General and Systematic Pathology

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Preface

This new textbook, intended primarily for medical students, presents pathology in the context of modern medicine and cellular biology.

We have adopted the long-established practice of dealing with general pathology (the principles of disease processes) before covering systematic pathology (specific diseases affecting individual body systems or organs). Each chapter in the systematic section begins with a brief account of the relevant normal structure and function of the organ or system, emphasising those aspects which are pertinent to a proper understanding of its pathology. After each major heading within a chapter, where it is considered appropriate, there is a summary panel listing key facts; these have two purposes: first, to provide the reader with a foundation of basic knowledge on which the subsequent details can be placed; second, to assist revision by scanning the text. Where relevant, there are brief comments on treatment and its relationship to the pathological features of a disease. Each chapter ends with a list of references to review articles or specialist texts for further reading.

Although pathology extends into the realm of molecular abnormalities, much of it has a visible expression. Illustrations are, therefore, essential. This book contains numerous colour illustrations of diseased tissues at a gross or microscopic level. The morbid images of disease also, in a modern textbook of pathology, should include radiographs, computerised tomography (CT) scans, and magnetic resonance images (MRI); these have been used when relevant. Clear drawings are used to depict important mechanisms or principles.

The full spectrum of diseases is covered and, anticipating an international readership, many infections and parasitic infestations which are relatively uncommon in the UK are included. The variable chapter length reflects, to some extent, the relative importance or complexity of the conditions described therein.

The book ends with a glossary of words used frequently in pathology, but which, by usage, have a meaning slightly different from that to be found in most dictionaries or in the public domain.

All chapters have been carefully reviewed by expert independent advisers and invariably edited in line with their recommendations. However, no new textbook could claim to be perfect. I hope that subsequent editions will benefit from comments received from medical students and their teachers.

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Chapter 1: Introduction to pathology

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 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 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. 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 was established early in the long history of medicine, the natture of the underlying disease was thought to be due to an excess or deficiency of the various *humours* - phlegm, black bile, and so on. These concepts are now firmly and irrevocably consigned to medical antiquity.

The first opportunity for the scientific study of disease came from the interanl examination of the body after death. *Autopsies* (necropsies or post-mortem examinations) have been performed scientifically from about 1500 AD 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, major contributions were made by Rokitansky and Aschoff, who meticulously performed and documented many thousand 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.

Pathology, and indeed medicine as a whole, was revolutionised by the application of *microscopy* to the study of diseased tissues from about 1800. Prior to this time, it was postulated that disease arose by a process of *spontaneous generation;* that is, by a process of 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, Pasteur's demonstration that micro-organisms in the environment could contaminate and impair the quality of wine was a major landmark in our perception of the environment and our understanding of its possible adverse effects, and it has had an enormous impact on medicine.

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 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.

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.

The 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. Pathology is, therefore, an integral part of modern medicine.

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 study in depth of tissue and body fluids from patients.

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. Fortunately, advances in cell culture technology have reduced the usage of laboratory animals in medical research and experimental pathology. However, it is extremely difficult to reproduce in cell cultures the physiological milieu that prevails in the intact human body.

Subdivisions of 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 (eg, investigation of death in suspicious circumstances).

These subdivisions are more important professionally (because each requires its own team of 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, 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. Clinical practice is only as good as its pathological basis.

Techniques of pathology

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

Light microscopy

Advances in the optical quality of lenses have resultwed 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 (eg, histochemistry, very urgen 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 (eg, 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.

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 adn 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 (eg, 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 advances are now coming from the relatively new science of molecular pathology, 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. Molecular pathology is manifested in various conditions, for example: abnormal haemoglobin molecules, such as in sickle cell disease (Ch 22); abnormal collagen molecules in osteogenesis imperfecta (Ch 5); and alterations in the genome governing the control of cell and tissue growth, now believed to play an important part in the development of tumours (Ch 9).

General and systematic pathology

Pathology is best taught and learnt in two stages:

- *general pathology:* the mechanismmms and characteristics of the principal types of disease process (eg, congenital versus acquired diseases, inflammation, tumours, degenerations)

- *systematic pathology:* the descriptions of specific diseases as they affect individual organs or organ systems (eg, 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 1 of this textbook and many specific diseases mentioned by way of illustration. It is essential that the principles of general pathology are 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.

