A TEXTBOOK OF PATHOLOGY

SECOND EDITION

Pathologic Anatomy in Relation to the Causes, Pathogenesis, and Clinical Manifestations of Disease

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Illustrated

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Preface to the Second Edition

The cordial reception given to the first edition of this textbook by both pathologists and clinicians, the helpful comments of many colleagues, and the decision of the publisher to reset the type, have combined to make possible an extensive and thorough revision.

The additions, deletions, substitutions, and changes may be reviewed in eight categories.

1. The addition of new chapters in order to round out the subject matter. There are new chapters on such subjects as "Disturbances in the Metabolism of Enzymes," "General Considerations of the Infectious Diseases," and "Diseases Peculiar to the Aged."

2. Subdivision of some longer chapters. The chapter on diseases caused by viruses has been divided into three chapters: dermotropic, viscerotropic, and neurotropic. The chapter on the alimentary tract has also been divided into three chapters: oral cavity and esophagus, stomach and duodenum, and intestine. The neoplastic and non-neoplastic diseases of the skin have been placed in separate chapters.

3. Rearrangement of chapters to improve correlation. In the first edition diseases of the kidney were discussed in three different chapters. These have now been brought together.

4. Rearrangement of chapters to take into account changing concepts. The previously scattered diseases which apparently are closely related because of primary effect on mesenchyme—the collagen diseases—are now collected into one chapter. Similarly the newer concept of the demyelinating encephalitides has led to arrangement in a single chapter.

5. Relocation of certain sections because of new information. The clear demonstration of a virus in epidemic hepatitis, in pretibial fever, and in Colorado tick fever, for example, has resulted in transfer of the discussion to the chapters on viral disease.

6. Addition of sections on topics or diseases inadvertently omitted in the first edition. Examples in this category include rubella, thalassemia, synovioma, and fibrous dysplasia of bone.

7. Addition of sections on topics or diseases which were unknown or did not appear to deserve attention at the time of the earlier edition. Many changes and additions have been made on this basis, for example, Coxsackie virus, rickettsialpox, viral diarrhea, effect of neutrons, effect of an atomic explosion, folic acid and vitamin B_{12}, retrolental fibroplasia, relation of rubella to congenital anomalies, and infectious lymphocytosis.

8. Revision of subject matter because of new or changing information. There are few sections which have escaped some change on the basis of this principle. A few examples are: hypoxic nephrosis (lower nephron disease), forward and backward failure of the heart, the unity of the malignant lymphoblastomas, adrenal insufficiency in the newborn, cystic and proliferative lesions of the breast (chronic cystic mastitis), granular cell neurofibroma (myoblastoma), and chronic (idiopathic) hypochromic anemia.

No attempt has been made to substitute systematically new references for old references unless information or ideas have changed or a new article in a widely distributed journal contains an up-to-date review. Most of the new references are to articles published since 1944.

Many friends and associates have assisted in the revision. I wish to thank particularly

Dr. Zola Cooper
Dr. Edward B. Smith

for their help on the chapters on diseases of the skin and on diseases of the blood forming tissues respectively. My other associates in the department of pathology at Washington University have made many useful suggestions

Dr. Margaret G. Smith
Dr. Lauren Ackerman
Dr. Gustave J. Dammin
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Dr. David E. Smith

As with the first edition, a search of the literature would not have been possible without the assistance of the staff of the library of the school under the supervision of

Miss Marion Murphy

Although no one person has served as an editorial alter ego, the secretaries in the dean's office and in the department of pathology have been most helpful.

Louise Jacoby
Dorothy Rinderer
Elizabeth Streeter
Helen Hendrix
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Dr. Fred T. Caldwell, Jr.
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The staff of the W. B. Saunders Company have been most considerate and cooperative despite delays occasioned by the press of my duties in other activities.

Once again my family have been tolerant and understanding of the many evenings, week-ends, and holidays spent away from home.

