mucus production in the bronchi may predispose to development of infection. Metaplastic tissue is structurally normal and itself carries no increased risk of development of cancer.

MECHANISMS OF INJURY OF CELL AND TISSUE

CAUSES OF CELL INJURY

A variety of injurious agents act on human tissues (Figure 1-7) to produce tissue damage either directly or indirectly. A noxious agent may act directly on the tissue and interfere with its structure or biochemical function. An example is a burn, in which heat causes immediate direct destruction of cell membranes, tissue components, and coagulation of intracellular proteins. However, an injurious agent may act at some site other than the tissue in question to produce an abnormality in the immediate environment of the cell or cause accumulation of some toxic substance, which in turn causes cell damage. Representative causes of indirect injury include accumulation of toxic products seen in kidney and liver failure or a change in extracellular pH, electrolyte concentrations, or core body temperature. These indirect injuries may result in cell damage to many different tissues throughout the body, e.g. structural and functional abnormalities in the brain from liver failure (hepatic encephalopathy).

1. Oxygen deprivation

Hypoxia is an extremely important and common cause of cell injury. Oxygen reaches the cells via arterial blood but is ultimately derived from the atmosphere. Most of the oxygen carried in blood is bound to hemoglobin. Lack of oxygen in the cells (hypoxia) may result from (1) **respiratory obstruction or disease**, preventing oxygenation of blood in the lungs; (2) **ischemia**, or failure of blood flow in the tissue, due either to generalized circulatory failure or to local vessel obstruction; (3) **anemia** (e.g. decreased hemoglobin in the blood), resulting in decreased oxygen carriage by the blood; or (4) **alteration of hemoglobin** (as occurs in carbon monoxide poisoning), making it unavailable for oxygen transport and leading to the same result as anemia.

2. Physical agents

Many forms of physical injury can be harmful to cells and tissues. For example, extremes of heat or cold (burns, heat stroke, heat exhaustion, frostbite, and hypothermia), mechanical injury (crush injury, fractures, lacerations, and hemorrhage), electric shock, radiation and sudden changes in atmospheric pressure all have direct effects on cells and tissues.

3. Chemical agents

A very large number of drugs and environmental chemical agents are capable of causing cell injury. The list includes inorganic compounds, ions, and organic molecules – including byproducts of normal metabolism and toxins synthesized by microorganisms. Two basic mechanisms of chemical injury are recognized: (1) a compound can react directly with some critical molecular component of the cell interfering with its function. For example, cyanide inactivates the enzyme cytochrome oxidase in mitochondria required for aerobic respiration. (2) A compound that is itself harmless to cells can be rendered toxic when it is metabolized and converted to a toxic substance (such as a free radical). This is the way in which acetaminophen overdose is toxic to the liver.

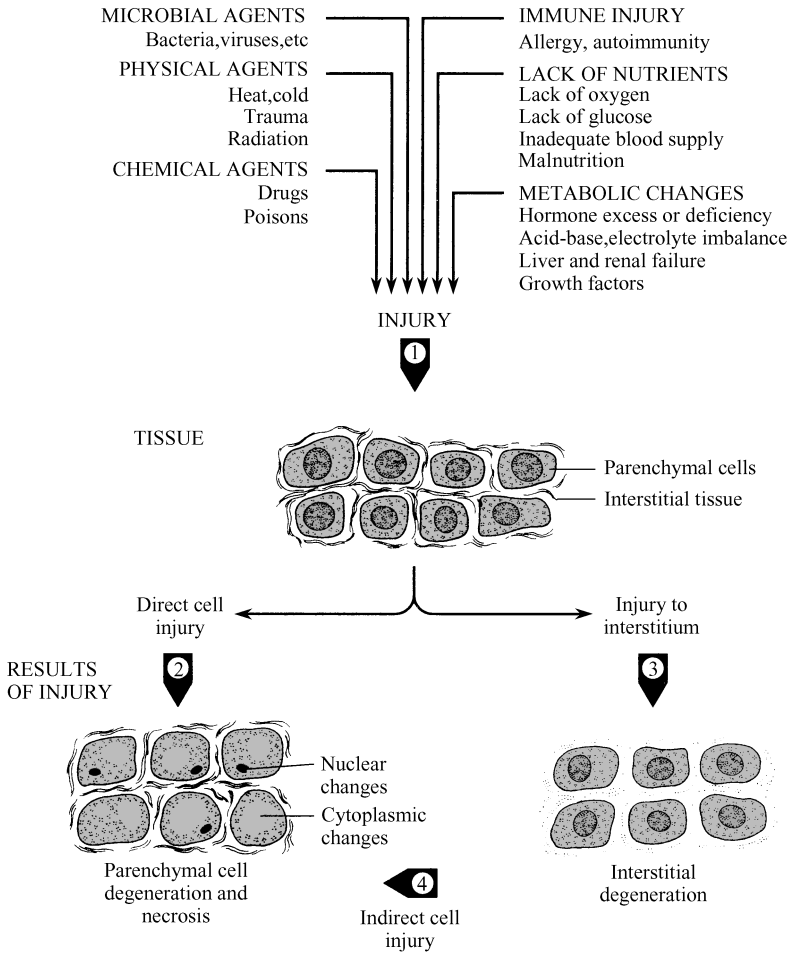

Figure 1-7 General causes and effects of tissue injury. Many different types of injuries act on tissues ① to cause direct parenchymal cell injury ② or interstitial injury ③ Interstitial abnormalities may cause indirect parenchymal cell injury④

4. Infectious agents

This very common category of cell injury results from the parasitization of the body by pathogenic viruses, bacteria, fungi, protozoa, or helminths. Pathogenic organisms produce disease by either: (1) replicating inside host cells and disrupting the structural integrity of the cell, (2) producing a toxin that is harmful to host cells, or by (3) triggering an inflammatory or immune response that inadvertently injures host cells.

