THE PRINCIPLES OF PATHOLOGY

BY

R. A. WILLIS

D.Sc., M.D., F.R.C.P.

PROFESSOR OF PATHOLOGY
IN THE UNIVERSITY OF LEEDS

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PREFACE

The main object of the book.—Thirty years ago, as an undergraduate student, I felt the need of a comprehensive outline of pathology expounded from its general principles, and without that artificial and repetitive subdivision of the subject into " general " and " special " parts which is still customary. My subsequent experience as a teacher of pathology convinces me that I was not peculiar in that respect ; and this book is an attempt to meet such a need. It aims to embrace the whole of pathology, at least as far as a senior medical student can reasonably be expected to assimilate it ; but descriptions of lesions in the various organs are included in the accounts of *the general processes and principles* which they exemplify. I firmly believe that this is the proper approach to the subject and the one which students can best appreciate.

Order of subjects.—The order in which the main processes of pathology are presented is the one which appears to me to be the most logical and to afford the most natural transition from normal anatomy and physiology. Uncomplicated repair is described first, because it is the most fundamental and physiological of all the processes studied by pathologists. Then follow inflammations evoked by microbic and other agents, and surveys of the ways in which inflammatory diseases vary according to the tissues affected and the particular bacteria responsible. The properties of bacteria, viruses and other parasites, and the phenomena of immunity, are discussed in detail sufficient for an understanding of pathological processes, but without any intention of providing a substitute for text-books of bacteriology and parasitology. The effects of extraneous foreign bodies and poisons and the effects of nutritional and metabolic disturbances then receive general consideration, but again without presuming to supplant text-books of toxicology, nutrition or pathological chemistry. The local effects of impaired circulation are next discussed, followed by an outline of disorders of the blood itself. The general accounts of tumours of each main class are amplified by descriptions of the main regional examples within the class. No excuse is offered for the length of the chapter on epithelial tumours ; this is no more than is appropriate to the importance of these tumours in human pathology. Consideration of endocrine disturbances is deliberately deferred until after the description of neoplasms, because so many endocrine diseases result from neoplasms of the ductless glands. So also, consideration of obstruction, dilatation and other mechanical effects in hollow organs is placed near the end of the book, because most of these are but the consequences of inflammatory and reparative diseases, parasites, foreign bodies or tumours, which have already been discussed in earlier chapters. A chapter is then allotted to a residuum of sundry diseases, the very nature of which is uncertain and which therefore cannot be confidently placed in earlier sections of the book. Although this method of disposal of these diseases is not as neat as that of the " special " pathologist, who can pop them into regional pigeon-holes, the present arrangement at least has the merit of focusing attention on the fact that their causes and nature are unknown. The final chapter is a general outline of the importance of antenatal factors in pathology and of the embryological principles necessary

to an understanding of malformations. But, because teratology is not of great importance to students, no detailed description of particular malformations is attempted.

Special pathology.—While the main object of the book is to present general principles, I have tried to incorporate all essential details regarding regional peculiarities of particular diseases, and to make the information easily accessible by means of plentiful cross references and a full index. To each chapter is appended a short list of selected papers and text-books which are recommended to students wishing to amplify their knowledge of particular subjects. In these ways, I hope that the needs of the student in "special" pathology are adequately met.

Illustrations.—Most of the 300 photographs and diagrams are intended to illustrate general principles rather than diseases of particular organs. I have deliberately introduced many low-power hand-lens magnifications, for they form a valuable and too-little-used bridge between gross and microscopic pathology. Relatively few photographs of gross specimens are included, because the student can become familiar with naked-eye appearances only by examining surgical, necropsy and museum specimens.

The three appendices.—These contain notes on the meaning of names, the history of pathology, and the art of observation. To encourage a man to use his eyes and mind is to do him a greater service than to cram his head with facts.

