PATHOLOGY

ANDERSON

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Edited by

W. A. D. ANDERSON, M.A., M.D., F.A.C.P.

Professor of Pathology and Bacteriology,
Marquette University School of Medicine,
Milwaukee, Wisconsin

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COLLABORATORS

ARTHUR C. ALLEN, M.D.

Assistant Pathologist, Memorial Hospital, New York; Consultant Pathologist, Army Institute of Pathology; Attending Consultant Pathologist, Veterans Administration, Kingsbridge Hospital, New York

W. A. D. ANDERSON, M.A., M.D., F.A.C.P.

Professor of Pathology and Bacteriology, Marquette University School of Medicine; Director of Laboratories, St. Joseph's Hospital, Milwaukee, Wisconsin

J. E. ASH, COLONEL U.S.A. (RET.)

Scientific Director, American Registry of Pathology, Army Institute of Pathology Washington, D. C.

ROGER DENIO BAKER, M.D.

Professor of Pathology, Medical College of Alabama, Birmingham, Alabama

WILLIAM H. BAUER, M.D., D.D.S.

Professor of Pathology; St. Louis University School of Dentistry, St. Louis, Missouri

GRANVILLE A. BENNETT, B.S., M.D.

Professor and Head of Department of Pathology, University of Illinois College of Medicine; Pathologist-in-Chief, University of Illinois Research and Educational Hospital, Chicago, Illinois

EDWARD L. BURNS, M.D.

Pathologist, Mercy Hospital, Toledo, Ohio

PAUL R. CANNON, M.D.

Professor of Pathology, University of Chicago, Chicago, Illinois

E. V. COWDRY, Ph.D.

Professor of Anatomy, The School of Medicine, Washington University; Director of Research, The Barnard Free Skin and Cancer Hospital, St. Louis, Missouri

CHARLES E. DUNLAP, M.D.

Professor of Pathology and Bacteriology, School of Medicine, The Tulane University of Louisiana, New Orleans, Louisiana

F. D. GUNN, A.B., M.D., Ph.D.

Professor of Pathology, University of Utah School of Medicine; Pathologist, Salt Lake County General Hospital; Consulting Pathologist, Veterans Hospital, Salt Lake City, Utah

ERNEST M. HALL, M.S., M.D., F.A.C.P.

Professor of Pathology, University of Southern California School of Medicine, Los Angeles, California

BÉLA HALPERT, M.D.

Professor of Clinical Pathology, Director of Laboratories, University of Oklahoma Hospitals, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma

HOWARD C. HOPPS, M.D.

Professor of Pathology, School of Medicine of the University of Oklahoma, Oklahoma City, Oklahoma

HELEN INGLEBY, M.B., M.R.C.P.

Pathologist, Jewish Hospital, Philadelphia, Pennsylvania; Formerly Professor of Pathology, Woman's Medical College of Pennsylvania

WALTER W. JETTER, M.S., M.D.

Assistant Professor of Legal Medicine, Harvard University Medical School, Boston, Massachusetts; Pathologist, Massachusetts Department of Mental Health; Associate Pathologist, Massachusetts Department of Public Safety

PAUL KLEMPERER, M.D.

Pathologist to Mount Sinai Hospital, New York City; Clinical Professor of Pathology, Columbia, University

ENRIQUE KOPPISCH, M.D.

Professor of Pathology, School of Tropical Medicine, San Juan, Puerto Rico

JOHN E. KRAUS, M.D.

Director of Laboratories, St. Francis Hospital, Peoria, Illinois; Formerly Professor of Pathology, University of Prague, and Visiting Professor of Pathology, Columbia University, New York

JOSEPH F. KUZMA B.S., M.D., M.S.

Assistant Professor of Pathology and Bacteriology, Marquette University School of Medicine; Director of Laboratories, Milwaukee County Hospital, Milwaukee, Wisconsin

MADGE THURLOW MACKLIN, A.B., M.D., LL.D.

Research Associate and Lecturer in Medical Genetics, Department of Medicine, Ohio State University, Columbus, Ohio

MORTON McCUTCHEON, M.D.

Professor of Pathology, University of Pennsylvania, Philadelphia, Pennsylvania

JEFF MINCKLER, M.D., Ph.D.

