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病理学 第二版

Pathology

SECOND EDITION

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Series editor
Daniel Horton-Szar
BSc (Hons), MB BS (Hons)
GP Registrar
Northgate Medical Practice
Canterbury
Kent

Faculty advisor
Professor Rosemary A Walker
MD FRCPath
Department of Pathology
Robert Kilpatrick Clinical Sciences Building
Leicester Royal Infirmary
Leicester

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SECOND EDITION

Daniel J O'Connor
BSc PhD, Medical student
Leicester Warwick Medical School
University of Leicester
Leicester

First Edition Author
Bethan Goodman Jones

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O'Connor
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3 Killiney Road, #08-01 Winsland Hose I, Singapore 239519
Tel: (65) 6349-0200
Fax: (65) 6733-1817

Preface

Pathology plays an integral part in all aspects of medicine. Each chapter of this Second Edition has been updated, incorporating our growing understanding of the disease process. Additional features include MCQs with a short clarifying answer statement and patient orientated SAQs. This Second Edition should provide a comprehensive reference guide in both the preclinical and clinical years. Its layout provides rapid reference and learning exercises for exams and coursework. I hope it proves to be useful.

Daniel J O'Connor

This Second Edition of Pathology Crash Course has been updated and expanded with regard to the molecular pathology of cancer, which reflects the background of the author who has a PhD in this area as well as studying medicine. It hopefully reflects the importance in understanding molecular and cell mechanisms and relating these to clinical pathology. Some of the systemic pathology has been reduced but overall this volume should provide a relevant background to the whole spectrum of pathology. Understanding the pathology of diseases is critical for the full appreciation of medicine. Understand and know this and you should be okay for all your medical course.

Professor Rosemary A Walker
Faculty Advisor

In the six years since the First Editions were published, there have been many changes in medicine, and in the way it is taught. These Second Editions have been largely rewritten to take these changes into account, and keep Crash Course up to date for the twenty-first century. New material has been added to include recent research and all pharmacological and disease management information has been updated in line with current best practice. We have listened to feedback from hundreds of students who have been using Crash Course and have improved the structure and layout of the books accordingly: pathology material has been closely integrated with the relevant basic medical science; there are more multiple-choice questions and the clarity of text and figures is better than ever.

The principles on which we developed the series remain the same, however. Medicine is a huge subject, and the last thing a student needs when exams are looming is to waste time assembling information from different sources, and wading through pages of irrelevant detail. As before, Crash Course brings you all the information you need, in compact, manageable volumes that integrate basic medical science with clinical practice. We still tread the fine line between producing clear, concise text and providing enough detail for those aiming at distinction. The series is still

written by medical students with recent exam experience, and checked for accuracy by senior faculty members from across the UK. I wish you the best of luck in your future careers!

Dr Dan Horton-Szar
Series Editor (Basic Medical Sciences)

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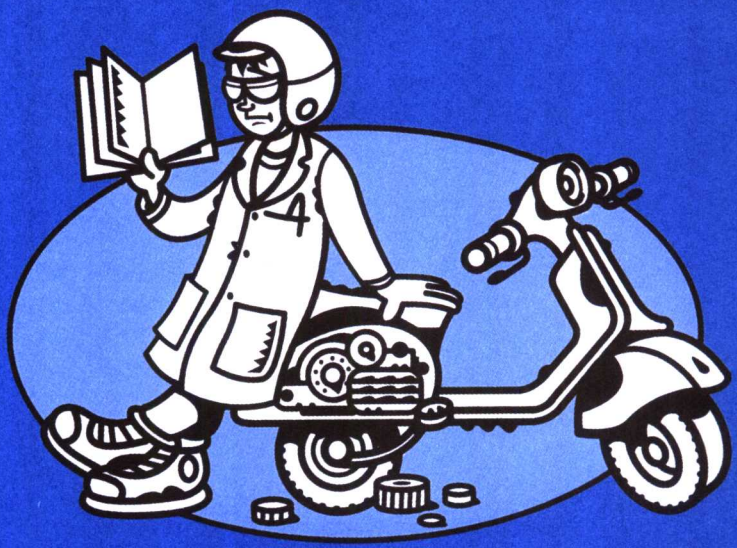
Dedication

