Color Atlas and Textbook of HISTOPATHOLOGY

WALTER SANDRITTER CARLOS THOMAS

Sixth Edition

Color Atlas & Textbook of Histopathology

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COLOR ATLAS & TEXTBOOK OF HISTOPATHOLOGY

SIXTH ENGLISH EDITION

with 11 Tables and 597 illustrations, including 464
color photomicrographs
and 65 electron photomicrographs

What is hardest of all to do?
What seems to you most easy:
To see clearly with your own eyes,
What your eyes lay before you.

GOETHE

To the memory of

LUDWIG ASCHOFF

October 1, 1866–June 24, 1942

Director of the Pathological Institute of the University of Freiburg

1906–1936

ARNOLD LAUCHE

September 14, 1890–September 29, 1959

Director of the Pathological Institute of the University of Frankfort on the Main

1943–1959

GEORG HERZOG

November 4, 1884–April 2, 1962

Director of the Pathological Institute of the University of Giessen

1926–1954

"In learning we develop the requisite process of thinking, and this training is not lost as long as we are possessed of our full mental vigor."

THEODOR BILLROTH

Preface to the English Edition

Thirteen years have passed since Professors Walter Sandritter and Julius J. Schorn, of the Justus-Liebig University, published their little book "Histopathologie." Ten years later the first English edition, with the new name "Color Atlas and Textbook of Tissue and Cellular Pathology," was published. Today, there are seven editions in German, six in English, two in Spanish, four in Japanese, one in Italian and one in French—an uncommon record to establish in only a baker's dozen of years. Professor Schorn, who was responsible for the beautiful photomicrographs in the first edition, died in an automobile accident before the book came out, and, until this edition, Professor Sandritter has been the primary author.

The original idea for the book was to consider pathology from the point of view of the microscopic signs of disease and to arrange these findings in an atlas. This was a reasonable approach, since much new and useful knowledge in both experimental and diagnostic pathology has come to us by way of the light and electron microscopes. Naturally, this approach has limitations, but the authors discovered ways to avoid some of the difficulties by adding short accounts of general pathology and gross pathology, along with some of the experimental and clinical aspects of disease. Subsequently, Professor Sandritter and Dr. C. Thomas wrote "Makropathologie," in which they gave a fuller account of gross pathology. Professor W. H. Kirsten, of the University of Chicago, translated the work into English under the title "Macropathology." This was followed by the publication of Sandritter and G. Beneke's "Allgemeine Pathologie," which in short order became a highly respected account of general pathology that has yet to be translated into English.

From the start, the beautiful color photomicrographs and the clear diagrams of the pathogenesis of a great number of the disease processes have been the chief attractions of all these books, particularly "The Color Atlas and Textbook of Tissue and Cellular Pathology," and they have accounted largely for the general appeal of the books. The care with which representative lesions have been selected, the expertness with which they have been photographed, and the beauty of the reproductions all contributed to the books' success. These works are clearly important additions to the writings in pathology.

New material has been added to each new edition of "Histopathology." For example, discoveries made with the electron microscope and chapters on the skin, blood and bone marrow, and fungi and parasites were added to the second edition; in the fifth edition, chapters on the kidney, specifically the account of glomerulonephritis, and on lymph nodes, the alimentary system and bones and joints were completely revised to reflect new knowledge about these diseases.

This new sixth edition (German seventh) has been the most thoroughly revised of all. In fact, it may be said that it is a new book, a fact that became clear to me as I made the translation again and discovered the extent of the changes and the amount of work needed to make them. There are now 372 pages and 597 illustrations, in comparison to 308 pages and 497 pictures in the previous edition. Much of the text has been rewritten. There are new accounts of the tumors, lymph nodes, blood and bone marrow, new sections on lesions of the breast, skin, gallbladder, oral cavity and genitalia, and an expansion of the discussion of cytodiagnosis. The tables and diagrams have been redesigned in color.

The result of all these additions and changes is a book that gives the student a clear and wide-ranging account of the facts of microscopic pathologic anatomy. So once again, as Ben Jonson put it, "Come forth thou bonny, bouncing book" and may your readers reward you with their approval.

William B. Wartman

Charlottesville and Christmas Cove
Summer 1977–78

Preface to the Seventh German Edition

One of the major purposes of a textbook of pathology is to utilize the accumulated empirical and experimental knowledge of this specialty to introduce the student to the field of clinical medicine. Of the many ways of doing this, there are clear advantages to one based on a visual or optical approach such as histopathology, or the microscopic pictures of diseased tissues. The "typical" histological structure thus becomes a continuing guide for the student during his clinical years and gives him a solid base on which to build his increasing knowledge of the complexities of disease. From this point of view, a textbook of pathological histology complements works of clinical medicine and general pathology and should be used along with them. Needless to say, no book can replace the study of actual histopathological preparations.