Director of Laboratories, Providence Hospital, Portland, Oregon

VIRGIL H. MOON, A.B., M.Sc., M.D.

Professor of Pathology, Jefferson Medical College, Philadelphia, Pennsylvania

ALAN R. MORITZ, M.D.

Professor of Legal Medicine, Harvard University, Boston, Massachusetts

S. B. PESSIN, M.D.

Associate Professor of Pathology and Bacteriology, Marquette University School of Medicine; Director of Laboratories, St. Mary's Hospital, Milwaukee, Wisconsin

HENRY PINKERTON, M.D.

Professor of Pathology, St. Louis University School of Medicine, St. Louis, Missouri

EDGAR R. PUND, A.B., M.D., F.A.C.P.

Professor of Pathology, University of Georgia School of Medicine, Augusta, Georgia

MAURICE N. RICHTER, M.D.

Professor of Pathology, New York University School of Medicine, Post-Graduate Division; Director, Department of Pathology, New York Post-Graduate Hospital

JOHN R. SCHENKEN, B.S., M.D.

Professor of Pathology and Bacteriology, College of Medicine, University of Nebraska; Director of Laboratories, Nebraska Methodist Hospital and Children's Memorial Hospital, Omaha, Nebraska

WALTER SCHILLER, M.D.

Pathologist, Women and Children's Hospital, Chicago, Illinois; Consultant Pathologist, Cuneo Memorial Hospital and Columbus Hospital, Chicago; Formerly, Director of Laboratories, Second Obstetrical and Gynecological Clinic, University of Vienna.

SHIELDS WARREN, M.D.

Director of Division of Biology and Medicine, Atomic Energy Commission; Pathologist, New England Deaconess and New England Baptist Hospitals, Boston, Mass.; Captain (M.C.), USNR

PREFACE

Pathology should form the basis of every physician's thinking about his patients. The study of the nature of disease, which constitutes pathology in the broad sense, has many facets. Any science or technique which contributes to our knowledge of the nature and constitution of disease belongs in the broad realm of pathology. Different aspects of a disease may be stressed by the geneticist, the cytologist, the biochemist, the clinical diagnostician, etc., and it is the difficult function of the pathologist to attempt to bring about a synthesis, and to present disease in as whole or as true an aspect as can be done with present knowledge. Pathologists often have been accused, and sometimes justly, of stressing the morphologic changes in disease to the neglect of functional effects. Nevertheless, pathologic anatomy and histology remain as an essential foundation of knowledge about disease, without which basis the concepts of many diseases are easily distorted.

In this volume is brought together the specialized knowledge of a number of pathologists in particular aspects or fields of pathology. A time-tested order of presentation is maintained, both because it has been found logical and effective in teaching medical students and because it facilitates study and reference by graduates. While presented in an order and form to serve as a textbook, yet it is intended also to have sufficient comprehensiveness and completeness to be useful to the practicing or graduate physician. It is hoped that this book will be both a foundation and a useful tool for those who deal with the problems of disease.

For obvious reasons, the nature and effects of radiation have been given unusual relative prominence. The changing order of things, with increase of rapid, world-wide travel and communication, necessitates increased attention to certain viral, protozoal, parasitic, and other conditions often dismissed as "tropical," to bring them nearer their true relative importance. Also given more than usual attention are diseases of the skin, of the organs of special senses, of the nervous system, and of the skeletal system. These are fields which often have not been given sufficient consideration in accordance with their true relative importance among diseases.

The Editor is highly appreciative of the spirit of the various contributors to this book. They are busy people, who, at the sacrifice of other duties and of leisure, freely cooperated in its production, uncomplainingly tolerated delays and difficulties, and were understanding in their willingness to work together for the good of the book as a whole. Particular thanks are due the directors of the Army Institute of Pathology and the American Registry of Pathology, for making available many illustrations. Dr. G. L. Duff, Strathcona Professor of Pathology, McGill University, Dr. H. A. Edmondson, Department of Pathology of the University of Southern California School of Medicine, Dr. J. S. Hirschboeck, Dean, and Dr. Harry Beckman, Professor of Pharmacology, Marquette University School of Medicine, all generously gave advice and assistance with certain parts

To the members of the Department of Pathology and Bacteriology at Marquette University, the Editor wishes to express gratitude, both for tolerance and for assistance. Especially valuable has been the help of Dr. R. S. Haukohl, Dr. J. F. Kuzma, Dr. S. B. Pessin, and Dr. H. Everett. A large burden was assumed by the Editor's secretaries, Miss Charlotte Skacel and Miss Ann Cassady. Miss Patricia Blakeslee also assisted at various stages and with the index. To all of these the Editor's thanks, and also to the many others who at some time assisted by helpful and kindly acts, or by words of encouragement or interest.

