Muir's textbook of
PATHOLOGY

Thirteenth edition

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Preface

In his preface in 1924 to the first edition of the textbook with which he has been eponymously linked, Sir Robert Muir wrote:

> The subject of Pathology has now become so extensive that in a book of this size selection of subjects is essential for any satisfactory treatment, and in considering their relative importance I have been guided by two considerations. I have endeavoured, in the first place, to give due weight to the scientific aspect of the general pathological processes and, in the second, to describe those pathological changes in the various organs, which are of special importance in relation to Clinical Medicine and Surgery. The subject-matter thus falls into two main portions corresponding roughly with General and Special Pathology, though these terms are not used, as it seems inadvisable, in a book of this nature, to draw any sharp distinctions.

These remarks remain, in part, apposite some 68 years later as we introduce this thirteenth edition of his textbook. The division into general and systematic sections which Muir reluctantly introduced was accepted in subsequent editions and we have continued with this pattern. The text is divided into a general section comprising 11 chapters, a systematic section comprising 13 chapters; a final chapter deals with parasitic diseases.

In embarking on the daunting task of preparing this new edition we were aware that pathology, the study of disease by scientific methods, had, in the past decade, extended its frontiers to encompass advances in molecular biology which had first been made in the basic sciences as distinct from the more applied medical sciences. These advances are of particular relevance to the teaching of general pathology but will become increasingly important also in helping our understanding of system and organ diseases. The section on general pathology, therefore, has been restructured and almost completely rewritten, emphasizing the impact of cellular and molecular biology on our understanding of disease. We have deliberately sought to have dual or multi-authorship of most chapters. Thus, in the general section, in order to broaden our scope we have had contributions from colleagues in cell biology, clinical chemistry, immunology, immunopathology, medical genetics, microbiology and pharmacology. In addition, clinical colleagues have not only been consulted but have also contributed to this section and to some of the systematic chapters, thus increasing the clinical emphasis.

Chapter 1 deals with the structure and function of normal cells and extracellular matrix and explains how abnormalities may lead to disease. This is followed by a chapter on the genetic basis of inherited disease and the application of recombinant DNA technology to the detection and characterization of these diseases. Haemostasis and its disorders are transferred from the haematology section to the chapter on disturbances of body fluids and blood flow since it is relevant to the discussion of haemorrhage and thrombosis. Inflammation, healing and repair are incorporated into one chapter to emphasize that healing and repair are two of the possible outcomes of the inflammatory response. More attention has also been given to the chemical mediators of inflammation and the role of cytokines in these processes as these are potential areas for therapeutic intervention. Whereas, originally, we intended to have a single chapter covering basic immunology and immunopathology we were unable to condense the massively expanded body of immunological knowledge into a single comprehensive chapter. Thus, as in the twelfth edition, we still have two chapters dealing with these topics. A new chapter on metabolic disorders draws together a miscellaneous group of conditions which, in previous editions, were dealt with in various parts of the systematic pathology section. The chapter on microbial infections describes the host–parasite relationship and the pathology of common microbial infections. As

these disorders often affect multiple organ systems and provide valuable examples of disease processes, this format is more appropriate. A full chapter is devoted to nutritional disorders; these, unfortunately, are probably still the commonest diseases of underdeveloped countries. The chapter dealing with growth and neoplasia describes and discusses the pathogenesis of tumours and their clinical behaviour. The last chapter in the general section deals with tissue injury produced by drugs and radiation; these diseases are often iatrogenic in origin. In contrast, drug abuse is usually a self-inflicted disease and the pathological mechanisms and consequences of this are briefly reviewed. The general section is extensively illustrated with some 200 line drawings.

In the systematic section we include diseases of the blood vessels and lymphatics in the chapter on the cardiovascular system. Emphasis is placed on the aetiology of the various diseases, their effects on structure and function and their clinicopathological correlations. Each chapter has been extensively revised and many recent advances have been included. The amount of systematic pathology covered is greater than most medical students require to assimilate during the undergraduate course in pathology, and students will therefore require guidance from their teachers. However, this book should continue to be of value throughout the 'clinical' years of the curriculum and indeed during vocational postgraduate training, not only in histopathology but in many disciplines. In some chapters, in order to provide comprehensive coverage, concise information has been provided in the form of extended tables. In every chapter a brief and limited list of further reading is included.