In order to achieve the purposes of this book, the material has been organized around the principles of special or systemic pathology; this should facilitate the correlation with clinical cases and enlarge the student's knowledge of general pathology. The comments on general pathology in the Introduction and the corresponding illustrations provide a useful review of the subject. This section was included for the special benefit of the beginner in order to guide him in understanding the photomicrographs in the latter part of the book. Similarly, the brief technical comments will help the student to use the microscope and to become familiar with the methods of preparation and staining of histopathological material.

The book is intended chiefly for medical students and young residents and assistants in pathology. However, as every experienced pathologist will recognize, there is such an abundance of material that careful selection is necessary to best serve these readers. We have taken pains to give special weight to representative and important lesions—a difficult task in view of the great number of disease illustrations. Diagrams have been inserted in an attempt to clarify and explain the course of the pathological events in didactic fashion.

The illustrations in this book are the central point of departure. The explanations supplied for them have been kept as concise as possible and placed on facing pages so that illustrations and text can be readily compared. Although the arrangement of the book in the form of an atlas has imposed certain limitations, we feel that the gains far outweigh the few losses that result from shortening the text. As far as possible the text has been arranged so that a general principle or short definition is given first, followed by an explanation that applies to the accompanying illustration and also describes possible variations. Short notes on the macroscopic appearance and often on the pathogenesis have been inserted where they seem important for an understanding of the microscopic findings. A short list of references to the literature, including both original and review papers and arranged according to subject, should make possible more intensive study of areas of special interest to the reader.

The above comments were written in 1964, for the preface to the first edition of this book. Since that time there have been widespread changes in the curricula of medical schools that seemingly have altered our teaching. But actually the course content has remained much the same; it has merely been served up in a different form. Knowledge of the fine tissue changes that occur in disease is still an essential part of medical learning, and the ability to "see with his eyes" is still one of the most important skills for a physician to acquire.

In the preparation of the seventh edition of this book, we have carefully taken into account many of the recent advances in medical knowledge. Fully 30% of the book is entirely new and the rest has been extensively revised and rewritten. There are new chapters on the pathology of the breast, skin, gallbladder, oral cavity and genitalia. The chapters on blood, bone marrow, spleen and lymph nodes, as well as the one on parasites, are now in accord with the newer classifications. In the chapter on tumors

special attention is given to precancerous lesions, with discussions of others such as fibromatosis and pseudosarcoma. The tumors of the different organs are now discussed under the appropriate organ systems. The tumor nomenclature of the World Health Organization (WHO) is used throughout the book.

Today it is quite clear that cytodiagnosis has taken a position of ever increasing importance in the diagnostic armamentarium of physicians. Because almost every organ can be sampled by needle biopsy and such samples examined both histologically and cytologically, the usefulness of cytodiagnosis has been greatly extended. It is of great diagnostic value not only in gynecology (investigation of the menstrual cycle, early detection of cancer) but also in other areas such as the prostate, breast, thyroid, liver and kidney. As a result of all these advances, every physician must have a basic understanding of the principles, the proper use, and the limitations of the method.

It is important for both medical students and young physicians to keep in mind constantly that, despite all the recent advances in laboratory diagnosis, histopathology has better than 90% reliability and that many diseases can be diagnosed only by biopsy. For example, there is no comparably reliable chemical test for cancer. For this reason it is important for physicians to have a sound knowledge of the histopathological changes that occur in diseased tissues, as well as an understanding of the language of the pathologist. Painstaking pathological work will be of little value if the physician attending the patient does not correctly interpret the pathologist's opinion.

The diagrams have been completely redesigned for this edition, a task for which we are specially indebted to Dr. U. Riede. He has also supplied the various codes used in the diagrams (e.g., red = inflammation). Mr. Tschörner, the artist for the publisher, has expertly redrawn the original rough sketches. Our thanks also go to numerous colleagues who have so freely given us light and electron microscope photographs. As always, the publisher has been a helpful partner. In particular we thank Professor Matis and Director Reeg.

