Thomas

Sandritter

Histopathology

Textbook and Color Atlas

Eighth Edition

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With 648 illustrations, 576 in color

1989
B.C. Decker Inc.
Toronto • Philadelphia

Publisher

B.C. Decker Inc
3228 South Service Road
Burlington, Ontario L7N 3H8

B.C Decker Inc
320 Walnut Street
Suite 400
Philadelphia, Pennsylvania 19106

Sales and Distribution

United States and Puerto Rico
The C.V. Mosby Company
11830 Westline Industrial Drive
Saint Louis, Missouri 63146

Canada
McAinsh & Co. Ltd.
2760 Old Leslie Street
Willowdale, Ontario M2K 2X5

Australia
McGraw-Hill Book Company Australia Pty. Ltd.
4 Barcoo Street
Roseville East 2069
New South Wales, Australia

Brazil
Editora McGraw-Hill do Brasil, Ltda.
rua Tabapua, 1.105, Itaim-Bibi
Sao Paulo, S.P. Brasil

Colombia
Interamericana/McGraw-Hill de Colombia, S.A.
Apartado Aereo 81078
Bogota, D.E. Colombia

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McGraw-Hill Book Company GmbH
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D-2000 Hamburg 63
West Germany

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MEDSI/McGraw-Hill
6, avenue Daniel Lesueur
75007 Paris, France

Hong Kong and China
McGraw-Hill Book Company
Suite 618, Ocean Centre
5 Canton Road
Tsimshatsui, Kowloon
Hong Kong

India
Tata McGraw-Hill Publishing Company, Ltd.
12/4 Asaf Ali Road, 3rd Floor
New Delhi 110002, India

Indonesia
P.O. Box 122/JAT
Jakarta, 1300 Indonesia

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McGraw-Hill Libri Italia, s.r.l.
Piazza Emilia, 5
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Italy

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06450 Mexico, D.F., Mexico

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McGraw-Hill Book Co. New Zealand Ltd.
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Manukau City, New Zealand

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McGraw-Hill/Interamericana, C.A.
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(entre avenida Casanova y Sabana Grande)
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Note: This is a faithful translation of the German text. The publisher has made every effort to ensure that the information contained herein is accurate. However, because there are differences in practice in Germany and elsewhere, the reader should consult a standard reference for local practice.

Authorized English edition of *Histopathologie*, 10 Auflage

Histopathology—8th English edition

ISBN 1-55664-204-0

Library of Congress catalog card number: 89-50852

10 9 8 7 6 5 4 3 2 1

Foreword

The study of disease encompasses general, special, and experimental pathology. A division into histopathology and macropathology is at best a compromise that is justified only by the emphasis placed on microscopic or macroscopic pathology in the various courses on general or special pathology. *Histopathology* and *Macropathology* complement each other and together constitute a single unit. In an atlas, the picture should be able to convey the information by itself and needs only a very brief supplementary text. It was never the goal of these two atlases to replace a conventional textbook, and hence they do not follow the traditional divisions of study. The atlases should not serve (primarily) to prepare students for examinations, but should serve (preferentially) the further education of students and young physicians. It is important to remember that in spite of the advances made in laboratory medicine and in diagnostic imaging (e.g., sonography, computed tomography) the pathologic diagnosis is still the most reliable (over 90 percent accurate) and cheapest method available. In the diagnosis of neoplasms it can be replaced by any other method. It is also important that the attending physician be familiar with the advantages, prognostic capabilities, and, last but not least, the limitations of this method. To do so, he or she must understand the "language" of pathology.

Pathology is by definition the focal discipline in medicine and thus carries a grave responsibility toward the students and young physicians who still have to rely on the experience of others. The rapid growth of scientific knowledge, with which they are confronted daily, places great demands not only on the student but also on the teacher, who must transmit this knowledge. In this context the old educational adage should be kept in mind: "Only that technical information should be taught that is likely to be valid five years hence!"