In memory of my father and dedicated to
my family and friends

Contents



PRINCIPLES OF PATHOLOGY

1. Introduction to Pathology

Disease

A disease is an alteration from the normal function/structure of an organ or system, which manifests as a characteristic set of signs and symptoms.

Pathology

Pathology is the scientific study of disease. It is concerned with the causes and effects of disease, and the functional and structural changes that occur. Changes at the molecular and cellular level correlate with the clinical manifestations of the disease.

Understanding the processes of disease assists in the accurate recognition, diagnosis, and treatment of diseases.

Divisions of pathology

Pathology is traditionally subdivided into five main clinical disciplines. The divisions are:

- Histopathology—the study of histological abnormalities of diseased cells and tissues.
- Haematology—the study of primary diseases of the blood, and the secondary effects of other diseases on the blood.
- Chemical pathology—the study of biochemical abnormalities associated with disease.
- Microbiology—the study of infectious diseases and the organisms that cause them.
- Immunopathology—the study of diseases through analysis of immune function.

Classification of disease

The causes of disease are numerous and diverse. For convenience, diseases are often classified as either congenital or acquired disorders. Congenital diseases are present from birth, whereas acquired disorders are incurred as a result of factors originating in the external environment.

Congenital

Congenital causes can be either genetic or non-genetic (for example cystic fibrosis or thalidomide anomalies).

Acquired

Acquired causes can be any of the following:

- Trauma.
- Infections and infestations.
- Radiation injury.
- Chemical injury.
- Circulatory disturbances.
- Immunological disturbances.
- Degenerative disorders.
- Nutritional deficiency diseases.
- Endocrine disorders.
- Psychosomatic factors.
- Iatrogenic disease.
- Idiopathic disease.

However, many if not most diseases are due to a combination of causes, and they are therefore said to have a multi-factorial aetiology.

It is important to have a logical and methodical approach to disease description. Fig. 1.1 illustrates the features of disease.

How pathology is covered in this book

Part I Principles of pathology

The number of tissue responses that underlie all diseases is limited. These responses are known as basic pathological responses. The first part of this book describes the principles of these in relation to our advancing knowledge of the molecular sciences.

Part II Systematic pathology

As well as an understanding of the basic pathological responses, it is also necessary to understand how they affect individual tissues and organs. The second part of this book describes the common pathology of the specific diseases as they affect individual organs or organ

Characteristics of disease	
Characteristic	**Explanation**
Definition	A clear, concise and accurate description
Incidence	Number of new cases of disease occurring in a population of a defined size during a defined period
Prevalence	Number of cases of disease to be found in a defined population at a stated time
Aetiology	Cause of disease
Pathogenesis	Mechanism by which a disease is caused
Morphology	Form and structural changes
Complications and sequelae	Secondary consequences of disease
Treatment	Treatment regimens, effectiveness and side effects
Prognosis	Expected outcome of the disease

Fig. 1.1 Features of disease include definition, aetiology, pathogenesis, treatment, and prognosis.

systems. This approach is termed systematic pathology, and it is illustrated by clinical examples of disease.

- Define 'disease'.
- Define 'pathology'.
- What are the divisions of pathology?
- What are the characteristics of a disease?
- Define congenital and acquired disorders.

2. Cancer

Definitions and nomenclature

Definitions

Tumour

A tumour can be defined as an abnormal mass of tissue resulting from autonomous disordered growth that persists after the initiating stimulus has been removed. A tumour results from genetic alteration and deregulated growth control mechanisms.

