General and Systematic Pathology

Edited by

JCE Underwood

CHURCHILL LIVINGSTONE

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Illustrations and chapter icons by Robert Britton

THIRD EDITION



CHURCHILL LIVINGSTONE An imprint of Harcourt Publishers Limited

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First edition 1992 Second edition 1996 Third edition 2000

ISBN 0-443-06285-4

International Student Edition ISBN 0-443-06286-2

British Library Cataloguing in Publication Data A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data A catalog record for this book is available from the Library of Congress

Note

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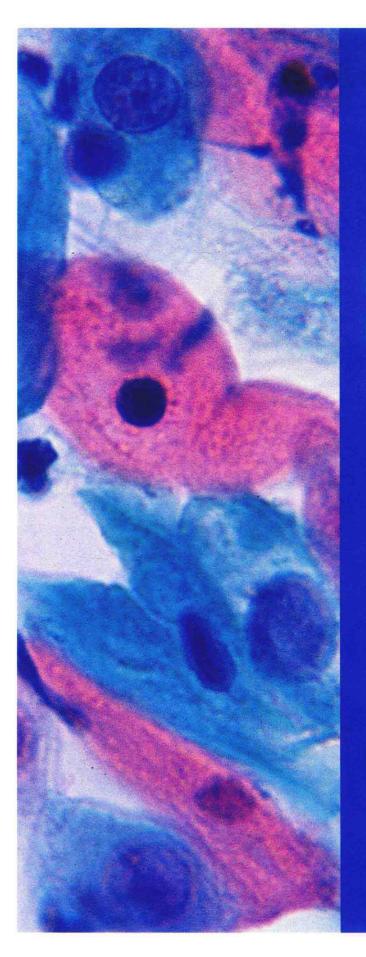
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Pathology is the *scientific study of disease*. In clinical practice and medical education, pathology also has a wider meaning: pathology constitutes a large body of scientific knowledge, ideas and investigative methods essential for the understanding and practice of modern medicine.

Pathology includes knowledge and understanding of the *functional* and *structural* changes in disease, from the molecular level to the effects on the individual.

Pathology is continually subject to change, revision and expansion as the application of new scientific methods illuminates our knowledge of disease.

The ultimate goal of pathology is the identification of the *causes* of disease, a fundamental objective that leads the way to successful therapy and to disease prevention.

HISTORY OF PATHOLOGY

The evolution of concepts about the causes and nature of human disease reflects the prevailing ideas about the explanation for all worldly events and the techniques available for their investigation (Table 1.1). Thus, the early dominance of animism, in the philosophies of Plato and Pythagoras, resulted in the attribution of disease to the adverse influences of immaterial or supernatural forces; it was therefore assumed that nothing could be learnt from the objective examination of the corpses of those who succumbed. Even when the clinical significance of many abnormal physical signs and postmortem findings was established early in the long history of medicine, the nature of the underlying disease was thought to be due to an excess or deficiency of the various humors—phlegm, black bile, and so on. These concepts are now firmly and irrevocably consigned to medical antiquity.

Morbid anatomy

The first opportunity for the scientific study of disease came from the thorough internal examination of the body after death. *Autopsies* (necropsies or postmortem examinations) have been performed scientifically from about 300 BC and have revealed much information that has helped to clarify the nature of many diseases. As these examinations were confined initially to the gross (rather than microscopic) examination of the organs, this period is regarded as the era of *morbid anatomy*. During the 19th century in Germany, medical science was advanced by Rokitansky and Aschoff, who meticulously performed and documented many thousands of autopsies and correlated their findings with the clinical signs and symptoms of the patients and with the natural history of a wide variety of diseases.

Microscopic and cellular pathology

Pathology, and indeed medicine as a whole, was revolutionised by the application of *microscopy* to the study of diseased tissues from about 1800. Before this, it was postulated that diseases arose by a process of *spontaneous generation*; that is, by metamorphosis independent of any external cause or other influence. This notion seems ridiculous to us today, but 200 years ago nothing was known of bacteria, viruses, ionising radiation, carcinogenic chemicals, and so on. So Louis Pasteur's demonstration that micro-organisms in the environment could contaminate and impair the quality of wine was a major advance in our perception of the environment and our understanding of its possible adverse effects, and it has had an enormous impact on medicine.