Since pathology encompasses all of medicine, its material is particularly broad and forces an author to make choices. The same is true during the revision of a textbook: emphasis must be placed carefully and only in selected areas. I have decided to emphasize the **infectious diseases** that have been largely neglected by both pathologists and clinicians. New diseases and the increased incidence of diseases that were considered curiosities, even a few years ago, confront us with difficult diagnostic problems. AIDS comes to mind immediately, as well as the numerous parasitic, mycotic, and viral diseases (*Pneumocystis* pneumonia, *Strongyloides* infestations, various systemic mycoses, and so on) that, in the context of congenital or acquired immune-deficient diseases, occur with increasing frequency. Tropical diseases once occurred only as isolated instances in Western countries, brought in by the long-distance tourist trade. With rapid increase in the numbers of foreigners seeking asylum in the Federal

Republic of Germany, however, these diseases have become routine diagnostic findings. I am grateful to Prof. Salfeld for the revision of this section.

The chapter on the **muscular diseases** was completely revised by Prof. Heene and Prof. Mennel. The introduction of enzyme histochemistry enabled us to define and classify these diseases. This technique can be used—with some reservations—in routine diagnostic work-ups. The same applies to the chapter on **neurologic diseases**. Prof. Mennel has completely revised the discussion of the degenerative central nervous system diseases. The last section that has to be mentioned particularly is the one on **pigment tumors**, discussed by Prof. Hagedorn with great attention to their classification and their prognostic criteria.

Textbooks like *Histopathology* and *Macropathology* can be created and, more important, kept current only by the joint efforts of a large group of collaborators. It is my very pleasant duty at this time to thank all the participants. This applies to my colleagues listed on the title page, to my co-workers in the Marburg Institute of Pathology, and to the Schattauer Publishing Company. Special thanks are due (to mention only a few) to Prof. Dr. Dr.h.c. Matis, Managing Director Bergemann, Mr. Haub (Grafische Kunstanstalt Brend'amour), and the artist, Mr. Tschorner.

C. Thomas
Marburg, September 1986

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Contents

A · Introduction — General Comments

In order to read a textbook profitably, certain practical knowledge and skills must be available. To use a microscope appropriately, a basic understanding of its construction and of the relationship of its various components is necessary. Evaluation of a histologic section is possible only if the evaluator is familiar with the methodology of preparing and staining such sections. In addition, a solid foundation in normal histology and general pathology is a requirement. The principles of general pathology are invariably applicable to the requirements of every instance of special pathology.

Technical Remarks

The Microscope and Its Use

A light source, a system of lenses, a diaphragm, and the eye must all be aligned properly for the optimal evaluation of the histologic section. The predominant yellowish-red light of the artificial light source must be brought closer to natural light by the use of a blue filter. The light is adjusted according to Kohler's principle: The field of the *light diaphragm* is projected through a condenser to the level of the slide and serves as the limiting factor in the size of the visual field. Reducing the size of the aperture will reduce the size of the visual field without affecting the intensity of the illumination. The *condenser diaphragm,* on the other hand, serves as an aperture diaphragm and reduces the numerical aperture (NA) of the condenser when its diameter is reduced (NA = $n \times$ sin alpha, where n is the refraction index of the medium before the objective lens, usually air, and sin alpha is the sine of half the aperture angle of the objective). Thus a reduction in the aperture darkens the image and enhances the contrast. In the absence of a phase-contrast microscope, unstained specimens are best examined with a maximally closed condenser diaphragm. When the image is "blurred," reducing the condenser diaphragm improves the contrast.

The microscopic image is generated in the posterior focal plane of the objective lens by the diffraction of the light by the structures of the histologic preparation (primary image). The secondary image that we see with the ocular lens is generated by the interference of the light in the primary image (Abbe's image generation theory).