Tumours are:

- Progressive—they are independent of normal growth control, and they continue to grow regardless of requirements, and in the absence of any external stimuli.
- Purposeless—abnormal mass serves no useful purpose.
- Parasitic—endogenous in origin but draw nourishment from the body while contributing nothing to its function.

All tumours have the suffix '–oma', which means a swelling.

Other related definitions are:

- Neoplasm (i.e. new growth)—synonymous with tumour.
- Neoplasia—the process of tumour growth.
- Cancer—a malignant neoplasm.
- Anaplastic neoplasm—a very poorly differentiated neoplasm.

Dysplasia

Dysplasia is the disordered development of cells resulting in an alteration in their size, shape, and organization. It may be reversible, but is also known to precede neoplasia. It is, therefore, referred to as a premalignant state in certain circumstances. For example, a tissue that can show dysplasia is the squamous epithelium of the uterine cervix following human papilloma virus (HPV) infection. This is referred to as Cervical Intra-epithelial Neoplasia (CIN) and three grades are observed. CIN I is mildly dysplasic; CIN II is moderately dysplasic; and CIN III is severely dysplasic.

Metaplasia

Metaplasia is the change from one type of differentiated tissue to another, usually in response to an irritating stimulus, e.g. a change from mucus-secreting epithelium to stratified squamous epithelium in the bronchial irritation associated with cigarette smoking. Metaplasia is reversible, and it often represents an adaptive response to environmental stress.

Benign versus malignant

Tumours are classified as either benign or malignant according to their appearance and behaviour (Fig. 2.1). Benign tumours are localized cancers that do not invade the surrounding tissues or metastasize to other organs. Critically malignant tumours are capable of invasion and spread to distant organs. This distinction is crucial in the clinic because malignant tumours are associated with significant morbidity and mortality.

Nomenclature of tumours

Tumour nomenclature (Fig. 2.2) is based on histological and behaviour patterns. Histology provides information about the type of cell from which the tumour has arisen, while behaviour provides information as to whether the cell is benign or malignant.

A few simple rules to follow:

- –oma: suffix for tumours. But there are some non-neoplastic '–omas', e.g. granuloma.
- Carcinomas: malignant tumours of epithelial origin; prefixed by tissue of origin.
- –sarcomas: suffix for malignant tumours of connective tissue origin.

Classification of carcinomas

Carcinomas are malignant tumours of epithelial tissue. Carcinomas of non-glandular epithelium are prefixed by the name of the epithelial cell type.

Characteristics of benign versus malignant tumour	
Benign	**Malignant**
Localized	Tumour spread
No invasion	Invasion
No metastases	Metastases
Slow growth rate	Rapid growth rate
Good differentiation	Poorly differentiated
Few mitoses	Many mitoses
Normal nuclear chromatin	Increased nuclear chromatin
Uniform size cells	Cells and nuclei vary in size
Exophytic	Endophytic
Compression of normal tissue	Invasion and destruction of normal tissue

Fig. 2.1 Characteristics of benign versus malignant tumours. Note that invasion is the only absolute distinguishing feature between benign and malignant neoplasms.

Malignant tumours of glandular epithelium are termed adenocarcinomas. Carcinomas can be further sub-classified according to their ability to invade or not, and behavioural information can be gained from histological grading of cellular differentiation.

Carcinoma *in situ*

This is an epithelial neoplasm that has all the cellular features associated with malignancy but which has not yet invaded through the epithelial basement membrane. The in-situ phase may not progress, or it may last for several years before invasion commences.

Intra-epithelial neoplasia

This covers the spectrum of changes short of invasive carcinoma:

- Mild dysplasia.
- Moderate dysplasia.
- Severe dysplasia/carcinoma *in situ*.

These three categories are clearly illustrated by the example of cervical intra-epithelial neoplasia (CIN).

Invasive carcinoma

This is an epithelial neoplasm that invades through the basement membrane. The tumour gains access to the vascular supply and lymphatics, and it will often metastasize to distant tissues.