Table 1.1 Historical relationship between the hypothetical causes of disease and the dependence on techniques for their elucidation

Hypothetical cause of disease	Techniques supporting causal hypothesis	Period
Animism	None	Primitive, though the ideas persist in some cultures
Magic	None	Primitive, though the ideas persist in some cultures
Humors (excess or deficiency)	Early autopsies and clinical observations	c. 300 BC to c.1500 AD
Spontaneous generation (abiogenesis)	Analogies with decomposing matter	Prior to 1800 AD
Environmental	Modern autopsy Cellular pathology (e.g. microscopy) Toxicology Microbiology Epidemiology	1850 to present
Genetic	Molecular pathology (e.g. DNA analysis) and clinical observations on inherited defects	20th century

Rudolf Virchow (1821–1902), a German pathologist and ardent advocate of the microscope, recognised that the cell was the smallest viable constituent unit of the body and contrived a new and lasting set of ideas about disease—cellular pathology. The light microscope enabled him to see changes in diseased tissues at a cellular level and his observations, extended further by electron microscopy, have had a profound influence. That does not mean to say that Virchow's cell pathology theory is immutable. Indeed, current advances in biochemistry are revolutionising our understanding of many diseases at a molecular level; we now have biochemical explanations for many of the cellular and clinical manifestations of disease.

Molecular pathology

The impact of *molecular pathology* is exemplified by the advances being made in our knowledge of the biochemical basis of congenital disorders and cancer. Techniques with relatively simple principles (less easy in practice) can reveal the change of a single nucleotide in genomic DNA resulting in the synthesis of the defective gene product that may be the fundamental lesion in a particular disease (Ch. 3).

Cellular and molecular alterations in disease

As a result of the application of modern scientific methods, we now have a clearer understanding of the ways in which diseases can be attributed to disturbances of normal cellular and a molecular mechanisms (Table 1.2). By continuing to study disease in this way, knowledge can be advanced and treatment improved.

SCOPE OF PATHOLOGY

Pathology is the foundation of medical science and practice. Without pathology, the practice of medicine would be reduced to myths and folklore.

Clinical and experimental pathology

Scientific knowledge about human diseases is derived from observations on patients or, by analogy, from experimental studies on animals and cell cultures. The greatest contribution comes from the detailed study of tissue and body fluids from patients. However, as a professional discipline, pathology has a key role in translational research by facilitating the transfer of knowledge derived from laboratory investigations into clinical practice.

Clinical pathology

Clinical medicine is based on a longitudinal approach to a patient's illness—the patient's history, the examination and investigation, the diagnosis, and the treatment. Clinical pathology is more concerned with a cross-sectional analysis at the level of the disease itself, studied in depth—the

cause and mechanisms of the disease, and the effects of the disease upon the various organs and systems of the body. These two perspectives are complementary and inseparable: clinical medicine cannot be practised without an understanding of pathology; pathology is meaningless if it is bereft of clinical implications.

Experimental pathology

Experimental pathology is the observation of the effects of manipulations on experimental systems such as animal models of disease or cell cultures. Although advances in cell culture technology have reduced the usage of laboratory animals in medical research and experimental pathology, it is extremely difficult to mimic in cell cultures the physiological milieu that prevails in the intact human body.

Subdivisions of clinical pathology

Pathology is a vast subject with many ramifications. In practice, however, it can be split into major subdivisions:

- histopathology: the investigation and diagnosis of disease from the examination of tissues
- *cytopathology*: the investigation and diagnosis of disease from the examination of isolated cells
- haematology: the study of disorders of the cellular and coagulable components of blood
- *microbiology*: the study of infectious diseases and the organisms responsible for them
- *immunology*: the study of the specific defence mechanisms of the body
- *chemical pathology*: the study and diagnosis of disease from the chemical changes in tissues and fluids
- genetics: the study of abnormal chromosomes and genes
- toxicology: the study of the effects of known or suspected poisons
- forensic pathology: the application of pathology to legal purposes (e.g. investigation of death in suspicious circumstances).