Acknowledgements.—While the book is based largely on notes prepared for student lectures and elaborated during the last 20 years, its final preparation was carried out in the last 3 years while I held the post of Pathologist to the Royal Cancer Hospital, London. Dr. J. W. Whittick, my assistant there, has my special gratitude; his careful and critical reading of the whole of the manuscript led to many improvements in it. Some sections were read also, and thereby improved, by Miss J. C. Tolhurst, Mr. K. B. Burnside, Professor Sunderland and Dr. W. King, all of Melbourne, Australia. Figures 85, 105, 186, 191–194, 219, 221, 225, 228, 233, 246, 256, 262 and 272 are from specimens in the museum of the Royal Cancer Hospital, and I am grateful to Miss J. Hunt and her staff for the photography of these. Many of the photomicrographs also are from sections prepared by Mr. C. G. Chadwin and photographed by Mr. L. A. Cowles, of the Pathology Department of the Royal Cancer Hospital, to both of whom I am much indebted. Plate X is the work of Miss Patricia Leicester, who helped me also in the preparation of Plate VIII. For access to the specimens depicted in Figs. 27–30, 48, 50, 51, 54, 55, 60–62, 106, 121, 130, 183, 266, 276 and 277, I am indebted to the Council of the Royal College of Surgeons, London. Figures 53, 66, 73, 74 and 79 are from specimens kindly lent by Professor H. E. Shortt of the London School of Hygiene and Tropical Medicine; Figs. 164–166, from sections prepared by Sir G. Lenthal Cheattle; Figs. 99 and 100, from specimens lent by Professor J. Gough of Cardiff; Figs. 8 and 9, from sections lent by Dr. H. A. Sissons; and Figs. 88, 89 and 96–98, from sections lent by Dr. J. W. Whittick. I am indebted to Professor E. R. Clark of Philadelphia for permission to use Fig. 5, and to Dr. Beatrice Pullinger and Sir Howard Florey for Fig. 6. Miss M. Walters greatly lightened my task in

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No writer could be more fortunate in his relations with his Publishers than I am.

RUPERT A. WILLIS

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TABLE OF CONTENTS

CHAPTER 1

WHAT IS PATHOLOGY ?

DEFINITION AND SUBDIVISIONS OF PATHOLOGY

Pathology is the science which studies the causes of, and the structural and functional changes accompanying, disease. It thus includes—(*a*) *aetiology*, the study of the causes of disease, (*b*) *pathological anatomy*, the study of the structural changes in disease, including *pathological histology* or *histopathology*, and (*c*) *pathological physiology*, the study of the alterations of function and metabolism in disease, including *pathological chemistry* or *chemical pathology*.

RELATIONSHIPS OF PATHOLOGY TO OTHER SUBJECTS

(1) To anatomy and physiology

Anatomy and physiology study normal structure and functions, i.e. the structure and functions of the genetically sound body maintained in a healthy or harmless environment. " Health " or " normality ", however, is difficult to define ; even the most healthy of us have some minor inherited imperfections or predispositions which we would be better without, and we are all constantly exposed to harmful environmental circumstances which leave their marks on us—physical injuries, chemical poisons, microbic infections, nutritional defects or excesses. However, anatomists and physiologists have succeeded in defining the main structural and functional norms or standards, anything outside which we recognize as clear evidence of disease or unhealth and therefore in the province of pathology. *Pathology is extended anatomy and physiology ; it is the study of all that the body and its tissues can be and do under all possible abnormal conditions.*

(2) To special sciences studying causes of disease

The general study of the causes of disease, *aetiology*, is a branch of pathology. But some of the groups of causes are so complex that they have become the subjects of special subsidiary sciences. Thus, *bacteriology* studies the properties of the many bacteria or microscopic vegetable parasites which can cause disease ; *parasitology* studies the numerous animal parasites of man and animals ; and *toxicology* studies the properties of chemical poisons and their effects. The pathologist must have a general knowledge of the main principles of these special sciences ; but he need not, indeed cannot, be versed in all their details. *Genetics*, the study of heredity, is another special science the principles of which are important for the pathologist ; for some diseases are transmitted genetically, and others, though acquired as the result of environmental factors, are more apt to develop in some families than in others because of an inherited predisposition, called a " diathesis ".

