Muir's Textbook of Pathology

Eleventh Edition

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Preface

It has long been appreciated that the undergraduate course in medicine cannot do more than lay the basis for further training, and that the newly-qualified doctor must undergo a further period of general training, followed by the appropriate specialist or vocational training, before commencing independent practice. There are, however, wide differences of opinion on what the undergraduate student should be expected to know, and this is nowhere better illustrated than by the variations in the time allocated to pathology in the curricula of medical schools. Clearly the authors of textbooks of pathology are faced with a problem, both in the selection of topics to be included and in the depth of treatment of each topic. The purpose of this book is to provide a text suitable for both undergraduate students and for doctors training or practising in various specialties, including junior trainees in pathology. It contains more than will be assimilated by most undergraduate students during their formal course in pathology, and students using it should receive guidance from their teachers on which topics deserve their closest attention. I hope it will continue to be of use throughout the clinically-oriented part of the curriculum and during subsequent training.

A brief introductory chapter defines pathology, explains its central position in medical education, and describes its importance in patient care and in the advancement of medical knowledge. The remainder of the book is divided into two main sections—'general' and 'systematic' pathology.

The twelve chapters on 'general' pathology describe pathological processes of fundamental importance—mechanisms and effects of cell injury, the inflammatory response to injury, healing and repair, the physiology of the immune response and its beneficial and harmful consequences, infection and host–parasite relationships, local and general disturbances of blood flow, and the causation, types and behaviour of tumours. It is in some of these basic processes that advance has been most rapid, and indeed this has necessitated production of this edition earlier than had been intended. The accounts of the cellular basis of immune responses and of the causation of tumours have been very largely rewritten and most of the other chapters have been changed considerably. These basic processes are applicable to a wide range of species and although they are, where possible, illustrated by human material, much of the text is based on the results of experimental work. The size of the general chapters has been determined not just by the clinical importance of the physiological and pathological processes they describe, but also by the amount of firm information that can usefully be imparted to students and trainee doctors. For example, the mediators of the inflammatory reaction and the basis of neoplasia are both subjects of considerable practical importance, but knowledge on them is still very limited and larger accounts would, I believe, be more likely to confuse than help the student. By contrast, the immunity system and its abnormalities are still relatively unimportant as the basis of primary illness in man, and yet they merit detailed consideration because they continue to be the subject of rapid scientific advance. In spite of our efforts at brevity, it has not been possible to avoid some increase in the length of the general section, which I hope will be of use both to medical students and to other biological scientists.

The 'systematic' section consists of fourteen chapters, each devoted to the more important diseases of man which affect a particular organ or system—the heart, lungs, blood and haemopoietic tissues, alimentary system, etc. Emphasis has been placed on the aetiology of those diseases, and their structural changes and effects on function, together with brief clinicopathological correlations. Every effort has been made to update these chapters. A section has been added on dental and related oral

pathology, while the disorders of the male and female reproductive systems have been rewritten as separate chapters with a brief account of sexually-transmitted diseases placed appropriately between them. Multi-authorship has been of particular value in the systematic chapters, for the expert who is also an experienced teacher knows how much emphasis to place on particular topics and, most important, what may be omitted. Although the number of illustrations has been increased and now includes approximately 1200 photographs and diagrams, some reduction in the text has been achieved in this section, the total length of which is virtually unchanged.

Bibliography (now given at the end of each chapter) is confined mainly to reviews and larger texts. We have included some references to classical work, and to original papers representing important advances, but in general have avoided the temptation to append long lists of references to recent, often unconfirmed reports. I believe that it is the duty of the teacher to guide the student in his search for further information.

A final point relates to the value of cross-references, which are numerous in this text. They are useful in saving repetition, but they can, of course, be ignored by those readers who find them a distraction.

Acknowledgements

I am grateful to all my fellow authors, not only for their contributions but also for granting me wide editorial licence. I have used this in order to achieve uniformity of style and nomenclature, to avoid unnecessary repetition, and hopefully to provide a balanced account. I accept responsibility for errors of fact and judgement.

In addition to named contributors, I have received help with the accounts of certain topics from a number of colleagues. They include Drs J. J. Brown, A. F. Lever and J. I. S. Robertson of the MRC Hypertension Research Unit (the renin-angiotensin system, the aetiology of hypertension and Conn's syndrome), Professor J. Hume Adams (diseases of muscle) and Dr C. D. Forbes (haemostasis, clotting and fibrinolysis). I am grateful also, for their helpful discussion and advice to Dr J. Douglas Briggs (renal diseases), Dr J. W. Kerr (atopic hypersensitivity) and Professor I. A. Ledingham (shock).

My thanks are due also to colleagues who have contributed to previous editions, parts of whose contributions may still be embodied in the text. They include Professors Sir Douglas Black, M. J. Davies, W. A. Harland and N. Woolf and Drs E. M. Murray and J. M. Vetters. The contributions of the late Drs R. F. Macadam and H. E. Hutchison are also gratefully acknowledged.

In addition to those who have contributed directly to the text, all my colleagues in this Department have been most helpful in making useful suggestions, providing illustrations and participating in the correction of proofs. Illustrations provided by former colleagues and others outwith the Department are acknowledged in the legends.

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The revision has involved much secretarial work, for which I am particularly grateful to Miss Helen Scott who has dealt successfully with a large amount of correspondence and a considerable amount of typing, often from scarcely legible manuscripts. In the latter, she has been ably assisted by Mrs Pat Bonnar, Miss Margaret Brough, Mrs Pat Johnson, Mrs Jean Lyall and Mrs Maureen Ralston.