W. Sandritter, C. Thomas

Freiburg i. Br.
Summer, 1977

Contents

Introduction – General Pathology

A certain amount of practical knowledge and skill, particularly with respect to use of the light microscope, is desirable on the part of the reader if he is to get the most good from reading a textbook of histopathology. Profitable use of the microscope requires knowledge of its construction and of the interrelations of its individual parts. Furthermore, it is only possible to interpret a histological slide after one is informed as to how the tissue has been prepared for cutting and how it has been stained. A solid foundation in normal Histology and General Pathology goes without saying, for the principles of General Pathology are used constantly in Special Pathology.

Preliminary Technical Remarks

Use of Microscope

The light source, the lens system with its diaphragms and the eye must all be correctly aligned with one another in order to obtain optimal information from a histological section. Artificial light, which consists predominantly of yellowish red light rays, can be corrected by a blue filter so that it will approximate daylight. Köhler's principle is commonly used to adjust the light source, since by using this principle it is possible to illuminate only the object area that is to be examined and that entirely uniformly. With a microscope with a built-in light source, swing in the front lens of the condenser. Focus the microscope on the specimen and stop down the *field diaphragm*. Rack up the condenser as far as possible and then lower it slowly, thus focusing the field diaphragm within the specimen area.

Center the condenser with the two centering screws if necessary (the condensers of many student microscopes are permanently centered so that this step may be omitted). Open the field diaphragm until its shadow disappears from the field of view. The field diaphragm should always be adjusted so that its image just disappears behind the edge of the eyepiece stop. Adjust image contrast and, if necessary, sharpness – but not image brightness – with the *condenser (aperture) diaphragm* by opening it entirely and then closing it down just far enough to remove glare from the specimen. Unstained objects can be seen best when the condenser diaphragm is closed as far as possible or with a phase contrast microscope. With blurred images, reducing the condenser diaphragm will increase the contrast.

The microscopic image is produced by diffraction of the light by the structures in the histological preparation in the focal plane at the back of the objective (primary image). The secondary image, which is the one observed in the ocular, arises from magnification of the primary image.

Objective and ocular must be properly matched. In usual histological practice, an ocular with a 10× magnification is used with the following objectives, in which the first number gives the magnification and the second the numerical aperture of the objective, which is a measure of its resolving power:

1. *Scanning lens:* objective 2.5 to 5.0 – magnification 25 – 50×.
2. *Low magnification:* objective 10/0.25 – magnification 100×.
3. *High dry magnification:* objective 40/0.65 – magnification 400×.

For still higher magnification, especially for examination of smears of cells (blood, lymph node), oil immersion objectives (100/1.25) are available with a magnification up to 1,000×.

When using the microscope, the following suggestions will prove helpful. With a monocular microscope, always keep both eyes open, since the adjustment for distance obtained in this way prevents rapid eye fatigue due to constant accommodation.

The lowest magnification should always be used before going to the other objectives because it is easier to orient the various structures under low magnification.

If the image is blurred, you should think of the possibility of the slide being upside down with the cover-slip resting on the stage of the microscope.

Preparation and Staining of Histological Sections

Sections are prepared from blocks of tissue measuring about 2 × 2 cm. The selected tissue is usually hardened and fixed in formol (ordinary 40% commercial formalin diluted with water 1:9 so that the resulting solution is about 4%). The *hardening* results from coagulation and denaturation of protein, while the *fixation* arrests autolysis and bacterial decomposition. In order to prepare sections 5–10 micra thick, the tissue must have a consistency suitable for cutting. To obtain this, the tissue may either be frozen (at −20°C.) with carbon dioxide snow and cut on the frozen-section microtome (this method is used particularly for demonstrating fat or for rapid diagnosis of biopsy specimens at the time of surgery) or the tissue can be processed through a series of alcohols (from 70 to 100%), methyl-benzoate, and benzol into paraffin with a melting point of 56° C. Liquid paraffin at 60° C. penetrates the finest tissue spaces and produces a good cutting consistency. After cutting on a microtome, the sections are mounted on microscopic slides and stained, after first being deparaffinized with xylol.

Note: Frozen sections permit demonstration of neutral fat–in paraffin sections, the fat is dissolved by alcohol and the droplets of fat appear as optically empty spaces in the tissue.

The methods used for *histological staining* have been developed empirically and the physical-chemical basis for them is not exactly known except in a few cases. Electrostatic binding, among other factors, plays a principal role. Negatively charged groups, for example, nucleic acids (phosphate groups) or proteins (−COOH groups) or the mucopolysaccharides (−COOH.SO_4), bind with the basic dye groups, which behave as cations. Acid dyes (e.g., eosin) with electron negative charges bind predominantly with positively charged protein groups (NH_2-groups). Excess and easily soluble dye in the tissue is removed after staining by differentiation in water, alcohol or weak acid. Finally, the water is removed with 70 and 96% alcohol, the section immersed in a clearing agent (xylol), mounted in Permount or Canada balsam and covered with a cover-slip.