Systemic 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 tumors; and so on.

Systematic pathology is covered in Part 2 of this textbook.

Learning pathology

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. For example, the term 'hyperplasia' means an increase in the size of an organ due to the proliferation of its constituent cells; this definition must be learnt before the student attempts to learn about the process of hyperplasia. In this book, each important term will be clearly defined in the main text or the glossary or both.

Disease mechanisms constitute general pathology, knowledge that can be applied to related diseases occurring in different organs or systems. It is absolutely vital to understand general pathology before attempting to study systematic pathology in depth. Systematic pathology deals more with specific diseases; the rules of general pathology apply, but there are many variations peculiar to the same disease process affecting different organs.

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

- incidence
- aetiology
- pathogenesis
- pathological and clinical features
- complications and sequelae
- prognosis (see Ch 2).

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; in addition to this textbook the student will no doubt have a fairly comprehensive course of relatively didactic lectures perhaps supplemented by tutorials, problem-solving-orientated practical classes involving the fross and microscopic examination of diseased tissues, demonstrations, and post-mortem teaching. If a student's curriculum lacks one or more of these features it should not be considered in any way deficient because there is no prescribed way of teaching the subject and each medical school will have evolved its own scheme based on local factors. Nevertheless, students of pathology should be encouraged to avail themselves of every opportunity to learn about diseases through a variety of media. Even the bedside, operating theatre and outpatient clinic provide ample opportunities for further experience of pathology; hearing a diastole cardiac murmur through a stethoscope should prompt the listening student to consider the pathological features of the narrowed mitral valve orifice (mitral stenosis) responsible for the murmur, and the effects of this stenosis on the lungs and the rest of the cardiovascular system.

Clinicopathological integration

Although medicine, surgery, pathology and other disciplines are frequently taught as separate subjects in the curriculum, students must develop an integrated understanding of disease. Diseases are compartmentalised in this way only so that all aspects can be taught in sufficient depth to provide a full and working understanding. In practice, no such boundaries exist.

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 experience and their knowledge of pathology.

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

- problem-oriented
- disease-oriented.

In clinical practice, the problem-orientated approach works best because patients present with problems (eg, cough, malaise, pain) rather than with any immediate knowledge of their disease. In learning pathology, the disease-orientated approach is more relevant because medical practitioners require knowledge of diseases (eg, pneumonia, cancer, ischaemic heart disease) so that correct diagnoses can be made and the most appropriate treatment given.

The problem-orientated approach

Historically, before diseases had been properly characterised, problems caused by diseases were 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-orientated approach is still the first step in the clinical diagnosis of disease. In many illnesses, symptoms alone suffice for diagnosis. In other illnesses, the diagnosis has to be supported by clinical signs (eg, abnormal heart sounds). In some instances, the diagnosis can be made conclusively only by special investigations (eg, laboratory analysis of blood or tissue samples, imaging techniques).

The disease-orientated approach

Modern pathological understanding of illnesses is based on a disease-orientated approach; knowledge of diseases and their clinical manifestations is fundamental to good medical practice.

The disease-orientated approach has also proved to be the most successful manner in which to impart 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-orientated 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 observing 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.

Having carried out this process in an individual patient, proof or strong suspicion of a particular disease eventually emerges as the diagnosis. If the diagnosis is still uncertain, a pragmatic approach to the problemmm can be adopted by observing the effects of a specific treatment or some other intervention.

Although experienced clinicians can diagnose many patients' diseases quite rapidly (and possibly 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), compute 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 algorithm, but these details are outside the scope of this book.

Diagnostic pathology

In living patients we investigate and diagnose their illness by applying pathological methods to the examination of *tissue biopsies* and *body fluids.* Subject to ethical constraints, and 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.

Biopsy and organ resections

Biopsies are samples of tissue removed from a patient for diagnostic purposes. Resection specimens (eg, gastrectomies, thyroidectomies) are the whole or part of an organ removed for a previously diagnosed condition. In addition to their diagnostic utility, much is being learned about the pathology of many diseases from the study of these tissue samples.

Biopsies can be obtained by a variety of methods:

- *needle biopsy:* from solid tissues using a thick-bored cutting needle

- *endoscopic biopsy:* visually-guided biopsy of an internal body surface (eg, alimentary or respiratory tracts)

- *incisional biopsy:* tissue removed by surgical incision (eg, wedge biopsy of liver).