(3) To the clinical arts

Medicine, surgery, obstetrics, and their many branch specialities (gynaecology, dermatology, ophthalmology, radiology, etc.) are not sciences but practical arts concerned with the diagnosis, prognosis and treatment of sick patients. The intelligent practice of these arts of course necessitates a sound knowledge of the relevant parts of several sciences—physics, chemistry, anatomy, physiology and pathology. The best practitioners (and by " best " is meant " best for their patients ", not " best for their pockets ") are they whose practice is based most firmly on the principles and progress of these sciences, especially pathology. Medical practice not so based—and there is much of it—is little better than quackery or witchcraft.

All three of the main functions of the clinician, diagnosis, prognosis and treatment, depend on a knowledge of pathology. *Diagnosis* is the identification of the disease from the symptoms and signs it has produced in the individual patient and from the results of special laboratory tests. Symptoms and signs—the former noticed by the patient himself, the latter detected by the examining physician —are the manifestations of the altered structure and function which constitute the pathology of the case. Symptoms and signs can be understood and properly interpreted only in the light of pathology. Throughout his career, both as student and doctor, the wise practitioner will assiduously cultivate the habit of relating symptoms and signs to pathological changes. The greater his knowledge of these changes, the better diagnostician he will be. For this reason, he will never lose touch with the laboratory and necropsy room, but will ensure that he actually sees the particular lesions removed surgically from his patients or revealed by post-mortem examination. Thus he will maintain his knowledge of real, as opposed to imaginary, pathology ; and this cannot fail to improve his interpretation of symptoms and therefore his diagnosis in future patients. Throughout this book, the writer has deliberately mentioned those main symptoms and signs which accompany, and are explained by, the lesions under discussion. *Prognosis*, the art of predicting the likely outcome of disease in the particular patient, clearly depends on a sound knowledge of pathology ; for it requires on the one hand an understanding of the natural history or progress of that disease in general, and on the other assessment of its severity and the extent of its lesions in the particular case—both of which are in the province of pathology *Treatment* also often depends on pathology ; for example, the operability or otherwise of a particular case can be decided only from a knowledge of the nature and distribution of the pathological changes present.

COMPARATIVE AND EXPERIMENTAL PATHOLOGY

(1) Comparative pathology

Comparative pathology is the study of the same or similar diseases in different species of animals Animals suffer from injuries, microbic and other parasitic diseases, tumours and nutritional disturbances identical with or closely similar to those of man ; and study of the progress and pathology of a disease in susceptible

animals has often shed light on the human disease. In another way, too, animal pathology is of special importance to human pathology ; some human microbic infections are acquired by transfer from infected animals, e.g. bovine tuberculosis, plague, anthrax and hydrophobia. Mammalian diseases are of course the most closely similar to those of man ; but the scientific student of pathology finds as great an interest also in the diseases of all classes of the animal kingdom. Birds, fishes, amphibians and reptiles suffer from their own peculiar varieties of tuberculosis and other bacterial infections ; tumours occur in all classes of vertebrates and even in some invertebrates, e.g. the honey-bee and the oyster ; much has been learnt from the study of regeneration and repair in amphibia and invertebrates ; and the fundamental phenomena of inflammation can be usefully seen in even so lowly a creature as the earthworm.