5. Immunologic agents

Although the immune system defends our body against foreign materials, exaggerated immune reactions (anaphylaxis, allergy) or the inappropriate targeting of the body's own cells by the immune system (autoimmunity) can result in acute or chronic inflammation and cell injury. Abnormal suppression of the immune system can increase vulnerability to microbial invasion.

6. Genetic defects

Inherited or acquired mutations in important genes can alter the synthesis of crucial cellular proteins leading to developmental defects or abnormal metabolic functioning. Acquired mutations to somatic cells during life can affect cell differentiation and replication leading to diseases such as cancer.

7. Nutritional Imbalances

Deficiencies or excesses in normal cellular sub-

strates (e. g. calories, proteins, carbohydrates, minerals and vitamins) can produce problems such as obesity, malnutrition, scurvy, iron deficiency anemia, etc.

MECHANISMS OF CELLULAR INJURY

Cell injury is associated with damage to the structural and functional molecules of the cell. Injury to a cell may be nonlethal or lethal (Figure 1-8).

Nonlethal injury to a cell may produce cell degeneration, which is manifested as some abnormality of biochemical function, a recognizable structural change, or a combined biochemical and structural abnormality. Degeneration is reversible but may progress to necrosis if injury persists. When it is associated with abnormal cell function, cell degeneration may also cause clinical disease.

Lethal injuries to the cell of a living individual cause cell death, including necrosis and apoptosis. Necrosis is accompanied by biochemical and structural changes (see below) and is irreversible. The

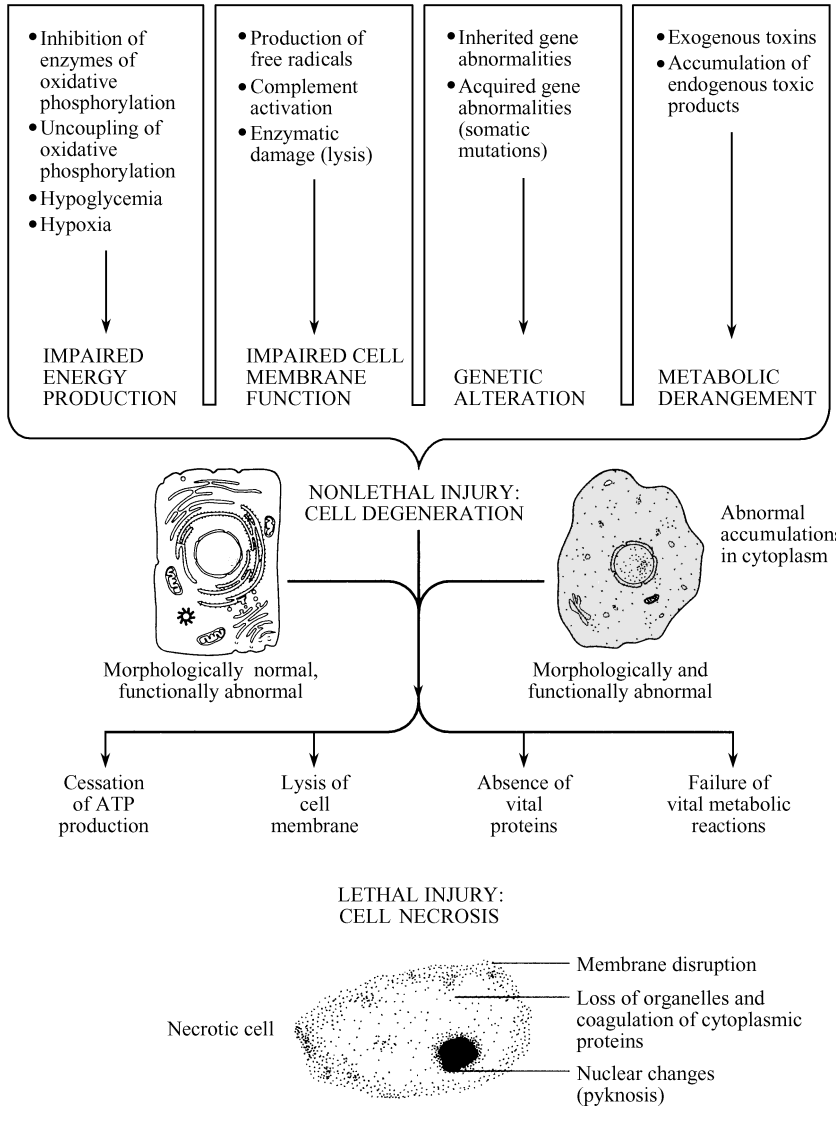

Figure 1-8 Mechanisms of injury leading to cell degeneration and necrosis

necrotic cells cease to function; if necrosis is sufficiently extensive, clinical disease results. Necrosis should be distinguished from apoptosis – genetically programmed cell death. In apoptosis, there is an orderly disassembly of cellular proteins and DNA with minimal disruption to normal tissue. Apoptosis is a normal physiologic process designed to eliminate unwanted, functionally abnormal, or senescent (old and worn out) cells. It plays an important role in the developing embryo, certain hormone-dependent tissues, and in aging. However, in some instances, apoptosis may be a pathologic process induced by cell injury (e. g. viral infection, radiation injury, etc.). The details of apoptosis are discussed later.

Mechanical Trauma

Mechanical trauma may cause subtle but significant dislocations of the intracellular organization of organelles or may destroy the cell by completely disrupting it. For example, a surgical incision or accidents can destroy the cells and tissues directly. Ice crystals which occur in freezing can mechanically injury the structure of the cell membrane.

Impaired Cell Membrane Function

Selectively permeable lipid membranes are essential for maintaining the internal environment of cells. By controlling what molecules enter and leave the cell, the plasma membrane helps conserve important resources, and keeps the cell in osmotic equilibrium with extracellular fluid. Energy-dependent protein "pumps" embedded in the plasma membrane establish differences in ion concentrations and electrical charge between the inside and outside of the cell (resting membrane potential).

