MUIR'S TEXT-BOOK OF PATHOLOGY

SEVENTH EDITION

REVISED BY

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PREFACE TO THE SEVENTH EDITION

In preparing this edition my object has been to meet primarily the requirements of medical undergraduates. I have followed the general pattern of previous editions as established by Sir Robert Muir, but the progressive expansion in knowledge has necessitated very careful selection of topics and, to avoid undue increase in size, the elimination or reduction of certain topics no longer so important in clinical medicine and surgery today. In so doing I have followed Sir Robert Muir's principle of relying primarily on my own observations and experience as a hospital pathologist, including such newer concepts as seem to me likely to be helpful to the young pathologist in training. The time is still far off when it will be possible to arrange the text under etiological headings alone, and I believe that it is best to discuss first the chief morbid processes and then in turn the various systems of the body with the diseases to which each is subject. It is fashionable today to say that students are taught too much detail and that more stress should be laid on the importance of general principles. But general principles can be derived only from a multiplicity of special examples ; accordingly I make no apology for retaining the previous arrangement in general or for the fact that this arrangement necessitates both detailed description and some repetition.

Considerable re-arrangement of the text has been carried out in the course of a thorough revision of sections which, I hope, incorporates the essential facts of new work and indicates the lines along which knowledge is advancing. The account of the process of repair in special tissues, e.g. bone, nerve, has been brought into the general Chapter III as more convenient for undergraduate instruction. The chapters on Tumours have been extensively remodelled, grouping both simple and malignant growths together according to their tissue of origin in Chapter VI, and incorporating brief accounts of certain rarer tumours which present special diagnostic or prognostic features. Chapter VII is therefore devoted to consideration of the etiology of neoplasms. Special attention has been paid to the rapidly advancing field of hæmatology, without overburdening the text with minutiae better studied in monographs, but the newer relationships of hæmatology and immunology have been indicated. The section of fluid and electrolytic balance has been revised in the light of much new work, with the help of Dr. D. A. K. Black, in view of its growing clinical importance.

The chapter on the endocrine glands has been virtually re-written, so great has been the progress in this field. About 100 additional illustrations have been incorporated and many of the older plates have been replaced by new and larger figures.

Pathology is the systematic study of the nature and causes of disease processes. Disease is the result *partly* of changes in the tissues brought about either by physical or chemical agents or living parasites, and *partly* of the reaction of the tissues to such changes. Disease has no independent existence in itself; its manifestations require for their development both the *action* of the exciting cause and the *reaction* of the individual patient. No man is quite as his neighbour and thus there is infinite variety in the manifestations of disease due to any single cause. Before the elaboration of the manifold techniques of laboratory and clinical investigation now in use, Pathology was very much the study of morbid anatomy and there is still nothing offered by the teacher of Pathology to his students which compares with the opportunity to learn by attendance at the necropsy. Here the culmination of the natural history of a disease, unfolded perhaps over many months or years, may be exposed at a stroke, and when the case-record is viewed in retrospect, the association of this morbid change with a particular physical sign or clinical symptom is impressed on the memory. This opportunity is afforded to most students of Medicine for only a brief period in their lifelong contact with disease. The importance of the necropsy in the teaching of Pathology can hardly be over-emphasised and there is no substitute for experience gained in the post-mortem room. The study of preserved tissues and photographs of diseased organs can be only supplementary to this, but the effort required in learning from them will be amply repaid, for museums have the advantage that they can be systematically arranged to illustrate the formal exposition of the subject, while variations of the same essential change can be exhibited side by side. Similarly, familiarity with microscopic preparations has a special value, for although few medical students are microscopists by inclination, such preparations have the advantage that those already accustomed to interpreting histology in the light of physiological function can often see more readily in the microscopic than in the gross specimen the morbid function implied in the morbid architecture. For this reason I have preserved and increased the ample illustration of the text by photomicrographs and it is my experience that the use of the systematic text-book beside the microscope is the quickest way of learning the steps by which morbid anatomy may be translated into the clinical signs of disease.