These subdivisions are more important professionally (because each requires its own team of expert specialists) than educationally. The subject must be taught and learnt in an integrated manner, for the body and its diseases make no distinction between these conventional subdivisions.

This book, therefore, adopts a multidisciplinary approach to pathology. In the systematic section (Part 3), the normal structure and function of each organ is summarised, the pathological basis for clinical signs and symptoms is described, and the clinical implications of each disease are emphasised.

TECHNIQUES OF PATHOLOGY

Our knowledge of the nature and causation of disease has been disclosed by the continuing application of technology to its study.

Table 1.2 Examples of the involvement of cellular and extra-cellular components in disease

Component	Normal function	Examples of alterations in disease
Cellular		
Nucleus	Genes encoded in DNA	Inherited or spontaneous mutations (e.g. inherited metabolic disorders, cancer)
		Site of viral replication
Mitochondria	Oxidative metabolism	Mutations of mitochondrial DNA
		Enzyme defects
Lysosomes	Enzymic degradation	Metabolic storage disorders
		Defects in microbial killing
Cell membrane	Functional envelope of cell	Defects in ion transfer (e.g. cystic fibrosis, hereditary spherocytosis)
Adhesion molecules	Cellular adhesion	Altered expression in inflammation
		Decreased expression in neoplasia
HLA molecules	Immune recognition	Aberrant expression associated with autoimmune disease
		Haplotypes correlate with risk of some diseases
Receptors	Specific recognition	Hormone receptors cause cells to respond to physiological or pathological hormone levels
		Lymphocyte receptors enable immune responses to antigens
Secreted products		
Collagen	Mechanical strength of tissues	Integrity of wounds
		Inherited defects (e.g. osteogenesis imperfecta)
Immunoglobulins	Antibody activity in immune reactions	Deficiency leads to increased infection risk
		Secreted by myeloma cells
	a a	Specific antibody activity may be in response to infection or a marker of autoimmune disease
Nitric oxide	Endothelium-derived relaxing factor causing vasodilatation, inhibition of platelet aggregation and of proliferation	Increased levels in endotoxic shock and in asthma
Hormones	Control of specific target cells	Excess or deficiency due to disease of endocrine organs
Cytokines	Regulation of inflammatory and immune responses and of cell proliferation	Increased levels in inflammatory, immunological and reparative tissue reactions
Free radicals	Microbial killing	Inappropriate or excessive production causes tissue damage

Gross pathology

Before microscopy was applied to medical problems (c. 1800), observations were confined to those made with the unaided eye, and thus was accumulated much of our knowledge of the *morbid anatomy* of disease. Gross or macroscopic pathology is the modern nomenclature for this approach to the study of disease and, especially in the autopsy, it is still an important investigative method. The gross pathology of many diseases is so characteristic that,

when interpreted by the experienced pathologist, a fairly confident diagnosis can often be given before further investigation by, for example, light microscopy.

Light microscopy

Advances in optics and the quality of lenses have resulted in a wealth of new information about the structure of tissues and cells in health and disease that can be gleaned from their examination by light microscopy. If solid tissues are to be examined by light microscopy, the sample must first be thinly sectioned to permit the transmission of light and to minimise the superimposition of tissue components. These sections are routinely cut from tissue hardened by permeation with and embedding in wax or, less often, transparent plastic. For some purposes (e.g. histochemistry, very urgent diagnosis) sections have to be cut from tissue that has been hardened rapidly by freezing. The sections are stained to help distinguish between different components of the tissue (e.g. nuclei, cytoplasm, collagen).

Histochemistry

Histochemistry is the study of the chemistry of tissues, usually by microscopy of tissue sections after they have been treated with specific reagents so that the features of individual cells can be visualised.

Immunohistochemistry and immunofluorescence

Immunohistochemistry and immunofluorescence employ antibodies (immunoglobulins with antigen specificity) to visualise substances in tissue sections or cell preparations; these techniques use antibodies linked chemically to enzymes or fluorescent dyes respectively. Immunofluorescence requires a microscope specially modified for ultraviolet illumination and the preparations are often not permanent (they fade). For these reasons, immunohistochemistry has become more popular; in this technique, the end product is a deposit of opaque or coloured material that can be seen with a conventional light microscope and does not deteriorate. The repertoire of substances detectable by these techniques has been greatly enlarged by the development of *monoclonal antibodies*.