Cell membranes can be disrupted by degrading phospholipids – the primary molecular component of biologic membranes. Damage to the plasma membrane increases the cell permeability to sodium and water. This causes the cell to swell, and may even lead to disruption of the cell (lysis). Potassium may leak out of the cell affecting its ability to maintain resting membrane potential. Injury to the membrane of mitochondria impairs energy metabolism. Lysosomal injury releases hydrolytic enzymes into the cytoplasm leading to auto-digestion of cellular proteins. Damage to the endoplasmic reticulum interferes with protein synthesis and the intracellular transport of biologically important compounds.

Impaired Energy Production

A. Normal Energy Production

High-energy phosphate bonds of adenosine triphosphate (ATP) represent the most efficient energy source for the cell. ATP is produced by phosphorylation of ADP, a reaction that is linked to the oxidation of reduced substances in the respiratory chain of enzymes. Oxygen is required (oxidative phosphorylation). Cells require a constant energy supply, mainly in the form of ATP, to drive metabolism and biosynthetic reactions.

B. Causes of Defective Energy (ATP) Production

1. Hypoglycemia

Glucose is the main substrate for energy production in most tissues and is the sole energy source in brain cells. Low glucose levels in blood (hypoglycemia) therefore result in deficient ATP production that is most profound in the brain.

2. Hypoxia

Depriving the cell of oxygen (hypoxia), or disturbing mitochondrial function, interferes with the cell's ability to utilize oxygen in generating adequate amounts of ATP. This, in turn, impairs the ability of the cell to utilize nutrients in synthesizing structural and functional proteins necessary for maintaining the cell. Depletion of ATP also shifts energy metabolism towards anaerobic glycolysis.

3. Enzyme Inhibition

Cyanide poisoning is a good example of a chemical interfering with a vital enzyme. Cyanide inhibits cytochrome oxidase, the final enzyme in the respiratory chain, causing acute ATP deficiency in all cells of the body and rapid death.

4. Uncoupling of oxidative phosphorylation

Uncoupling of oxidation and phosphorylation occurs either through chemical reactions or through physical detachment of enzymes from the mitochondrial membrane. Mitochondrial swelling, which is a common change associated with many types of injury, causes uncoupling of oxidative phosphorylation.

C. Effects of Defective Energy Production

Generalized failure of energy production will first affect those cells with the highest demand for oxygen because of their high basal metabolic rate. Brain cells are maximally affected. The earliest clinical signs of hypoxia and hypoglycemia are disturbances of the normal level of consciousness.

Genetic Alteration

Damage to cellular DNA interferes with cell replication, and impairs the synthesis of important structural and functional proteins.

Inherited genetic abnormalities are passed from generation to generation, frequently in predictable fashion according to Mendelian laws. **Acquired genetic abnormalities** are somatic mutations resulting from damage to genetic material by any of several agents, including ionizing radiation, viruses, and mutagenic drugs and chemicals. The clinical and pathologic effects of genetic abnormalities depend on (1) the severity of damage, (2) the precise gene or genes damaged, and (3) when the damage was sustained. When genetic damage is inherited or occurs during gametogenesis or early fetal development, clinical effects may be present at birth (congenital genetic disease). Acquired genetic disease results when genetic damage occurs postnatally.

The Role of Oxygen-derived Free Radicals

When mitochondria generate energy by reducing molecular oxygen to water, small amounts of partially reduced forms of oxygen (superoxide, hydrogen peroxide, and hydroxyl radicals) are produced in the process. These "free radicals" are short-lived molecules containing an unpaired electron in an outer orbital – an electron that is not contributing to normal intramolecular bonding. These are essentially "free chemical bonds" which are energetically unstable and highly reactive. Free radicals are generally transient products of oxidation-reduction reactions or result when a covalent bond is broken and one electron from each pair remains with each atom. Although free radicals play an important physiologic role in intracellular oxidation-reduction reactions and the bacteria killing function of white blood cells, they can also interact with biologically important molecules-removing electrons or hydrogen atoms and disrupting covalent bonds. Fortunately, cells normally produce only very small amounts of oxygen-derived free radicals, and they also have molecular scavengers (anti-oxidants) to neutralize them before they can do any harm.

When cells are injured, large amounts of free radicals can accumulate-rapidly depleting anti-oxidants and allowing free radicals to react with critical biochemical components of the cell. Free radicals can attack the double bonds of unsaturated phospholipids in cell membranes which eventually degrade the structural integrity of cell membranes. Free radicals also impair the functions of enzymes by causing fragmentation of polypeptide chains or the cross-linking of sulfhydryl (–SH) groups in proteins. Free radicals also cause strand breaks or abnormal cross-linking in DNA.

Denaturation of Cellular Enzymes or Structural Proteins

Almost all vital cellular processes are dependent on enzymes-protein catalysts that facilitate biochemical reactions inside the cell. Without enzymes, synthesis and metabolic reactions would occur too slowly to be useful to the cell.

Damage to structural proteins can impair the intracellular transport system of cells and disrupt the supportive protein cytoskeleton of cells.

REVERSIBLE INJURY OF CELL AND TISSUE

Under some conditions, many normal or abnormal amounts of various substances may be accumulated either in the cytoplasm or in the interstitial tissues. These may be harmless or may cause varied degree of injury. This is also named as degeneration.

Degeneration and accumulation of endogenous substances are seen Table 1-3.

HYDROPIC DEGENERATION

Hydropic degeneration, or **clouding swelling**, is an early and reversible effect of cell injury, including hypoxia, toxins and so on. These injurious agents can cause dysfunction of the energy-dependent sodium pump in the plasma membrane, and resulting influx of sodium and water into cell.

