Muir's Textbook of Pathology

Tenth Edition
Edited by J. R. Anderson

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B.Sc., M.D., F.R.C.P.(Glas.), M.R.C.P.(Lond.), F.R.C.Path., F.R.S. Edin.
Professor of Pathology, University of Glasgow
Pathologist to the Western Hospitals Group, Glasgow
Consultant Pathologist to the Greater Glasgow Area Health Board

Edward Arnold

First published 1924
by Edward Arnold (Publishers) Ltd.
25 Hill Street, London W1X 8LL

Reprinted, 1924, 1926, 1927
Second edition, 1929
Reprinted, 1930, 1932
Third edition, 1933
Fourth edition, 1936
Fifth edition, 1941
Reprinted, 1944, 1946
Sixth edition, 1951
Reprinted, 1956
Seventh edition, 1958
Eighth edition, 1964
Reprinted, 1968
Ninth edition, 1971
Reprinted, 1972, 1973, 1975
Tenth edition, 1976

ISBN: 0 7131 4268 5

Filmset in 'Monophoto' Times 10 on 11 pt. by
Richard Clay (The Chaucer Press), Ltd., Bungay, Suffolk
and printed in Great Britain by
Fletcher & Son Ltd., Norwich

Preface

It is with sadness that I record the death, on 13 February 1976, of Professor D. F. Cappell, whose contribution in preparing the 6–8th editions of this book was enormous.

In preparing this edition, the intention has been, as before, to provide an illustrated text in pathology suitable for medical students and yet sufficiently comprehensive to be used by graduate trainees in various branches of medicine, including junior trainees in pathology.

Progress in the biological sciences, including human and experimental pathology, has once again necessitated drastic changes in the text. In order to include the more important recent developments without making the book much bigger, it has been necessary to re-write approximately half of the text and to modify the rest considerably. It has not been my intention to provide the minimum, and the book contains more than will be assimilated readily by most medical students during their formal course in pathology. Methods of teaching have become more varied, and so have the contents of the curricula of different medical schools: students reading this book should receive guidance from their teachers in deciding which aspects of the subject deserve their closest attention.

As before, the text is in two major sections: the first 12 chapters are devoted to the important basic pathological processes—types of cell injury, inflammation, immunological reactions, infections, neoplasia, etc. The remainder of the book consists of 13 chapters, each of which gives an account of the more important pathological changes affecting a particular system—the heart, alimentary tract, skin, etc. The general section has been increased to approximately 300 pages at the expense of shortening some of the systematic chapters, and any increase in size is due mainly to the greater space now allocated to the 1000 or so illustrations, about a quarter of which are new.

Although this book is concerned especially with human pathology, it includes accounts of experimental work which has made important contributions to the understanding of disease processes, and some topics, particularly in the general section, are considered at length mainly because of their basic scientific importance. I believe that this section of the book may be of interest also to non-medical biologists.

In re-writing the systematic chapters, care has been taken to preserve from the previous edition those descriptions of structural changes which are based on a large cumulative personal experience and which are still of importance. Sections on clinico-pathological correlations have also been retained and sometimes extended, and the temptation to expound dogmatic views on subjects which are controversial has, in general, been resisted. Although most of the general chapters were re-written for the 9th edition, the accounts of inflammation, the mononuclear-phagocyte system, the cellular basis of immunity, hypersensitivity reactions and the nature and causation of tumours have been almost completely replaced. Extensive changes have also been made in the systematic chapters, particularly in those on the heart, the respiratory system, the blood and bone marrow, lymphoid tumours, the liver, kidney and endocrine system. A section on those diseases of the eye which are of general importance has been added to the chapter on the nervous system. As before, brief accounts of some of the more important tropical parasitic diseases are included, but for diseases occurring predominantly in tropical countries reference should be made to texts by those with the appropriate experience.