ROBERT A. MOORE

Saint Louis

Preface to the First Edition

Pathology occupies a pivotal position in the medical curriculum. Anatomy, biochemistry, physiology, and bacteriology are prerequisites. Clinical medicine and surgery follow it. In pathology the student must learn to apply the facts and theories of anatomy, biochemistry, physiology, and bacteriology to an elucidation of the causes, processes, and effects of disease. He must learn to reach ahead into the clinical branches of medicine and correlate the anatomic and physiologic changes with the signs and symptoms in the patient. He must learn to study the causes of disease with a view to prevention and control. Finally he must gain a clear understanding of the alterations in form and disturbances of function that take place in disease, so as to be ready for the next step in his medical education—the so-called "clinical years."

Medical education is at the graduate level of university teaching. The students have completed two to four years of college. In this textbook I have attempted to present the subject in a manner consonant with the objectives of higher education. I have tried to avoid being dogmatic, and yet present to the reader clear concepts. The presentation of controversial material is intended to stimulate rather than to confuse, and by including it I have hoped to cultivate in the mind of the student a speculative and reasoning approach to the subject. The answers to the questions "Why?" and "How?" are as important as the answer to the question "What?" Specifically applied to pathology "Why?" and "How?" deal with cause and pathogenesis, while "What?" is concerned with pathologic anatomy. In terms of energy and motion "What?" is static; "Why?" and "How?" are dynamic.

The arrangement of the book may require a word of explanation: The broad division of the subject into general and special pathology will probably evoke no controversy; nor will the further division of general pathology into disturbances of metabolism, inflammation, and tumors. The approach by disturbances of metabolism rather than by the anatomic types of degeneration is a departure. It represents an attempt to give more emphasis to the physiologic and chemical aspects of general pathology.

In my experience the most desirable classification of disease is one based on cause; hence in the section on special pathology, diseases with similar causes have been grouped together. Those diseases of which the causes are unknown or obscure have been considered according to the organ or system in which they occur. My confidence that preventive medicine will play an important part in the future of medical science prompted the arrangement of the bacterial diseases according to the portal through which the bacterium enters the body and the source of the bacterium.

I have been guided in the selection of illustrations by certain principles: an illustration should expand the text; it should fix in the mind of the reader the important facts or observations about a disease; it should serve to correlate the pathologic with clinical observations; and it should stimulate the reader to further study. Illustrations are therefore not confined to gross and microscopic photographs, but radiographs, photographs of patients, reproductions of the frontispieces of classical monographs, pictures of the great men of medicine in the past, photographs from the field of paleopathology, and maps showing the distribution of disease, have been selected. Occasionally diagrams and drawings are advantageous, but so far as possible only actual photographic reproductions have been used.

References in a textbook serve two purposes: they indicate accessible works in which additional information on a subject can be found, and they call attention to the names of those who have made significant contributions to the sum of knowledge. The lists of references in this book have been compiled with a

full realization that there are many other contributions of equal value. So far as possible I have selected reports which answer these criteria: that the author has made many other contributions to the literature on the subject; that the journal is likely to be found in even small medical libraries; that the work is in English; that the bibliography is sufficient to point the way to future reading; and that the work has been published within the last few years. The number of citations varies from chapter to chapter, and is intended roughly to indicate the trend of present-day research, and conversely to point out chapters of medicine where investigation is most needed. The names of authors whose work is referred to are usually enclosed in parentheses in the text in order to familiarize the student with the names of men and women who are advancing the limits of knowledge in a certain field. The references are inserted for use and not for appearances, hence the preponderance in English is not a mark of provincialism, but a frank and practical acknowledgment that few Americans read any language except their own. Lists of journals are included at the end of some chapters to indicate sources of current literature. The date after the name of the journal is the year of first publication. If the publication of a journal has been discontinued a second date is included.