Table 1-3 Endogenous substances accumulating in tissues as a result of deranged metabolism

Accumulated Substance	Effects in Parenchymal Cells	Effects in Interstitial Tissues
Water	Cloudy swelling Hydropic change	Edema
Lipid		
Triglyceride	Fatty change	
Cholesterol		Atherosclerosis Xanthoma
Complex lipids (phospholipids)	Lipid storage disease	
protein	Ubiquitin/protein Complexes Heat shock proteins	Amyloidosis
Glycogen	Glycogen storage diseases	
Mucopolysaccharide	Mucopolysaccharidoses	Myxoid degeneration
Minerals		
Iron	Hemochromatosis	Localized hemosiderosis
Calcium	Contributes to necrosis	Calcification
Copper	Wilson's disease	Wilson's disease
Pigments		
Bilirubin	Kernicterus	Jaundice
Lipofuscin	Brown atrophy	
Urate		Gout
Homogentisic acid		Alkaptonuria

Morphologically, in the hydropic swelling of the organs or tissues there is an increasing weight and turgor. The parenchyma cells are enlarged in various degrees and crowded together, and the cytoplasm is translucent and stains more lightly. Sometimes these large round cells are called balloon-like enlarged cells. The nucleus is usually in the center of the cell. Some small, clear vacuoles may be seen within the cytoplasm on microscopy (Figure 1-9). The vacuoles represent distended cisternae of the endoplasmic reticulum or sequestered remnants of it.

FATTY CHANGE (Fatty Degeneration)

Fatty change is the accumulation of triglyceride in the cytoplasm of parenchymal cells. It is common in the liver and rare in the kidney and myocardium and occurs as a nonspecific response to many types of injury.

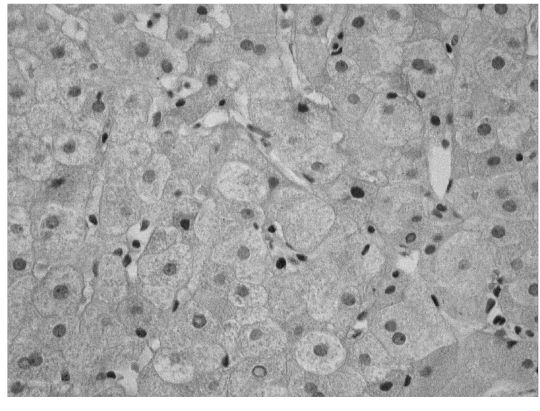

Figure 1-9 Hydropic swelling of hepatocytes. The cytoplasm of the liver cells is lucent. Some of the liver cells are enlarged with translucent cytoplasm that appears as a vacuole, also called balloon-like enlarged cells

Normal Triglyceride Metabolism in the Liver

The liver plays a central role in triglyceride metabolism. Free fatty acids are carried in the blood to the liver, where they are converted to triglycerides, phospholipids, and cholesteryl esters. After these lipids form complexes with specific lipid acceptor proteins (apoproteins), which are also synthesized in the liver cell, they are secreted into the plasma as lipoproteins. When triglycerides are metabolized normally, there are so little triglycerides in the liver cell that it cannot be seen in routine microscopic sections.

Causes of Fatty Liver

Accumulation of triglycerides in the cytoplasm of liver cells (fatty liver) represents an abnormality of the metabolic pathway and occurs in the following conditions: (1) When there is increased mobilization of adipose tissue, resulting in an increase in the amount of fatty acids reaching the liver, e. g. in starvation and diabetes mellitus. (2) When the rate of conversion of fatty acids to triglycerides in the liver cell is increased because of overactivity of the involved enzyme systems. This is the main mechanism by which alcohol, a powerful enzyme inducer, causes fatty liver. (3) When oxidation of triglycerides to acetyl-CoA and ketone bodies is decreased, e. g. in anemia and hypoxia. (4) When synthesis of lipid acceptor proteins is deficient. Protein malnutrition and several hepatotoxins, e. g. carbon tetrachloride and phosphorus, cause fatty liver in this way.

Types of Fatty Liver

A. Acute Fatty Liver

Acute fatty liver is a rare but serious condition associated with acute liver failure. In acute fatty liver, triglyceride accumulates as small, membrane-bound droplets in the cytoplasm (microvacuolar fatty change, Figure 1-10).

B. Chronic Fatty Liver

Chronic fatty liver is much more common. It is associated with chronic alcoholism, malnutrition, and several hepatotoxins. Fat droplets in the cytoplasm fuse to form progressively larger globules

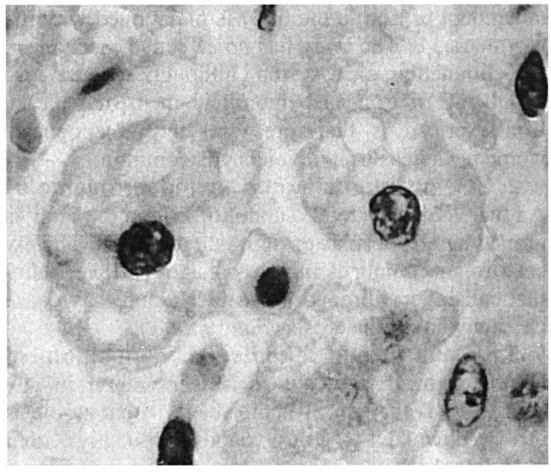

Figure 1-10 Acute microvacuolar fatty change of the liver in Reye's syndrome. The cytoplasm of the liver cells is filled with numerous small vacuoles representing the lipid that has been dissolved out of the tissue during processing. The nuclei are centrally located

(macrovacuolar fatty change, Figure 1-11). The distribution of fatty change in the liver lobule varies with different causes (Figure 1-12). Grossly, the fatty liver is enlarged and yellow, with a greasy appearance when cut. Even when severe, chronic fatty liver is rarely associated with clinically detectable liver dysfunction.