The objective and ocular lenses must be properly coordinated. In a course in histology an ocular lens with a 10× magnification is usually used in combination with the following objective lenses:

1. Low magnification (general overview, hand lens magnification): objective lens 2.5/0.08,[1] magnification 25×
2. Median magnification: objective lens 10/0.25, magnification 100×
3. High magnification: objective lens 40/0.85, magnification 400×

For maximal magnification, particularly for the study of smears (lymph nodes, blood, and so on), oil-immersion lenses (100/1.25) with a magnification of 1,000× (ocular: 10×) or a magnification of 1,250× (ocular: 12.5×) are available.

[1] The first number after the word "objective" indicates the magnification; the second number indicates the numerical aperture of the objective.

Note: When a monocular microscope is used, both eyes should be kept open. This assures that the eyes will be adjusted for distance and that the fatigue of constant accommodation will be avoided.

The low magnification is preferred to all others since it makes possible optimal surveying of the tissues.

If the picture is not sharp, the slide may be upside-down.

Histologic Sections and Stains

The sections are prepared from tissue blocks measuring approximately 2×2 cm. The tissue is usually fixed in formol (commercial formalin, 40 percent, diluted with water 1 : 9 so that a 4 percent solution is obtained). Fixation produces a denaturation and coagulation of the tissue proteins. Fixation also inhibits autolysis, heterolysis, and bacterial decomposition. In order to produce sections 5 to 10 μm thick, the tissues must have the appropriate consistency. This can be accomplished by freezing with carbon dioxide snow and cutting with a frozen-section microtome at −20°C (this technique is used to demonstrate fat or for rapid, intraoperative, surgical diagnostic purposes); it can also be accomplished by dehydration using a series of alcohols, methylbenzoate, benzol, and paraffin with a melting point of 56°C. The liquid paraffin enters all tissue spaces at 60°C and renders the tissue suitable for sectioning. After cutting, the sections are floated onto a slide and stained. Prior to staining, the paraffin is removed with xylol.

Note: Frozen sections permit an inspection of the neutral fats. In paraffin sections the fats are removed by the alcohol, and the fat droplets in the tissues appear as optically empty spaces.

The staining of histologic sections is accomplished by methods that were developed empirically and whose physicochemical mechanism is known only in very few instances. In addition to other mechanisms, electrostatic bonds are the most important factors. Negatively charged groups, such as the nucleic acids (phosphate groups), or the proteins (—COOH-groups), or the mucopolysaccharides (—COOH, SO_4), combine with basic dyes that function as cations. Acid dyes (e.g., eosin) having electronegative charges are attached predominantly to the positively charged groups of the proteins (NH_2-groups). After staining, the excess and freely soluble dyes are removed by differentiation with water, alcohol, or weak acid solutions. Lastly, the water is removed with 70 percent and 96 percent alcohol, and the section is immersed in xylol, covered with Canada balsam, and sealed with a cover slip.

Histochemistry demonstrates chemically distinct substances in the tissues, such as nucleic acids, certain proteins, carbohydrates, enzymes, and so forth, both qualitatively and quantitatively.

Artifacts in the histologic sections are usually due to improper fixation, embedding (tears), or staining (e.g., lighter and darker spots).

Table 1 provides a review of the currently used dyes.

When a fluorescence microscope is used, even minute concentrations of fluorescent dyes can be identified, since the ultraviolet light used (e.g., 350 mμ) produces a secondary luminescence in the visible range. Lipids, porphyrins, and elastic fibers have their own fluorescence.