ROBERT A. MOORE

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Air-borne Infections: Bacteria, Viruses

Exogenous or Hematogenous Routes of Infection: Bacteria

Portal of Entry the Alimentary Canal: Bacteria, Spirochetes

Venereal Diseases: Bacteria, Spirochetes, Viruses

I

The History and Scope of Pathology

Pathology, as it is practiced today, may be defined as that branch of medicine which deals with the causes, the processes, and the effects of disease.

The origin of disease is lost in antiquity, but there is abundant evidence that at least some diseases have been present on this earth for over a hundred million years. Thus there are excellent examples of arthritis deformans in the spines and in the joints of prehistoric mammals and reptiles.

Greek and Roman Medicine. The contribution of the Greek physicians of the classical period was not concerned with the nature of disease, nor with the exact changes which occurred in the body as the result of disease, but was rather the elucidation of the principle of exact and careful clinical observation. They further crystallized these observations into a system of medicine. The same in general is true of the Roman physicians, typified by Galen. With one notable exception, human dissection was not practiced; and there was no opportunity to study the structural changes of disease, except as these changes appeared on the surface of the body. The exception was Alexandria during the reign of the Ptolemies, but even there human dissection was used largely for purposes of studying anatomy rather than pathology.

At that time the disease was thought to be due either to supernatural intervention or to the operation of "humors" within the body. The humoral theory of disease postulated that the body was composed of four humors and that disturbance in the ratio of these humors was the basic cause of all disease.

Medieval Ages. This period is frequently spoken of as the Dark Ages, because of the lack of interest in literature and in art. Medicine also suffered neglect during this era and no significant original contributions were made from the time of Galen until the Renaissance. There were, however, a few isolated persons who made attempts to break down the dogma of Galen, notably Paracelsus and Fracastoro. The latter propounded an entirely sound theory of the contagiousness of disease.

Anatomic Pathology. Beginning in a small way in the sixteenth and seventeenth centuries, through the published works of Benivieni in 1507 and of Bonetus in 1679, the autopsy took its place in medicine. The work of these anatomists culminated in the three-volume compendium of autopsies published by Morgagni in 1761. In these volumes are recorded systematically seven hundred complete autopsies, with comments on the relation of structural change to the signs and symptoms which the patient presented during life. Pathology was then largely a purely morphologic science, and was concerned only with clinical correlation. This was rapidly followed by the work of many others. Matthew Baillie in 1793 published in England the first systematic textbook of pathologic anatomy in any language.

At about this same time the French physician Bichat was developing his ideas of histology, in contrast to organology. Although Bichat is usually known as an anatomist or histologist, he carried his ideas over into pathology, and was the first to propose that disease attacked specific tissues rather than specific organs.

Period of Clinical Correlation. As the result of these basic changes in the theories of disease there grew up in France and in England, during the first forty years of the nineteenth century, a school of combined clinicians and pathologists. In most instances, the same person observed the patients on the wards and carried out the autopsies. Many diseases

which are known today by a proper name date from this period. Thus in France there were Corvisart, Laennec, Louis, and Cruveilhier; and in Britain, Carswell, Hodgkin, Bright, Addison, Cheyne, Stokes, Adams, Corrigan, and Graves.

At this time, pathology was not a separate science, but rather was an adjunct to clinical medicine. In a few isolated places, however, pathology was recognized as a distinct academic discipline, and the first professorship of pathology in the world was created at Strassburg in 1819. Lobstein was appointed to this chair. Soon thereafter in 1831, Carswell was made professor of pathology at the University College of London, and in 1836 Cruveilhier was appointed professor of pathology in the University of Paris.

