What is pathology?

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disease
diagnosis
pathology
history
Pathology is the **scientific study of disease**. Pathology comprises scientific knowledge and diagnostic methods essential, first, for understanding diseases and their causes and, second, for their effective prevention and treatment. Pathology embraces the **functional** and **structural** changes in disease, from the molecular level to the effects on the individual patient, and is continually developing as new research illuminates our knowledge of disease.

The ultimate goal of pathology is the identification of the causes and mechanisms of disease leading to successful therapy and disease prevention. Without pathology, the practice of medicine would still rely on myths and folklore, and consequently be ineffective.

**HISTORY OF PATHOLOGY**

Evolving concepts about the causes and nature of human disease reflect prevailing explanations for all worldly events and also the techniques available for their investigation (Table 1.1). Thus the early dominance of animism, for example in the philosophies of Plato (424–348 BC) and Pythagoras (c. 580–c. 500 BC), led to the belief that disease represented the adverse effects of immaterial or supernatural forces, often as punishment for wrongdoing. Treatments were often brutal and ineffective.

When many symptoms, signs and postmortem findings were first believed to have natural explanations, the underlying disease was postulated to be due to an imbalance (‘isonomia’) of the four humours — phlegm, black bile, yellow bile and blood — as proposed by Empedocles (490–430 BC) and Hippocrates (c. 460–370 BC). These concepts are now obsolete.

Galen (129–c. 200) built on Hippocrates’ naturalistic ideas about disease by giving them an anatomic and physiological basis. However, it was probably Ibn Sina (980–1037) — commonly known as Avicenna — who, by his *Canon of Medicine*, pioneered advances in medicine through scientific discovery by observation, experimentation and clinical trials.

**Morbid anatomy**

Some of the greatest advances in our understanding of disease emerged from internal examination of the body after death. **Autopsies** (necropsies or postmortem examinations) have been performed since about 300 BC and have 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**. A notable landmark was the publication in 1761 of *De Sedibus et Causis Morborum per Anatomem Indagatis* by Giovanni Morgagni (1682–1771). During the 18th and 19th centuries in Europe, medical science was further advanced by Matthew Baillie (1761–1823), Carl von Rokitansky (1804–1878) and Ludwig Aschoff (1866–1942). They meticulously performed and documented many thousands of autopsies and, crucially, correlated their findings with the clinical signs and symptoms of the patients and with the natural history of numerous 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. Previously, it was commonly believed that tissue alterations in disease resulted from a process of **spontaneous generation**; that is, by metamorphosis independent of any external cause or other influence. Today, this notion seems ridiculous, but 200 years ago nothing was known of bacteria, viruses, ionising radiation, carcinogenic chemicals, and so on. Louis Pasteur’s (1822–1895) demonstration that microorganisms in the environment could contaminate and impair the quality of wine was a major advance in our perception of the environment and our knowledge that pathogens within it, invisible to the naked eye, cause disease.

Rudolf Virchow (1821–1902), a German physician and pathologist and an ardent advocate of the microscope, recognised that cells were the smallest viable constituent units...
of the body. Building on the work of Theodor Schwann (1810–1882) he formulated a new and lasting set of ideas about disease — cellular pathology. The light microscope enabled diseased tissues to be viewed at a cellular level. His observations, extended further by electron microscopy, have had a profound and enduring influence. But Virchow’s cell pathology theory is neither complete nor immutable; advances in biochemistry have revolutionised our understanding of many diseases at a molecular level.

Molecular pathology

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

Cellular and molecular alterations in disease

Modern scientific methods have resulted in a clearer understanding of the ways in which diseases result from disturbed normal cellular and molecular mechanisms (Table 1.2).

SCOPE OF PATHOLOGY

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

Clinical pathology

Clinical medicine involves a longitudinal approach to a patient’s illness — the patient’s history, the examination and investigation, the diagnosis, the treatment and follow-up. 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 effectively without understanding pathology; pathology is meaningless if it lacks clinical significance.

Approximately 70% of clinical diagnoses rely on pathology investigations. In the USA, c. 90% of the objective data in electronic patient records are derived from pathology laboratories.

Pathology in clinical practice includes:

- **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 use of pathology for legal purposes (e.g. investigation of death in suspicious circumstances).

These subdivisions are more important professionally (because each requires its own team of trained specialists) than educationally at the undergraduate level. Pathology must be taught and learnt in an integrated manner, for the body and diseases make no distinction between these professional 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 growing knowledge of the causes and mechanisms of disease has emerged from advances in science and technology.

Gross pathology

Before microscopy was applied to medical problems (c. 1800), observations were limited to those made with the naked 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, is still important. The gross pathology of some diseases is so characteristic that, when interpreted by an experienced pathologist, a fairly confident diagnosis can be given before further investigation by, for example, light microscopy.

Light microscopy

Advances in optics have yielded much new information about the structure of tissues and cells in health and disease. Before solid tissues are 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 usually cut from tissue hardened by embedding in wax or, less often, transparent plastic. For urgent or intraoperative diagnosis, sections are cut from tissue hardened by rapid freezing. Tissue sections are stained to help distinguish between different components (e.g. nuclei, cytoplasm, collagen).

The microscope can also be used to examine cells from cysts, body cavities, sucked from solid lesions or scraped
### Table 1.2 Examples of the involvement of cellular and extracellular components in disease

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

HLA, Human leukocyte antigen.
from body surfaces. This is cytology and it is used widely in, for example, cancer screening.