Epidemiological aspects of cancer

Cancer in the UK

As a cause of mortality in the UK, cancer is the second biggest killer (after cardiovascular disease). Its incidence (Fig. 2.3) is as follows:

- Almost 1 in 3 of the population will develop cancer during their lifetime.
- Almost 1 in 4 of the population will die of cancer.
- Incidence of cancer deaths increases with increasing age.
- Incidence of cancer varies between males and females.

Cancer worldwide

The incidence of different cancers varies from country to country, and this variation provides clues to the causes of the cancers.

For example, in Japan, gastric carcinoma is 30 times more common than in the UK, whereas pancreatic cancer is much rarer. However, migration of a subset of the Japanese population to different geographical areas (e.g. USA, UK) alters the incidences of these diseases within that population.

These findings suggest that environmental factors (such as diet and occupational, social, and geographic effects) rather than genetic causes account for most of the observed differences between countries.

Molecular basis of cancer

Oncogenes and tumour suppressor genes

Cell proliferation and division is usually tightly regulated by two sets of opposing functioning genes. These are the growth promoting genes—called proto-oncogenes—and the negative cell cycle regulators—called tumour suppressor genes (TSGs). Abnormal activation of proto-oncogenes and loss of function of tumour suppressor genes leads to the transformation of a normal cell into a cancer cell.

Proto-oncogenes

Proto-oncogenes are genes that are expressed in normal cells. These genes code for oncoproteins, which positively regulate cell growth and

Important tumour nomenclature		
Histological type	**Benign**	**Malignant**
Epithelial		
Glandular	Adenoma	Adenocarcinoma
Non-glandular	Papilloma	Carcinoma
Connective tissue		
Adipose	Lipoma	Liposarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Voluntary muscle	Rhabdomyoma	Rhabdomyosarcoma
Blood vessels	Angioma	Angiosarcoma
Nerve	Neurofibroma	Neurofibrosarcoma
Nerve sheath	Neurilemmoma	Neurilemmosarcoma
Glial cells	Glioma	Malignant glioma
Others		
Haemopoietic	*	Leukaemia
Lymphoreticular	*	Lymphoma
Melanocytes	*	Malignant melanoma
Germinal cell	Benign teratoma	Malignant teratoma

Fig. 2.2 Examples of tumour nomenclature. * represents those tumours that are always malignant and do not have benign counterparts.

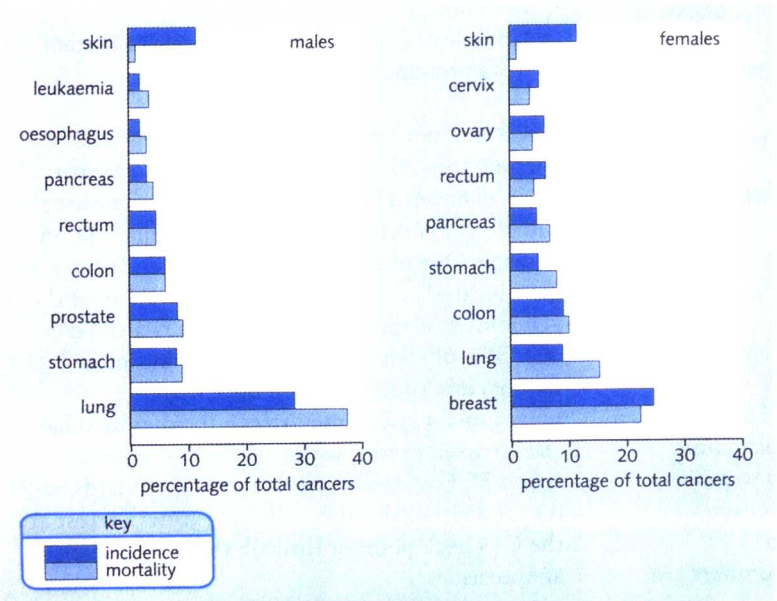


Fig. 2.3 Incidence and mortality of common cancers in men and women in the UK. (Adapted from Underwood, 2000.)