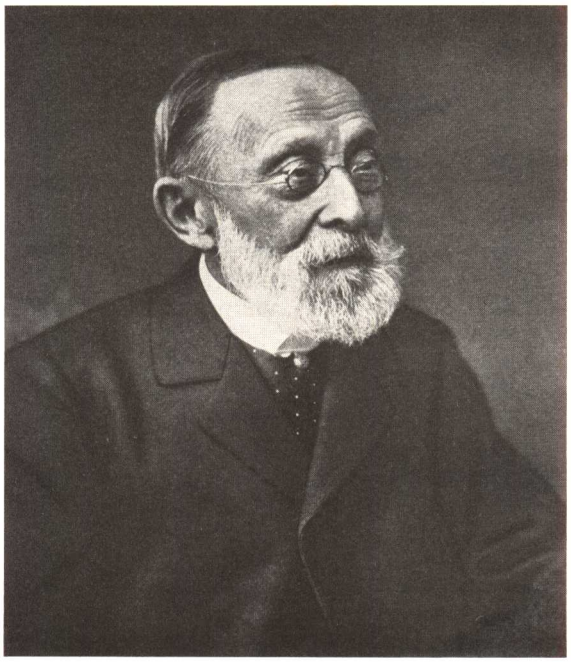

Fig. 1. Rudolph Virchow (1821–1902). (College of Physicians, Philadelphia.)

Germanic Pathology. Although the French and the English brought pathology from the realm of speculation into the field of objective observation of diseased tissue, it remained for the Austrians and the Germans to complete the revolution. In Vienna Rokitansky, the supreme descriptive pathologist of all time, firmly established the structural basis of disease. As the result of his observations in the autopsy room, the work of Skoda, Semmelweiss, and Billroth was made possible.

While this progress in morbid anatomy and clinical correlation was taking place, the microscope had been invented; but for some reason it never occurred to a pathologist to use the microscope to study disease until the middle of the nineteenth century. In Berlin, under the influence of Johannes Müller, the cellular nature of all animal tissues had been proved by Schwann. Into this atmosphere came Rudolf Virchow, who studied under Müller, and who, on graduation, was appointed assistant prosector to the Charité. He immediately applied the microscope and the cellular theory to pathology and, in 1846, the first edition of "Cellular Pathology" appeared. This book revolutionized the concepts of the nature of disease and the means which could and should be used to study it. Through his students, Virchow influenced the further development of pathology: through Cohnheim into the dynamic concepts of experimental pathology, through Klebs into the field of the bacterial causes of disease, through Hoppe-Seyler into the field of biochemistry, and through many students into the field of morbid anatomy.

American Pathology. The developments initiated by Virchow are of particular interest to Americans because American pathology

stems from this period, and has adopted the concepts and the methods of the Germanic school of pathology of the last half of the nineteenth century. It is true that there were a few isolated contributions to American pathology before this time, notably the textbook of Horner in 1829 and the classic work of Samuel Gross in 1839. It is also true that many of the great physicians and surgeons of Philadelphia, New York, and Boston brought back to America the ideas of the English and French schools of clinical pathology. But it was not until the students of Virchow and his associates returned to America that pathology was recognized as a distinct science. The greatest of these were Welch, Councilman, Mallory, Prudden, Hektoen, Ophüls, and Warthin. William Henry Welch, a student of Cohnheim, in 1884 was appointed Professor of Pathology at Johns Hopkins University School of Medicine. Welch, more than anyone else, influenced American pathology and American medicine. His students occupy many of the important chairs of pathology in the United States, and there are few pathologists today who have not at one time studied under Welch or under one of his students. Welch and the others brought to America the dynamic concepts of an integrated pathology, and it is along those lines that pathology has evolved in the United States.

The Present and Future. Pathologists are at one and the same time morbid anatomists, histopathologists, physiologic pathologists, and chemical pathologists. Pathology is a science which has no methods of its own. It applies to problems of disease the methods and the procedures of the anatomist, the chemist, and the physiologist. With this concept there is no limit to the field.