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Many readers have sent me useful comments and criticisms on the previous edition. This is most helpful and I hope it will continue.

For all this help, I offer my grateful thanks.

Finally, I wish to thank my wife for many things. Not only has she advised me on bacteriological topics and helped with proof reading, but she and our family have been unfailing in their support in spite of my pre-occupation and irritability during the preparation of this edition.

J. R. ANDERSON

Glasgow
July, 1980

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Introduction

What is pathology?

Pathology is the study of disease by scientific methods. Disease may, in turn, be defined as an abnormal variation in the structure or function of any part of the body. There must be an explanation of such variations from the normal—in other words, diseases have causes, and pathology includes not only observation of the structural and functional changes throughout the course of a disease, but also elucidation of the factors which cause it. It is only by establishing the cause (*aetiology*) of a disease that logical methods can be devised for its prevention or cure. **Pathology may thus be described as the scientific study of the causes and effects of disease.**

Methods used in pathology

These include (*a*) **histology** and **cytology**, in which the structural changes in diseased tissues are examined by naked-eye inspection, or by light and electron microscopy of tissue sections or smears; (*b*) **biochemistry**, in which the metabolic disturbances of disease are investigated by assay of various normal and abnormal compounds in the blood, urine, etc.; (*c*) **microbiology**, in which body fluids, mucosal surfaces, excised tissues, etc., are examined by microscopical, cultural and serological techniques to detect and identify the micro-organisms responsible for many diseases.

These methods may be applied to the study of individuals suffering from a disease, and to animals in which a model of the disease occurs naturally or has been induced experimentally. The development of special techniques to investigate some types of disease has led to further specialisation in pathology. For example, the diagnosis of disorders of the blood involves various quantitative tests on, and morphological examination of, the cells of the blood and haemopoietic tissue, assay of the factors involved in clotting, investigation of the metabolism of iron, vitamin B_{12}, etc., the detection of abnormal antibodies to cells of the blood and blood group serology. The many techniques involved have required the establishment of **haematology** laboratories: application of techniques to determine chromosome anomalies has led to the establishment of **cytogenetics** laboratories, and microbiology has divided into **bacteriology** and **virology**. Finally, **immunology**, a subject of enormous interest in biology and of increasing clinical significance, now requires special laboratory facilities. It will be apparent that pathology covers a wide spectrum of techniques, both in the diagnosis of patients and in research into the causes of various diseases. The relative importance of the several branches of pathology varies for different types of disease. In some instances, for example in diabetes mellitus, biochemical investigations provide the best means of diagnosis and are of the greatest value in the control of therapy. By contrast, recognition of the nature of many diseases, for example tumours, and so the choice of the most appropriate therapy, depend very largely on examination of the gross and microscopic features. For most diseases, diagnosis is based on a combination of pathological investigations. To give an example, biochemical tests may indicate that a patient is suffering from impairment of renal function, but the nature of the renal disease responsible for this commonly requires removal of a piece of renal tissue for histological examination (*renal biopsy*). Another example is provided by the condition of anaemia, which may have many causes. The changes in the cells of the blood and the bone marrow may suggest deficiency of a factor essential for erythropoiesis, and biochemical and physiological tests are then indicated to con-

firm the deficiency, e.g. of vitamin B_{12} or folic acid. Alternatively, anaemia may result from blood loss and this may be due to a structural lesion of the gastro-intestinal tract or of the endometrium, diagnosis of which may require histological examination.

The hospital pathologist is becoming much more clinically orientated. He must co-operate closely with clinicians, not only in diagnosis, but also by applying his skills to assessment of the effects of treatment, e.g. by examination of multiple biopsies of cancers and other lesions, removed serially during the course of treatment. He must also monitor patients for unwanted effects of treatment, e.g. the harmful effects of some drugs on the cells of the liver, kidney or haemopoietic tissue.

Finally, it is important to emphasise the continuing value of the clinical necropsy. In the past, when diagnostic procedures were relatively limited and primitive, a high proportion of diagnoses were made in the post-mortem room. In many cases, the more sophisticated diagnostic procedures now available have not diminished the value of necropsy, even in hospitals providing a very high standard of patient care (Cameron, 1978). The important role of post-mortem examination in elucidating the natural history of disease processes is well illustrated by the extensive studies of Willis (1973) on the spread of tumours within the body. This role of the necropsy is still important, for it is revealing the changes in the patterns of many diseases, and also new and unwanted effects, resulting from use of the ever-increasing number and variety of powerful drugs and therapeutic procedures available to the clinician.

Why learn pathology?

Most medical students are not going to become pathologists. It is nevertheless essential that the medical school curriculum should include a course of pathology which provides a clear account of the causes, where these are known, and of the pathological changes, of the more important diseases. Most disease processes bring about structural changes and these usually provide a logical explanation for the symptoms and signs and commonly also for the biochemical changes. A basic knowledge of the pathological processes of disease thus aids the doctor in the correct interpretation of the clinical features of the patient's illness. This applies not only to the clinical diagnostician but also to the surgeon who must recognise the nature of the structural changes exposed at operation and act accordingly, and to the radiologist who must be familiar with the structural changes of diseases in order to interpret the shadows they cast on an x-ray film. To the research worker, histopathology and electron microscopy are superb techniques; both can be adapted to enzymic and other chemical investigations (**histochemistry**), including immunohistological techniques which make use of the exquisite specificity of antigen–antibody reactions to detect tissue and cell constituents and abnormal substances (see Fig. 22.20, p. 819 and Fig. 26.1, p. 1005).

Accordingly, pathology is of central importance to the medical student, regardless of the branch of medicine he intends to pursue.