**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 biochemical features of individual cells can be visualised.

**Immunohistochemistry and immunofluorescence**

Immunohistochemistry and immunofluorescence use 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 modified for ultraviolet illumination and the preparations are often not permanent (they fade). For these reasons, immunohistochemistry is 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 range of substances detectable by these techniques has been enlarged greatly 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 vital 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 blood levels of cardiac enzymes and troponin 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**

Molecular pathology reveals 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, specific genes or their messenger RNA can be visualised in tissue sections or cell preparations. Minute quantities of nucleic acids can be amplified by the use of the polymerase chain reaction using oligonucleotide primers specific for the genes being studied. Microarrays can be used to determine patterns of gene expression (mRNA). This powerful technique can reveal novel diagnostic and prognostic categories, indistinguishable by other methods.

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 (Ch. 6); and genomic alterations disturbing the control of cell and tissue growth, playing a pivotal role in the development of tumours (Ch. 10).

**LEARNING PATHOLOGY**

Pathology is best learnt in two stages.

**Disease mechanisms**

The causation, mechanisms and characteristics of the major categories of disease are the foundations of pathology. These aspects are covered in Part 2 of this textbook, with many specific diseases mentioned by way of illustration. Ideally, the principles of disease causation and mechanisms should be understood before studying systematic pathology.

**Systematic pathology**

Systematic pathology is our current knowledge of specific diseases as they affect individual organs or systems. Systematic pathology comprises Part 3 of this textbook. (‘Systematic’ should not be confused with ‘systemic’. Systemic pathology would be characteristic of a disease that affected all body systems!) Each specific disease can be attributed usually to the operation of one or more causes and mechanisms. Thus acute appendicitis is acute inflammation affecting the appendix; carcinoma of the lung is the result of carcinogenic agents
acting upon cells in the lung, and the behaviour of the cancerous cells thus formed follows the pattern established for malignant tumours, and so on.

Building knowledge and understanding

There are two difficulties commonly facing new students 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 practice. However, learning the language is not sufficient; learning the mechanisms of disease and the effects on individual organs and patients is vitally important for clinical practice. In this book, each important term will be clearly defined in the main text or the glossary, or both.

There is a logical and orderly way of thinking about diseases and their characteristics. For each disease entity, students should be able to list the chief characteristics:

- 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 prompt the memory and enable students to organise their knowledge.

Pathology is learnt through a variety of media. 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 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 still taught as separate subjects in some curricula, students must develop an integrated understanding of disease.

To encourage integration, this textbook emphasises the pathological basis of common clinical signs so that students can relate their everyday clinical experiences to their knowledge of pathology. An index of symptoms lists the diseases that may cause them (pp. x–xvii).

In general, a clinicopathological understanding of disease can be achieved 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

The problem-oriented approach is the first step in the clinical diagnosis of a disease. In many illnesses, symptoms (the patient’s problem) alone suffice for diagnosis. In other illnesses, the diagnosis has to be supported by clinical signs (e.g. abnormal heart sounds). In some cases, 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).

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

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

ECG, Electrocardiogram.

The disease-oriented approach

The disease-oriented approach is the most appropriate way of presenting pathological knowledge. It would be possible to produce 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 achieve 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 feature 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; it enables the patient to benefit from treatment that is known, or is at least likely, to be effective, its effects having been observed in 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 it helpful to follow a series of logical steps leading to the gradual exclusion of various possibilities and the emergence of a single diagnosis including these examples.
  - First decide which organ or body system seems to be affected by the disease.
  - From the signs and symptoms, decide which general category of disease (inflammation, neoplasia, 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.

**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, a series of samples can be examined to monitor the course of the disease and response to treatment.

The applications of pathology in clinical diagnosis and patient management are described in Chapter 12.

**Autopsies**

Autopsy (necropsy and postmortem examinations 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 to directly inspect and analyse 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 12.

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, patients and populations**

Although pathology, as practised professionally, is a clinical discipline focused on the care of individual patients, our knowledge about the causes of disease, disability and death has wide implications for society.

**Causes and agents of disease**

What actually constitutes the cause of a disease can be controversial. Some may argue that the science of pathology leads to the identification of merely the agents of diseases rather than their underlying causes. For example, *Mycobacterium tuberculosis* is the bacterium resulting in tuberculosis but, because many people exposed to it alone do not develop the disease, social deprivation and malnutrition (both of which are associated with increased risk of tuberculosis) might be regarded as the actual causes. Without doubt, the marked fall in the incidence of many serious infectious diseases during the 20th century was 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**

Pathology enables reliable diagnoses to be made, either during life by biopsy or after death by autopsy, and thereby has an important role in accurately documenting the incidence of disease in a population. Cancer registration data are most reliable when based on histologically proven diagnoses, as happens in most cases. Epidemiological data derived from death certificates are notoriously unreliable unless verified by autopsy. The 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 to 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 risk of death from cancer of the cervix is reduced by screening programmes. In many countries, and sometimes in combination with testing for human papillomavirus, women are invited to have their cervix scraped at regular intervals and the exfoliated cells examined microscopically to detect the earliest changes associated with development.
of cancer. Screening for breast cancer is primarily by mammography (radiographic imaging of the breast); any abnormalities are further investigated by microscopically examining either cells or tissue from the suspicious area.

**Pathology and personalised medicine**

For many patients, pathological diagnosis of the type of disease is sufficient for decisions about best treatment. For others, particularly those with cancer, choosing the most effective treatment requires not only the type of disease (e.g. invasive adenocarcinoma) but also its **grade** (aggressiveness or degree of malignancy) and **stage** (extent of spread). Now, however, better understanding of the molecular pathology of cancer and the development of therapies specifically targeting molecular abnormalities in disease have led to an era of personalised medicine. Based on the molecular profile of an individual patient’s tumour, for example, treatment can be selected to achieve the best prospect of survival.

**FURTHER READING**