Where uncertainty exists about the interpretation of clinical observations or experiments I have thought it desirable to show both sides of the argument, because dogma is of less value to the student than the training of his critical faculties. If he is disappointed to find many diseases still with unknown etiology and some with no apparent

morbid anatomy, he will none the less discover that medical or surgical treatment is most likely to be successful where the etiology and morbid physiology of the disease process are known. In the practice of clinical medicine the Art of knowing how to deal with the sick person and his environment still contributes in no small measure to the success of therapy, but the position of Medicine as a Science is steadily advancing. The last fifty years have seen greater advances in the treatment of disease than all the rest of the five hundred years and more since this University was founded, and this progress is almost wholly the outcome of pursuit of knowledge in the basic sciences.

There are certain specialities with which it is no longer possible to deal at any useful length in a text of this kind, and for the details of parasitology, as long since for bacteriology, reference must be made to the readily accessible works on these subjects. At the end of the text there is a brief bibliography which is not intended to be exhaustive but to introduce the student to a selection of literature which may be read with interest and profit. Some of the works cited are of great historical interest and are included in order to give the actual words of those who made the original discoveries, others provide further details of the present state of knowledge on particular subjects. In the latter category I have thought it more helpful to quote only one or two authoritative references in each section rather than to provide an extensive list from which the student would require to make a choice.

It is a pleasure to thank my colleague, Professor J. W. Howie, and members of my staff, Drs. H. E. Hutchison, J. R. Anderson, B. Lennox, G. B. S. Roberts, J. A. Milne, A. T. Sandison, P. Macfarlane, A. J. Watson, R. B. Goudie and Mary A. Catto, for help in various ways in the revision of the text.

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To my secretary, Mrs. Margaret Morton, and to my departmental librarian, Miss Audrey Carbis, I am deeply grateful for their meticulous help in many ways but above all in the reading of proofs and preparation of the index.

Finally, it is with pleasure and gratitude that I acknowledge my indebtedness to my wife not only for her practical help in the revision

of the text and index but for her unfailing sympathy and understanding which have sustained me at all times and without which this increasingly difficult revision could not have been accomplished.

D. F. CAPPELL.

University of Glasgow, 1958.

PREFACE TO THE FIRST EDITION

This book is intended primarily as a text-book for students of medicine. It is based on the course of instruction which I have given in Glasgow University, and various expansions and additions have been made, with a view to rendering it more generally useful. The subject of Pathology has now become so extensive that in a book of this size selection of subjects is essential for any satisfactory treatment, and in considering their relative importance I have been guided by two main considerations. I have endeavoured, in the first place, to give due weight to the scientific aspect of the general pathological processes, and, in the second, to describe those pathological changes in the various organs, which are of special importance in relation to Clinical Medicine and Surgery. The subject-matter thus falls into two main portions corresponding roughly with General and Special Pathology, though these terms are not used, as it seems inadvisable, in a book of this nature, to draw any sharp distinction. I have been guided mainly by my experience as a teacher and as a hospital pathologist in carrying out the selection referred to. While the work deals chiefly with the structural changes in disease, I have made it my object also to show the bearing of these on disturbances of function, as studied by the clinician, and to incorporate the principal results of experimental and chemical research.

In conformity with the usual practice nowadays, Systematic Bacteriology has been omitted, as have also the subjects of Diseases of the Special Senses and of the Skin, Tropical Diseases, Parasitology, and Teratology, as these can be satisfactorily treated only by specialists in separate works. I have given for convenience, however, an account of the more important parasites in connection with the lesions produced by them, and of the chief congenital abnormalities in relation to the several organs. I have relied as far as possible on my own observations, but I am, of course, greatly indebted to the works of others. These are too numerous to mention in full, but I should wish to state my obligation to the works on Pathological Anatomy by Aschoff and by Kaufmann, for details in connection with the less common lesions. I have given in footnotes references to other books which have been of value and which are recommended to the student.