How to learn pathology

Pathology is no exception to the general rule that learning is dependent mainly on the student's own effort. Most medical schools provide lectures and/or small-group tutorials, demonstrations and practical classes in pathology, but self-education by reading, preferably supplemented by audio-visual aids, is essential. The student should also take full advantage of opportunities to compare the clinical features of patients' illnesses with the underlying pathology. Clinico-pathological conferences on selected cases, held for teaching purposes, are helpful but one of the best places to see pathology and to compare the clinical features of disease with the pathological changes is the post-mortem room. A well-conducted necropsy, presented jointly by a clinician who cared for the patient and the pathologist performing the necropsy, is still unsurpassed as a teaching method. Students should also gain experience by following the progress of the patients they examine, noting the results of laboratory investigations and where possible examining the lesions removed surgically or revealed at necropsy.

Pathology in the medical curriculum

There is a logical sequence in the pattern of teaching of most medical schools. After courses

in the basic sciences—chemistry, physics, biology—often provided before starting at medical school, the student is introduced to normal human structure (anatomy and histology) and function (physiology and biochemistry), followed by courses in pathology (the causes, features and effects of diseases) and pharmacology, and finally concentrates on the clinical subjects, i.e. the diagnosis and treatment of patients. Classically, the subjects are dealt with on a broad front. For example, the courses in anatomy, etc. deal with the whole of the body. In many medical schools, this policy has been replaced by what is variously termed 'integrated', 'topic' or 'systems' teaching, in which each of the body's major systems (cardiovascular, alimentary, respiratory, etc.) is the subject of a teaching course provided by a multidisciplinary team. Thus the course on, say, the alimentary system will include its anatomy, physiology, biochemistry, pathology, pharmacology and clinical aspects. Each method has its advantages, but it has become abundantly clear that the second method requires considerable organisation, and good co-operation between departments in the preparation and delivery of the course on each system. At present, there is a tendency to revert to the classical type of curriculum, or to compromise between the two.

One of the great advantages of a course in pathology, spanning the gap between the preclinical and clinical subjects, is that it provides the student, in the early part of his hospital experience, with a basic knowledge of the diseases he is likely to encounter most often in the wards and clinics. By contrast, the integrated course must either be brief and intensive or must extend over much of the curriculum, with the result that some systems come very late, leaving little time for their personal clinical study by the student.

Pathological processes

It was first pointed out by Virchow that all disturbances of function and structure in disease are due to cellular abnormalities and that the phenomena of a particular disease are brought about by a series of cellular changes. Pathological processes are of a dual nature, consisting firstly of **the changes of the injury** induced by the causal agent, and secondly of **reactive changes** which are often closely similar to physiological processes. If death is rapid, as for example in cyanide poisoning, there may be little or no structural changes of either type. Cyanide inhibits the cytochrome-oxidase systems of the cells and thus halts cellular respiration before histological changes can become prominent. Similarly, blockage of a coronary artery cuts off the blood supply to part of the myocardium and death may result immediately from cardiac arrest or ventricular fibrillation. When this happens, no structural changes are observed in the myocardium. If, however, the patient survives for some hours or more, the affected myocardium shows changes which occur subsequent to cell death and the lesion becomes readily visible both macroscopically (Fig. 15.9, p. 404) and microscopically (Fig. 2.5, p. 11). Reactive changes may be exemplified by enlargement of the myocardium in the patient with high blood pressure (Fig. 4.31, p. 100). In this condition, there is an increase in the resistance to blood flow through the arterioles and consequently the normal rate of circulation can be maintained only by a rise in blood pressure. Reflex stimulation of the heart results in more forcible contractions of the left ventricle, and in accordance with the general principle that increased functional demand stimulates enlargement (**hypertrophy**) and/or proliferation (**hyperplasia**) of the cells concerned, the myocardial cells of the left ventricle increase in size. Although part of a disease state, the reactive hypertrophy of the myocardium in hypertension is closely similar to the physiological hypertrophy of the skeletal muscles in the trained athlete. To give another example, the invasion of the body by micro-organisms, in addition to causing injury, stimulates reactive changes in the lymphoid tissues, with the development of immunity. The distinction between the changes due to injury and those due to reaction are not usually so well defined as in the above examples. In many instances where cell injury

persists without killing the cells, the cytological changes are complex and those due to injury often cannot be distinguished from those due to reaction. Some examples of the various types of cell injury and reaction are provided in Chapter 2.

In order to facilitate the understanding of pathological processes, it is helpful to group together those which have common causal factors and as a consequence exhibit similarities in their structural changes. For example, bacterial infections have certain features in common, and may with advantage be further sub-divided into acute and chronic infections. The features and behaviour of neoplasms (tumours) are sufficiently similar to classify most tumours into two categories, benign and malignant, and to provide a general account of each group. The changes resulting from a deficient blood supply are similar for all tissues. Accordingly, the next twelve chapters of this book are of a general nature and deal with the commoner pathological processes. The remaining chapters are systematic and go on to describe the special features of disease processes as they affect the various organs and systems.

The causes of disease

Causal factors in disease may be genetic or acquired. **Genetically-determined disease** is due to some abnormality of base sequence in the DNA of the fertilised ovum and the cells derived from it, or to reduplication, loss or misplacement of a whole or part of a chromosome. Such abnormalities are often inherited from one or both parents. **Acquired disease** is due to effects of some environmental factor, e.g. malnutrition or micro-organisms. Most diseases are acquired, but very often there is more than one causal factor and there may be many. Genetic variations may influence the susceptibility of an individual to environmental factors. Even in the case of infections, there is considerable individual variation in the severity of the disease. Of the many individuals who become infected with poliovirus, most develop immunity without becoming ill; some have a mild illness and a few become paralysed from involvement of the central nervous system (Fig. 21.44, p. 759). This illustrates the importance of **host factors** as well as causal agents. Spread of tuberculosis is favoured by poor personal and domestic hygiene, by overcrowding, malnutrition and by various other diseases. Accordingly, disease results not only from exposure to the major causal agent but also from the existence of **predisposing** or **contributory factors**.