Glasgow — R. N. M. MacSween
January 1992 — K. Whaley

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We are deeply grateful to our fellow authors for their contributions. It is with much sadness that we record the death of Professor David Flenley; his contribution to Chapter 13 was virtually complete at the time of his death and has been incorporated with minor modifications. We thank all our authors for their tolerant acceptance of our editing of their manuscripts and for keeping to increasingly tight deadlines in order to meet the demand to publish by a specified date. The published text is our final responsibility; we earnestly hope we have achieved the correct balance in terms of content and that we have not introduced errors of fact or judgement.

In addition to named contributors we have received helpful advice from many of our colleagues in this department who have read chapters and commented on the balance of the content. They provided stimulating discussions on a number of topics, advised on lay-out and design and, most painstakingly of all, undertook proof reading duties. They include Dr M. E. Catto, Dr I. Gibson, Dr M. P. MacSween, Dr A. McPhaden and Dr E. A. Mallon. We gratefully acknowledge the contribution of Professor J. R. Anderson, co-editor or editor of the previous four editions. He encouraged us in our task and not only gave us a free hand with text material, but allowed us unrestricted use of many illustrations for this edition. Illustrations provided by colleagues from other departments are acknowledged in the legends. Dr A. J. Krajewski and Dr C. M. Steel kindly advised on some of the illustrations in Chapter 15.

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Glasgow
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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 sought and developed for its prevention or cure. Pathology may thus be described as the scientific study of the causes and effects of disease.

Pathology as defined in this way embraces a number of scientific specialties including: (a) histology and cytology in which the structural changes in diseased tissue are examined by naked eye inspection (macroscopic features) or by light and electron microscopy of tissue sections or smears (microscopic features); (b) clinical chemistry, 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; (d) haematology – investigation of abnormalities of the cells of the blood and their precursors in haemopoietic tissue and of the haemostatic, including the clotting, mechanism; and (e) clinical genetics, in which inherited chromosomal abnormalities in the germ cells or acquired chromosomal abnormalities in somatic cells are investigated using the techniques of molecular biology.

These divisions of pathology have resulted from increasing specialization in techniques and from expanding knowledge within each discipline. They are each, however, of importance in the scientific study of disease. Even a cursory look at any of the systematic chapters in this book will immediately make the student appreciate how closely interlinked the disciplines are and how each variously contributes to our understanding of disease processes. Furthermore, it has to be emphasized that the pathologist, while sometimes removed from immediate patient contact, is nevertheless a clinical specialist who is frequently the first to establish a clinical diagnosis and whose experience is vitally important in clinical management and treatment. There is a compelling need therefore to learn pathology, irrespective of the branch of medicine the student intends to pursue. The pathological sciences are, and will continue to be, among subjects constituting the core course in medical curricula.

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 first of the injurious effects of 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 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. If, however, the patient survives for some days or more, the affected myocardium

shows reactive changes which occur subsequent to cell death and the lesion becomes readily visible both macroscopically (p. 490) and microscopically (p. 493). Reactive changes may also, however, be closely similar to physiological processes. The increase in skeletal muscle size (i.e. hypertrophy) which is readily recognized as a normal adaptive response in the athlete is a similar process to the cardiac enlargement which occurs in the patient with high blood pressure and which, if the blood pressure is not controlled, may lead to cardiac failure. During the normal menstrual cycle the endometrium undergoes considerable increase in bulk by a process of hyperplasia, i.e. increase in cell numbers, but this ceases and the endometrium is shed during menstruation, the whole cycle being under hormonal control. If, however, there is hormonal imbalance then the hyperplasia may become an abnormal reactive response and the endometrium shows microscopic abnormalities.