It is a great pleasure to me to record my indebtedness to those who have helped me in the work. To my sister, Miss S. C. Muir,

who has corrected the proofs, and to my colleague, Professor C. H. Browning, who has read the manuscript and given me valuable criticism, I offer my sincere thanks ; likewise to Professors J. Shaw Dunn and G. Haswell Wilson for several photomicrographs ; to Professor R. Stockman for illustrations from his work, *Rheumatism and Arthritis* ; to Drs. John Cowan and W. T. Ritchie for illustrations from their book, *Diseases of the Heart* ; to Dr. A. H. Drew, Professors A. M. Kennedy, J. H. Teacher, and M. J. Stewart for photographs or blocks ; to Professor E. H. Kettle, Drs. A. Ninian Bruce, J. W. S. Blacklock, D. F. Cappell, E. M. Dunlop, G. W. St. C. Ramsay, and Douglas S. Stevenson, for the loan of microscopic preparations. To all these I offer my grateful acknowledgments. The sources of the figures referred to are indicated in the text. Unless where otherwise stated, the drawings are by Mr. Richard Muir of the Pathological Department, University of Edinburgh, and the photographs of naked-eye specimens and the photomicrographs are by Mr. John Kirkpatrick of the Pathological Department, University of Glasgow, who has assisted me also in the preparation of the Index. In thanking them also, I desire to express my appreciation of the skill and care which they have given to the work. Most of the photographs of specimens are from preparations in the Museum of the Western Infirmary, Glasgow.

R. M.

GLASGOW,
August, 1924.

TEXT-BOOK OF PATHOLOGY

INTRODUCTION

Pathology is the science of disease, i.e. the study of disease by scientific methods. Its scope is wider still, however, as it deals with anything abnormal, and abnormalities in structure may not be attended by disease in the ordinary meaning of the term. The methods of study are those of physiology, and are thus of various kinds—physical, chemical, and anatomical; and they are applied both in observation and in experiment. Disease is manifested alike by subjective symptoms resulting from disturbance of function, and by objective signs and changes which can be scientifically investigated. The change or abnormality is ordinarily described as being either morphological or chemical in type or both. One important department of pathology thus comes to be a search for and study of abnormalities in structure, which underlie and are the causes of symptoms and disturbances of function. From an evolutionary standpoint, function ultimately governs structure, in that structure has been progressively modified to subserve changing functional requirements. In disease, however, alterations in structure may be rapidly brought about by morbid processes, and acute derangements of function then result. Thus in disease altered structure often, though not invariably, precedes and determines altered function. Such structural changes may be of a gross kind and visible to the naked eye, or they may be detectable only by the microscope. We have thus the two departments of study, *pathological anatomy* and *pathological histology*. Again, it may not be possible to find any visible alteration, or *lesion* as it is usually called. In fever, for example, there is abnormal metabolism, notably of proteins, as is shown by alterations in excretion and in other ways, but frequently we cannot point to a visible change in the tissues which indicates that this has occurred. So also many rapidly-acting poisons may cause death without producing a visible lesion, but we may be able to detect and identify the alteration in cellular enzymatic activity which will explain the fatal result. Thus the poisonous action of cyanides is so rapid that no lesion may be visible, but biochemical investigations have shown that the effects depend on selective inhibition of the cytochrome-oxidase systems of

the cells and thus that death is attributable to cessation of intracellular respiration. Accordingly, whilst the presence of a structural change as a cause of disturbed function is taken as a working principle, there are cases in which the lesion is too minute to be discoverable as yet; and, after all, alterations which are not visible except with the highest powers of the microscope are nevertheless relatively gross in nature. From the practical point of view it is important to distinguish between lesions which are capable of resolution or cure so that the part returns to normal, and those which are permanent to a greater or less degree. In an acute catarrh, for instance, complete recovery may take place, whereas, if there are repeated attacks or if the condition becomes chronic, then changes of a permanent character often follow.