differentiation (growth factors, transcription factors, and receptor molecules). In healthy cells, transcription of these genes is tightly controlled. Inappropriate expression of oncoproteins leads to abnormal cell growth and survival. Normally-functioning proto-oncogenes can be activated into cancer-causing oncogenes in two ways:

- A mutation can produce an oncoprotein that is functionally altered and abnormally active. For example, intracellular signalling is affected by the hyperactive mutant ras protein.
- A normal oncoprotein can be produced in abnormally large quantities because of enhanced gene amplification (the *myc* oncogene in neuroblastomas) or enhanced transcription (formation of the Philadelphia chromosome from a translocation between chromosomes 9 and 22).

Oncogenes can be classified according to the function of the gene product. Oncogenes include genes which express:

- Nuclear binding proteins (e.g. *c-myc*).
- Tyrosine kinase proteins (e.g. *src*).
- Growth factors (e.g. platelet derived growth factor; PDGF).
- Receptors for growth factors (e.g. c-*erb*B-2/HER-2 which is related to epidermal growth factor receptor (EGFR).
- GTP binding proteins (e.g. *ras*).

Expression of abnormal oncogene products corresponds to the behaviour and appearance of transformed cells. These include:

- Independence from the requirement of extrinsic growth factors.
- Production of proteases which assist tissue invasion.
- Reduced cell cohesiveness which assist metastasis.
- Ability to grow at higher cell densities.
- Abnormal cellular orientation.
- Increased plasma membrane and cellular motility.

Tumour suppressor genes

Tumour suppressor genes (e.g. p53 and Rb1) encode proteins that prevent or suppress the growth of tumours. Inactivation of TSGs results in increased susceptibility to cancer formation. Genetically increased susceptibility to cancer formation was first proposed by Knudson who studied the childhood retinal cancer retinoblastoma. In some cases the tumours are bilateral and familial, but in other cases they are unilateral and sporadic. He proposed that familial retinoblastoma resulted in a high risk of bilateral eye tumours because of the predisposition to cancer from a germline mutation in one copy of the RB1 gene. Therefore, only one further mutation was required for tumour formation. In contrast, sporadic retinoblastoma occurs in patients who have an initially fully functioning RB1 gene. These tumours are rare and unilateral because two somatic mutations are required. This has been coined the 'two hit' hypothesis.

Examples of dysfunctional TSGs involved in human cancers are:

- APC implicated in colorectal tumours and located on chromosome 5q
- NF1 implicated in neurofibrosarcoma and located on chromosome 17q
- RB1 implicated in retinoblastoma and located on chromosome 13q
- BRCA1 implicated in breast and ovarian cancer and located on chromosome 17q
- p53 implicated in many tumours and located on chromosome 17p

Loss of function of TSGs or their protein products can result in uncontrolled neoplastic cell growth. TSGs can lose their normal function by a variety of mechanisms:

- Mutations (hereditary or acquired).
- Binding of normal TSG protein to proteins encoded by viral genes, e.g. human papilloma virus proteins E6/E7.
- Complexing of normal TSG protein to mutant TSG protein in heterozygous cells.

TSGs function by maintaining the integrity of the genome through arrested cell growth and repair of DNA damage. They also function to promote cell suicide or apoptosis in cells with sustained DNA damage. One of the most studied TSGs is the p53 gene located at 17p—termed 'the guardian of the genome'. It is mutated or functionally altered in over 50% of all human cancers. In addition a familial inherited mutation is found in Li–Fraumeni syndrome. Affected individuals have an increased predisposition to several tumour types. P53 can recognize damaged DNA and can respond either through cell cycle growth arrest at the G_1 check point or through the initiation of apoptosis.