Electron microscopy

Electron microscopy has extended the range of pathology to the study of disorders at an organelle level, and to the demonstration of viruses in tissue samples from some diseases. The most common diagnostic use is for the interpretation of renal biopsies.

Biochemical techniques

Biochemical techniques applied to the body's tissues and fluids in health and disease are now one of the dominant influences on our growing knowledge of pathological processes. The clinical role of biochemistry is exemplified by the importance of monitoring fluid and electrolyte homeostasis in many disorders. Serum enzyme assays are used to assess the integrity and vitality of various tissues; for example, raised levels of cardiac enzymes in the blood indicate damage to cardiac myocytes.

Haematological techniques

Haematological techniques are used in the diagnosis and study of blood disorders. These techniques range from relatively simple cell counting, which can be performed electronically, to assays of blood coagulation factors.

Cell cultures

Cell cultures are widely used in research and diagnosis. They are an attractive medium for research because of the ease with which the cellular environment can be modified and the responses to it monitored. Diagnostically, cell cultures are used to prepare chromosome spreads for *cytogenetic analysis*.

Medical microbiology

Medical microbiology is the study of diseases caused by organisms such as bacteria, fungi, viruses and parasites. Techniques used include direct microscopy of appropriately stained material (e.g. pus), cultures to isolate and grow the organism, and methods to identify correctly the cause of the infection. In the case of bacterial infections, the most appropriate antibiotic can be selected by determining the sensitivity of the organism to a variety of agents.

Molecular pathology

Many important advances are now coming from the science of molecular pathology revealing defects in the chemical structure of molecules arising from errors in the genome, the sequence of bases that directs amino acid synthesis. Using *in-situ hybridisation* it is possible to render the presence of specific genes or their messenger RNA visible in tissue sections or cell preparations. Minute quantities of nucleic acids can be amplified by using the *polymerase chain reaction* using oligonucleotide primers specific for the genes being studied.

Molecular pathology is manifested in various conditions, for example: abnormal haemoglobin molecules, such as in sickle cell disease (Ch. 23); abnormal collagen molecules in osteogenesis imperfecta (Chs 7, 25); and alterations in the genome governing the control of cell and tissue growth, playing an important part in the development of tumours (Ch. 11).

LEARNING PATHOLOGY

Pathology is best learnt in two stages:

- general pathology: the mechanisms and characteristics of the principal types of disease process
 (e.g. inflammation, tumours, degenerations)
- systematic pathology: the descriptions of specific diseases as they affect individual organs or organ systems (e.g. appendicitis, lung cancer, atheroma).

General pathology

General pathology is our current understanding of the causation, mechanisms and characteristics of the major categories of disease.

These processes are covered in Part 2 of this textbook and many specific diseases mentioned by way of illustration. The principles of general pathology must be understood before an attempt is made to study systematic pathology. General pathology is the foundation of knowledge that has to be laid down before one can begin to study the systematic pathology of specific diseases.

Systematic pathology

Systematic pathology is our current knowledge of specific diseases as they affect individual organs or systems. ('Systematic' should not be confused with 'systemic' in this context. Systemic pathology would be characteristic of a disease that pervaded *all* body systems!) Each specific disease can usually be attributed to the operation of one or more categories of causation and mechanism featuring in general pathology. Thus, acute appendicitis is acute inflammation affecting the appendix; carcinoma of the lung is the result of carcinogenesis acting upon cells in the lung, and the behaviour of the cancerous cells thus formed follows the pattern established for malignant tumours; and so

Systematic pathology is covered in Part 3 of this textbook

Building knowledge and understanding

There are two apparent difficulties that face the new student of pathology: language and process. Pathology, like most branches of science and medicine, has its own vocabulary of special terms: these need to be learnt and understood not just because they are the language of pathology; they are also a major part of the language of clinical medicine. The student must not confuse the learning of the language with the learning of the mechanisms of disease and their effects on individual organs and patients. In this book, each important term will be clearly defined in the main text or the glossary or both.