In previous editions, the help of colleagues has been acknowledged in the preface. With increasing specialization the number of contributors has grown steadily, and I have thought it

appropriate, in the list of contents which follows, to state who has been mainly responsible for the revision of each chapter. In addition, a number of colleagues have kindly revised or contributed smaller sections: they include Dr. J. Stewart Orr, D.Sc. (the effects of ionising radiations), Dr. Morag Timbury (virus infections), Drs. J. J. Brown, A. F. Lever and J. I. S. Robertson of the M.R.C. Hypertension Research Unit (the renin–angiotensin system; Conn's syndrome), Sir Douglas Black (whose account of oedema has still not required much change), Professor G. P. McNicol (haemostasis, clotting and fibrinolysis) and Professor J. Hume Adams (diseases of muscle). Parts of the chapter on the endocrine system have been revised by Professor R. B. Goudie (thyroid), and Dr. R. M. N. McSween (endocrine pancreas). For the respiratory system, I have been fortunate to enlist the help of Professor Donald Heath and Dr. J. M. Kay of the Pathology Department of Liverpool University; they have rewritten most of the chapter and have provided a lucid and up-to-date account. I must acknowledge also the work of colleagues who helped with the previous edition but who, for various reasons, have not been involved this time. This includes Drs. R. F. Macadam and J. M. Vetters, Professor W. A. Harland and the late Dr. H. E. Hutchison, much of whose contribution to the haematology chapter has been retained. The book has gained in authority from this multiple authorship, and I am grateful to my colleagues, not only for their contributions, but also for affording me wide editorial licence, which I have used in an endeavour to ensure uniformity of style and nomenclature, to avoid unnecessary overlap between chapters, and hopefully to provide a balanced account. I accept responsibility for errors of fact and judgement.

I am grateful for much useful advice and suggestions provided by Dr. J. Douglas Briggs on the urinary system. Dr. M. J. Davies and Professor N. Woolf on the heart, and Dr. J. W. Kerr on atopic hypersensitivity. I have been helped also by the many useful suggestions made in letters from readers of the 9th edition and hope that this source of advice will continue. I am indebted also to members of the departmental staff and others who have provided illustrations: the latter are acknowledged individually in the legends.

I wish to thank Mr. Robin Callander, F.F.P.A., M.M.A.A. for preparing diagrams, to Messrs. William Carson, F.I.M.L.T and Norman Russell, F.I.M.L.T. for maintaining the high standard of technical work necessary for the production of suitable material for illustrations, Mr. David McSeveney, F.I.M.L.T. for his outstanding electron microscopy preparations, and Mr. Peter Kerrigan for a very large amount of painstaking and skilful photography. My gratitude is due to various members of staff, and to my wife, for helping with correction of the proofs.

The revision has included much secretarial work: the help of Mrs. Margaret Morton and Miss Helen Scott with communications and correspondence has been invaluable, and they have shared the major task of typing (often from semi-legible manuscripts) with Mrs. Norma McCulloch, Mrs. Anne McLeod, Mrs. Maureen Ralston and Mrs. Pat Bonnar. To all these I express my grateful thanks.

It is a pleasure once again to thank Messrs. Edward Arnold, and particularly Miss Barbara Koster, for their enthusiastic co-operation and determination to overcome delays in publication. Both they and the printers have dealt so successfully and efficiently with the preparation of the new edition that I have been kept under considerable pressure.

Finally, I would like, once more, to thank my wife and family who have faced with sympathetic understanding my preoccupation and bad temper during the revision.

J. R. ANDERSON

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, 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 various 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 histological examination of renal tissue (*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 confirm 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.

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. An appreciation 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 can only interpret the significance of shadows on an x-ray film on the basis of the structural changes of disease. 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. 21.18, p. 761 and Fig. 24.1, p. 940).

From what has been said above, pathology is important to the medical student, regardless of the branch of medicine he intends to pursue. The pathologist is concerned mainly in the diagnosis and in elucidating the nature and causes of disease. He must co-operate fully with his clinical colleagues, both in the diagnosis of individual patients, and in the conduct of clinico-pathological meetings for teaching purposes. One of the best places to learn pathology and to correlate the patient's illness with the structural changes of his disease is the post-mortem room, and a well-conducted necropsy, attended by the clinicians who looked after the patient during life, is unsurpassed as a teaching method.

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 apparent. Similarly, blockage of a coronary artery cuts off the blood supply to part of the myocardium and death may be immediate, when no myocardial changes will be found: if, however, the patient survives for some hours or more, the affected myocardium shows the structural changes which occur subsequent to cell death and the lesion becomes readily visible both macroscopically (Fig. 14.9, p. 352) and microscopically (Fig. 1.4, p. 4). Reactive changes may be exemplified by enlargement of the myocardium in the patient with high blood pressure (Fig. 3.32, p. 82). 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 1.