W. A. D. ANDERSON.

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PATHOLOGY

Chapter 1

INTRODUCTION

PAUL KLEMPERER

Pathology is that branch of natural science which is concerned with the search for the cause and mechanism of disease. In this general sense the term applies to disease of all living organisms. Human pathology is primarily concerned with disease in man but does not exclude the insight which is gained from the study of disease in animals and plants. Fundamental facts of morbid life are revealed by exact observation and purposeful experiments on animals and plants.

The everyday word "disease" is an abstraction, and abstractions obviously cannot be the immediate object of natural science, which is necessarily founded upon observation of natural phenomena. The concept of disease has been established by extracting and totaling those characteristics of the sick which differ from the norm. In our observation of the sick and the healthy we study manifestations of life, and life presents itself to our senses as form and action. These manifestations are investigated with methods involving precise measurement. Anatomy—gross and microscopic—is concerned with normal form. Physiology inquires into normal function. Life, however, is also experienced subjectively by the mind, and investigations of mind belong to the realm of psychology.

Sickness in the individual is recognized by manifestations of life which are different from those of normal life and are designated as symptoms. These evidences of disease are both subjective and objective. Subjective symptoms, such as pain, itching, nausea, discomfort, and emotional or intellectual disturbances, are of great importance in the recognition of ill-health but have not yet been subjected to the same qualitative and quantitative analysis which has been applied to objective symptoms. It has long been recognized, however, that subjective symptoms can and should be correlated with the outward manifestations of illness. The application of biochemistry and biophysics to the investigation of psychopathic persons and the study of mental disturbances in persons afflicted with obvious physical ailments illustrate the endeavor to align diseases of the mind with those of the body. The attempt to understand the mind at the level of somatic organization (or in terms of bodily function) must not be regarded as the only scientific approach to mental diseases. Man as a social animal cannot be completely understood apart from his social environment, and the impact of the forces of society upon his mind require to be considered no less attentively than the influences exerted by chemical or physical factors upon his body.

Manifestations of disordered life which can be perceived by the senses constitute the objective symptoms of disease. From the earliest days of civilization, disease has been an object of intense interest to mankind. The medical records of the ancient Greeks are still a source of inspiration for us; their golden merits continue to shine in the light of modern science and exemplify the eternal value of accurate observation. Yet upon a mere perplexing multitude of symptoms and signs no lasting edifice of medicine can be erected. While the intuitive Hellenic genius recognized connections which modern medicine is scarcely beginning to understand, the Hippocratic system of pathology was doomed because it lacked the firm foundation of anatomy and rational physiology.* For more than a thousand years the progress of medicine was largely arrested. It began anew with the advancement of anatomy and physiology, but centuries had to pass until it was realized that the search for the intrinsic reason of disease must originate in observations of altered form and function of the living organism.

Having briefly outlined the purpose of pathology, we must now consider how investigations in pathology have proceeded and what they have accomplished. In pathology, as in all natural sciences, understanding must begin with observation and description. The earliest observations were concerned with obvious manifestations of abnormality of the patient during life—e.g., variations in the rate and quality of pulse or respiration, fever of varying type and intensity, abnormalities of excretion and secretion, and changes in bodily appearances and behavior. Empiricism, mingled with mysticism and vague philosophical theories of

*Genius is revealed in a delicate feeling which correctly foresees the laws of natural phenomena. But we must never forget that correctness of feeling and fertility of idea can be established and proved only by experiment (Claude Bernard).

nature and man, led to the concept that disease was a living being which existed independently within the body of the patient. Numerous diagnostic terms, which are still in use today, such as cancer and lupus, are vestiges of this period. Other terms, such as typhus and rheumatism (flowing pain), are derived from conspicuous objective or subjective symptoms of disease. These signs, however, are by no means the most important ones in the light of present knowledge.