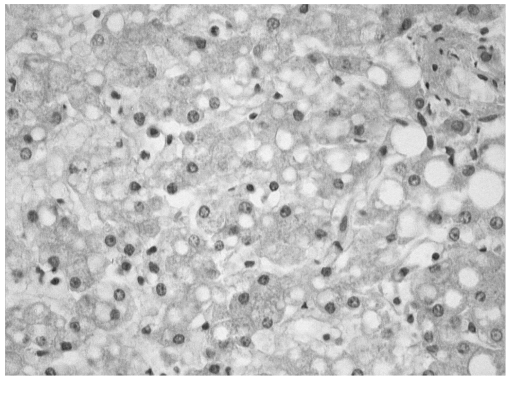

Figure 1-11 Macrovacuolar fatty change of the liver in chronic alcoholism. The large fat globules in the cytoplasm appear as empty spaces that have displaced the nucleus to the side

Fatty Change of the Myocardium

Triglyceride deposition in myocardial fibers occurs

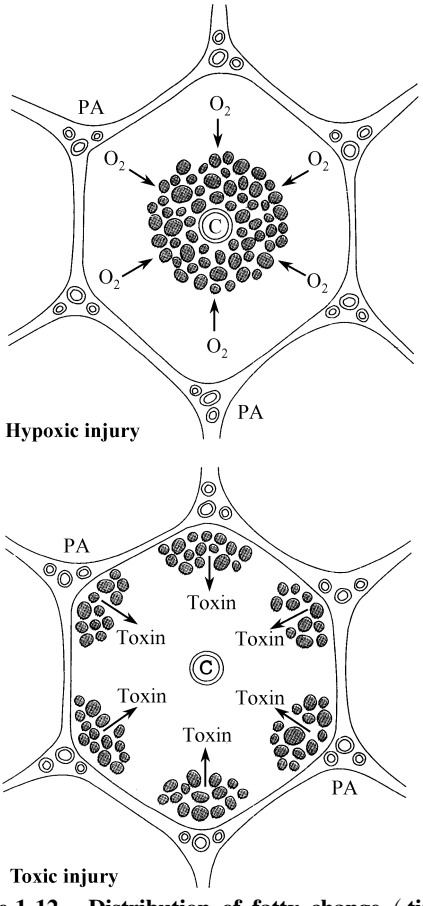

Figure 1-12 Distribution of fatty change (tinted circles) in the liver in hypoxic and toxic liver injuries. In hypoxic injury, fatty change occurs centrizonalling; in toxic injury, fatty change occurs around the portal areas, The rules relating to this distribution, which are dependent on the mode of entry of oxygen and toxins into the liver lobule, are not without exception. Carbon tetrachloride, for example, causes centrizonal fatty change

in chronic hypoxic states, notably severe anemia. In chronic fatty change, bands of yellow streaks alternate with red-brown muscle ("thrush breast" or "tiger skin" appearance); this usually causes no clinical symptoms. Toxic diseases such as diphtheritic myocarditis and Reye's syndrome produce acute fatty change. The heart is flabby and shows diffuse yellow discoloration; myocardial failure commonly follows.

Microscopic Features of Fatty Change

Any fat present in tissues dissolves in the solvents that are used to process tissue samples for microscopic sections. In routine tissue sections, therefore, cells in the earliest stages of fatty change have pale and foamy cytoplasm. As fat accumulation increases, cytoplasmic vacuoles appear. Positive demonstration of fat requires the use of frozen sections made from fresh tissue. Fat remains in the cytoplasm in frozen sections, where it can be demonstrated by fat stains such as oil red O and Sudan black B.

HYALINE DEGENERATION

Hyaline degeneration is applied to material of homogeneous, glassy, usually eosinophilic appearance seen on microscopy of hematoxylin and eosin stain. It is a purely descriptive adjective, and many different formed tissue elements, as well as cell cytoplasm or interstitial tissue, may assume a hyaline appearance.

A. Hyaline of Connective Tissue

It commonly occurs in dense collagenous fibrous scar which may assume a homogeneous pink hyaline appearance grossly. Microscopic examination shows excessive collagen as thick, hyalinized bands.

B. Hyaline of the Arterial Wall

In the kidney, brain, spleen, retina and other organs, the walls of arterioles usually become thickened. Hyalinization in arteries occurs in longstanding hypertension. The hyaline material arises by intramural deposition of plasma protein and lipids and reduplication of the intimal basement membrane. The narrowing of the lumens usually result in the ischemia of organs (Figure 1-13).

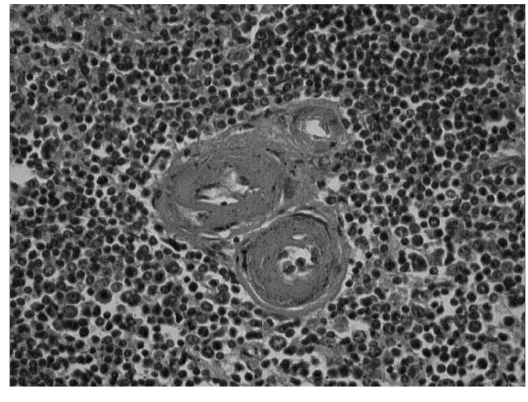

Figure 1-13 Hyaline degeneration of the central artery of the spleen, showing numerous homogenous eosinophilic material deposit under the intima, which results in thickened of the parts of the central artery as well as narrowing of the lumen

C. Intracellular Accumulation of Protein

In many injuries, overabundant proteins deposition in cell cytoplasm results in morphological changes of tissue. On microscopy the round, eosinophil droplets usually can be seen in cytoplasm. These droplets can appear as homogeneous, filament-like and crystalloid by electron microscopy. For example: (1) In many conditions such as glomerulonephritis, abnormal amounts of plasma proteins leak into the glomerolar filtrate, part of the protein is resorbed by the tubular epithelium where it is seen as hyaline droplets. (2) Russell bodies in plasma cells constitute spherical hyaline immunoglobulin deposits, it usually occurs in some chronic inflammation. (3) Mallory hyaline appears in the hepatocyte cytoplasm in alcoholics, particularly when it has led to cirrhosis of the liver, and certain other forms of liver cell injury (Figure 1-14). And (4) Lewy bodies appears in neurons of Parkinson's disease.