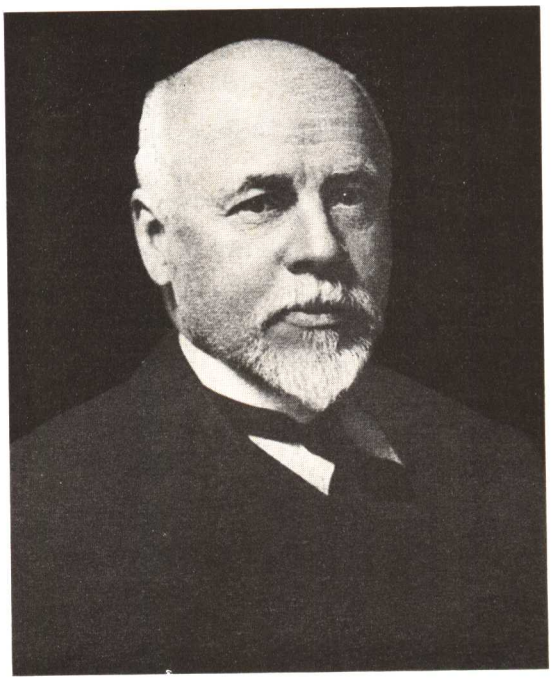

Fig. 2. William Henry Welch (1850–1934). (College of Physicians, Philadelphia.)

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PART I

GENERAL PATHOLOGY

II

Disturbances in the Metabolism of Proteins

The proteins are universal constituents of plant and animal tissue. Mulder, the Dutch chemist who in 1839 first suggested the term "protein," characterized it as "unquestionably the most important of all known substances in the organic kingdom." The role of proteins in life and metabolism is manifold: they are important in determining the osmotic relations between extracellular and intracellular fluids; many enzymes have the properties of proteins (pepsin); some hormones are either proteins or derived from proteins (thyroxine); and the substances associated with humoral resistance to disease are proteins.

Nature. Specificity. Amino acids are joined in peptide linkage to form polypeptides and proteins with molecular weights up to 7,000,000.

Each species of animal and plant, and frequently each cellular type or tissue, tends to construct a characteristic protein. It is probable that these differences are based on the quantitative and qualitative content and the special arrangement of the amino acids in the molecule, but this has not been proved. Present methods for the determination of the specificity of proteins are largely immunologic and depend on the phenomena of anaphylaxis, allergy, and the formation of antibodies.

Protein in the Body. *Requirements. Sources. Nitrogen Balance.* Nitrogenous substances are needed for general metabolism and for the building of new cells and tissues, as in growth, pregnancy, and lactation. If the dietary protein is adequate, the nitrogen of the diet (chiefly protein) is equal to the nitrogen of the excreta (chiefly in the urine). When the dietary nitrogen is in excess, a person is said to be in a positive nitrogen balance, whereas when the excreted nitrogen is in excess, the person is said to be in a negative nitrogen balance.

With an all vegetable diet the daily requirement for adults is about 2.9 gm. of nitrogen per square meter of body surface, and with a meat diet it is about 2.4 gm. of nitrogen (Hegsted, Tsongas, Abbott, and Stare).

In most human diets the protein is derived from animal products (meats, eggs, fish, and milk), cereal, grains, legumes, and nuts. In the United States, animal protein makes up about 50 per cent of the total (Lewis).

Dynamic Equilibrium. The protein of the animal body may be considered as a single pool and may flow from cell to plasma or the reverse, depending upon the conditions of the moment (Whipple and Madden). The largest pool of stored protein and the chief center of manufacture is the liver.

Plasma Proteins. The normal plasma protein value for white adults is 7.19 gm., with 4.65 gm. of albumin and 2.59 gm. of globulin (Milam).

Fractionation of the plasma proteins has yielded many products useful in treatment, such as globulin for immunization and fibrin foam for hemostasis (Cohn, Oncley, Strong, Hughes, and Armstrong Cohn).

Demonstration of Protein in Tissue. Most chemicals used for the fixation of tissue are protein precipitants and, in the subsequent treatment with aqueous and organic solutions, most carbohydrate and lipid are removed. Hence the greater part of the material seen in sections of tissue is protein. The density of the cytoplasm is a rough index of the concentration of protein. Basophilism of the cytoplasm indicates the presence of nucleoproteins, particularly ribonucleic acid (Opie). Some of the specific tests for the identification of protein may be used histochemically, such as the biuret and xanthoproteic reactions.