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 or 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 first 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 of a genetic nature 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 in fact 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. 20.43, p. 698). 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 polyposis coli, which is transmitted by a dominant abnormal gene (see below) and is characterised by multiple tumours of the colonic mucosa, appearing in adolescence or adult life (Fig. 18.71, p. 592). 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, containing 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 additional 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 gene, or combination of genes, from one or both parents, commonly termed *mutations*. 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. 16.50, p. 501), or from the presence of two abnormal corresponding genes, 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 arterial hypertension 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 radio-active 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, for example the barbiturate drugs affect especially the neurones, paraquat causes severe injury to the lungs (Fig. 15.37, p. 432), while many substances cause death of the cells of the liver and of the renal tubules.

(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. Harmful effects, both local and general, can result from the reaction of antibody or sensitised cells with foreign antigenic material. Asthma, hay fever, and skin rashes following exposure to various chemicals are examples of such *hypersensitivity* reactions, but they are many and complex, and hypersensitivity to penicillin and other drugs sometimes causes a fatal reaction. Disease may result also from the development of *auto-immunity*: the immunity system develops antibodies and sensitised cells which react specifically with constituents of normal cells or tissues, and injury results from such reactions. Examples are 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 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. 19.23, p. 620) and causes various neurological and mental disturbances, while cigarette smoking is the major cause of lung cancer (Fig. 15.45, p. 444), 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. 18.23, p. 550), high blood pressure and coronary artery disease (Fig. 14.12, p. 354). 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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Errata

p. 52, col. 2, line 29. For 'lesions may' read 'lesions (p. 54) may'.
p. 72, Fig. 3.21 caption, line 6. For 'fibula is' read 'cortex is'.
p. 115, col. 2, lines 24–25. For '($C\bar{1}$ to $C\bar{9}$)' read '($C\bar{1}$, $C\bar{2}$, etc.)'.
p. 117, col. 1, line 18. For '5′-monophosphate (Cyclic AMP)' read '5′-monophosphate (Cyclic) AMP'.
p. 204, col. 2, line 9. For 'thrombosis commonly occurs' read 'embolism commonly occurs'.
p. 253, Table 10.2, col. 1. For 'Thyroid hormone' read 'Thyroid stimulating hormone'.
p. 368, col. 1, in paragraph on **Classification.** Transpose 'former' (3rd line) and 'latter' (5th line).
p. 508, col. 1, line 13. For 'macrocytes' read 'macrophages'.

Contents

1

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. Unfortunately our knowledge of this large and important subject is still in its infancy because of the slow development of methods for investigating it, and the extremely complex interrelationship of biological activities within the cell. Nevertheless progress in biochemistry and molecular biology is now bringing the pathology of cell damage within our grasp.

In at least one disease, sickle-cell anaemia, we probably know the entire sequence of events leading to cellular destruction and this can be taken as an illustration of the kind of understanding which is our object for the future in other forms of cellular injury. 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 the protein moiety 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. The change in structure is of no account 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. Accordingly the beta chains of deoxygenated sickle haemoglobin can 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; furthermore, haemoglobin is one of the few proteins whose molecular structure is known in detail.

The mechanism of most other forms of cell damage is much less clear. For example, the mode of action of carbon tetrachloride on liver cells has been the subject of much study. In liver cells of rats poisoned with this substance there are abnormalities of protein, fat and carbohydrate metabolism, and electron microscopy shows damage first to the granular endoplasmic reticulum and later to other cellular organelles. Attempts to establish the primary site of action of carbon tetrachloride by study of liver cell homogenates have not been successful. Several other poisons, e.g. thioacetamide, cause similar effects on liver cells and it is evident that various different injuries lead to a train or trains of common secondary effects preceding cell death. McLean *et al.* (1965) compare the structure and chemistry of a cell to a net. When a net is pulled, all the links are disturbed, and the weaker links will tend to break no matter where the stress is applied. A damaged part of the cell, detected by methods currently available, may likewise be only indirectly related to the cause of the injury.