Congenital disease. Diseases may also be classified into those which develop during fetal life (congenital) and those which arise at any time thereafter during post-natal life. Genetically-determined diseases are commonly congenital, although some present many years after birth, a good example being adenomatosis (polyposis) coli, which is due to a dominant abnormal gene (see below) and consists of multiple tumours of the colonic mucosa, appearing in adolescence or adult life (Fig. 19.79, p.652). Congenital diseases may also be acquired, an important example being provided by transmission of the virus of rubella (German measles) from mother to fetus during the first trimester of pregnancy. Depending on the stage of fetal development at which infection occurs, it may result in fetal death, or involvement of various tissues leading to mental deficiency, blindness, deafness or structural abnormalities of the heart. The mother may also transmit to the fetus various other infections, including syphilis and toxoplasmosis, with consequent congenital disease. Ingestion of various chemicals by the mother, as in the thalidomide disaster, may induce severe disorders of fetal development and growth. Another cause of acquired congenital disease is maternal–fetal incompatibility. Fetal red cells exhibiting surface antigens inherited from the father may enter the maternal circulation and stimulate antibody production: the maternal antibody may pass through the placenta and react with the fetal red cells, causing a haemolytic anaemia.

Genetically-determined disease

As already mentioned, this results from abnormalities in the DNA which forms the genome. In some instances the abnormality consists of gain or loss of a whole chromosome or of part of a chromosome. Such gross abnormalities can now be detected by cell culture techniques. Most of them probably arise by non-disjunction of chromosomes in the meiosis which precedes germ-cell formation, and only a few appear to be compatible with life, e.g. an addi-

tional chromosome 21, which is the usual cause of Down's syndrome (mongolism).

A very large number of diseases result from the inheritance of an abnormal (mutant) gene, or combination of genes, from one or both parents. The development of abnormal genes (**mutation**) can be provoked by irradiation, mutagenic chemicals and probably by viruses, but in most instances the cause of mutations in man remains unknown. Examples of the many conditions resulting from an abnormal gene are colour blindness, albinism, haemophilia, sickle-cell anaemia, dystrophia myotonica and polyposis coli. The abnormal gene may be dominant, i.e. may induce an abnormality in spite of the presence of a normal corresponding gene from the other parent, or it may be recessive; i.e. causing disease only in the absence of a corresponding normal gene. The latter circumstance arises most usually in abnormalities of genes on the X chromosome, males being thus affected (Fig. 17.50, p. 555), or from the presence of two abnormal corresponding genes, one from each parent, the likelihood of which is enhanced by inbreeding.

In addition to those diseases due to mutations or recognisable chromosomal anomalies, there are many which show a **familial tendency**, but in which the mode of inheritance has not been elucidated. Examples include diabetes mellitus, chronic thyroiditis (see (6) below) and some of the commoner cancers, e.g. of the breast and of the bronchus. It is likely that both genetic and environmental factors are of causal importance in these conditions.

Acquired disease

The major causal factors may be classified as follows:

(1) Deficiency diseases. Inadequate diet still accounts for poor health in many parts of the world. It may take the form of deficiency either of major classes of food, usually high-grade protein, or of vitamins or elements essential for specific metabolic processes, e.g. iron for haemoglobin production. Often the deficiencies are multiple and complex. Disturbances of nutrition are by no means restricted to deficiencies, for in the more affluent countries obesity, due to overeating, has become increasingly common, with its attendant dangers of high blood pressure and heart disease.

(2) Physical agents. These include mechanical injury, heat, cold, electricity, irradiation and rapid changes in environmental pressure. In all instances, injury is caused by a high rate of transmission of particular forms of energy (kinetic, radiant, etc.) to or from the body. Important examples in this country are mechanical injury, particularly in road accidents, and burns. Exposure to ionising radiations cannot be regarded as entirely safe in any dosage. While radiation is used with benefit in various diagnostic and therapeutic procedures, any pollution of the environment with radioactive material is potentially harmful to those exposed to it and probably to subsequent generations.

(3) Chemicals. With the use of an ever increasing number of chemical agents as drugs, in industrial processes, and in the home, chemically-induced injury has become very common. The effects vary. At one extreme are those substances which have a general effect on cells, such as cyanide (see above) which causes death almost instantaneously, with little or no structural changes. Many other chemicals, such as strong acids and alkalis, cause local injury accompanied by an inflammatory reaction in the tissues exposed to them. A third large group of substances produces a more or less selective injury to a particular organ or cell type. Because of their important and complex metabolic activities, hepatocytes are injured by many chemical substances, including paracetamol and alcohol in high dosage. Many toxic chemicals or their metabolites are excreted by the kidneys, and because of their concentrating function the renal tubular epithelial cells are exposed to high levels of such substances. Accordingly toxic hepatic and renal tubular cell death are common. Fortunately both types of cell have a high regenerative capacity. Specific effects of chemicals are illustrated also by injury of neurones by overdosage of barbiturates and lung injury by paraquat (Fig. 16.37, p. 486).