Effects of a Deficiency of Protein

A deficiency of protein may be related to decreased intake as in starvation, defective absorption as in disease of the intestines, increased loss as in certain renal diseases and after injury, or decreased synthesis as in some diseases of the liver. Changes in the plasma proteins chiefly take the form of a decrease in albumin (Muntwyler).

Within a few hours after the loss of from 20 to 30 gm. of plasma protein by hemorrhage the volume of the blood is restored by the withdrawal of fluid from the tissues, and within six to twelve hours the protein concentration of the blood has been restored to normal. In chronic depletion there is a maximum regenerative capacity, which in the dog is in excess of 70 gm. of plasma protein per week under optimum conditions (Whipple and Madden).

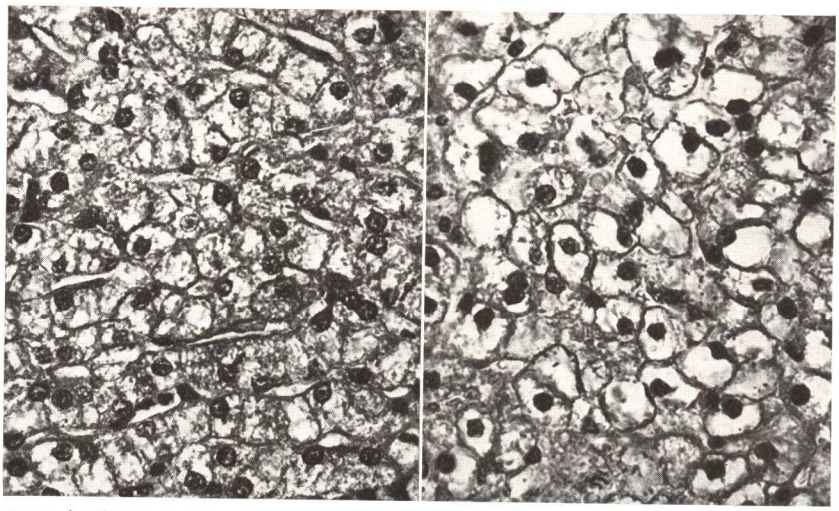

Fig. 3. Two stages in the depletion of protein from hepatic cells. (Tissue by courtesy of Dr. Robert Elman.)

Hypoproteinemia. Nutritional Edema. Maintenance of the dynamics of the circulation is dependent on the blood pressure and the osmotic pressure of the plasma proteins. Fluid is held within the blood vessels by the osmotic pressure against the force of the blood pressure, which tends to drive it into the tissues. Perfect maintenance of the balance between the fluid within the blood vessels and the extravascular fluid thus depends on the maintenance of the level of the plasma proteins at about 7 gm. per 100 cc. of plasma. Any decrease of protein tends toward the passage of fluid into the tissues. When the level of plasma protein reaches about 4 gm. per 100 cc., the differential between osmotic pressure and blood pressure is sufficiently low that fluid passes out of the blood vessels. This fluid contains only a small amount of protein, and there is a direct correlation between specific gravity and the concentration of protein (Paddock). This phenomenon of nutritional edema is common during war time (Chen).

Anatomic Changes. In man it is difficult to separate the changes caused by a deficiency of protein from those resulting from a grossly deficient diet, leading to starvation. In starvation there is a deficiency not only of protein but of carbohydrates, fats, and vitamins. As the anatomic changes in starvation are more concerned with the metabolism of fats, this subject will be discussed in detail in the chapter on fats (Chapter V, p. 39).