In the following account only a few of the many possible examples of cellular damage have been selected. The topic is frequently mentioned 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 anaesthetic drugs given in therapeutic doses. 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 while they still form part of the living body, and implies permanent cessation of their integrated function. Necrosis may occur suddenly, for example when cells are exposed to heat or toxic chemicals, or cell death 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 the result of 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. 208). Different cells can withstand anoxia resulting from impaired blood flow for different periods, nerve cells, for example, dying 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 acts directly on 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 in the proximity of the bacteria but also in organs remote from the infection due to dissemination of toxins by the bloodstream and other routes. The necrosis accompanying bacterial infection may be partly due to interference with the circulation brought about by severe inflammation in addition to the effect of toxins.

(c) Immunological injury. As will be described in Chapter 5, cell injury results in various ways from immune reactions. This is a feature of many infections, including tuberculosis in which tuberculoprotein, a nontoxic derivative of the tubercle bacillus, evokes an immune reaction which, though possibly protective in function, paradoxically leads 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. Most viruses kill infected cells in tissue culture (cytopathic effect) and an analogous destructive effect *in vivo* is probably the cause of necrosis 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. 1.1 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 poisoning with such substances as

carbon tetrachloride but detail of the mode of interaction between poison and cell is usually obscure.

(f) Physical agents. Cells are very sensitive to the action of heat and, depending on the origin of the cells, they die after variable periods of exposure to a temperature of 45 °C. Low temperatures are much less injurious and, provided certain precautions are taken, cell suspensions and even whole animals can be frozen without being killed. Necrosis after frostbite is due to

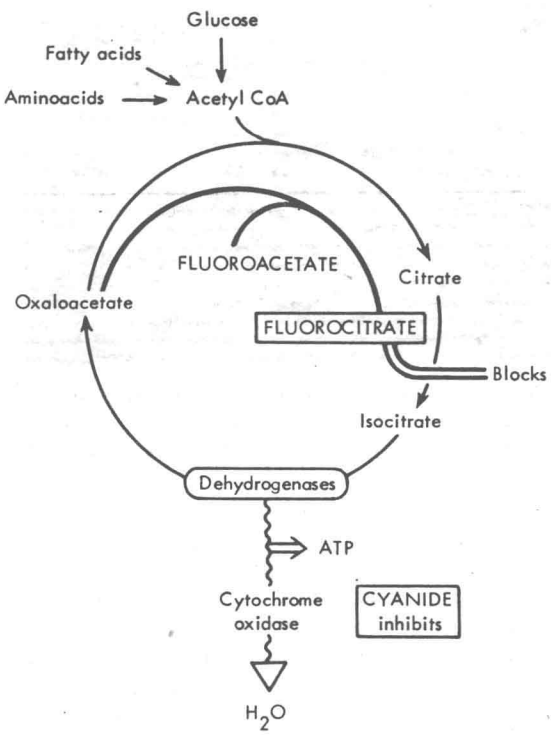

Fig. 1.1 The effects of fluoroacetate and of cyanide on cellular metabolism. Note that fluoroacetate is converted to fluorocitrate which inhibits aconitase.

damage to capillaries which results in thrombosis that may even extend to the arteries. Radiation damage, also a cause of necrosis, is considered on p. 23. 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 unnoticed mechanical trauma consequent upon 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. 1.2). Alternatively, membranous components of the living cells may be labelled with radioisotopes such as Cr^{51} or P^{32};

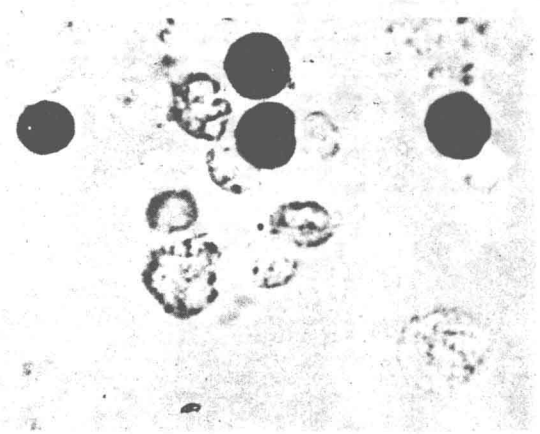

Fig. 1.2 A suspension of lymphocytes treated with cytotoxic iso-antibody and complement. Some of the cells have been killed, and have become stained by trypan blue dye present in the suspending fluid: other cells have survived and are unstained. (Phase microscopy.) (Miss Patricia Bacon.)

subsequent severe injury to the cell, probably lethal, is recognised by release of the radioactive label from the cells into the culture medium.