TABLE 1 Staining Techniques

Method	Result		Comments
Hematoxylin-Eosin (HE)	Blue Hematoxylin Basophilic cytoplasm, bacteria, nuclei, calcium	Red Eosin Cytoplasm, connective tissue fibers, and everything else	See p. 62
van Gieson (v.G.)	Yellow Picric acid Cytoplasm, muscles, amyloid, fibrin, fibrinoid	Red Fuchsin Connective tissue Hyalin	Black Iron hematoxylin, nuclei, e.g., p. 58
Elastica stain	Black Resorcin-fuchsin Elastic fibers	Red Nuclear-fast red Nuclei	See, p. 82
Elastica-van Gieson (E.v.G.)	In combination, as above		See p. 78
Azan	Azocarmine Nuclei, erythrocytes, fibrin, fibrinoid, acidophilic cytoplasm, epithelial hyalin	Aniline blue-orange G Collagen fibers, connective tissue hyalin, basophilic cytoplasm, mucus	See p. 80
Silver stain	Black Ammoniac. $AgNO_3$ Reticulum fibers, nerve fibers		Brown Collagen fibers
Fat stain	Red Sudan III, scarlet red Neutral fats	Blue Hematoxylin Nuclei, cytoplasm	See p. 78
Congo red	Red Congo red Amyloid	Blue Hematoxylin Nuclei	See p. 188
Weigert's fibrin stain	Blue Lugol's solution, crystal violet Fibrin, bacteria	Red Nuclear-fast red Nuclei	No specific fibrin stain See p. 110
Prussian blue reaction	Blue Potassium ferrocyanate Hemosiderin, Fe^{+++}	Red Nuclear-fast red Nuclei	See p. 98
Giemsa (May-Grunwald-Giemsa)	Blue Methyl violet Nuclei, bacteria, all basophilic substances	Red Azure-eosin Eosinophilic cytoplasm and granules, collagen fibers	Metachromatic: Mast cells, violet Melanin, green See p. 338
Ladewig	Blue–gray-blue Aniline blue Parenchyma-mesenchyma	Red-orange Acid fuchsin–gold-orange Muscles, fibrin	Black Iron hematoxylin Nuclei
Masson-Goldner	Red-orange Azofuchsin Parenchyma, fibrin	Green Light green Mesenchyma	Black Iron hematoxylin Nuclei See p. 190

Table continues

TABLE 1 Continued

Method	Result		Comments
Myelin stain (Spielmeyer's)	Blue-black Iron-alum hematoxylin Myelin, erythrocytes		See p. 314
Ziehl-Neelsen	Red Carbolfuchsin Acid-fast rods, *Mycobacterium tuberculosis, M. leprae*	Blue Iron-alum Nuclei	
Periodic acid-Schiff reaction (PAS)	Purple-red Schiff's reagent Adjacent hydroxyl-groups and amino-alcohols	Blue Hematoxylin Nuclei	Neutral and acid polysaccharides; see p. 140 Preferred for demonstration of fungi, parasites; See p. 322
Levaditi	Black $AgNO_3$-reduced Pyrogallic acid *Spirocheta pallida* *Listeria monocytogenes*		See p. 158
Thionine, Toluidine blue	Blue Basophilic cytoplasm	Blue Nuclei	Metachromatic with mucins and lipids
Papanicolaou's stain for smears	Blue-violet Hematoxylin Nuclei, bacteria	Orange-red Orange-G Cellular glycogen, keratin Blue-green/green/pink E.A. 36 dye mixture (pale green, Bismarck brown, eosin) Blue-green: cytoplasm, basophilic cells Pink: cytoplasm, acidophilic cells Green: mucus	

From Observation to Diagnosis

An outstanding physician, Franz Vollhard, once said "The gods placed diagnosis before therapy." This must be amplified by the statement that before a diagnosis can be made, careful observation and assessment of the findings must occur. As in every other science, analysis must precede synthesis. With analysis comes the distinction between the subjective and the objective. With careful observation comes comparison and differentiation, separation of the typical from the atypical, the general from the particular. The organization and color, size and form of the tissue components, and their spatial relationship to each other are the hallmarks of the structures under study. These observations cannot be made entirely without some assumptions.