The restrictions placed upon the cultural development of man during the centuries which followed the decline of the Roman Empire were finally lifted by the Renaissance. The revival of medicine was characterized by intense interest in the human body. Anatomic investigations were encouraged by enlightened rulers and the secrets of the fabric of the human body were rapidly revealed and divulged. These disclosures, coinciding with discoveries of universal laws of nature, stimulated inquiries into the mechanism of the human body. It is beyond the scope of this introductory chapter to depict even in rough outline the history of this natal period of modern medicine; yet the principles of pathology can never be fully understood without an appreciation of the labor of the creators.

Descriptive anatomy had established the norm of the structure of the human body. Superstitious fear of the dead had given way to the relentless curiosity which delved into the human body in an attempt to explain the mysteries of life. It was inevitable that medicine, challenged by the riddle of disease, should turn to anatomy for the answer. As structural alterations of organs were discovered, pathologic anatomy became established as a descriptive science and the symptoms of disease came to be correlated with the organic alterations revealed at autopsy. In 1761 the monumental work of Morgagni appeared; the anatomic conception entered the system of medicine and dominated it for nearly a century. It revolutionized medical diagnosis by providing a foundation to which the fluctuating symptoms of disease could be anchored. It now became the aim of scientific physicians to anticipate during the life of the patient the organic changes which would be disclosed at autopsy. Exact methods of physical examination, such as auscultation, percussion, and palpation, could be developed only after pathologic anatomy had disclosed the actual gross organic changes in disease. Not satisfied with these indirect methods of perception, ingenious investigators aimed at direct visualization of the organic alterations and invented instruments such as the laryngoscope and the cystoscope. X-ray diagnosis is likewise based largely upon the existence of physical changes in diseased organs. Thus the development of this important branch of medicine is founded upon the information supplied by pathologic anatomy.

For nearly a century Morgagni's idea of descriptive and correlative morbid anatomy held the lead in the progress of pathology. Yet, almost from the beginning of the era of pathologic anatomy, there were minds which challenged the primacy of a descriptive doctrine as the ultimate goal of pathology. They questioned the identification of disease with morbid alteration, and they ridiculed the overestimation of anatomic diagnosis as the final aim in the search for the nature of disease. It is the eternal contribution of Rudolf Virchow to have recognized the inevitable sterility of a merely static appraisal of the structural alteration associated with disease. In prophetic articles as well as by means of original investigations in pathologic anatomy and histology he stated precisely the leading idea of pathology and produced a "regulative principle" (Royce) for future research. His dictum, "disease is life under altered conditions," is the master plan of a rational pathology. Life as form and function is the object of investigation—not form alone and not function alone. Altered life is under inquiry as it is seen at the sickbed, in the experimental animal, and in its final manifestation at the autopsy table. Each goal is approached by different methods; but the ultimate aim is integration into one science: pathologic physiology, the true science of medicine. This refers not to physiology in the narrow sense of the academic curriculum, but to physiology in its original sense, the proximate reason of the nature of man. Merely a century has passed since the first issue of his *Archiv,* in which Virchow originally announced his new doctrine. In the same year he formulated the principle which up to the present time has remained the axiom of research in pathology: to understand the inception and evolution of morbid states.

The pathologist concerned with the structural aspect of disease cannot confine himself to mere description. Pathologic anatomy originated as a branch of normal anatomy; it employed identical methods of gross and microscopic observation and description; but anatomic science advanced from mere description to an inquiry into the evolution of form. Morphology, concerned with the intrinsic reason of form, aims at an understanding of the formation and transformation of organic nature (Goethe: Zur Botanik, 1817). The concept of morphogenesis stimulated the development of embryology and comparative anatomy as components of normal anatomy. Pathologic anatomy utilizes the disclosures of these sciences in the interpretation of human monstrosities. Teratology and comparative pathologic anatomy have developed into an important field of biology; but beyond these special applications, the morphologic conception is a fundamental principle of pathologic investigation. Morphology rests upon the recognition that organic structure is constantly undergoing transformation. It is founded upon the comparison of different phases of organic life. Morphologic pathology compares normal with altered structure and correlates different states of pathologic lesions. It establishes relations between facts ascertained by observation, it correlates the morbid with the norm, and it teaches us that structural phenomena not only exist but that they pass through developmental stages. It introduces the dimension of time into the interpretation of static facts and it places them in the movement of life.