The changes which are adaptive, as distinct from changes due to injury or those which are due to reaction, are often not as well defined as in the examples given above. Furthermore, the processes involved are often much more complex and this textbook sets out to provide an account of the mechanisms which are involved. In order to help in the understanding of these processes it is of value to introduce here a broad classification of causal factors in disease, citing a few examples.

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 fertilized 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 the 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 adults who become infected with hepatitis B virus, most develop immunity without becoming ill, some have a mild illness and a few (less than 10%) develop chronic liver disease which progresses to cirrhosis. 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 postnatal life. Genetically-determined diseases are commonly congenital, although some present many years after birth, a good example being adenomatous polyposis coli, which is due to an abnormal gene and consists of multiple tumours of the colonic mucosa, appearing in adolescence or adult life. 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 can result in fetal death, or involvement of various tissues leading to mental deficiency, blindness, deafness or structural abnormalities of the heart. The mother can 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 can enter the maternal circulation and stimulate antibody

production: the maternal antibody may pass across the placenta and react with the fetal red cells, causing a haemolytic anaemia.

Acquired Disease

The major causal factors may be classified as follows:

(1) Deficiency diseases (p. 338). 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 trauma, 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 ionizing radiations cannot be regarded as entirely safe in any dosage (p. 430).

(3) Chemicals. With the use of an ever increasing number of chemical agents as drugs, in industrial processes, in agriculture 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. Hepatocytes play a major role in absorbing and metabolizing many toxic chemicals. They are therefore liable to injury by such substances, including paracetamol and alcohol in high dosage (p. 413). 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.

(4) Infective micro-organisms (p. 279). These include bacteria, protozoa, small metazoa, lower fungi and viruses. In spite of advances in immunization 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 multiply in host cells, usually with a direct cytopathic effect: features of virus disease depend largely on which cells are invaded and on the response of the host. Some viruses also become integrated, i.e. viral genes are inserted into the genome of the host cell, and this is probably a contributory cause in some forms of cancer (p. 391). Of the protozoa, the malaria parasite is of enormous importance as a cause of chronic ill health in whole populations.

(5) Metazoan parasites (p. 1142) are also an important cause of disease in many parts of the world. Hookworm infection 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 micro-organisms 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 immune system does not distinguish between harmful and harmless foreign antigenic materials and injury may result from immune reactions to either. Such hypersensitivity reactions (p. 204) 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, can cause generalized, sometimes fatal, reactions. Hypersensitivity reactions may also result from the development of autoimmunity in which antibodies and lymphocytes react with and injure normal cells and tissues; examples include chronic thyroiditis, commonly progressing to hypothyroidism, and the excessive destruction of red cells in autoimmune haemolytic anaemia.

In another group of disorders there is immune deficiency and the patient lacks defence against micro-organisms. This may result from abnormalities of fetal development, as an effect of various acquired diseases, most notably in infection by the human immunodeficiency virus (HIV) with the development of the acquired immunodeficiency syndrome (AIDS), or it may be induced by immunosuppressive therapy.

(7) Psychogenic factors. The mental stresses imposed by conditions of life, particularly in technologically advanced communities, are probably contributory factors in three important and overlapping groups of diseases. First, acquired mental disease such as depression, for which no specific structural or biochemical basis has yet been found. Second, diseases of addiction, particularly to alcohol, various drugs and tobacco. The heterogeneous third group, sometimes referred to as the psychosomatic disorders, includes peptic ulcer (p. 699), hypertension (p. 451) and coronary artery disease (p. 488); in these three conditions, anxiety, overwork and frustration (all of which are experienced by editors of textbooks) may be causal factors, although their modes of action are obscure.

Contents

1

Cells and Tissues in Health and Disease

Pathology is the study of disease by scientific methods; it involves the study of abnormality, of the failure of normal systems to operate, or their collapse following insult. Problems can arise either internally, through defects in the organism, or from external causes, such as infection or trauma. Not only is the study of pathology essential in understanding disease, it often provides valuable clues as to the functioning of normal systems. Equally, the pathologist must draw upon a range of disciplines to understand malfunction.