Cytology

Cytology involves the examination and interpretation of dispersed cells rather than solid tissues, usually for the diagnosis of cancer and pre-cancerous lesions. These cells can be obtained by a variety of methods according to the organ being investigated:

- *exfolifative cytology:* cells shed from, or scraped or brushed off, an epithelial surface (eg, bronchus, cervix)

- *fluid cytology:* cells withdrawn with the fluid in which they are suspended (eg, peritoneal and pleural effusions, urine)

- *washings:* cells flushed out of an organ using an irrigating fluid (eg, bronchial washings from the lung)

- *fine-needle aspiration cytology:* cells sucked out of a solid tissue (eg, breast lump) using a thin needle attached to a syringe.

Blood

Blood is easy to sample by venepuncture; arterial blood is necessary only when gas analyses (eg, O_2, CO_2) are to be performed. Many observations and measurements can be made on blood smaples; for example:

- *blood cells:* the morphology and concentration in the blood are important in the investigation and diagnosis of anaemias, leukaemias, infections, and immune status

- *plasma:* for the investigation of abnormalities of blood coagulation

- *serum:* commonly used (because it does not coagulate) for biochemical assays of electrolytes, enzymes, proteins, etc.

Excretions and secretions

Urine and faeces are commonly investigated by microbiological methods in cases of suspected infection of the urinary tract and gastrointestinal tract respectively. In some non-infectious conditions, biochemical analyses are helpful.

Sputum is an important source of diagnostic material in respiratory tract disease. Malignant cells may be shed from the surface of a bronchial tumour and expectorated in the sputum where they can be found by cytological examination. In lower respiratory tract infections (bronchitis and pneumonia) the causative organisms can often be found in the sputum by microbiological methods.

Effusions and exudates

Effusions of fluid into body cavities (eg, peritoneal, pleural) may be due to a variety of causes. Measuring the protein concentration in the fluid may be helpful in distinguishing between different mechanisms by which the fluid might have accumulated. Of greater value, however, is cytological examination for neoplastic cells.

Effusions and exudates (eg, pus and pathological discharges) may also be provoked by infections. Microbiological examination of the material is vitally important in such cases so that the casative organism can be identified and the most appropriate treatment prescribed.

Autopsies

Autopsy (necropsy and post-mortem examination are synonymous) means to 'see for onself'. 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.

Autopsies are not restricted to the study of just those diseases that have proved fatal; during the course of an autopsy, particularly in the elderly, it is not unusual to find evidence of other diseases that have not contributed to death but which are nevertheless important to note for epidemiological and other purposes.

From cadavers, we are able to obtain much information about the extent of a disease and the way in which it has fatal consequences. Post-mortem autolysis, however, means that there are limitations to how much detailed knowledge can be obtained; the proteolytic enzymes naturally resident in tissues leak out of the lysosomes in which they are normally sequestrated and slowly digest the cells. In some cases electron microscopy is helpful, though this depends on the degree of autolysis. Post-mortem biochemistry is often useful, particularly in toxicology or the detection of severe abnormalities of, for example, electrolytes and blood lipids.

There has been a regrettable decline in the autopsy rate in most hospitals during the latter half of the 20th century. Formerly, it was not unusual to find that the autopsy rate (as a percentage of deaths) was 60% or higher; now, in many hospitals in the developed world, it is 25% or lower. There are several reasons for this decline.

The relatives of deceased patients seem to be increasingly reluctant to give their consent for an autopsy. They may feel that the examination is disfiguring and repugnant, that the deceased has 'suffered enough', or there may be objections on religious grounds. All of these objections are understandable and demand a sympathetic hearing. Request for a consent for an autopsy is a very sensitive issue for most relatives.

Many clinicians directly responsible for patient care (eg, physicians and surgeons) seem increasingly disinterested in the autopsy. They may feel that, having investigated the patient during life, using all modern methods, there is nothing more to be learned from an autopsy. They may feel absolutely confident about their diagnosis. However, several recent studies in the UK and USA have shown that up to 30% of major clinical diagnoses are not confirmed at autopsy. The autopsy makes, therefore, a major contribution to clinical audit by verifying or refuting diagnoses made during life and by revealing hitherto unsuspected disease.

For the medical undergraduates and postgraduates, 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.