Life is manifested in structure and in function; the two cannot be dissociated. The maintenance of normal structure of living substance is guaranteed by the fundamental functions of assimilation and reproduction, and proper function is maintained by normal structure. This holds true for life in its most primitive as well as in its highest organization. A morphologic approach to structure implies a correlation between form and function. Thus, morphologic pathology guides us in visualizing aberration of function and makes structural change intelligible in terms of process. It leads us to the realization that pathology must strive for an understanding of the mechanisms of disease. The complexity of the human body compels us to correlate structural and functional alterations at different levels of organization. Only on the plane of organs or complex tissues can changes of circulation and homeostasis become visually manifest, while alterations of metabolism and reproduction are revealed at the level of cells or intercellular substances.

While morphologic pathology is obviously dependent upon structural organization, it must always be remembered that living form is inseparably connected with matter (Needham). Biochemistry in its application to the analysis of organs and tissues is engaged in the search for the ultimate constitution of living matter without consideration of structure. Histochemistry, however, attempts to identify the chemical nature of morphologically separable units of cells and tissues. On the one hand, histochemistry employs the principle of anatomy—to separate separable things (Bensley). In addition to conventional histologic technique it utilizes the most refined methods of separation, such as microdissection, ultracentrifugation, and electronic microscopy. On the other hand, it adapts certain methods of analytic and enzyme chemistry and of physics, such as ultraspectroscopy and x-ray diffraction, to the investigation of cells and intracellular substances. A combination of such methods has already promoted research in histology, embryology, cytology, and genetics. The pathologist concerned with the structural aspect of disease must realize that a fuller understanding of life, normal and abnormal, will only be achieved by recognition of the chemical and physical constitution of the living substance and its regulation by the laws disclosed by natural science. Such recognition ties morphologic pathology to biochemistry, biophysics, and to biology in general. Thus the pathologist must keep abreast of every advance in these sciences.

Biology, as a science concerned with the manifestations of life, investigates also the conditions under which normal life is maintained in form and function. The living organism can scarcely be imagined outside of its natural environment but should be viewed as a part of the universe. Biologic sciences also must include in the scope of their inquiry the forces of the environment and mechanisms by which the living organism is adapted to their influence; they must attempt to interpret phenomena of life as a result of interaction between the forces of the organism and those of the external environment. Pathology, conceiving of disease as life under altered conditions, tries to understand life in terms of a change in this interaction. Complex external and internal factors determine disease. It is the final object of pathology to recognize all fundamental factors in their action and interaction, in order to investigate causality in disease. Exact observation and correct correlation lead to inferences of causality which must be tested by experiment. The recognition of external factors as causes of disease does not complete the search. Oertel clearly states: "Any perfect causal explanation must include the complete and connected chain of all events which are responsible for phenomena, and these, moreover, must be in their proper position." In other words, etiology is not synonymous with pathogenesis. We must realize that the search for causality in disease must not stop with the recognition of external cause but must progress to demonstrate the mechanism by which the cause acts. Pathologists cannot rest merely with the reproduction of phenomena of disease by experiment; they must strive to "dissociate all the complex phenomena successively into more and more simple phenomena" (Claude Bernard). Only if we recognize the elementary principles of the causative factors and their action upon the animal and human body, will the ultimate aim of pathology be reached. Disease is the experiment of nature; we see only the results, while we are ignorant of the conditions under which the experiment has been performed. Step by step, pathology must unveil these conditions. It progresses from observation to correlation, from correlation to deduction, in order that rational experimentation may accomplish the final synthesis.

An introductory chapter to a textbook of pathology should not refer to facts which will be presented in detail in the various chapters of the text. This principle has been adhered to not for lack of illustrative material but rather despite an abundance of such material.