(4) Parasitic micro-organisms. These include bacteria, protozoa, lower fungi and viruses. In spite of the advances in immunisation procedures and the extensive use now made of antibiotics, many important diseases still result from infection by micro-organisms, and the danger of widespread epidemics, e.g. of influenza and cholera, has been enhanced by air travel. The

disease-producing capacity of micro-organisms depends on their ability to invade and multiply within the host, and on the possibility of their transmission to other hosts. The features of the disease produced by infection depend on the specific properties of the causal organism. Bacteria bring about harmful effects mainly by the production of chemical compounds termed **toxins**, and the biological effects of these, together with the response of the host, determine the features of the disease. Viruses colonise host cells, and have a direct cytopathic effect: features of virus disease depend largely on which cells are colonised, the rate of viral replication, the nature of the cytopathic effect, and the response of the host. Of the protozoa, the malaria parasite is of enormous importance as a cause of chronic ill health in whole populations.

(5) Metazoan parasites are also an important cause of disease in many parts of the world. Hookworm infestation of the intestine and schistosomiasis are causes of ill health prevalent in many tropical countries.

(6) Immunological factors. The development of immunity is essential for protection against microbes and parasites. Harmful effects, both local and more widespread, can, however, result from the reaction of antibodies and lymphocytes with parasites, microbes and their toxic products. Also, the immunity system does not distinguish between harmful and harmless foreign antigenic materials, and injury may result from immune reactions to either. Such **hypersensitivity reactions** are numerous and complex. Local examples include hay fever, asthma and some forms of dermatitis, while hypersensitivity to many foreign materials, including penicillin and other drugs, sometimes causes fatal generalised reactions. Hypersensitivity reactions may also result from the development of **auto-immunity** in which antibodies and lymphocytes develop which react with and injure normal cells and tissues: examples include chronic thyroiditis, commonly progressing to myxoedema, and the excessive destruction of red cells in auto-immune haemolytic anaemia.

In another group of disorders, the immunity system is deficient, and the patient lacks defence against micro-organisms: this may result from abnormalities of fetal development, as an effect of various acquired diseases, or may be induced by immuno-suppressive therapy.

(7) Psychogenic factors. The mental stresses imposed by conditions of life, particularly in technologically advanced communities, are probably largely responsible for three important and overlapping groups of diseases. First, acquired mental diseases such as schizophrenia and depression, for which no specific structural or biochemical basis has yet been found. Second, diseases of addiction, particularly to alcohol, various drugs and tobacco: these result in their own complications, for example alcohol predisposes to liver damage (Fig. 20.27, p. 682) and causes various neurological and mental disturbances, while cigarette smoking is the major cause of lung cancer (Fig. 16.45, p. 498) and chronic bronchitis, and is concerned also in peptic ulceration and coronary artery disease. The third group of diseases is heterogeneous, and includes peptic ulcer (Fig. 19.28, p. 609), high blood pressure and coronary artery disease (Fig. 15.12, p. 406). In these three important conditions, anxiety, overwork and frustration appear to be causal factors, although their modes of action are obscure.

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2

Cell Damage

All metabolic activities of the body are carried out and regulated by the cells of the tissues, and since the time of Virchow cell injury has been recognised as the central problem in pathology. It is clearly important to know what factors cause cell damage and how these lead to the cellular disorders which result in the states we recognise as diseases. Our knowledge of this large and important subject has been slow to develop due to the extremely complex interrelationship of biological activities within the cell. Recently, however, there have been rapid advances, partly due to greatly improved techniques of biochemical analysis, fractionation of subcellular organelles and microscopy, and partly to the use of homogeneous experimental systems such as cultures of clones of genetically identical cells (bacterial or mammalian). Equally important has been the strategic use of cellular disorders in which the initial damage affects only one molecular constituent of the cell, thereby providing information about the normal and abnormal function of that constituent and its relationship to other activities of the cell. For this reason the most instructive forms of cellular damage are those due to abnormality of a single gene or to the effects of a selective poison.

Single gene defects. In at least one disease, sickle-cell anaemia, we probably know the entire sequence of events leading to cellular destruction. The sickle-cell abnormality is an inherited defect characterised clinically by rapid destruction of red blood cells. Apparently an error has occurred in copying one base in the sequence of 146 base triplets in the DNA constituting the gene for the beta polypeptide chain of haemoglobin. This error, transcribed through messenger RNA, results in the insertion of the amino acid valine instead of glutamic acid in position 6 from the N terminal end of the beta polypeptide chain and the shape of that end of the chain is altered. This abnormality does not matter when haemoglobin is oxygenated, but as the haemoglobin molecule gives up oxygen it expands and the abnormal parts of the two beta chains come to project from the surface of the molecule and unite with alpha chains of adjacent molecules. Masses of long helical fibres of polymerised deoxygenated haemoglobin form and these impart to the red cells abnormal rigidity and a characteristic sickle shape which make them unduly prone to mechanical injury and subsequent phagocytosis within the spleen. It should be noted that, compared with most cells, red cells have a very simple structure and are easily obtained for study. Also, haemoglobin is one of the few proteins whose molecular configuration and amino acid sequences are known in detail, so that the substitution of a single amino acid is detectable and indicates, in turn, a single error in the DNA base sequence.

Many other defects of single genes result in clearly defined primary lesions. There may be absence of a particular enzyme with predictable effects such as accumulation of substrate and deficiency of the product of the missing enzyme, but these effects often lead to secondary, more complex abnormalities which may result also from various other primary defects. Genetic disorders are further considered on p. 14.