Basic, theoretic understanding and a certain amount of experience are necessary. The ability to draw or to describe findings in a few well-chosen words is essential to acquiring a facility to interpret histologic findings accurately and competently. This ability will enable the observer to emphasize the essential elements and de-emphasize the inessential ones. Sketching is therefore mandatory in many courses on histology.

Synthesis, i.e., diagnosis, can come only as a second step, following the stage of observation and after the introduction of certain conceptual considerations. Rapid, careless study can easily lead to erroneous results. *Diagnosis* implies the orderly consideration of the findings and their arrangement into a working conceptual system that must also include a working hypothesis and that must be based on experience and general agreement. It is the nature of a diagnosis that it is final and can change only with new scientific developments. Therefore a careful description evidently maintains its validity indefinitely, while the interpretation of the findings and the diagnosis may change with time.

From a practical point of view the evaluation of a histologic section should follow a regular sequence. First the section is inspected with the *naked eye.* The shape and distribution of the structures—recognized by the differences in staining—allow definite conclusions about the topography of the tissues and affect the subsequent analysis to a very considerable degree. The ocular lens, removed from the scope and reversed, can be used as a magnifying glass and can give a general impression of the slide. This step is followed by an examination under *low magnification* and an identification of the structures previously seen or suspected. A sketch is prepared of the essential structural elements. An inspection under *median magnification* allows the recognition of more detail, e.g., the size and position of nuclei and the connective tissues. The most time is spent at this magnification, since a tenfold enlargement permits identification of all essential structures, without obscuring the overall structural relationships of the individual components. Typically, a sketch is prepared at this time. Practically all histologic elements can be identified under median magnification. *High magnification* is useful only to look at details, e.g., the form and distribution of nuclear chromatin, mitotic forms, etc. Such a systematic, orderly progression of study is absolutely essential for careful assessment and correct diagnosis.

The didactic value of histology lies in the development of the ability to make a careful assessment of a finding that does not change. A histologic preparation is an ideal means to learn to distinguish between the essential and the nonessential in a mass of observations. This ability is an absolute requirement of every physician caring for sick patients.

Comments on the Schematic Illustrations

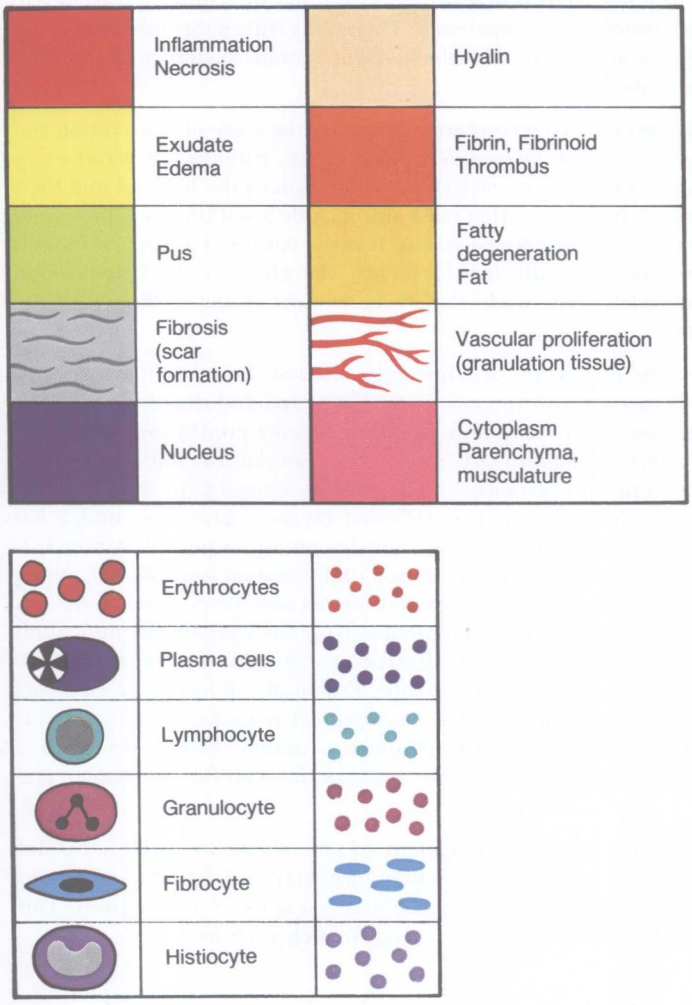

Figure 1 Explanation of the colors and symbols used in the schematic drawings throughout the book.