In animals in the laboratory specific histologic changes result from the administration of a diet which is deficient only in proteins. In dogs, after periods of two to three weeks, the liver is smaller than normal, grayish brown, and soft. The hepatic cells, especially those about the hepatic vein, are enlarged, and the cytoplasmic substance is not recognizable. The cell wall is thick and prominent, and in the center or at the side of a clear space there is a relatively small hyperchromatic nucleus (Elman, Smith, and Sachar).

Effect on Resistance to Disease and Toxic Agents. It is a well known observation that

the animal organism depleted of protein is more susceptible to infection (Cannon) and to toxic agents (Nutrition Reviews). The mechanism of this is not fully understood but in the former it would appear to be an impairment of capacity to fabricate antibody gamma globulin (Cannon, Chase, and Wissler), and in the latter an interrelation between sulfhydryl groups and the liver.

Effect on the Healing of Wounds and the Restoration of Tissue. A protein deficient diet also influences the rate of regeneration of hepatic tissue following partial hepatectomy (Rous and McMaster). The hypertrophy of a remaining kidney, adrenal, or ovary may be delayed (Addis and Lew). The healing of wounds progresses more slowly in dogs fed a diet deficient in protein than in normal dogs (Thompson, Ravdin, and Frank).

Post-traumatic Negative Nitrogen Balance. Following injury or surgical operation there is usually a negative nitrogen balance due to decreased intake, increased catabolism of protein, and loss of plasma protein (Elman; Madden and Clay). The condition may be corrected by an increased intake of protein (Elman).

EFFECTS OF A DEFICIENCY OF SPECIFIC AMINO ACIDS

Rose has demonstrated that ten amino acids are required for the normal growth of the white rat. These are lysine, tryptophane, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine, and arginine. Small quantities of arginine can be synthesized by the animal organism, but not sufficient to maintain growth. Observations on the dog and in man indicate that these same ten acids will maintain nitrogen balance and serve for synthesis of plasma protein (Madden and Whipple).

A beginning has been made in the study of each amino acid separately. Lack of lysine in man leads to nausea, dizziness, hypersensitivity to sound, and increased excretion of nonketonic organic acids (Albanese, Holt, Frankston, Kajdi, Brumbach, and Wangerin). A deficiency of arginine in man is associated with aspermia (Holt, Albanese, Shettles, Kajdi, and Wangerin). A histidine deficient diet in man results in weight loss and increased excretion of an indican-like substance, but no negative nitrogen balance (Albanese, Holt, Frankston, and Irby). In the rat, deficiency of tryptophane causes changes in the teeth, eyes, and testes (Albanese, Randall, and Holt), but in man there are no clinical alterations (Holt, Albanese, Frankston, and Irby).

A deficiency of cystine in mice retards the occurrence of both spontaneous and of induced tumors (Nutrition Reviews).

Although there is no evidence on the results of a deficiency of glutamic acid, there is clear evidence that additional amounts in a supposedly normal diet will increase the intellectual ability of both animals and man.

Effects of an Excess of Protein

So far as is known the ingestion of an excess of protein has little deleterious effect upon the animal organism other than to produce a certain degree of obesity. This phase of the subject will be discussed in the chapter on disturbances in the metabolism of fats (Chapter V). Rats on a diet containing 10 per cent of *l*-tyrosine show purulent keratitis, and swelling and redness of the feet and legs (Hueper and Martin), and both degenerative and fibrotic lesions in the viscera. On the other hand, studies of men who lived for a year on a diet of meat failed to show any harmful effects (McClellan and Du Bois).

Hyperproteinemia. A value of the plasma proteins above 8.5 gm. per 100 cc. is pathologic and is seen in hepatic disorders, venereal lymphopathy, certain acute and chronic infections, and in extreme dehydration. There are no demonstrable associated histologic lesions (Cardon, Atlas, Brunner, Aron, and Teitelman).

EFFECTS OF AN EXCESS OF SPECIFIC AMINO ACIDS

Aside from indefinite changes in animals there is only one very clear effect of an excess of a specific amino acid—cystine.