Experimental poisoning. Many genetic defects are incompatible with cell survival and so cannot readily be investigated. Accordingly, toxic chemicals have been widely used to investigate more severe forms of cell injury, for example the impairment of oxidative phosphorylation by fluoroacetate or cyanide (p. 9). Much information has been obtained by use of drugs known to have a specific effect on particular cellular functions: examples include actinomycin D which inhibits transcription of

DNA to mRNA, and colchicine which interferes with microtubular function. Various bacterial and other biological toxins have specific effects, for example cholera toxin disturbs the sodium pump and α-bungarotoxin from snake venom blocks acetylcholine receptors. It is possible, however, that such substances have additional effects on other cellular mechanisms. The action of some other poisons is indirect and less specific. Thus the classical experimental poison carbon tetrachloride is toxic to liver cells because it is metabolised by the microsomal enzyme P450 to produce free CCl_3^+ and Cl^- radicals which lead to peroxidation of mRNA and of unsaturated fatty acids in cell membranes, and also to secondary disturbances of protein, fat and carbohydrate metabolism: electron microscopy shows damage to rough endoplasmic reticulum and later to other cellular organelles. Several other poisons cause similar effects on liver cells and, as in genetic abnormalities, it is evident that various different injuries cause trains of common secondary events, some of which lead to cell death.

In the following account only a few examples of cellular damage have been selected. The topic arises frequently in later chapters and our superficial treatment of this important subject is merely a reflection of our present basic ignorance.

It is convenient to consider the effects of cellular injury under two main headings: **(1) cell death** or *necrosis*, in which irreversible changes take place in the cell so that no further integrated function such as respiration or maintenance of selective membrane permeability is possible: **(2) lesser forms of damage** (sometimes described as degenerations) in which functions important for the economy of the cell or body are diminished or lost but in which integrated vital functions such as respiration and selective membrane permeability remain possible. Many lesser forms of cellular damage are reversible when the cause is withdrawn, for example the injury to neurones by therapeutic doses of anaesthetic drugs. Others, not resulting in cell death, are irreversible, e.g. radiation damage to chromosomes resulting in non-lethal genetic mutation.

Necrosis

Necrosis means the death of cells or groups of cells. It may occur suddenly, for example when cells are exposed to heat or toxic chemicals, or may be preceded by gradual and potentially reversible damage in which case the term **necrobiosis** is occasionally used.

Causes of necrosis

(a) Marked impairment of blood supply, usually due to obstruction of an end-artery (that is, one without adequate collaterals) is a common and important cause of necrosis, the necrotic area being known as an **infarct** (p. 246). Different cells can withstand the anoxia which results from ischaemia (impaired blood flow) for different periods, nerve cells, for example, die after only a few minutes, while fibrocytes survive much longer periods of anoxia.

(b) Toxins. Certain bacteria, plants, and animals such as snakes and scorpions, produce toxic organic compounds which even in very small quantities can cause cell damage amounting to necrosis. Some toxins have identifiable enzyme activity; for example, the causal organism of gas gangrene, *Clostridium welchii*, forms a lecithinase which digests the lipoprotein of cell membranes. Diphtheria toxin appears to inhibit cellular protein synthesis by indirect interference with the transfer of aminoacyl–tRNA to ribosomes. Certain bacterial toxins, including those mentioned above, exert their effects not only locally, but are distributed via the bloodstream and other routes and so injure the cells of organs remote from the infection. The necrosis accompanying bacterial infection may be partly due to interference with the circulation brought about by toxic injury to the vascular endothelium with inflammation and sometimes thrombosis.

(c) Immunological injury. As will be described in Chapter 6, cell injury results in various ways from immune reactions. This is a feature of many infections, including tuberculosis in

which tuberculoprotein, a nontoxic product of the tubercle bacillus, evokes an immune reaction which, though protective in function, paradoxically leads also to necrosis of cells in the neighbourhood of the organism.

(d) Infection of cells. In certain infections, notably by viruses, the infecting agent proliferates within cells. Many viruses kill infected cells in tissue culture (cytopathic effect) and this is probably the cause of necrosis *in vivo* of the anterior horn cells of the spinal cord in poliomyelitis.

(e) Chemical poisons. Many chemicals in high concentration cause necrosis by non-selective denaturation of the cellular proteins (e.g. strong acids, strong alkalis, carbolic acid, mercuric chloride). Cyanide and fluoroacetate are much more selective poisons and in low concentrations quickly cause cell death by interfering with oxidative production of energy from glucose, fatty acids and amino acids. As shown in Fig. 2.1 cyanide inhibits the enzyme cytochrome oxidase, thereby preventing the use of oxygen, while fluoroacetate forms a powerful competitive inhibitor of the enzyme aconitase which normally converts citrate to isocitrate in the Krebs citric acid cycle. Necrosis of liver or other specialised cells results from the effects of poisoning, but in many instances the mode of interaction between poison and cell is obscure.

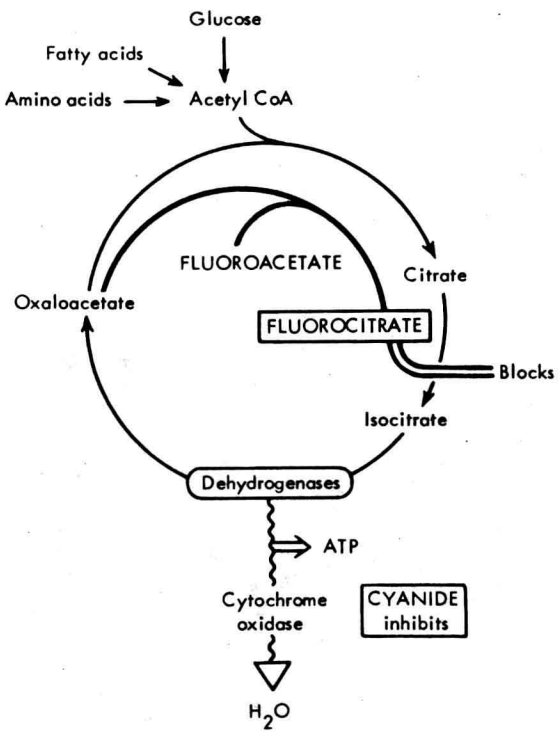

Fig. 2.1 The effects of fluoroacetate and of cyanide on cellular metabolism. Note that fluoroacetate is converted to fluorocitrate which inhibits conversion of citrate to isocitrate by aconitase.