For further details on histological techniques, see Davenport, Lilly, Humason, etc.

Histochemistry deals with specific and sometimes quantitative identification of chemical substances in tissues, such as nucleic acids, certain proteins, carbohydrates, enzymes, etc. (see Pearse, 1960).

Artifacts in histological sections are caused chiefly by improper fixation, embedding (cracks or tears) or staining (transparent, unstained flaws).

Table 1 reviews the features of some commonly used stains. *Fluorescence microscopy*, in which tissues are stained with fluorescing dyes and examined under ultraviolet light, allows detection of certain substances, e.g., immunologically active proteins, because the ultraviolet light rays (e.g., 350 Mμ) liberate secondary rays in the visible range (compare p. 220). Some substances show self fluorescence, e.g., lipids, porphyrins and elastic fibers.

Table 1. **Staining Methods**

Method	Results		Remarks
Hematoxylin-eosin (H & E)	**Blue** *Hematoxylin* Basophilic cytoplasm, nuclei, bacteria, calcium	**Red** *Eosin* Cytoplasm, connective & all other tissues	p. 40
van Gieson (v. G.)	**Yellow** *Picric Acid* Cytoplasm, muscle, amyloid, fibrin, fibrinoid	**Red** *Fuchsin* Connective tissue, hyalin	**Black** *Iron Hematoxylin* Nuclei p. 52
Elastic stain	**Black** *Resorcin-fuchsin* Elastic fibers	**Red** *Nuclear fast red* Nuclei	p. 70
Elastic-van Gieson (E.v.G.)	used in combination		p. 62
Azan	**Red** *Azocarmine* Nuclei, erythrocytes, fibrin, fibrinoid, acidophilic cytoplasm, epithelial hyalin	**Blue** *Aniline blue, Orange G* Collagen fibers, basophilic cytoplasm mucus	p. 160
Silver stain	**Black** *Ammoniacal $AgNO_3$* Reticulum fibers, nerve fibers		Collagen fibers brown
Fat stain	**Red** *Sudan III, Scarlet Red* Neutral fat	**Blue** *Hematoxylin* Nuclei, cytoplasm	p. 38
Congo red	**Red** *Congo red* Amyloid	**Blue** *Hematoxylin* Nuclei	p. 164
Weigert's fibrin stain	**Blue** *Lugol's solution, Crystalviolet* Fibrin, bacteria	**Red** *Nuclear fast red* Nuclei	Not specific for fibrin p. 100
Berlin-blue reaction	**Blue** *Calcium ferrocyanide* Hemosiderin, Fe^{III}	**Red** *Nuclear fast red* Nuclei	p. 82
Giemsa (May-Grünwald-Giemsa)	**Blue** *Methyl violet* Nuclei, all basophilic substances	**Red** *Azur-eosin* Eosinophils, cytoplasm & its granules, collagen fibers	Metachromatic: Mast cells violet Melanin green p. 238
Ladewig	**Blue-greyblue** *Aniline blue* Parenchyma Mesenchyma	**Orange red** *Acid fuchsin-gold-orange* Muscle Fibrin	**Black** *Iron hematoxylin* Nuclei p. 248
Mason-Goldner	**Orange red** *Azofuchsin* Parenchyma Fibrin	**Green** *Light Green* Mesenchyma	**Black** *Iron hematoxylin* Nuclei p. 166

Table 1. **Staining Methods** (con'd)[1]

Method	Results		Remarks
Spielmeyer's myelin stain	**Blue-black** *Iron-alum hematoxylin* Myelin, erythrocytes		p. 280
Ziehl-Neelsen	**Red** *Carbofuchsin* Acid-fast rods, Tb bacilli, lepra bacilli	**Blue** *Hemalum* Nuclei	
Periodic Acid-Schiff Reaction (PAS)	**Red** *Schiff reagent* Adjacent hydroxyl groups and amino-alcohols		Neutral and acid polysaccharides p. 180 Demonstration of Fungi, parasites
Levaditi	**Black** *$AgNO_3$-reduced* *Pyrogallic acid* Spirocheta pallida Listerella mono-cytogenes		p. 318
Thionine, Toluidine Blue	**Blue** Basophilic cytoplasm	**Blue** Nuclei	Mucus, mucin, lipids are metachromatic p. 270

[1]See pp. 12 and 317, for other special stains.