Disease manifests itself in alteration of form and function. Anatomic pathology deals with alteration of form, structural as well as material, while alteration of function is the domain of clinical investigation. An integrated knowledge of altered form and function is the ultimate aim of pathology and is the cornerstone of modern medicine. This integration requires not only a knowledge of facts but also a certain attitude of mind which must guide the future physician in the study of disease. This attitude of mind can only be developed if the student is trained to advance from exact observation to correlation of facts and from correlation to deduction. Alteration of structure, as disclosed by anatomic pathology, is easier to perceive than alteration of function; the analysis of changes in structure, as they occur in disease, is therefore a simpler preparation for the inquiry into the mechanism of disease. Moreover, as has been indicated previously, many methods used for the recognition of disease in the living are founded upon the knowledge of structural alterations in the dead. All this accounts for the position of anatomic pathology as a preclinical subject and for the requirement that a textbook of pathology shall be devoted primarily to exact description and interpretation of structural anomalies observed in disease. No textbook of pathology with its spatial limitations can fully achieve this object. It can attempt to present in concise form the results of investigation, it can never give a full account of the long road which has led from the original observation of lesions to the understanding of their causation; but by well-chosen references to literature, it can stimulate the student to a historical review of the problems of pathology. Thus the student can spiritually repeat the investigative efforts which have advanced our knowledge.* In this way he will develop the attitude of mind which will later enable him to make his own contribution to the ultimate object of medicine: to recognize the intrinsic reason of disease.

*It is of great advantage to the student of any subject to read the original memoirs on that subject, for science is always most completely assimilated when it is in the nascent state (James Clerk Maxwell).

Chapter 2

CELLS AND THEIR BEHAVIOR

E. V. Cowdry

Fluid Environment

The body is a complex system of regulated fluid streams in which cells live and function. As indicated in Fig. 1 the principal stream enters the alimentary tract and escapes mainly in the urine. The circulating blood plasma is about 5 per cent of body weight, the more sluggish interstitial fluid (tissue fluid + lymph) 15 per cent, and the innumerable lakelets of intracellular fluid 50 per cent.

All living cells are aquatic but they are not all bathed in blood as protozoa attached to the rocks of the bed of a stream are bathed in water passing by—a much mistaken simile. Only the endothelial cells which limit the blood stream and the blood cells within it are directly in contact with blood. A fundamental feature in the architecture of the body is the protection of all other cells from direct contact with blood.

The vast majority of cells live in tissue fluids which are shielded from the blood stream by a layer of vascular endothelium through which transfer of material is limited. These tissue fluids are not seen to be of large extent on naked-eye examination, but in relation to the size of their cellular inhabitants they are of considerable volume. They are certainly larger pools of fluid in vivo than when viewed in microscopic preparations in which there has been a shrinkage of 10 to 20 per cent. The preparations are therefore deceptive.

Walter B. Cannon[18] has written eloquently about the factors which maintain like states (homeostasis) in the blood stream. In the tissue fluids, unlike states, or conditions, are established to provide the special fluid environments required by many kinds of cells; and these environments are regulated so that the cells are not subjected to injury by the imposition of too great changes in their manner of life. Thus, heterostasis in the tissue fluids is imposed upon the homeostasis in the blood—a concept which is gaining ground rapidly. These different states in tissue fluids owe their origin and maintenance to local differences in:

1. **Permeability of Vascular Endothelium.**—Exchange between blood and tissue fluid depends on permeability. Where there is a high degree of vascular permeability (spleen and liver), exchange is greater than where it is lower (extremities).

2. **Blood Supply.**—Contribution from blood to tissue fluid and drainage from tissue fluid into the blood also depend on availability of the blood stream to the tissue. From avascular tissues, such as epidermis, cornea, and cartilage, blood is held at a distance so that their tissue fluids are less conditioned by it than are those of tissues having a rich blood supply.

3. **Lymphatics.**—Some components of tissue fluids unable to leave them through vascular endothelium can get out through lymphatic endothelium because it is more permeable. Tissue fluids of alymphatic tissues (brain, bone marrow, etc.) are consequently less effectively drained than are those provided with many lymphatics (intestinal mucous membrane, dermis, etc.).

4. **Cellular Inhabitants.**—Obviously, their influence on the tissue fluid depends on what they take from it, what they give to it, and whether they are surrounded by much or little of it.

5. **Fibrous Components.**—Where elastic and collagenic fibers exist in the tissue fluids, these may be expected to influence the composition of the fluids because they provide surfaces for adsorption (cf., iron and calcium encrustation in blood vessel walls).