Chemical changes in the tissues and fluids of the body in disease, which may be regarded as the expression of disturbances of the functional activities of cells, are of high importance, and our means of investigating them are being steadily improved. Many such changes can be detected by ordinary qualitative or quantitative methods, while for others the development of reliable quantitative methods using only minute amounts—*microchemical methods*—has enabled notable advances to be made. By the combination of chemical tests with subsequent microscopic examination—*histochemical methods*—further insight has been gained, and a valuable addition to these methods has been the incineration of microscopic sections and subsequent chemical study of the mineral residues. It is, however, essential to recognise that many of the most important changes in the body are as yet inaccessible to ordinary chemical methods; for instance, in infection most of the symptoms and tissue changes are due to toxins formed by micro-organisms, but there is no chemical means of detecting these poisonous substances. Their presence and mode of action are discoverable only by indirect or by biological reactions, which will be afterwards described. The *presence* of certain substances known generally as antibodies, which appear in the blood in association with the development of immunity, is of much importance in connection with the diagnosis and treatment of disease and is detectable by refined quantitative chemical and physical methods, e.g. by electrophoresis, but their *specificity* can be determined only by biological tests.

The pathologist, however, has to study not only particular changes in the tissues and organs in any condition of disease, but has to elucidate the methods by which they have been brought about. As was established first by the work of Virchow, all disturbances of function and structure in disease depend upon alteration of the life of cells, evidenced partly by damage and partly by increased activity. By his dictum, that all cells are formed by the proliferation of pre-existing cells—*omnis cellula e cellula*, Virchow placed pathology on a scientific basis as *cellular pathology*, and showed that the basis of the phenomena of any one disease was a series of changes occurring in

the cells of the body. The body, however, is something more than a collection of cells with certain properties and potentialities; it is a co-ordinated whole, as is, of course, evident in normal growth and development, and equally so in conditions of disease. This co-ordination is seen not only in the interdependence of structurally related parts, but in the reciprocal control of the various endocrine organs by hormones, a rise in the blood level of which is normally followed by a fall in the output of the corresponding trophic hormone, e.g. thyroxine inhibits thyrotrophic hormone production.

In the study of the changes in the body in a particular disease, the purposes in view will be found to be mainly of twofold nature. (*a*) Firstly we have to discover a lesion and trace its evolution. Each particular change found represents a stage in a series of changes, and the nature and sequence of these have to be elucidated. For example, the appearance of an acutely inflamed tissue forms a complex picture, and we have to study each individual phenomenon and show how the departure from the normal has been reached. We have thus to deal with certain *pathological processes*, as they are called, and these are for the most part of a general character, and present the same main features wherever they are found. (*b*) Secondly we have to discover the *cause* which has started the particular pathological process and has led to the departure from the normal. As we have indicated, Virchow and his co-workers established the importance of structural change in relation to functional disturbance, and showed the nature of the pathological processes concerned. But for a considerable time no explanation of their mode of origin could be given. Such a process as inflammation could be minutely studied and its whole course traced, but nothing could be said of its etiology except in a very general way. It was only when bacteria were shown to be the causes of most inflammatory changes and of many specific fevers, that the causation of disease became intelligible. The start, course and termination of inflammatory processes were seen to depend on the vital activity of bacteria, and the problem of the course of the pathological change came to be one of the conditions regulating the life and death of bacteria in the tissues. Structural pathology thus had many of its problems elucidated by bacteriology. But if bacteria are to be regarded as the *seeds* of disease, it is now realised clearly that the *soil* is also fundamentally important and the behaviour of the tissues determines whether exposure to infection will result in a typical attack of a disease, an abortive attack (recovery in either case being followed by subsequent immunity) or complete failure of the infecting micro-organisms to establish a foothold in the tissues. There is already suggestive evidence that unless a micro-organism can establish a chemical link with tissue constituents it will fail to exercise any effect. Ultra-microscopic viruses also were found to behave in a similar way to bacteria and to produce like effects.