(2) Experimental pathology

Experimental pathology greatly amplifies our knowledge of naturally developing diseases in man and animals, and this in the following different ways. (i) When a disease has been of unknown causation, its cause has often been discovered by ascertaining how to reproduce it experimentally in animals. This applies not only to most of the microbic infections, but also to vitamin deficiency diseases, endocrine diseases, many kinds of toxic and nutritional disturbances, and to some kinds of tumours. (ii) Animal experiments have often elucidated the routes of entry of particular infections in the human body, e.g. of the pneumococcus into the lungs, or of the virus of infantile paralysis into the central nervous system. (iii) When a patient is suffering from a disease of obscure nature, appropriate animal tests may enable its cause to be identified ; e.g. a fluid or discharge from a lesion suspected of being tuberculous may, on injection into a guinea-pig, give the animal obvious and easily identifiable tuberculosis, thus establishing the diagnosis. (iv) The progress of a disease and the development of its lesions can often be followed more completely in affected animals killed at different stages than in human cases. For example, the development of tuberculosis in guinea-pigs inoculated with tubercle bacilli, or of skin cancers in mice painted with carcinogenic substances, or of cirrhosis of the liver in animals given carbon tetrachloride, can be examined at all stages in large series of animals killed at selected intervals. (v) The effectiveness of a method of treatment or prevention can often be tested on suitable experimental animals ; e.g. the protective value of immunization against bacterial infections, or the value of particular drugs in the treatment of established infections. Experiments on animals also enable us to assess the importance of such general factors as impaired nutrition, vitamin deficiencies, or blood loss, on the susceptibility to, or the progress of, particular infections or other diseases. (vi) Breeding experiments have clarified the part played by genetic factors in certain inherited diseases or in diseases with an inherited predisposition.

For the foregoing reasons, the modern pathologist needs to know not only the structural and functional changes produced by disease in human tissues, but something also of the corresponding diseases in animals, and of the scope of experimental work in elucidating the causes of disease and the progress of pathological lesions.

DIFFICULTIES ENCOUNTERED BY BEGINNERS IN PATHOLOGY

Many a student, coming fresh from his study of normal anatomy and physiology, which seem so precise and clear, finds pathology a perplexing subject. There are three main reasons for this, namely (*a*) the diverse appearance of diseased tissues, (*b*) the diverse causation of disease, and (*c*) uncertainties as to the nature and causes of some diseases. It will be helpful to consider these points more fully.

(1) The diverse appearance of diseased tissues

While anatomy and physiology deal with nearly invariable or standard structures and processes, the abnormal structures and processes studied by pathology are very diverse in both nature and degree. The organs and tissues of two normal human beings closely resemble each other, but diseased organs and tissues are variable in their naked-eye and microscopic appearance. No two examples of a disease are ever exactly alike. To take concrete examples, if you have learnt the gross and microscopic structure of the lungs of one healthy man, then, except for minor and negligible differences, you know the structure of the lungs of all other healthy men. But this does not apply to diseased lungs; pneumonia in the lung of one man looks very different from that in another, according to its extent, stage, severity and the particular germ which has caused it; so also tuberculosis of the lung is infinitely variable in its appearance, extent and complications; fatal cancer of the lung in one man may appear as a tiny focus found only with difficulty, and in another as a huge mass almost completely replacing the organ and perhaps many other intrathoracic structures as well. Not only does each kind of disease appear in many different guises and stages; but two different diseases may closely resemble each other in gross appearance and even in microscopical structure. For example, from the naked-eye appearance of a mass of abnormal tissue in a lung it may be impossible to say with certainty whether it is due to simple pneumonia, tuberculosis or cancer. The beginner in pathology naturally finds this diversity of appearances very confusing; but let him take heart; all pathologists once felt just as confused as he, and even the most experienced can still make mistakes when confronted by unusual examples of quite common diseases. Constant experience in seeing and handling specimens is the only way to become proficient in pathological anatomy; therefore the student should take every possible opportunity of seeing operation, post-mortem and museum specimens. He cannot see too many of even the most common and obvious lesions.