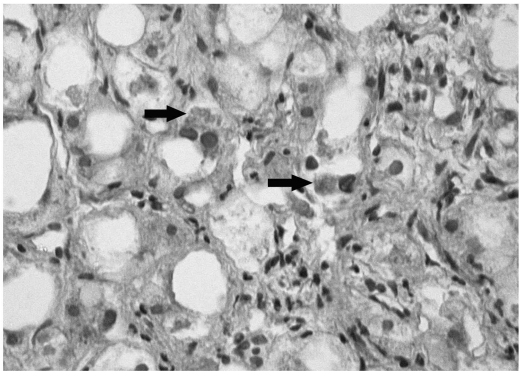

Figure 1-14 Mallory body, so called "alcoholic hyaline" in the cirrhosis associated with alcohol abuse. The irregular dark configuration within the liver cells (arrow)

ACCUMULATION OF MUCOPOLYSACCHARIDES (Myxoid Degeneration)

An increase in the amount of mucopolysaccharides (glycosaminoglycans) in the ground substance of the interstitium is termed myxoid (myxomatous) degeneration. Special stains (e.g. alcian blue, colloidal iron) are necessary to demonstrate mucopolysaccharides; myxoid degeneration appears on microscopic examination of hematoxylin and eosin-stained sections as loose, weakly basophilic material.

Myxoid degeneration of the interstitium occurs in hypothyroidism (myxedema) through an unknown mechanism. Myxoid degeneration is common in joint capsules, where it may lead to formation of a cystic tumor (ganglion) on a tendon or aponeurosis. Myxoid degeneration also occurs in the stroma of neoplasms such as neurofibromas.

A form of myxoid degeneration may occur in the aorta and cardiac valves, especially the mitral valve. This change is common in Marfan's syndrome (see above) and may be associated with valvular incompetence and aortic rupture. A similar form of myxoid degeneration – largely confined to the mitral valve leaflets – occurs in otherwise normal individuals and is the most common cause of mitral valve incompetence (floppy valve syndrome).

DEPOSITION OF AMYLOID (Amyloidosis)

The term amyloid denotes a variety of fibrillary proteins deposited in interstitial tissues in certain pathologic conditions. All types of amyloid have the following physicochemical characteristics:

a. In histologic sections, amyloid stains as follows:

- With Congo red stain, amyloid appears red with apple-green birefringence when viewed under polarized light.
- With H and E, it stains homogeneous pink.
- Amyloid may also be stained immunohistochemically using antibodies specific to the various subtypes of fibrils.

b. On electron microscopy, amyloid appears as nonbranching fibrils 7.5–10 nm wide.

c. On x-ray diffraction, amyloid exhibits a pleated β-sheet structure that renders the protein very resistant to enzymatic degradation, contributing to its accumulation in tissues.

Chemical Composition

The chemical structure of amyloid protein is quite variable (see Table 1-4, where AL, AA, etc are explained).

A. Amyloid of Immunoglobulin Origin

In AL amyloid, the protein is composed of fragments of the light chains of immunoglobulin molecules. AL is produced by neoplastic plasma cells

Table 1-4 Amyloidosis

Amyioid Protein	Principal Constituent	Associated Diseases	Distribution
AL	Lmmunoglobulin light chain	Primary amyloidosis Plasma cell myeloma B cell malignant lymphoma	Tongue, heart, gastrointestinal tract liver, spleen, kidney (primary distribution)
AA	Serum A protein (α_1-globulin)	Rheumatoid arthritis	Tongue, heart, gastrointestinal tract (primary distribution)
AA	Serum A protein (α_1-globulin)	Chronic infections (tuberculosis, leprosy bronchiectasis, osteomyelitis) Hodgkin's disease Inflammatory bowie disease	Liver, kidney, spleen (secondary distribution)
AA	Serum A protein (α_1-globulin)	Familial Mediterranean fever	Liver, kidney spleen
AF	Prealbumin	Familial amyloidosis (Portuguese, Swedish, etc)	Peripheral nerves, kidney
AS	Prealbumin	Senile amyloidosis Cardiac amyloidosis Cerebral amyloid angiopathy	Heart, spleen, pancreas Heart Cerebral vessels
AE	Peptide hormone precursors (e.g. calcitonin)	Medullary carcinoma of thyroid Pancreatic islet cell adenomas	Locally within the neoplasm
AD	Unknown	Lichen amyloidosis	Skin (dermis)
Alzheimer	A_4 peptide[1] or beta amyloid precursor protein	Alzheimer's disease Down's syndrome	Neurofibrillary tangles, plaques, and angiopathy

[1] A_4 peptide = Alzheimer 4000-MW peptide (derived from a 40,000-MW precursor protein found in serum and cerebrospinal fluid; encoded in chromosome 21).

(myeloma) and B lymphocytes (B cell lymphomas). Amyloid light chains resemble the free light chains (Bence Jones proteins) or light chain fragments that are produced by the neoplastic plasma cells or B lymphocytes.

B. Amyloid of Other Origin

Other amyloid fibrils are composed of (1) serum amyloid-associated protein, an acute phase protein (MW 18,000) produced by the liver during any inflammatory process; (2) prealbumin; and (3) other peptide fragments (Table 1-4). In addition, all amyloids contain small amounts of amyloid P protein and, usually, heparan sulfate.

Classification

The clinical classification of amyloidosis is based on protein type and tissue distribution.

A. Systemic Amyloidosis

1. Primary pattern of distribution

In systemic amyloidosis with a primary distribution, amyloid is found in the heart, gastrointestinal tract, tongue, skin, and nerves. This distribution is seen in primary amyloidosis and neoplasms of B lymphocytes (plasma cell myeloma and B cell malignant lymphomas). An underlying plasma cell neoplastic process with a monoclonal immunoglobulin is detectable in serum in more than 90% of patients with primary amyloidosis. In these cases, amyloid is AL. In rheumatoid arthritis, a nonimmunoglobulin amyloid (AA) is deposited in this primary pattern.

2. Secondary pattern of distribution

In systemic amyloidosis with a secondary distribution, amyloid is found in the liver, spleen, kidney, adrenals, gastrointestinal tract, and skin. It occurs secondarily to chronic inflammatory diseases such as tuberculosis, leprosy, chronic osteomyelitis, chronic pyelonephritis, and inflammatory bowel disease (reactive systemic amyloidosis, secondary amyloidosis). The amyloid protein is AA and is derived from plasma α_1-globulins.