Histological Interpretation and Diagnosis

A famous physician (FRANZ VOLHARD) once said: *"The Gods have put diagnosis before therapy—man must put careful observation and interpretation before diagnosis." Analysis must precede synthesis* as it does in all other branches of knowledge. Analysis begins with the examination of the subject with a clear-cut objective in mind. *Careful observation* of similarities and dissimilarities, the separation of the typical and the atypical, the general from the special, all contribute to the desired knowledge of the subject. The arrangement, color, size and form of the tissue elements and their relations to one another all help to determine the essential characteristics of the various structures under consideration. As such observations cannot be obtained without adequate preparation, a thorough theoretical grounding and a certain amount of experience become essential.

The beginning student will find it helpful in getting exact histological details either to make drawings or to set down his observations in abbreviated, outline form. The student is thus forced to emphasize the essential features and to de-emphasize unessential ones.

After first carefully making the necessary observations, it is then possible to take the second step, that is, to synthesize the observations and make a diagnosis. On the other hand, hasty, careless examination will often lead to an incorrect opinion. In order to arrive at a *diagnosis,* the histological observations need to be classified in some logical manner, usually one which has been reached through a compromise of experience and hypothesis. But, by its very nature, no diagnosis can be considered final, since it can change with the progress of scientific knowledge. Thus, it is understandable that an exact description retains its validity indefinitely, even when the interpretation and diagnosis of a section have already been revised.

The student will therefore be well advised to put his chief effort into a careful description of a microscopic section. In examinations, this is always graded higher than a diagnosis unsupported by accurate description.

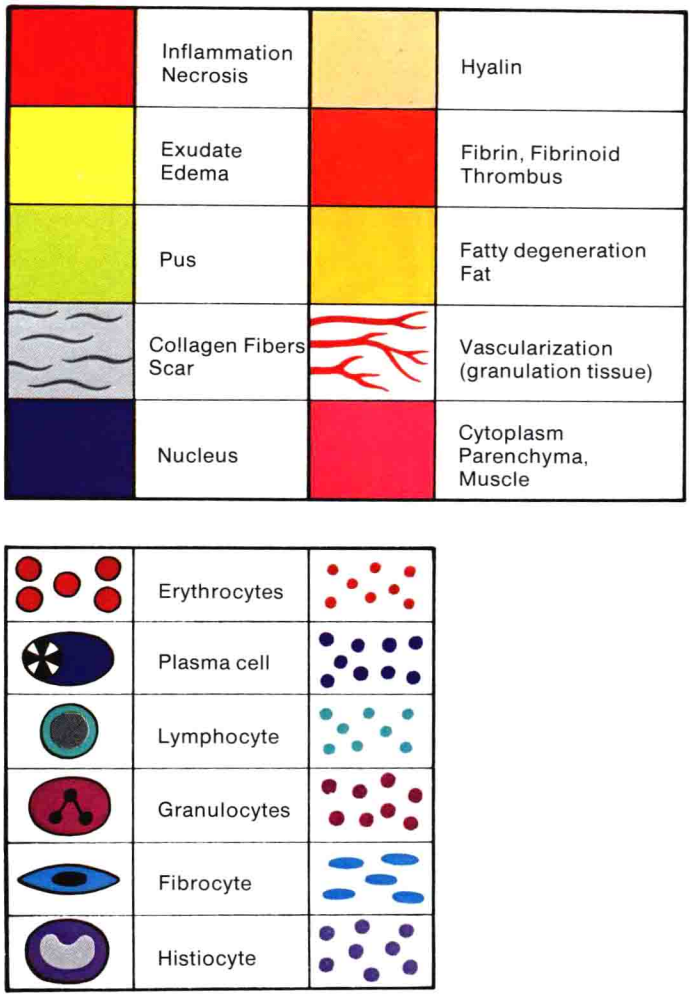

Fig. 1. Explanation of the colors and symbols used to depict lesion components and pathological processes.