(2) The diverse causation of disease

Pathology includes a very difficult aspect from which anatomy and physiology are exempt—that of causation. The pathologist's task is not ended when he has described the structural and functional changes in tissues; he must then identify, if he can, the abnormal factors which evoked those changes. This task is sometimes easy, sometimes difficult and sometimes impossible. To revert to the lung as an example; the pathologist sees in a diseased area the gross and microscopic appearances characteristic of tuberculosis; it is usually a simple matter to prove this by demonstrating the presence of tubercle bacilli. On the

other hand, seeing changes characteristic of pneumonia, he knows that some microbic infection has been at work ; but it may be difficult or impossible to name the causative microbe, which might be any one of half a dozen different species and which may not be easily identifiable in the pneumonic tissue. A great deal of a pathologist's time is devoted to detective work, i.e. to the search for parasitic, chemical or other agents responsible for lesions the causation of which is not at once obvious. Now the causes of disease are many and diverse ; the pathologist must become familiar with them all and with the kind of changes they evoke in living tissues. This complex subject of causation or aetiology is a great source of confusion to the beginner, who cannot at once appreciate in which diseases our knowledge of causation is clear and definite and in which it is still obscure. This brings us to the third point, namely—

(3) Uncertainties as to the nature and causes of some diseases

Our knowledge of the causes of some main classes of disease is very full, though still not complete ; this applies, for example, to the great majority of parasitic diseases, whether due to viruses, bacteria, fungi, protozoa or metazoa. On the other hand, our knowledge of the causes of tumours, though advancing, is still fragmentary. There are many other common diseases the causation of which is often unknown or obscure, e.g. nephritis, " cirrhosis " of the liver, gastric and duodenal ulcers, many blood diseases and many endocrine diseases. Because these diseases are of unknown or doubtful causation, many opposing hypotheses have been advanced regarding them ; and it is very difficult for the beginner in pathology to distinguish between established facts and hypothetical speculations. One of the greatest services the teacher can do is to make this distinction plain in every subject discussed. He should often tell his students, " These are our speculations, but we really do not know ". In this book I try to distinguish clearly between established knowledge and mere speculation on controversial topics.

THE CAUSES OF DISEASE

Man is a very complex organism set in a very complex physical, chemical and biological environment. His mechanical ingenuity and his physical restlessness, in mechanized industry, in traffic and in war, make him much more liable than other species to physical accidents. He is exposed to great changes of temperature and humidity ; he is bathed in sunlight or immersed in fog. The air he breathes (especially in workshops, mines and populous cities) contains many kinds of gaseous impurities and dusts. The food he eats is extremely complex and diverse ; he consumes also many artificial chemical substances such as drugs, flavouring agents, dyes and antiseptics. He encounters and contends with many other species of living creatures, some of which have become adapted to a parasitic residence in his body. His crowding in great cities makes some of these parasites a special menace, spreading quickly as they do from victim to victim in epidemics.

In man's complex environment we find the causes of most of his ills. But man himself is a variable creature. Men differ intrinsically from one another, not only in the shapes of their noses and the colour of their hair and the quality

of their brains, but also in their susceptibility to disease. The intrinsic differences between men are partly inborn or genetic, and partly acquired because of differences of nutrition and other environmental factors. We must therefore group the causes or antecedents of disease into two main classes as follows :

I : ABNORMAL ENVIRONMENTAL FACTORS

(1) *Physical injuries or trauma:*	Mechanical, thermal, chemical, radiational, electrical.
(2) *Parasites:*	Bacteria, fungi, viruses, protozoa, metazoa.
(3) *Harmful inanimate substances:*	(*a*) Inert, insoluble material or "foreign bodies". (*b*) Soluble poisonous or toxic substances.
(4) *Nutritional abnormalities:*	(*a*) General ; deficiency or excess of particular food substances, vitamins, minerals or water. (*b*) Local ; from impaired blood supply.
(5) *Carcinogenic or tumour-evoking agents :*	Chemical, physical, parasitic.

II : ABNORMAL CONSTITUTIONAL FACTORS

(1) *Genetic or inherited factors:* determining or predisposing to the development of particular diseases.

(2) *Non-genetic factors* predisposing to particular diseases, e.g. previous defective nutrition or previous disease.

A few explanatory comments will clarify this tabulation.