A logical and orderly way of thinking about diseases and their characteristics must be cultivated; for each entity the student should be able to list the chief characteristics that apply to any disease:

- epidemiology
- · aetiology
- pathogenesis
- pathological and clinical features
- complications and sequelae
- prognosis
- treatment.

Our knowledge about many diseases is still incomplete, but at least such a list will serve to prompt the memory and enable students to organise their knowledge.

Pathology is learnt through a variety of media. Even the bedside, operating theatre and outpatient clinic provide ample opportunities for further experience of pathology; hearing a diastolic cardiac murmur through a stethoscope should prompt the listening student to consider the pathological features of the narrowed mitral valve orifice (mitral

Table 1.3 The problem-oriented approach: examples of combinations of clinical problems and their pathological basis

Problems	Pathological basis (diagnosis)	Comment
Weight loss and haemoptysis	Lung cancer or tuberculosis	Can be distinguished by finding either cancer cells or mycobacteria in sputum
Dyspnoea and ankle swelling	Heart failure	Due to, for example, valvular disease
Chest pain and hypotension	Myocardial infarction	Should be confirmed by ECG and serum assay of cardiac enzymes
Vomiting and diarrhoea	Gastroenteritis	Specific microbial cause can be determined
Headache, impaired vision and microscopic haematuria	Hypertension	May be due to various causes or, more commonly, without evident cause
Headache, vomiting and photophobia	Subarachnoid haemorrhage or meningitis	Can be distinguished by other clinical features and examination of cerebrospinal fluid

stenosis) responsible for the murmur, and the effects of this stenosis on the lungs and the rest of the cardiovascular system.

Pathology in the problem-oriented integrated medical curriculum

Although medicine, surgery, pathology and other disciplines are frequently taught as separate subjects in the curriculum, students must develop an integrated understanding of disease.

To encourage this integrated attitude, in this textbook the pathological basis of common clinical signs is frequently emphasised so that students can develop an interface between their everyday clinical experiences and their knowledge of pathology.

In general, the development of a clinicopathological understanding of disease can be gained by two equally legitimate and complementary approaches:

- problem-oriented
- · disease-oriented.

In learning pathology, the disease-oriented approach is more relevant because medical practitioners require knowledge of diseases (e.g. pneumonia, cancer, ischaemic heart disease) so that correct diagnoses can be made and the most appropriate treatment given.

The problem-oriented approach

Historically, before diseases had been properly characterised, the problems (symptoms and signs) caused by diseases constituted all that was known about them. The classification of disease was based almost entirely upon symptomatology supported by a limited range of clinical signs.

The problem-oriented approach is still the first step in the clinical diagnosis of a disease. In many illnesses, symptoms alone suffice for diagnosis. In other illnesses, the diagnosis has to be supported by clinical signs (e.g. abnormal heart sounds). In some instances, the diagnosis can be made conclusively only by special investigations (e.g. laboratory analysis of blood or tissue samples, imaging techniques).

The links between *diseases* and the *problems* they produce are emphasised in the systematic chapters (Part 3) and are exemplified here (Table 1.3).

Justifications for the problem-oriented approach are that:

- Patients present with 'problems' rather than 'diagnoses'.
- Some clinical problems lack a known pathological basis (this is true particularly of psychiatric conditions such as depressive illness).
- Clinical treatment is often directed towards relieving the patient's problems rather than curing their disease (which may either remit spontaneously or be incurable).

The disease-oriented approach

Modern pathological understanding of illnesses is based on a disease-oriented approach; knowledge of diseases and their clinical manifestations is essential for good medical practice.

The disease-oriented approach is also the most successful way of presenting pathological knowledge. It would be possible to compose a textbook of pathology in which the chapters were entitled, for example, 'Cough', 'Weight loss', 'Headaches' and 'Pain' (these being problems), but the reader would be unlikely to come away with a clear understanding of the diseases. This is because one disease may cause a variety of problems—for example, cough, weight loss, headaches and pain—and may therefore crop up in several chapters. Consequently, this textbook, like most textbooks of pathology (and, indeed, of medicine) adopts a disease-oriented approach.

MAKING DIAGNOSES

Diagnosis is the act of naming a disease in an individual patient. The diagnosis is important because it enables the

patient to benefit from treatment that is known, or is at least likely, to be effective from having observed its effects on other patients with the same disease.