(f) Physical agents. Cells are very sensitive to heat and, depending on the type of cell, they die after variable periods of exposure to a temperature of 45°C. Cold is much less injurious and, provided certain precautions are taken, cell suspensions and even small animals can be frozen without being killed. Necrosis after frostbite is due to damage to capillaries, resulting in thrombosis which may even extend to the arteries. Radiation damage, also a cause of necrosis, is considered on p. 32. Mechanical trauma such as crushing may cause direct disruption of cells. Certain disorders of the nervous system are sometimes accompanied by necrotic lesions in the limbs; these 'trophic' lesions were previously attributed to an ill-defined effect of denervation on tissue nutrition but are now thought to result from mechanical trauma which occurs unnoticed because of sensory loss.

The recognition of necrosis

As a rule it is not possible to determine exactly when a particular cell becomes necrotic—i.e. when the disintegration of its vital functions has reached an irreversible stage. Many of the changes by which necrosis is recognised occur *after* cell death and are due to the secondary release of lytic enzymes normally sequestrated within the cell, e.g. in the lysosomes; this process of **autolysis** is described below.

Necrosis of cell suspensions in tissue culture can be studied conveniently by observing changes of permeability of cell membranes to dyes such as neutral red or trypan blue. These dyes are normally excluded from the nucleus but when cells die, the nuclei become stained due to increased permeability of the membranes of the cell (Fig. 2.2). Alternatively, membranous components of the living cells may be labelled with radioisotopes such as ^{51}Cr or ^{32}P; subsequent severe injury to the cell, probably lethal, is recognised by release of the radio-active label from the cells into the culture medium.

In organised tissues such as liver or kidney,

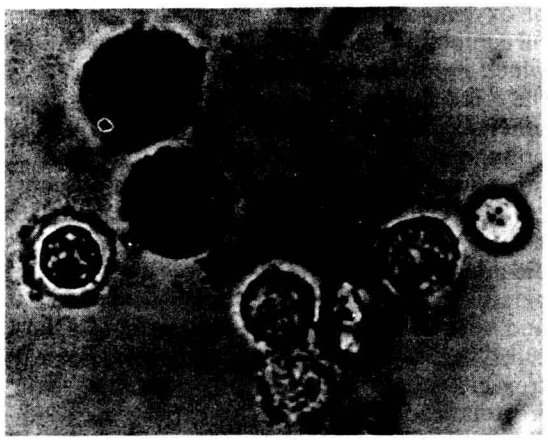

Fig 2.2 A suspension of lymphocytes treated with cytotoxic iso-antibody and complement. Some of the cells have been killed, and have become stained by trypan blue dye present in the suspending fluid: other cells have survived and are unstained. × 1250.

necrosis is usually recognised by secondary changes seen on histological examination. In preparations stained with haematoxylin and eosin, the nuclei may gradually lose their characteristic staining with haematoxylin so that the whole cell stains uniformly with eosin (Fig. 2.3), although the nuclear outline may persist; this change, the result of hydrolysis of chromatin within the cell after its death, is called **karyolysis**. Sometimes the chromatin of necrotic cells, especially those with already dense chromatin such as polymorphonuclear leukocytes, forms dense haematoxylinophilic masses (**pyknosis**) and these may break up (**karyorrhexis**) to form granules inside the nuclear membrane or throughout the cytoplasm (Fig. 2.4). In many necrotic lesions the outlines of swollen necrotic cells can be recognised but the cytoplasm is abnormally homogeneous or granular and frequently takes up more eosin than normal. In other tissues, e.g. the central nervous system, necrotic cells absorb water and then disintegrate, leaving no indication of the architecture of the original tissue; the lipids derived from myelin etc. persist in the debris of the necrotic tissue. The activities of certain enzymes, e.g. succinic acid dehydrogenase, diminish rapidly after cell death and appropriate tests provide useful indicators of recent tissue necrosis.

Electron microscopy of cells which have undergone necrosis shows severe disorganisation of structure. Gaps are seen in the various membranes and abnormal polymorphic inclusions, presumably derived from membranes, lie in the ground substance. Fragmentation and vacuolation of endoplasmic reticulum and mitochondrial membranes precede the disap-

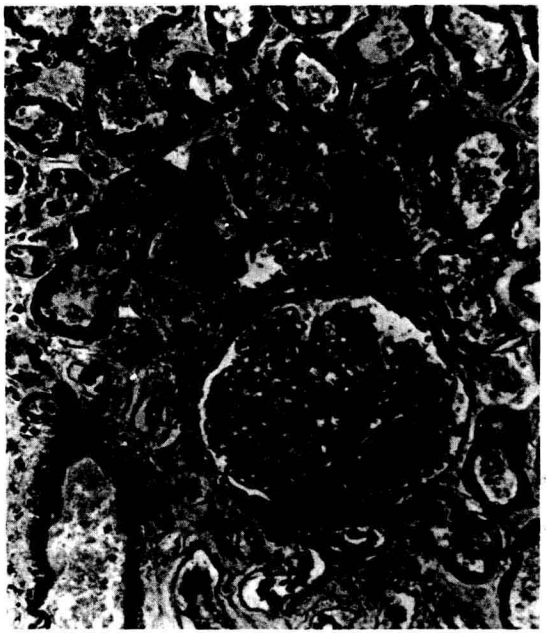

Fig. 2.3 Part of an infarct of kidney, showing coagulative necrosis. A glomerulus and tubules are seen, but the nuclei have disappeared and the structural details are lost. × 172.

