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Textbook of General Pathology for Dental Students

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Dedication

To

Newell W Johnson, who has inspired and motivated hundreds of students and collegues in their academic pusuits.

Foreword

Whilst the study of general pathology is incredibly interesting, for many students, it can often be overwhelming and not always immediately relevant to clinical dental practice. Dental practitioners encounter pathology every day, and whilst, fortunately, it is not always serious, it is important that practitioners can appreciate the basic principles that underlie these presentations so that appropriate management can be implemented—as health practitioners, dentists need to understand pathology.

The importance of pathology is sometimes overlooked and at risk of being overshadowed by the various clinical disciplines and other areas that "compete" for time in dental programmes. Understanding the basic principles of pathology is essential for all dental students. It underpins a comprehensive understanding of oral and maxillofacial pathology, for which dental practitioners should be considered the experts. Furthermore, this is reinforced by the increasing understanding of the links between oral and systemic disease.

Historically, general pathology has been taught by external faculty rather than dental academics and oral pathologists. As mentioned previously, students, particularly undergraduate students, often find this approach daunting and miss the relevance of these basic pathological sciences to clinical dentistry. This textbook helps address this issue.

With clear explanations and coverage of a wide range of topics, including an overview of oral pathology, this book is an essential resource. Professor Prabhu's extensive teaching experience and deep understanding of the subject matter make this an invaluable tool for anyone looking to gain a deeper understanding of the fundamental principles of pathology at exactly the right level for dental students. I have known Professor Prabhu since my own undergraduate days and remember fondly his passion for oral pathology; it is exciting that there is now a general pathology textbook written especially for dental students, which can also be a useful reference for postgraduate students and practicing dental practitioners.

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Preface

Understanding the basic principles of pathology is essential for students pursuing dentistry. Although excellent books on pathology are available, they are primarily targeted at medical students. Dental students often find these books too voluminous with too much basic detail, particularly from the undergraduate students' points of view. Worse, pathology books primarily targeted at dental students are hard to find. It is heartening to note that globally there is a trend developing to shoulder the responsibility of teaching general pathology topics by oral and maxillofacial pathologists. With this scenario, a need for a book on general pathology topics authored by oral and maxillofacial pathologists is real. *Textbook of General Pathology for Dental Students* is aimed at fulfilling this need.

This book deals with fundamental concepts and mechanisms underlying various human diseases in 18 chapters. Chapters on introduction to pathology, cellular pathology, homeostasis, and tissue healing set the scene for diseases and disorders of inflammatory, genetic, infectious, and neoplastic background. Because of their relevance to clinical dental practice, chapters on ageing, imbalances in fluids and electrolytes, acids and bases, haemodynamic disorders, thrombosis, infarction and shock, and environmental and nutritional pathology are included in the book. A chapter on pain is presented to provide essential basic knowledge of pain pathways. Brief details of dental, oral, and maxillofacial and salivary gland diseases are presented to introduce these topics to the preclinical dental student. Because of the strong, often bidirectional link between systemic and oral diseases, organ system-based pathology is discussed briefly as an introduction to general medicine topics taught later in the clinical years of training. Illustrations and tables are expected to reinforce the information presented in the text. Pathologic terms, most of which are new to a dental student in preclinical years, are defined in the glossary at the end of the book.

It is my earnest hope that this book will be helpful to dental students globally.

Brisbane, QLD, Australia — S. R. Prabhu
November 2022

Contents

Introduction to Pathology

1

1.1 Introduction

The history of pathology is closely intertwined with the history of medicine. Today, pathology is practised as a medical discipline and is regarded as the foundation of many aspects of patient care, including diagnostic testing, prognostication, and advice on treatment modalities. *The word pathology comes from the Greek words "pathos" and "logy." 'Patho' means suffering or disease, and 'logy' means study*. It is a speciality of medical science concerned with the cause, development, structural/functional changes, and natural history associated with diseases. Disease refers to a definable deviation from normal with observable characteristics evident via patient complaints (symptoms) and careful examination (signs) measurements. The cause of the disease is referred to as its aetiology. The process of disease development is referred to as its pathogenesis. The pathogenesis can refer to the changes in the structure or function of an organism at the gross/clinical level. Pathology, therefore, deals with nature, causes, processes, development, and consequences of diseases. The term pathophysiology is also commonly used in the study of disease to include the study of disordered function and the breakdown of homeostasis. Pathophysiology mainly focuses on alterations in function rather than alterations in structure. Pathology mainly focuses on alterations in structure. However, because structural and functional changes are closely related, a clinician must have basic knowledge of physiology and anatomy before one embarks on the study of disease. The disease is an abnormal variation in the structure or function of any part of the body. Diseases can be distinguished based on differences at the molecular, cellular, tissue, fluid chemistry, and individual organism level. A pathologist is an individual who specialises in pathology.