(1) Abnormal environmental factors

(*a*) *Physical injury or trauma*

This is the most obvious and direct kind of injury inflicted by environmental factors. Such factors may be purely mechanical, producing incised or lacerated wounds, contusions (bruises), fractures of bones, dislocations of joints, or tearing of muscles, ligaments or tendons. Thermal injuries comprise burns produced by subjecting tissues to excessive temperatures, and chilblains and frost-bite produced by subnormal temperatures. Caustic chemical substances, such as strong acids or alkalis, destroy tissues as effectively as heat and produce chemical burns. Various kinds of radiations damage tissues, as in sunburn, X-ray burns and radium burns. Electrical discharges may produce local burns or may disorganize internal parts and cause instantaneous death.

(*b*) *Parasites*

Plant or animal parasites capable of residing and multiplying in the tissues of human and other hosts, form the largest class of extrinsic causes of disease. We speak of them as *pathogens*, i.e. disease-producers ; and in ascending order of size they include viruses, bacteria, fungi, protozoa and metazoa. *Viruses* are the smallest pathogenic organisms; many of them are ultramicroscopic, while others are just visible microscopically. There are about 30 species of viruses which are known to be pathogenic for man, the diseases which they cause including such important ones as influenza, small-pox, measles, and infantile paralysis. *Bacteria* are microscopically easily visible unicellular vegetable organisms, about 40 distinct species of which produce human diseases ; these include boils and other purulent (i.e. pus-producing) infections, tuberculosis, typhoid fever,

diphtheria, tetanus and plague. *Fungi*, closely allied to bacteria, but of filamentous or multicellular colonial types, cause about a score of distinct human diseases, e.g. thrush, ringworm and various other skin infections. *Protozoa* which are pathogenic for man include the amoeba of amoebic dysentery, the three types of plasmodia or sporozoa which cause malaria, and the flagellate trypanosome of sleeping sickness. *Metazoa* or multicellular animals parasitic for man may reside on the surface of the body, e.g. mites, ticks or fleas ; or in the alimentary canal, e.g. tapeworms or hookworms ; or they may infest the tissues or blood stream, e.g, hydatid cysts, trichina, or filaria.

(*c*) *Harmful inanimate substances*

Many kinds of harmful foreign substances may enter the body through the respiratory or alimentary passages or through wounds. Some of these are insoluble or chemically inert particulate masses which are harmful only mechanically, and are called " foreign bodies ", e.g. a peanut or grass-seed inhaled into the lungs, a swallowed bone or denture obstructing the oesophagus or intestine, or a needle or fragment of glass which has penetrated and become embedded in the tissues. A rather special class of extraneous foreign substances which are insoluble or only slightly soluble comprises those which are inhaled as fine dusts. These include carbon, silica and several kinds of silicates, and the diseases of the lungs due to them are collectively called " pneumoconioses ". Ingested or inhaled noxious substances which are more or less soluble are of enormous variety; their sources, chemical properties and effects are the subject matter of the science of toxicology. Some of them have long been recognized as occupational or accidental poisons ; others are drugs which, though used in treatment, sometimes produce serious toxic effects ; others are present in small quantities in our food or the atmosphere and their toxic properties are less clearly recognized.

(*d*) *Nutritional abnormalities*

Nutritional disturbances may be general, affecting the body as a whole because of alterations of diet ; or they may be local, affecting only part of the body, usually because of locally impaired blood supply. Examples of general nutritional disturbances are starvation and its effects, vitamin deficiency diseases such as rickets and scurvy, and mineral deficiency diseases such as iron-deficiency anaemias and iodine-deficiency goitres. Local nutritional disturbances are mainly due to interferences with the blood supply of parts. Clearly, if the arterial blood supply of a vascular part is cut off completely, the part will die ; if the supply is much reduced, the tissues of the part will show varying degrees of atrophy or degeneration. Arterial obstruction is the essential cause of many common pathological lesions, e.g. gangrene or death *en masse* of the distal parts of limbs, atrophy or softening of the brain, atrophy or degeneration of the myocardium. Bulky tumours which have outgrown the available blood supply, or have obstructed their own vessels, often show extensive degenerative changes or death of tissue.