The process of making diagnoses involves:

- taking a clinical history to document symptoms
- examining the patient for clinical signs
- if necessary, performing *investigations* guided by the provisional diagnosis based on signs and symptoms.

Although experienced clinicians can diagnose many patients' diseases quite rapidly (and usually reliably), the student will find that it is helpful to adopt a formal strategy based on a series of logical steps leading to the gradual exclusion of various possibilities and the emergence of a single diagnosis. For example:

- First decide which organ or body system is likely to be affected by the disease.
- From the signs and symptoms, decide which general category of disease (inflammation, tumours, etc.) is likely to be present.
- Then, using other factors (age, gender, previous medical history, etc.), infer a diagnosis or a small number of possibilities for investigation.
- Investigations should be performed only if the outcome of each one can be expected to resolve the diagnosis, or influence management if the diagnosis is already known.

This strategy can be refined and presented in the form of decision trees or diagnostic algorithms, but these details are outside the scope of this book.

Diagnostic pathology

In living patients we often investigate and diagnose their illness by applying pathological methods to the examination of *tissue biopsies* and *body fluids*. If there are clinical indications to do so, it may be possible to obtain a series of samples from which the course of the disease can be monitored.

The applications of pathology in clinical diagnosis and patient management are described in Chapter 4.

Autopsies

Autopsy (necropsy and postmortem examination are synonymous) means to 'see for oneself'. In other words, rather than relying on clinical signs and symptoms and the results of diagnostic investigations during life, here is an opportunity for direct inspection and analysis of the organs.

Autopsies are useful for:

- determining the cause of death
- audit of the accuracy of clinical diagnosis
- education of undergraduates and postgraduates
- research into the causes and mechanisms of disease
- gathering accurate statistics about disease incidence.

The clinical use of information from autopsies is described in Chapter 4.

For the medical undergraduate and postgraduate, the autopsy is an important medium for the learning of pathology. It is an unrivalled opportunity to correlate clinical signs with their underlying pathological explanation.

PATHOLOGY AND THE SOCIAL CONTEXT

Although pathology, as practised professionally, is a laboratory-based clinical discipline focused on the care of individual patients and the advancement of medical knowledge, our ideas about the causes of disease, disability and death have wide implications for society.

Causes and agents of disease

There is socially (and politically) relevant controversy about what actually constitutes the cause of a disease. Critics argue that the science of pathology leads to the identification of merely the agents of some diseases rather than their underlying causes. For example, the bacterium Mycobacterium tuberculosis is the infective agent resulting in tuberculosis but, because many people exposed to the bacterium alone do not develop the disease, social deprivation and malnutrition (both of which are epidemiologically associated with the risk of tuberculosis) might be regarded by some as the actual causes. Without doubt, the marked fall in the incidence of many serious infectious diseases during the 20th century has been achieved at least as much through improvements in housing, hygiene, nutrition and sewage treatment as by specific immunisation and antibiotic treatment directed at the causative organisms. This distinction between agents and causes is developed further in Chapter 3.

The health of a nation

Because the methods used in pathology enable reliable diagnoses to be made, either during life by, for example, biopsy or after death by autopsy, the discipline has an important role in documenting the incidence of disease in a population. Cancer registration data are most reliable when based on histologically proven diagnoses; this happens in most cases. Epidemiological data derived from death certificates are notoriously unreliable unless verified by autopsy. The pathologically-based information thus obtained can be used to determine the true incidence of a disease in a population and the resources for its prevention and treatment can be deployed accordingly where they will achieve the greatest benefit.

Preventing disability and premature death

Laboratory methods are used increasingly for the detection of early disease by population screening. The prospects of cure are invariably better the earlier a disease is detected.

For example, the incidence of death from cancer of the cervix is lowered by screening programmes; in many countries, women have their cervix scraped at regular intervals and the exfoliated cells are examined microscopically to detect the earliest changes associated with development of cancer. Screening for breast cancer is primarily by mammography (X-ray imaging of the breast); any abnormalities are further investigated either by examining cells aspirated from the suspicious area or by histological examination of the tissue itself.

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