The schematic illustrations and general views in this textbook are arranged so that the various pathogenic processes are represented uniformly with the same symbols and the same color (Fig. 1). This makes the material more impressive and also emphasizes the recurrent, consistently identical events in general pathology. The individual elements in each schematic image have an appropriate symbol, and these are based wherever possible on the impressions gained in gross pathology and microscopy (e.g., pus is greenish-yellow; collagen fibers are shown as curly lines).

Comments on General Pathology

These brief, almost telegraphic remarks on general pathology should make the illustrations in the sections on special pathology more readily understandable. Reference to the corresponding illustrations should facilitate the use of this textbook according to the principles of general pathology.

General pathology provides the basis for understanding the fundamentals of the disease processes. This knowledge and these principles can be applied to all special problems, since the organism can respond to the wide variety of pathologic stimuli with only a limited number of response patterns. These are transient or permanent increases (anabolism) or decreases (catabolism) of metabolism or general dysfunctions. More complex tissue responses are represented by circulatory disturbances, various forms of inflammation, and neoplasms.

Pathologic stimuli can reach the cells and tissues in a variety of ways (Fig 2): (1) directly (trauma, radiation); (2) via the circulation [e.g., toxins, changes in the circulating fluids, (thrombi)]; (3) indirectly, by attacking the vessel walls; a secondary circulatory disturbance triggers cellular damage, e.g., neural damage or disturbances of permeability); or (4) they can originate in the lumen of the vessels. Finally, it is also possible that primary (i.e., congenital) metabolic abnormalities trigger cellular disturbances by a secondary mechanism. Figure 3 illustrates schematically the various reactions with which an organism can respond to pathologic stimuli.

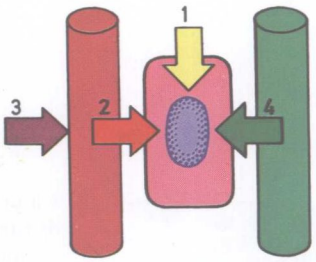

Figure 2 See text.

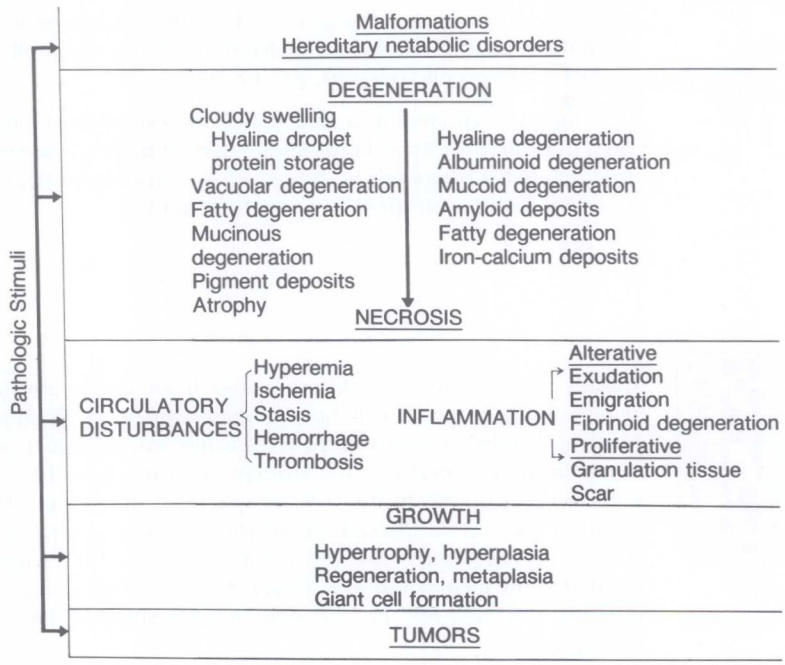

Figure 3 Schematic overview of the possible tissue reactions to pathologic stimuli.