(*e*) *Carcinogenic agents*

These comprise chemical, physical or parasitic agents which can evoke neoplasms or true tumours. Chemical agents of this kind include certain polycyclic aromatic hydrocarbons, certain azo-dyes and certain aromatic amines.

Carcinogenic physical agents include ultra-violet rays, X-rays and gamma-rays. A few special parasites are capable of evoking neoplasia in the tissues infested by them; they probably do so by producing chemical carcinogens in the tissues. Some peculiar tumours in birds are produced by filterable virus-like agents which multiply in the tumours as they grow.

(2) Abnormal constitutional factors

(a) Genetic or inherited causes of disease

The causes of most diseases are wholly or mainly environmental; in only a small number are genetic peculiarities the sole or main cause. A bullet, a burn or a bacterium will play havoc with you no matter what your ancestry; and there are no genes which will protect you from starvation or malaria or tape-worms. However, there are a few diseases which are due entirely to inherited chromosomal anomalies, and which develop irrespective of the environment. Examples of such purely genetic disorders include—familial jaundice accompanied by abnormal fragility of the red blood corpuscles; the bleeding disease, haemophilia, which is transmitted by females but affects males only; colour blindness, cleft iris, retinal tumours in infants, and some other anomalies of the eyes; webbed digits, supernumerary digits and some other malformations of the limbs; hereditary ataxia, and several other rare diseases of the central nervous system.

(b) Non-genetic factors predisposing to disease

It is but common-sense and everyday knowledge that people's resistance or susceptibility to particular acquired diseases depends on their previous nutrition and state of health. General undernourishment and vitamin deficiencies predispose to tuberculosis and other bacterial infections. One bacterial disease often predisposes the patient to another, e.g. influenza or whooping cough predisposes to pneumonia. On the other hand previous attacks of many infective diseases, e.g. small-pox, measles, typhoid fever and diphtheria, leave behind a more or less permanent immunity which protects the person from subsequent attacks.

This is the place to mention the importance of *mental factors in the causation of disease*. In the first place, through their ignorance, carelessness and lack of hygiene, mentally inferior persons—whether inferior by inheritance or training, nature or nurture—are more liable than others to various injuries, infections and nutritional disturbances. In the second place, in otherwise healthy people, severe mental strain or emotional upsets may produce important bodily effects culminating in disease. Thus, hurry, worry and emotional stress are well recognized factors in the causation of gastric and duodenal ulcers, arterial disease and hypertension, and exophthalmic goitre.

THE MAIN KINDS OF PATHOLOGICAL CHANGES IN TISSUES

Living tissues, when injured by the extrinsic causes just outlined, may display one or more of the following distinct kinds of pathological changes:

(1) Repair
(2) Hyperplasia
(3) Inflammation
(4) Neoplasia
(5) Retrogressive changes
(6) Developmental malformations

(1) Repair

Repair is proliferation of tissues to fill a breach caused by injury or disease. The simplest examples are seen in the healing of wounds and the union of fractures. Such gaps in the tissues become filled in by new reparative tissue consisting of young multiplying blood vessels and fibroblasts (or, in bone, osteoblasts) produced by multiplication of these elements from the surrounding tissues. Later this young reparative tissue changes into a scar in soft tissues, or effects bony union of a fractured bone.

(2) Hyperplasia

Hyperplasia is proliferation of cells of a particular kind either (a) as a compensatory response to loss of tissue of the same kind, or (b) as a result of disturbed hormonal control of the tissue. Examples will make these meanings clear. If liver tissue is lost, either by excision or by damage by poisons, new liver cells are freely produced by mitotic proliferation from surviving liver tissue ; removal of part of an endocrine gland is usually followed by proliferation of the cells of the remainder so that the normal amount of the tissue is almost or quite restored ; loss of blood is followed by hyperplasia of the red bone marrow and increased haemopoiesis. These are examples of compensatory hyperplasia or regeneration. Such compensatory regeneration is allied to repair, from which however it differs in the specificity of the regenerated cells and in the fact that the regeneration is not restricted to the site of tissue loss. The function of repair is to fill a breach ; the function of regenerative hyperplasia is to compensate for the loss of cells of a specific kind. The second kind of hyperplasia, that due to hormonal disturbances, is seen in the endocrine glands or in organs which are under endocrine control, such as the breast and uterus. The cyclical changes in cellular proliferation and function in the cells of the breast or of the endometrium depend on cyclical variations in the balance of various hormones. Clearly then, an improper balance of the hormones concerned may bring about abnormal proliferations of the special cells of the breast or endometrium even when there is no proper physiological call on them.