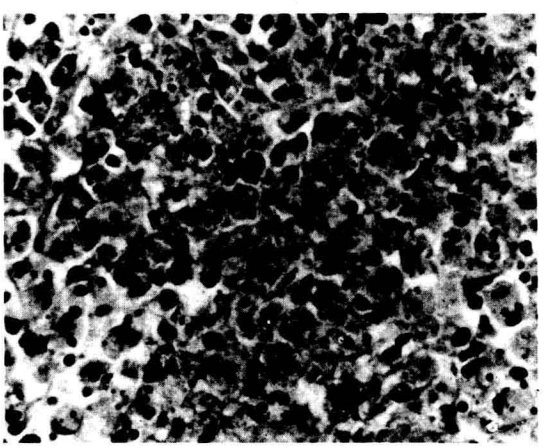

Fig. 2.4 Spreading necrosis with karyorrhexis in lymph node in typhoid fever. Note destruction of nuclei and numerous deeply-stained granules of chromatin. × 412.

pearance of these structures. Curious lamellar structures with concentric whorling form from the cell membrane, especially where there have been microvilli. Ribosomes and Golgi apparatus are unrecognisable from an early stage. There is loss of density of the nucleoplasm and large chromatin granules accumulate just inside the nuclear membrane before it disappears.

Less severe injury affecting single cells sometimes leads to **shrinkage necrosis**, a gradual process in which water is lost from the cell so that the nucleus becomes condensed and the cytoplasm appears strongly eosinophilic due to the closely packed organelles. Later the cell breaks into rounded fragments with preservation of ultrastructure and some functional activities which persist until the fragments are phagocytosed and digested by neighbouring parenchymal cells or macrophages. The circular Councilman bodies formed from hepatocytes are examples of this form of necrosis which can be an expression of normal cell turnover in the parenchyma of tissues like liver and adrenal cortex. The term **apoptosis** ('dropping off') has also been used in this context.

Necrosis can often be recognised macroscopically when large groups of cells die. The necrotic area may become swollen, firm, dull and lustreless, and is yellowish unless it contains much blood. This appearance is often found in kidney, spleen and myocardium. Histologically the outlines of the dead cells are usually visible (Figs. 2.3 and 2.5) and the firmness of the tissue may be due to the action of tissue thromboplastins on fibrinogen which together with other plasma proteins has been shown to diffuse through the damaged membranes of necrotic cells. This type of necrosis is appropriately described as **coagulative necrosis**. By contrast, necrotic brain tissue, which has a large fluid component, becomes 'softened' and ultimately turns into a turbid fluid (**colliquative necrosis**) with profound loss of the previous histological architecture.

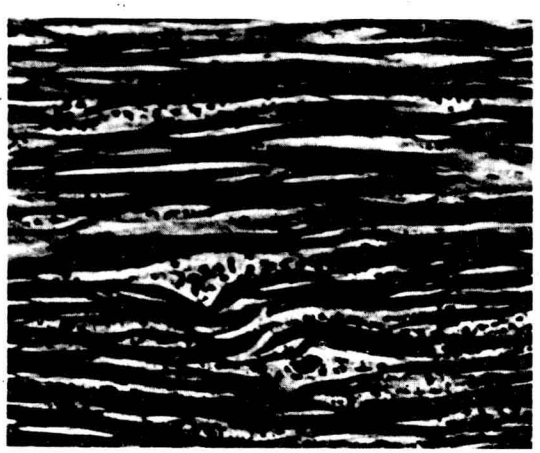

Fig. 2.5 Coagulative necrosis in infarction of heart muscle. The dead fibres are hyaline and structureless; remains of leukocytes, which have migrated from the venules, are present between them. ×125.

Certain necrotic lesions develop a firm cheese-like appearance to the naked eye and microscopy shows amorphous granular eosinophilic material lacking in cell outlines; a varying amount of finely divided fat is present and there may be minute granules of chromatin. Because of its appearance this lesion is described as '**caseation**'. It is very common in tuberculosis but essentially similar changes are occasionally seen in infarcts, necrotic tumours and in inspissated collections of pus.

Necrotic lesions affecting skin or mucosal surfaces are frequently infected by organisms which cause putrefaction, i.e. the production of foul-smelling gas and brown, green or black discoloration of the tissue due to alteration of haemoglobin. Necrosis with putrefaction is called **gangrene** (Fig. 2.6). It may be primarily due to vascular occlusion, e.g. in the limbs or bowel where the necrotic tissue is exposed to putrefactive bacteria, but it may also result from infection with certain bacteria, namely the clostridia which cause gas gangrene (p. 203) or fusiform bacilli which result in **noma** (p. 205).

The special features of **fat necrosis** are described on pages 717 and 972.

Autolysis

The structural disintegration of cells as a result of digestion by their own enzymes is largely responsible for the softening of necrotic tissues and the associated loss of histological structure. In the intact cell, the enzymes concerned do not have general access to the protoplasm. For example, various hydrolytic enzymes are associated with endoplasmic reticulum, mitochondria and lysosomes. The hydrolases confined within the lysosomal membranes include proteases which are most effective at low pH, a state which prevails in necrotic cells due to acid production from anaerobic glycolysis and the