Many peculiarities of different tissue fluids have been reported and others are to be expected.[1] Only those most easily collected have thus far been analyzed. Cerebrospinal fluid differs very materially from joint fluid. The fluid in the anterior chamber of the eye appears to be unique in that species differences are lacking which in other areas are present and prevent successful transplantation into them of tissue from alien species. One of the potentially most useful advances recently made has been the discovery of polysaccharides in the dermal tissue fluids which give them a gel-like consistency so that mechanical resistance is offered to the spread of entering substances whether infective or otherwise. This resistance is overcome by so-called spreading factors which break down the gel. The best known is the factor, hyaluronidase, acting on the polysaccharide, hyaluronic acid.[2]

To be more precise, tissue fluids are of two orders. The first and basic order of tissue fluid is simply separated from the blood stream by vascular endothelium. This is represented in light stiple in Figs. 2 and 3.

The second order of tissue fluid is separated from the blood stream by vascular endothelium, plus tissue fluid of the first order, plus another membrane. In the case of intraocular tissue fluid, one of the second order, this membrane is ectodermal epithelium; while in the case of peritoneal tissue fluid, likewise one of the second order, this membrane is mesothelial.

Kinds of Cell Lives

In addition to an appreciation of local tissue fluid environments as controlling factors in cellular behavior, it is important to remember that fundamental differences exist in the kinds of lives which cells live. From this point of view there are two great classes of cells, each divisible into two subclasses, making four kinds in all.[3]

1. **Intermitotics.**—These cells exist as individuals from the mitosis which gives them birth to the next following mitosis when each divides forming two other individual cells. Their intermitotic lives do not end in death but in cessation of individualty. They do not become senile, but throughout their lives are young.

Some intermitotics are through long years the reservoirs in the body of new cellular life. These are the *vegetative intermitotics.* The primitive blood cells—whatever hematologists may ultimately decide that they look like or may call them—end their individual lives when

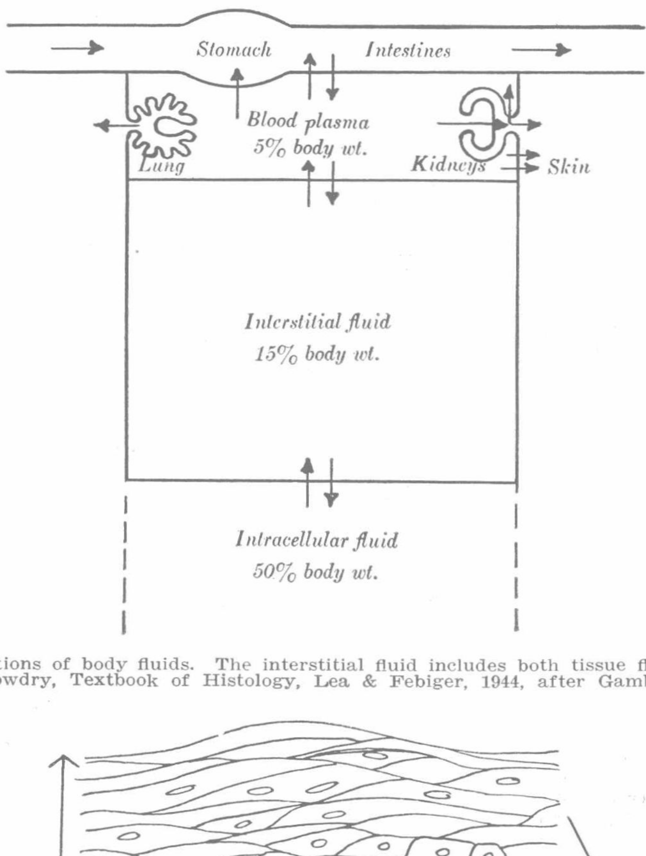

Fig. 1.—Proportions of body fluids. The interstitial fluid includes both tissue fluid and lymph. (From Cowdry, Textbook of Histology, Lea & Febiger, 1944, after Gamble, 1937.)