The human body is a clone of about 10^{13} cells together with the extracellular matrix they have made; complicated control mechanisms are required to keep it working in a co-ordinated fashion. Abnormalities may arise because of faulty genomic information or because of incorrect or untimely interpretations of the primary code. Obviously an inaccurate plan is likely to give rise to an abnormal system (Chapter 2) but it is less easy to see how the inappropriate expression of normal cellular information will cause abnormality. Thus, 'normal' behaviour in an abnormal site can cause serious problems.

One way of reducing the impact of malfunction is to have a repair and maintenance system, yet it is in these that we often see defects. This conundrum becomes understandable if we consider that if a primary system collapses then there is no body (or cell) to exhibit pathological features whilst a defective repair system leads to slow degenerative changes after a period of apparent normality. Thus, total failure of DNA replication would leave just a zygote whereas deficiency in the DNA repair

system (e.g. in xeroderma pigmentosum – p. 390) leads to a high incidence of skin tumours. It is important to realize that biological structures at both cellular and tissue level are labile. Not only must the correct organization arise during embryonic development, it must be constantly maintained and renewed.

In this chapter, we will first discuss the structure and function of normal cells and tissues, concentrating on systems which cause problems if disturbed and draw attention to those areas of cell biology which help in understanding pathological mechanisms. Thereafter, we will examine some of the effects which result from tissue damage.

Normal Cell Structure and Function

A high level of complexity occurs in unicellular eukaryotic organisms (e.g. amoeba): here intracellular compartmentalization occurs with the development of intracytoplasmic organelles each with specific function (Fig. 1.1). There is a cost in terms of the informational energy required to establish and maintain compartments but this is offset by the ability to concentrate reactants and increase reaction rates. A multicellular mode of existence allows even more specialization, this time at the cellular level but more sophisticated control mechanisms are required to co-ordinate the functions of each cell type and the interaction between cell types.

Ultrastructural study of mammalian cells provides a fixed 'snapshot' of the cell at a particular time. The recent introduction of enhanced-contrast video microscopy has revealed dramatic movement within the cytoplasm, and has shown that even cytoskeletal elements may have half-lives of only minutes or seconds (Table 1.1).

Nucleus

The nucleus is the largest single compartment of the cell and is its central data store. Control arises through the interaction of nucleus and cytoplasm and neither one is autonomous as a controller. It is enclosed by the double membrane of the nuclear envelope which is perforated by nuclear pores, allowing passage of molecules including proteins and nucleic acids between nucleus and cytoplasm. The nuclear shape is stabilized by a group of polypeptides (**lamins**) which show some homology with intermediate filaments (see Table 1.3). The lamins bind to proteins of the inner membrane and form an electron dense layer on its nuclear aspect, the **nuclear lamina**.

Within the human nucleus are 46 chromosomes. Each consists of a single molecule of DNA approximately 5 cm long packed in a complex fashion (Fig. 1.2) with positively charged structural proteins (**histones**) to form a string of particles known as **nucleosomes**. Closely packed nucleosomes form electron dense **heterochromatin**, which is thought to be transcriptionally inactive, and is often concentrated at the periphery of the nucleus. In contrast, most RNA synthesis occurs in the more loosely arranged and thus electron lucent **euchromatin**. The arrangement of chromosomes within the nucleus appears to be non-random. For example, several chromosomes contain repeated genes for ribosomal RNA synthesis and these are clustered together to form nucleoli.

While the haploid set of chromosomes of each cell carries all the information needed for the entire organism, this information will only be correctly interpreted if the nucleus is in the cytoplasmic environment. The nucleus and cytoplasm are interdependent in the control of gene expression. An unusual feature of the nuclear compartment is that it is transient; at every cell division the nuclear membrane is broken down and then reformed. It is likely that nuclear structure and function are highly conserved since any major loss of content or alteration in function would be fatal to the organism. Minor alterations in the genetic code which