(3) Inflammation

Inflammation is the immediate vascular and exudative reaction of tissues to injuries. When tissues are injured by physical or chemical agents or by microbic parasites, they become inflamed, red and swollen. The redness and swelling are due to dilatation of the small blood vessels and to exudation of fluid and leucocytes from the blood into the tissue spaces. These changes subside when the products of the damaged tissues have been absorbed and the invading microbes have been destroyed. Inflammation and repair, though often seen together, should be distinguished from one another ; the one is a prompt vascular and exudative response, involving no cellular multiplication, and its function is removal of the damaging agent and of the products of tissue damage ; the other is a slower proliferative response, the function of which is to fill the breach created by the injury in the tissues.

(4) Neoplasia

Neoplasia is an abnormal mode of growth of tissues which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner

after cessation of the stimuli which caused it. The abnormal mass of tissue produced is called a neoplasm or true tumour. Tumours form a very important class of pathological lesions; dangerous types of them are popularly called "cancers". The distinctive feature of tumours is that they continue to grow progressively, irrespective of the structural and functional requirements of the body. In this they differ fundamentally from masses of reparative or hyperplastic tissue, in which of course the cellular multiplication is limited in amount and duration in accordance with structural and functional needs. Neoplasia involves a permanent irreversible change in the cells, manifesting itself in excessive multiplication, and transmitted indefinitely to the descendants of the affected cells. The extrinsic causes of this persistent excessive habit of growth are called carcinogenic agents or carcinogens. Those so far discovered include various special chemical substances (e.g. certain hydrocarbons, azo-dyes and organic amines) and radiations of short wave-lengths (ultra-violet light, X-rays and *gamma* rays). The external causes of many kinds of tumours are still unknown, but more of them are gradually being discovered. Of the all-important cellular change which they evoke and which is the real secret of the neoplastic habit of growth, we as yet know next to nothing.

(5) Retrogressive changes

This is a very heterogeneous group of changes in cells and tissues, resulting from many different causes—the action of poisonous substances, disturbances of nutrition or oxygen supply, metabolic disturbances, etc. The most extreme examples are those of necrosis or death of tissues *en masse*, whether from deprivation of blood supply, e.g. gangrene of the limbs or softening of the brain from occlusion of the arteries, or from the action of poisons, e.g. necrosis of the liver from carbon tetrachloride. Short of total necrosis, however, tissues which are starved or poisoned may survive but may show a great variety of degenerative structural changes—e.g. intra-cellular or extra-cellular accumulations of various lipoid substances, abnormal proteins, glycogen, pigments or calcium salts. Or they may show wasting or atrophy of the more specialized parenchymatous cells —secreting epithelia, muscle fibres or nerve cells.

(6) Developmental malformations

These form a special class of structural abnormalities, due to disturbances of development of the young organism either from damaging environmental agencies or from genetic defects. Damage inflicted on a young embryo, whether by chemical poisons, microbic toxins or nutritional defects, may kill it outright; but, if it survives, it may have suffered such injury to growing parts that these now develop imperfectly. There may be arrest of development of particular parts which may remain stunted and deformed, or which may fail to coalesce as they should; or there may be abnormal persistence of embryonic structures which normally disappear, e.g. the thyroglossal duct or the vitelline duct; or there may be extensive deficiencies of large parts of the body; or, if the disturbing agencies have acted very early in embryonic life, there may be duplication, bifurcation or other anomalies in the formation of the primary axis, leading to double monsters. Malformations of these various kinds are due much more often to