In organised tissues such as liver or kidney, 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. 1.3), 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 haematoxyphilic masses (**pyknosis**) and these may break up (**karyorrhexis**) to form granules inside the nuclear membrane or throughout the cytoplasm (Fig. 1.5). 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

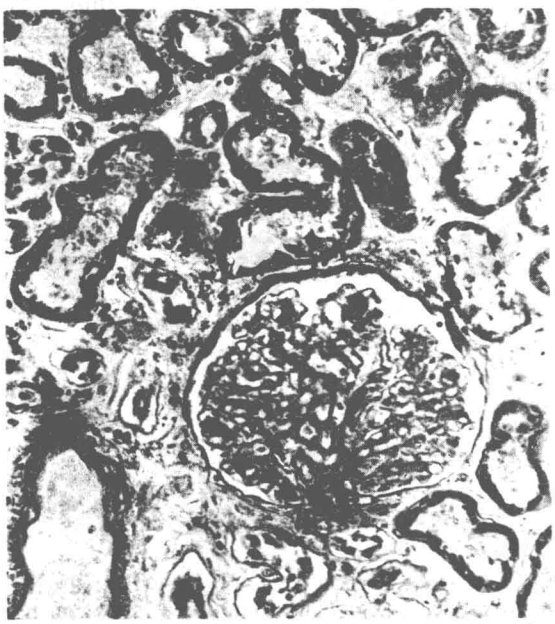

Fig. 1.3 Portion of infarct of kidney, showing coagulative necrosis. A glomerulus and tubules are seen, but the nuclei have disappeared and the structural details are lost. × 172.

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

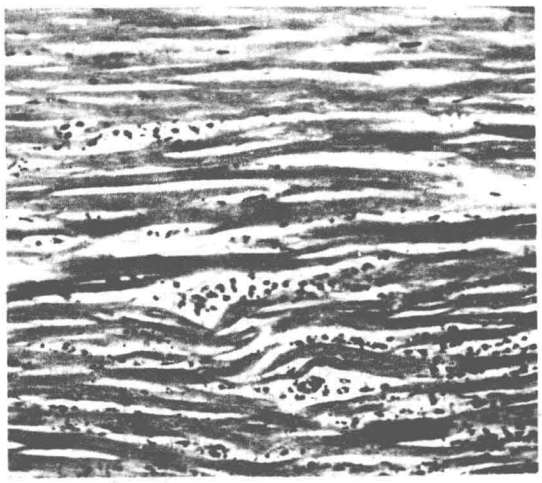

Fig. 1.4 Coagulative necrosis in infarction of heart muscle. The dead fibres are hyaline and structureless; remains of leukocytes are present between them. × 125.

mitochondrial membranes precedes the disappearance 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. 1.3 and 1.4) 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 liquid (**colliquative necrosis**) with profound loss of the previous histological architecture.

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.

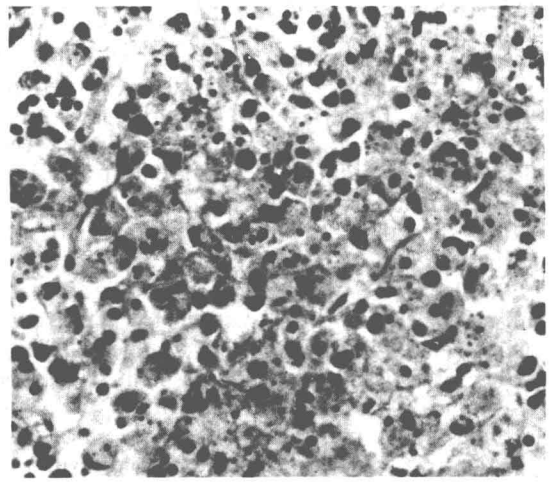

Fig. 1.5 Spreading necrosis with karyorrhexis in lymph node in typhoid fever. Note destruction of nuclei and numerous deeply-stained granules of chromatin. × 412.

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

Fig. 1.6 Gangrene of toes.