Pathological Processes. When the cells of the body are placed

under abnormal conditions or are injured, we see a series of changes taking place ; in other words, a pathological process is started. We shall have to enquire whether such processes are new or peculiar to disease, or whether they merely represent physiological processes in abnormal conditions. In the great majority of instances the latter is the case. The changes following injury or damage are always of two essentially distinct types :

(A) In the first place, there is the direct result of the injury—the extreme degree is the death of the cells, but all degrees of degeneration, short of actual death, are met with. This simply means that living cells are necessarily vulnerable, and some of the changes which follow are the direct effect of the damage done. Such changes are sometimes called *retrogressive*, and they indicate merely that the conditions for healthy cell life have been disturbed.

(B) In the second place, when damage has been done or the conditions are abnormal, a series of *reactive* processes comes into play. They have for their object the removal of the irritant or abnormal state, and the repair of the damage. The reactions are thus *defensive* and *reparative* in nature and they are of two main kinds, viz. (*a*) increased functional activity and (*b*) increased formative activity. These correspond to processes seen in normal conditions. Increased functional activity, katabolism followed by anabolism, is exemplified by increased muscular contraction, increased secretion, increased leukocytic activity, etc. For example, emigration of leukocytes in inflammation, and their action after emigrating, are not new phenomena ; they are represented by the normal activities of leukocytes on a mucous membrane exposed to bacterial action. Increased formative activity occurs in a variety of conditions, but a typical example is seen in the process of repair. The cells in relation to the injury actively divide and afterwards form matrix, and they will continue to do so until the breach is filled. This is an example of the lighting up again of a process seen in early growth and development, and proceeds on similar lines. It is therefore not a new process. Functional and formative activities are usually present in an inverse proportion to one another at a given time, but when the former is increased unduly, involving excessive katabolism, enlargement or hypertrophy of the tissue often follows. Such hypertrophy is seen especially in muscular and glandular tissues, and is compensatory or adaptive in nature. A hypertrophied heart is an abnormal heart, but hypertrophy itself is not an abnormal process, it is merely an exaggeration of the normal state with the effect of restoring the balance between functional capacity and functional demand ; the particular condition which brings it about is, of course, abnormal. Accordingly, in all these reactive changes we see nothing peculiar to disease—the processes observed correspond with those met with in the normal development and life of the individual.

There is, however, one phenomenon of disease which cannot be

explained on these lines, namely tumour growth. Here we have to deal with a proliferative process which, however it may begin, is, at least in the end, not of a reactive nature—an indefinite and independent proliferation of cells, which have ceased to respond to the normal controlling influences of the body.

To summarise : In pathology we have to investigate by scientific methods the basis of disease—the changes underlying its symptoms, and its functional disturbances. Some of these changes can be seen, others can be detected by chemical or biological reactions, whilst in other cases no important changes have yet been demonstrated. The various changes met with represent in part the result of damage, and in part are of a reactive nature ; they are to a large extent defensive and reparative.

Etiology of Disease. In searching for causes of disease, the general principle may be accepted that a healthy organism will remain healthy unless it is affected by some disturbing cause from outside. Disease does not occur spontaneously, as no change occurs without a cause. Of some phenomena, however, no explanation can be given ; for example, the cycle of events in the life history of the individual, notably the occurrence of senescence. In the great majority of cases the disease or abnormal state is due to some disturbance acting after birth, that is, it is *acquired*. In a relatively small proportion of instances it is present at the time of birth and is then spoken of as *congenital* ; and in this type the abnormality may arise during fœtal life in various ways, and sometimes in the same manner as in the acquired form, e.g. congenital syphilis is merely infection of the fœtus *in utero*. Causes of disease are sometimes spoken of as external and internal, but the terms are inadvisable, as little is as yet known regarding internal causes in the strict sense—that is, the causes of inherent defects or abnormalities of cells though it is thought that damage to the germ cells by irradiation and by certain viruses may cause inherent defects in the progeny. We may say that every *known* disturbance is external or comes from without as far as the affected cells are concerned.