B. Localized Amyloidosis

Localized amyloidosis may take the form of nodu-

lar, tumor-like masses that occur rarely in the tongue, bladder, lung or skin. These amyloid tumors are commonly associated with localized plasma cell neoplasms. In Alzheimer's disease, deposits of a special form of amyloid occur in the extracellular brain substance (plaques).

C. Amyloid in Neoplasms

Amyloid is present in the stroma of many endocrine neoplasms, e. g. medullary carcinoma of the thyroid. The amyloid protein is AE, usually derived from precursor molecules of certain peptide hormones (e. g. calcitonin).

D. Heredofamilial Amyloidosis

Familial amyloidosis has been reported in only a few families. The amyloid type is AF or AA. Familial amyloidosis is classified as neuropathic, nephropathic, or cardiac, depending on the site of maximal involvement. Familial Mediterranean fever, a disease transmitted by autosomal recessive inheritance, is characterized by fever and inflammation of joints and serosal membranes.

E. Senile Amyloidosis

Small amounts of amyloid (AS type) are frequently found in the heart, pancreas, and spleen in the elderly. In the late stages of diabetes mellitus, amyloidosis occurs in the abnormal pancreatic islets. This may be a distinct type of amyloid composed of islet amyloid polypeptide, which has been shown to have hormonal activity, affecting glucose uptake in muscle.

Effects of Amyloid Deposition

Amyloid is deposited in interstitial tissue, commonly in relation to the basement membrane of cells and small blood vessels. Tissues affected by amyloidosis are often enlarged (hepatosplenomegaly, cardiomegaly, thickened peripheral nerves, macroglossia). Affected tissues are also firmer and less flexible or distensible than normal tissues. Therefore, blood vessels affected by amyloidosis do not constrict normally and tend to bleed after injury; diagnostic biopsy may be followed by hemorrhage for this reason. The gross appearance of involved tissue appears pale gray and waxy. Pathologic and clinical effects of amyloidosis are illustrated in Figures 1-15 and 1-16.

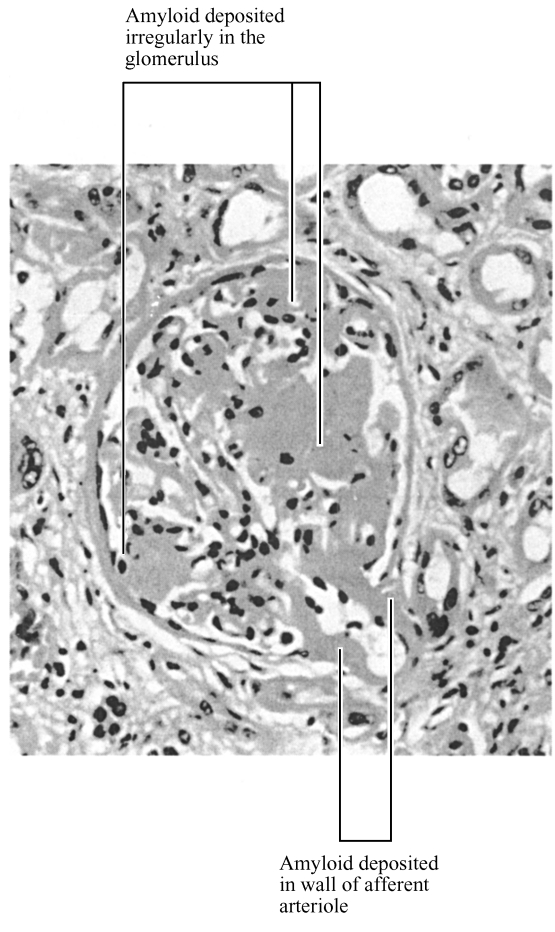

Figure 1-15 Amyloidosis involving a glomerulus. Amyloid appears as a homogeneous acellular material that stains pink with hematoxylin and eosin

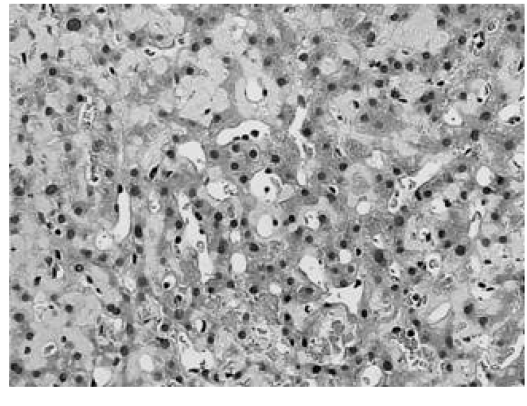

Figure 1-16 Amyloidosis of the liver. Amyloid is deposited in the space of Disse and compresses the liver cell plates

INTRACELLULAR ACCUMULATION F GLYCOGEN

Glycogen accumulation is encountered in patients having deranged carbohydrate or glycogen metabolism. Intracellular accumulation of glycogen usually occurs in **diabetes mellitus** or **glycogen storage disease**. In diabetes mellitus, increased glucose is reabsorbed by the renal tubular epithelial cells, especially affecting the terminal straight portion of the proximal convoluted tubules and the loop of Henle. Glycogen accumulates and causes clear vacuolation of the cytoplasm of the cell in these tubules on H. E section. On PAS stained sections, glycogen appears rose-red color. Glycogen accumulation in the diabetic is also encountered in hepotocytes, myocardium and β-cell of pancreatic islets. In the glycogen storage disease, there is a genetic lack of one or more of the enzymes involved in either the mobilization of glycogen or the synthesis of normal glycogen, and glycogen also accumulates intracellularly.

DEPOSITION OF PATHOLOGICAL IGMENTS

Pigments are the colored substances in tissues. Some pigments exist in normal tissues such as melanin in skin, but other's occur in abnormal conditions such as hemosiderin in lung. They are either exogenous, coming from outside the body (example as carbon), or endogenous, synthesized within body itself (example as lipofuscin, melanin and hemosiderin).