Experiments in rats and mice indicate that the normal state of the liver and kidneys depends on the dietary balance between cystine on the one hand, and choline and methionine on the other hand. With high cystine and low choline there is fatty metamorphosis of the liver and, in young animals, there is also a hemorrhagic lesion of the kidneys (Griffith and Wade).

The direct application of this knowledge to

disease in man is not clear, but choline is useful in the treatment of patients with cirrhosis of the liver.

Disturbances in the State of Intracellular Proteins

Under normal conditions the protein in the cytoplasm of cells is in an evenly distributed, homogeneous, colloidal state. In some pathologic conditions the even distribution, the homogeneity, or the colloidal state may be disturbed. These lesions are classified as degenerations and include cloudy swelling, hydropic degeneration, hyaline droplet formation, and Zenker's hyaline degeneration.

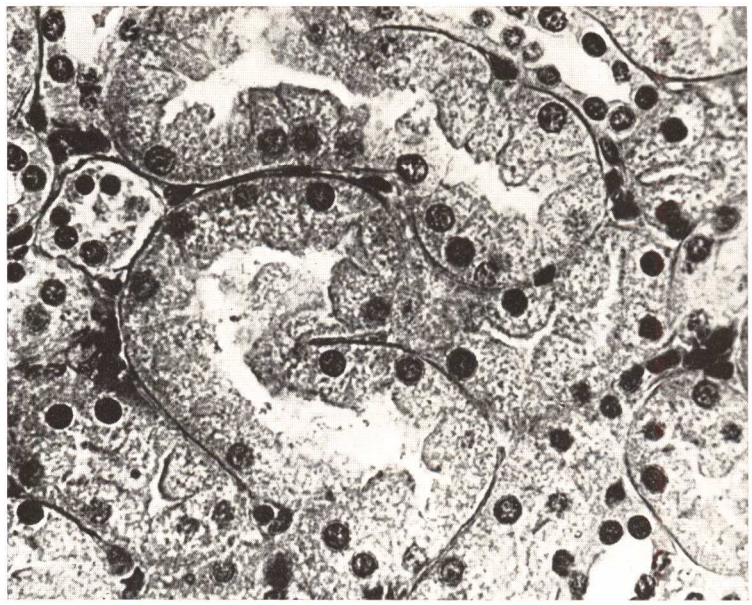

Fig. 4. Cloudy swelling of the renal epithelium. Note the granularity of the cytoplasm and variation in the chromatism of the nuclei.

Cloudy Swelling. In many pathologic states the parenchymatous viscera are enlarged and turgid, and do not have the transparency of normal tissue. In fact the tissue appears as though it had been dipped in boiling water—parboiled. When sectioned, the parenchyma bulges from beneath the capsule, and the substance of the organ is gray, semi-opaque, soft, and friable, and the architecture is partially obscured. If a small piece of the organ is crushed between a slide and a cover slip, or if an unfixed frozen section is prepared, the cells are observed to be enlarged, the cytoplasm cloudy and granular, and the nuclei indistinct. The granules in the cytoplasm are soluble in dilute acetic acid and alkalis and give the xanthroproteic reaction, indicating that they are proteins. Virchow was impressed with the cloudy appearance of the cell, and suggested the term "cloudy swelling." Others, with a chemical turn of mind, have proposed the name "albuminous degeneration," while still others, with an anatomic approach, have adopted the designation "parenchymatous degeneration." Until we know more about the exact physical and chemical nature of the condition it seems best to use the original term "cloudy swelling."

In fixed and stained sections the cells are observed to be enlarged 25 to 100 per cent above normal, and the cytoplasm is increased to a greater extent than is the nucleus, although both participate in the process (Davidman and Dolley). The cytoplasm is finely or coarsely granular (depending on the type of fixation and other technical procedures), and the nucleus may show a slight degree of hyperchromatism or hypochromatism. There is no histologic evidence that the granules are derived from the mitochondria. Early the cell walls are conspicuous, and late they may become indistinct and a part of the cytoplasm