With regard to the causation of disease, as in all biological phenomena the matter is complicated, and a number of circumstances may be necessary to bring about a given result. We speak of the tubercle bacillus as the cause of tuberculosis in the sense that the disease is not met with apart from the bacillus, but the converse is not necessarily true and the presence of the bacillus is not invariably followed by the disease. In tuberculosis, contributory factors may be necessary in order to allow the action of the bacillus to become effective. There must be susceptibility to infection, and this may be congenital or acquired. Accordingly, with regard to many conditions we have to speak of predisposing, contributing or auxiliary causes. This question of causation will be met with in a more complicated form still when we come to consider the etiology of tumour

growth. Except for certain infectious diseases which are invariably associated with a specific micro-organism, it is no longer supposed that each disease or illness has a single specific cause which is the *sine qua non* of the state, and some well-known clinical conditions are to be regarded as *syndromes* rather than as specific morbid entities. The modern conception of disease leads to the conclusion that a disturbance of health may result from interference with the normal chain of biochemical processes, interruption of which at any one of several points may produce the same impairment of function without notable morbid anatomical changes, e.g. diabetes mellitus. Megalocytic anæmia, too, offers a good example of a condition in which a similar morphological change in the blood may be induced by disturbance of the process of hæmopoiesis at any one of several points in the cycle of development. Again, similar gross morbid anatomical changes may result from the action of widely different agents, and it may be impossible to arrive at an accurate estimate of the fundamental nature of the disease without a detailed clinical history and investigation of the case ; cirrhosis of the liver is a good example of such a disorder.

We shall merely sketch the chief causes of disease as, at this stage, it would not be of advantage to the student to have them enumerated in detail.

(A) In the first place, reference may be made to abnormal states which are present at birth ; these are of various kinds. Some are hereditary in the strict sense, depending on abnormalities in the genes, and we assume that such abnormalities have arisen in the past by mutation. Of such truly hereditary conditions, we may mention as examples, colour blindness, albinism, hæmophilia, some diseases of muscles, skin, etc. Predisposition or susceptibility to certain diseases also is transmitted by heredity, just as are peculiarities in external configuration. In some instances, disease present at birth is the result of intra-uterine infection of the fœtus, e.g. congenital syphilis. There is also the group of congenital abnormalities due to errors in development. The causes of all of these cannot be correctly assigned, but in some instances intra-uterine disturbances—traumatic, nutritive and infective—are responsible, a conspicuous example being the tendency of maternal rubella and less commonly other exanthematous fevers in early pregnancy to result in congenital malformations of the heart, eyes, etc.

(B) With regard to the causes operating after birth, the following are the main types :

(1) *Improper or Insufficient Food Supply* : with this may be classed insufficient supply of oxygen. A defect in the amount of food as a whole leads to wasting, and when this is extreme, as in starvation, a condition of inanition is produced which may lead to death. Deficiency in any of the main classes of foodstuffs also brings about harmful results. For example, a variety of œdema is known to be mainly the result of gross protein deficiency in the diet. Of great importance

are the ' vitamins ' or accessory food principles, the presence of which in sufficient amount is necessary for a state of health. Many of these act by forming essential links in certain intra-cellular enzyme systems and insufficiency or lack thus cause important disorders, such as beri-beri, scurvy, rickets, etc. These are known accordingly as *deficiency diseases.* At first there is no morphological change in the cells and the state may be regarded as a ' pure biochemical lesion ' (Peters) which is rapidly reversible, but later, if the deficiency continues, morphological changes of various kinds appear. Thus lack of choline and other lipotropic substances leads to fatty changes in the liver. There is no doubt that recent biochemical researches have afforded a remarkable insight into some of the intimate changes which underlie certain pathological states. Furthermore, it may be added that definite pathological effects may be produced by deficiency in the intake or absorption of various inorganic substances, such as iron, calcium, chlorides, sodium, potassium, etc., especially when there is excessive loss.