Malformations: Inborn Errors of Metabolism

During the embryonal period (first 3 months of gestation) or the fetal period (after the third month of gestation) congenital abnormalities in the genetic material or pathologic stimuli can produce *malformations* or *errors of metabolism.* These can manifest as agenesis (absence of an enzyme, e.g., galactosemia; absence of an organ primordium), or aplasia or hypoplasia (incomplete development of an existing primordium). There are a large number of such manifestations.

Degeneration

The various forms of *degeneration* are manifestations of metabolic disturbances that can affect the morphology of the cells (Fig. 3, left column) or of the intercellular substance (connective or supportive tissues; Fig. 3, right column).

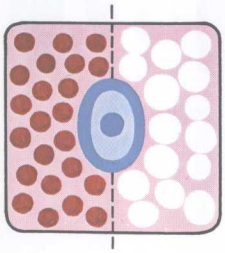

Figure 4 Cloudy swelling *(left);* vacuolar degeneration *(right).*

Cloudy swelling and vacuolar degeneration (Fig. 4) are the results of a disturbance in the metabolic system that maintains the ionic milieu ("ionic pump"). If these regulatory mechanisms fail, sodium and water enter the cell and potassium is lost. The mitochondria swell and the cytoplasm appears to be filled with fine "protein granules" *(cloudy swelling).* This turbidity is the result of an increased dispersion of light (the Tyndall effect). The mitochondria can be transformed into water-containing blisters (*vacuolar degeneration* of mitochondria). Water can also accumulate in the enlarged vesicles of the endoplasmic reticulum or in the ground plasma *(vacuolar degeneration).* (See light micrographs, p. 184; electron micrographs, pp. 17, 67.)

The nucleus can swell in a similar fashion *(degenerative nuclear swelling).* This process must be differentiated from the *functional nuclear swelling* that is frequently accompanied by nucleolar enlargement and is a manifestation of increased metabolic activity.

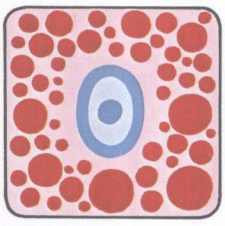

Figure 5 Hyaline droplet protein storage.

Cloudy swelling must be differentiated from *hyaline droplet protein storage* (Fig. 5), which can have a similar microscopic appearance. Hyaline droplet protein storage is an active work product of the cell (anabolism) and results in the storage of proteins in the cytoplasm, e.g., in reabsorption in the tubular system of the kidney. This reabsorption takes place through pinocytosis and through the sequestration of tiny vesicles from the cell membrane (see p. 17). Phagocytosis is defined as the incorporation of larger, formed particles, e.g., bacteria, into the cell (see pp. 11, 20; light micrographs, p. 184; electron micrographs, p. 192).

Fatty degeneration (more accurately, fatty metamorphosis)—the appearance of microscopic fat droplets—can be in the form of fine (Fig. 6, right) or large globules (Fig. 6, left). The size of the droplet depends on the neutral fat-to-phospholipid ratio (large globules indicate less phospholipid). The absorpton of fat takes place via pinocytosis in the form of fatty acids. These are synthesized into triglycerides, attached to phospholipids or proteins, and released into the blood stream. Any disparity between the amount of triglyceride (e.g., increased dietary intake) and protein (e.g., hunger) and phospholipids (e.g., lack of choline) or lack of energy (hypoxia, enzyme depletion) leads to fatty infiltration (obesity). (See light micrographs, p. 58: electron micrographs, p. 177.)