Coal Dust

Coal dust is the most common exogenous pigment; usually occurring in the coal miner and the urban dweller. When inhaled into alveoli and deposited, some black pigment can be seen in lung grossly. Then the dusts are phagocytosed by alveolar macrophages and transported through lymphatic channels to the tracheobronchial lymph nodes. Aggregates of the dust blacken the draining lymph nodes and pulmonary parenchyma. Heavy accumulations may induce emphysema or pulmonary sclerosis that can result in serious lung disease.

Melanin

Melanin, which is normally present in skin, hair follicles, iris, choroids and other sites, is synthesized in melanocytes by the tyrosinase-mediated oxidation of tyrosine to dihydroxyphenylalanine (DOPA). It is an endogenous dark brown granular cytoplasmic pigment. Melanin synthesis is under adrenal and pituitary control. Adrenal steroids suppress and pituitary adrenocorticotropic hormone (ACTH) stimulates its synthesis. Aggregates of these melanophores create freckles which darken after exposure to sunlight because of the actinic stimulation of melanin synthesis in melanocytes. The local aggregate of melanin can occur in melanotic nevus, melanoma and other diseases.

Lipofuscin

With light microscopy, lipofucin appears as yellow-brown, fine cytoplasmic granules which present in certain normal cells, such as the epithelial cells of the epididymis, the interstitial cells of the testis and the ganglion cells of the hippocampus. However, larger amounts of lipofucins are found in cells undergoing slow regressive changes, such as that which occurs in the atrophy accompanying advanced age and in chronic injury (Figure 1-17). Lipofucin granules represent residual bodies containing depolymerized indigestible residues of organellar membranes.

Figure 1-17 Myocardial fiber with lipofuscin pigment in the perinuclear region. On sections stained with hematoxylin and eosin, lipofuscin has a golden brown color (arrow)

Deposition of Iron (Hemosiderosis and Hemochromatosis)

A. Normal Iron Metabolism

Iron metabolism is normally regulated so that the total amount of iron in the body is maintained within a narrow range. The body has no effective mechanism for eliminating excess iron, although women lose 20 – 30 mg of iron each month in menstrual blood. Iron overload is therefore rare in premenopausal women, whereas iron deficiency is common.

B. Hemosiderosis and Hemochromatosis

An increase in the total amount of iron in the body is termed hemosiderosis or hemochromatosis. The excess iron accumulates in macrophages and parenchymal cells as ferritin and hemosiderin and may cause parenchymal cell necrosis (Figure 1-18).

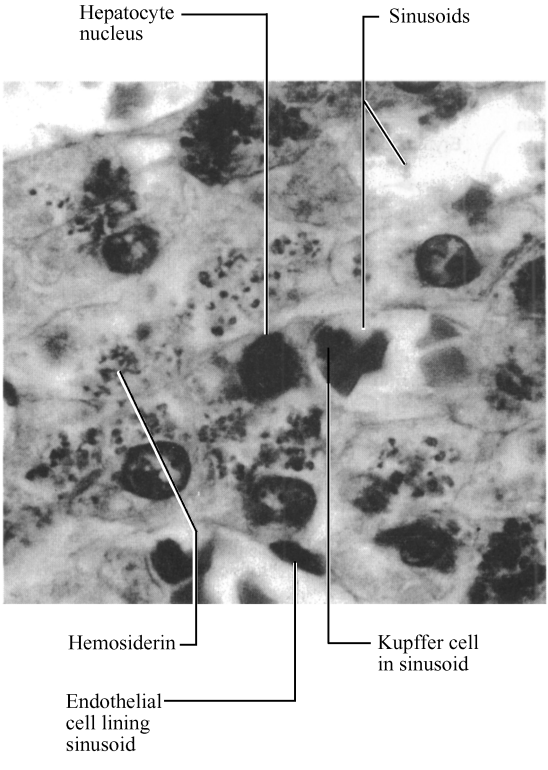

Figure 1-18 Hemochromatosis of the liver, showing hemosiderin pigment deposited in hepatocytes and Kupffer cells. Hemosiderin stains golden brown with hematoxylin and eosin and deep blue with Prussian blue stain

C. Causes and Effects of Deposition of Iron

Localized hemosiderosis is common, in any tissue that is the site of hemorrhage. Hemoglobin is broken down and its iron is deposited locally; either in macrophages or in the connective tissue, in the form of hemosiderin (as in a bruise). Localized hemosiderosis has no clinical significance.

Generalized hemosiderosis is less common, occurring with relatively minor iron excess following multiple transfusions, excessive dietary iron, or excess absorption of iron in some hemolytic anemias. The excess iron is deposited as hemosiderin in macrophages throughout the body, notably in bone marrow, liver, and spleen. Generalized hemosiderosis can be diagnosed in bone marrow and liver biopsies and, apart from indicating the presence of iron overload of minor degree, has no clinical significance.

Hemorrhage is the presence of blood in interstitial tissue outside the blood vessels. Hemorrhage results from escape of erythrocytes across intact vessels (diapedesis) or from vascular rupture.

Erythrocytes are rapidly broken down in interstitial tissue, and the iron in hemoglobin molecules is ingested by macrophages in the interstitium and converted to **hemosiderin**, which appears as a brown, granular pigment in the cytoplasm of macrophages. Hemosiderin may spill over from macrophages to be deposited in interstitial connective tissue (localized hemosiderosis). The porphyrin in the hemoglobin molecule is broken down by local macrophages to form bilirubin, which may be absorbed in the blood or deposited in interstitial connective tissue as a golden-yellow, crystalline pigment called **hematoidin**. Neither hemosiderin nor hematoidin deposited in interstitial tissues cause cellular dysfunction.

Deposition of Calcium (Calcification)

Deposition of calcium in the interstitium is common and takes one of two forms.

A. Metastatic Calcification

Metastatic calcification is due to an increase in serum calcium or phosphorus levels. Calcification occurs in previously normal tissues, most commonly the arterial walls, alveolar septa of the lung, and kidneys.