(2) *Overwork or Overstrain.* Each organ has a reserve power so that additional functional demands may be made without injury. When, however, these demands are excessive, a condition of exhaustion may result, and when this is severe or occurs repeatedly, permanent damage may take place. An organ of impaired reserve power may be sufficient for the performance of normal function but may fail when abnormal demands are made on it, and serious results may follow. The effects of exhaustion are seen especially in connection with the circulatory and nervous systems. Further, in the circulatory system, overwork, when continued for some time, leads to a condition of hypertrophy of the specialised cells, and this may be followed eventually by a failure of the hypertrophic process. In this manner permanent changes of an important kind, both in the heart and in the arteries, may be brought about. Muscular fatigue may also increase the susceptibility of the tissues to infection, notable examples being seen in typhoid fever, infective hepatitis and poliomyelitis.

(3) *Trauma or Mechanical Injury.* The effects of trauma need no explanation, but it is important to recognise that, apart from the grosser effects, damage may result in the internal organs from such conditions as concussion. Such damage is of all degrees of severity, and in the case of the central nervous system, important functional disturbances may be produced even when there is little or no discoverable structural lesion.

(4) *Physical Agencies*—Heat, Electricity, X-rays, etc. Both local and general effects may be produced by extremes of heat and cold. The effect of heat applied locally is the production of burns of varying degree, extreme damage being an actual charring of the tissues. Exposure to a temperature sufficient to cause coagulation of the cell proteins will of course cause death of the cells ; but at a temperature lower than this, serious damage may be inflicted, and marked inflammatory reaction is a common result. The local action of cold, sometimes

resulting in frost-bite, is chiefly on the blood vessels, and leads to a condition in which the circulation can no longer be maintained through a part. Here again, varying degrees of ultimate damage are met with.

As regards general effects, exposure to a hot atmosphere, especially when it is associated with moisture, may lead to pyrexia and other serious results, which are described under the heading of heat-stroke, the symptoms being largely attributable to disturbances in the electrolyte balance of the body fluids. Exposure to cold, resulting in a chill, was formerly regarded as a fruitful cause of various inflammatory conditions, but we now recognise that it acts mainly by leading to vasoconstriction and to a diminished resistance of the tissues to invasion by bacteria. Accordingly, most of the diseases which arise in this way are really of the nature of infections.

Important results, both local and general, may be caused by certain forms of irradiation, and in this atomic age, the hazard to mankind from this source is likely to increase substantially. Acute *generalised* exposure to a massive dose of ionising irradiation causes profound destructive effects on the marrow and lymphoid tissues resulting in virtual disappearance of the circulating leukocytes and death from fulminating infections. Less acutely lethal dosage is followed by an increased incidence of leukæmia and certain other neoplastic disorders, especially in children subjected to irradiation *in utero* or in the early post-natal period. It is probable that in man, as in the animal kingdom generally, long-continued exposure to even small doses of ionising radiation is harmful and may lead to an increased incidence of genetic mutations. *Local* effects of irradiation are seen especially after repeated application of inadequately screened X-rays or radium, or after excessive dosage, and these may take the form of an X-ray burn, the effects of which may become distinctly manifest only some time after exposure, and then gradually increase in severity.

Sudden death may be caused by *electric currents* of high voltage, e.g. lightning stroke, and burning or even laceration of the tissues may be present; there may, however, be little change discoverable.

(5) *Micro-organisms.* Under this term may be included bacteria, protozoa, lower fungi and various ultra-microscopic viruses. Many serious diseases and, in fact, all infective fevers are produced in this way. The special feature of micro-organisms, as a cause of disease, is their power of multiplication in the tissues, and the possibility of their being transferred to other individuals. The action of such organisms in relation to disease will be referred to frequently, but it is important to recognise that their harmful effects are due to toxic substances which are set free by their action. Infection is thus of the nature of intoxication, and the peculiarity is that there is a progressive manufacture of the poison during the growth of the organisms. An important result of the presence of the infecting organisms may be to render the tissues supersensitive to their products.

(6) *Other Parasites.* Disease may result from invasion of the tissues