In practice, the first step in examining a histological preparation is to look at the section with the *unaided eye*. The shape and the various components of the tissue structures–easily recognized by differences in staining–often provide essential topographical information and have an important influence on the next step in the analysis of the section. An inverted ocular used as a scanning lens will provide an over-all view of the tissue at very low magnification. Ordinary *low-power magnification* can then be used to examine in greater detail the structures already seen with the inverted ocular. In this way, a rough over-all picture of the essential elements of the lesion is formed. Further details can also be distinguished with *low magnification*, such as the size and position of the nuclei and the structure of the cytoplasm. This magnification is probably the most useful of all, for at a magnification of about one hundred-fold, all the essential structures are well seen without losing the over-all architectural relationships. A drawing at this stage of the examination will fix the typical findings firmly in mind. Practically all histological preparations can be diagnosed with low magnification. *Higher magnification* is used only to clarify individual details, such as the shape and division of nuclear chromatin, mitoses, and so forth.

Such a methodical approach is an essential prerequisite for profitable observation and correct diagnosis. In studying histopathological slides the student gets the knowledge required to separate essential from nonessential observations–knowledge that a physician uses at the bedside.

Notes on General Pathology[1]

These brief, almost stenographic, introductory remarks about general pathology are intended only as a means of making it easier to understand the complexities of special pathology. Reference to the appropriate illustrations of the book permits its use as a guide to the principles of general pathology.

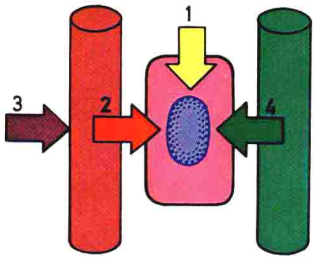

Fig. 2. See text for explanation.

In the schematic diagrams and tables the same symbols and colors are used for similar pathological processes throughout the book (Fig. 1). The individual components of a lesion or process are indicated by colors or symbols based, unless otherwise noted, on the gross (e.g. pus-greenish yellow) or microscopic appearance (e.g., collagen fibers-curly lines).

A knowledge of general pathology is an excellent foundation for the study of disease. The knowledge so obtained can be applied in nearly all special situations, since *the host in reacting to the many different pathological stimuli that may affect it has only a limited number of possible responses available.* These originate essentially from either transient or permanent increase *(anabolism)* or decrease of metabolism *(catabolism)* or from *work failure.* In addition, complex tissue responses occur in *circulatory disturbances*, the various forms of *inflammation* and in *tumors.*

In theory, pathological stimuli can reach the cells and tissues in various ways (Fig. 2):

1) *directly* (e.g., trauma, radiant energy). 2) by way of the *blood stream* or the *lymphatics* with resultant direct cell injury (e.g., toxins, alterations of the vascular contents as in thrombosis). 3) *indirectly*, when the stimulus acts on the *vessel walls*, a secondary circulatory disturbance then causing the cell injury (e.g., nervous derangement of permeability). 4) the pathological stimulus can come from the *alimentary tract.* Finally, primary (e.g., inborn) defects of metabolism may cause secondary cellular reactions.

The following diagram sets out the possible reactions of the organism to pathological stimuli in simple fashion (Fig. 3).

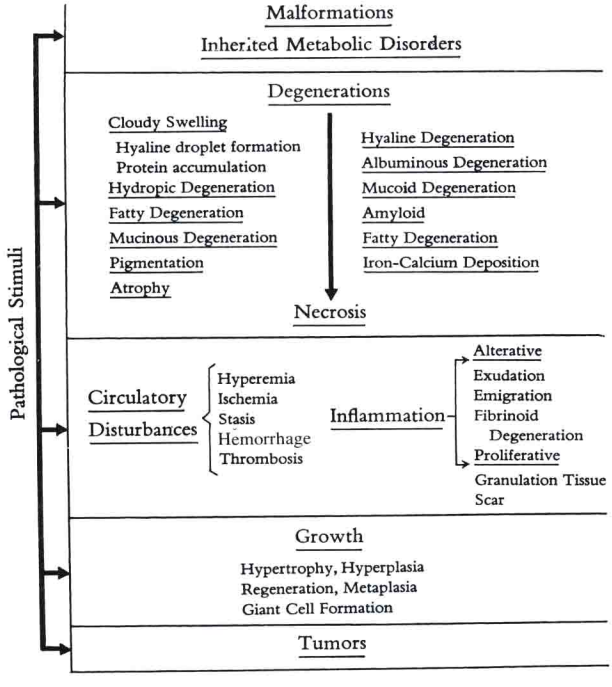

Fig. 3. Schematic survey of possible host reactions to pathological stimuli.

1 For a more detailed treatment of the subject see the textbooks of Anderson, Boyd, Florey, Montgomery, Muir-Cappell, Perez-Tamayo and Robbins, Walter and Israel, Sandritter and Benecke: Allgemeinen Pathologie (Schattauer-Verlag, 1974).