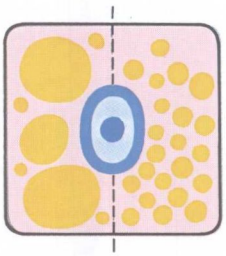

Figure 6 Fatty degeneration: large droplets *(left)*, small droplets *(right)*.

Fat phanerosis occurs in cases of necrobiosis (morphologically evident death of cells), at which time the fat originally attached to tissues coalesces into microscopically visible droplets.

Disturbances in carbohydrate metabolism may appear as glycogen storage (e.g., in the kidney in diabetes) or as mucoid degeneration (mucopolysaccharide production in the absence of secretion), e.g., in mucinous carcinomas (signet-ring cells, Fig. 7; see also page 141). *Mucoid dyscrinism* results in an obstruction of the excretory channels (e.g., cystic fibrosis of the pancreas). See page 150. The *glycogen storage diseases* represent an inborn error of carbohydrate metabolism.

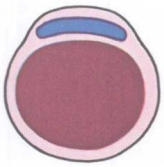

Figure 7 Signet-ring cells.

Pigments are substances that have their own color and are deposited in the cells in a diffuse or granular form. Their primary components are either building blocks of protein (melanin), lipids (lipopigments, e.g., lipofuscin) or hemoglobin derivatives (hemosiderin, siderin, hematoidin, bile pigments). There are also a large number of exogenous pigments. See the following examples:

Lipofuscin, pp. 10, 56
Melanin, p. 249
Hemosiderin and siderin, pp. 98, 170
Bile pigments, p. 152
Malaria melanin, p. 152
Hematoidin, pp. 10, 276
Exogenous pigments, pp. 10, 276

Table 2 presents the distinguishing characteristics of the various pigments.

Cellular *atrophy* (Fig. 8) can be due to inactivity or to chronic malnutrition and may appear as a decrease in cell size (simple atrophy) or, eventually, as a decrease in the number of cells (numerical atrophy). *Hypertrophy* indicates an increase in cell size usually resulting from hyperactivity.

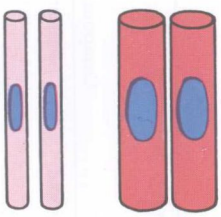

Figure 8 Atrophy; hypertrophy.

TABLE 2 Pigments

Type	Components	Location	Iron Reaction	Fat Stain	H_2O_2	Acid	Base	PAS[1]	$AgNo_3$[2]	Fluorescence[3]	Gmelin test
Lipofuscin (p. 56)	Unsaturated oxidized fatty acids	Parenchymal cells	−	(+)	(+)	−	−	+	+[4]	+	−
Ceroid	Unsaturated oxidized fatty acids	Intracellular (mesenchymal)	−	+	−	−	−	+	±	+	−
Melanin (p. 249)	Tyrosine derivatives	Intracellular	−	−	+	−	(+)	−	+[5]	−	−
Siderin	Iron	Intracellular	+	−	−	+	−	+	+	−	−
Hemosiderin (pp. 98, 170)	Glycoprotein	Intracellular	−	−	−	+	+	−	−		+
Hematoidin (p. 276)	Bilirubin	Extracellular	−	−	−	+	+	−			+
Bile pigments (p. 152)	Bilirubin Biliverdin	Intra- and extracellular	−	−	−	+	+	−			+
Malaria melanin	Hemoglobin derivatives	Intracellular	(+)	−	+	+	+		−		
Formalin pigment (p. 276)	Protoporphyrin	Extracellular	−	−	−		+	−		−	
Exogenous pigments (p. 276)	Carbon, silver, etc.	Intra- and extracellular	−	−	−			−			−

[1] PAS reaction to demonstrate polysaccharides (α-glycols).
[2] Reduction of silver.
[3] Primary fluorescence without staining.
[4] Brown.
[5] Black.