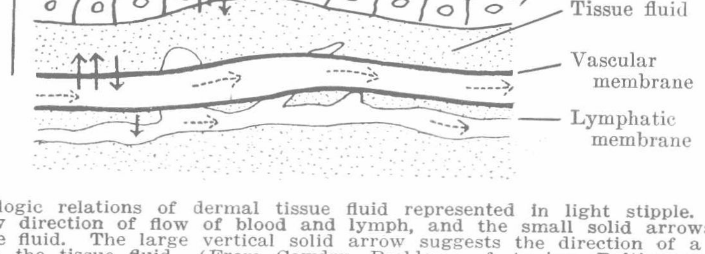

Fig. 2.—Histologic relations of dermal tissue fluid represented in light stipple. The broken arrows show direction of flow of blood and lymph, and the small solid arrows the movements of tissue fluid. The large vertical solid arrow suggests the direction of a deprivation gradient in the tissue fluid. (From Cowdry, Problems of Ageing, Baltimore, 1942, Williams & Wilkins Co.)

they divide, each producing two others. Among these daughter cells some remain in the same place and repeat in their persons the same vegetative kinds of lives.

Other daughter cells are perhaps edged a little away from their birthplace, and in the tissue fluid are subjected to slightly different conditions so that their lives are altered. These, in turn, are the *differentiating intermitotics.* When they divide, their daughter cells carry on from about the stage of differentiation which their parents attained, and they pass on to their own descendents the still higher stage of differentiation which they themselves achieve.

It is an interesting exercise to survey the cells of the body in search of still other vegetative and differentiating intermitotics, many of which will be found. Among the former are basal cells of the epidermis and spermatogonia of the testicle, and among the latter, spinous epidermal cells and spermatocytes.

2. **Postmitotics.**—By contrast these cells do age and die. Their lives are ordinarily postmitotic, not intermitotic. They are highly specialized cells, completely fitted by their differentiating intermitotic ancestors to serve in many capacities—secretion, conduction, and so on.

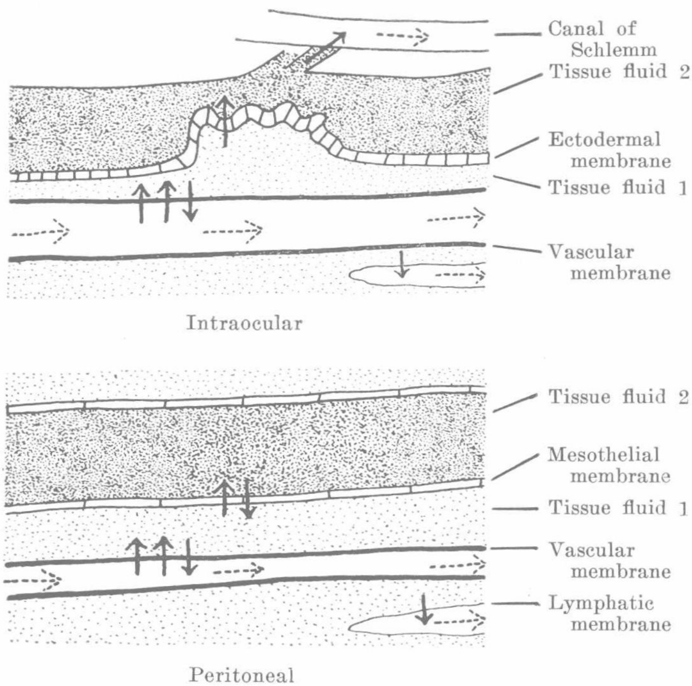

Fig. 3.—Intraocular and peritoneal tissue fluids of second order in dense stipple. (From Cowdry, Problems of Aging, Baltimore, 1942, Williams & Wilkins Co.)

However, some of them can, if the demand is urgent, revert to a condition in which they do divide—kidney cells for example, when many other kidney cells have died or have been excised—so cells possessing this property are called *reverting postmitotics.* Smooth muscle cells and several others will be found to belong to this same category.

Nerve cells (in children after about 2 years of age), neutrophilic leukocytes, corneal cells of the epidermis, and a host of others cannot revert to a state capable of mitosis and are, therefore, known as *fixed postmitotics.* Inevitably, these age and die but at different rates. Individual nerve cells, for instance, live several thousand times as long as leukocytes. Their lives are terminal. We look to all others, but not to fixed postmitotics, as possible sources of cancer.

Types of Cells

Nobody knows how many different types of cells exist in the body, but there are two large groups—the "surface cells" and the "fill-in cells."

The surface cells make up epithelium, endothelium, and mesothelium. *Epithelium* enjoys the position of seniority as to date of introduction, since this term can be traced to Ruysch in 1703. As now used, it covers: (1) cells closely packed together side by side in