Pathology is divided into general and systemic pathology (systematic pathology) for pedagogical reasons. General pathology (Basic Pathology) covers the basic mechanisms of diseases, whereas systemic pathology covers conditions as they occur in the individual organ system. General pathology is the foundation of knowledge that must be acquired before studying the mechanisms involved in the pathology of various organ systems. Systemic pathology describes multiple aspects of a disease by studying its aetiology (cause), pathogenesis (mechanisms), morphologic changes (gross and microscopic structural alterations), and functional derangements (signs and symptoms).

1.2 History of Pathology

In prehistoric times, the disease was associated with religion, magic ("evil eye of the spirits"), and divine influences ("curse from God"). Herophilus, one of the great Greek physicians, along with Erasistratus, provided a beginning for anatomical pathology and autopsy. Greek philosophers Socrates, Plato, and Aristotle introduced philosophical concepts to medicine. Hippocrates was an eminent Greek Physician who disassociated medicine from magic and religion. He believed in symptoms from patients' histories and described methods of diagnosis. He is also instrumental in forming rational and ethical principles in medical practice (Hippocratic Oath). Roman physician Cornelius Celsus is credited with introducing cardinal signs of inflammation (*rubor, tumour, calor, and dolour*), and Claudius Gallen postulated humoral theory. Around 200 AD, Indian physicians Charaka and Sushruta described aspects of disease and medical and surgical remedies in books *Charaka Samhita* and *Sushruta Samhita,* respectively.

Pathology developed only as science advanced. Some prominent individuals contributed to the development of pathology in the seventeenth and eighteenth centuries. Antony van Leeuwenhoek (1632–1723) invented the first microscope, and Marcello Malpighi (1624–1694) used the microscope to study skin and lymphoid tissue in the spleen and has been credited as the father of histology. Giovanni Morgagni (1682–1771) laid the foundation for clinicopathologic methods in the study of disease. Other notable clinicians responsible for the advancement of pathology and the

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study of medicine included Sir Percival Pott (1714–1788), John Hunter (1728–1793), William Hunter (1718–1788), Edward Jenner (1749–1823), Thomas Addison (1793–1860), Thomas Hodgkin (1798–1866), Louis Pasteur (1822–1912), Paul Ehrlich (1854–1915), Christian Gram (1853–1938), D L Romanowsky (1861–1921), Robert Koch (1843–1910), Sir William Leishman (1865–1926), Rudolph Virchow (1821–1905), Karl Landsteiner (1863–1943), G N Papanicolaou (1883–1962) and Willian Boyd (1885–1979).

1.3 Making a Diagnosis

The steps involved in arriving at a diagnosis are as follows:

- Taking an appropriate clinical history of symptoms and collecting and recording relevant data
- Physical examination
- Generating a provisional and differential diagnosis. (Developing a list of the possible conditions that might produce a patient's symptoms and signs).
- Investigations (ordering, reviewing, and interpreting test results)
- Reaching a final diagnosis
- Consultation (referral to seek clarification if indicated)

Chapters 2 and 3 provide further information necessary to understand the disease process better.

1.4 Diagnostic Investigations in Pathology

Pathologists use gross, microscopic, immunologic, genetic, and molecular modalities to determine the presence of disease and frequently work closely with surgeons, radiologists, and oncologists. Pathologists can sub-specialise in different areas, such as gastroenterology, gynaecologic pathology, blood diseases, clotting disorders, microbiology, and lung and breast cancers. For every subspecialty in medicine or surgery, there is a pathologist counterpart, helping to make the correct diagnosis and guide the patient's care. In the diagnosis of disease, the following techniques are used.

1.4.1 Gross Pathology

Gross pathology refers to macroscopic disease manifestations in organs, tissues, and body cavities. Anatomical pathologists commonly use this term to refer to diagnostically useful findings made during the gross examination of specimen processing or an autopsy.

1.4.2 Biopsy

A biopsy is a procedure that removes a tissue sample from a living body to provide the pathologist with a representative, viable specimen for microscopic (histopathologic) interpretation, and diagnosis. There are many different types of biopsy procedures. The most common types include (1) incisional biopsy, in which only a sample of tissue is removed; (2) excisional biopsy, in which an entire lump or suspicious area is removed; and (3) needle biopsy, in which a sample of tissue or fluid is removed with a needle. The procedure is called a core biopsy when a wide needle is used. When a thin needle is used, the process is called a fine-needle aspiration biopsy.

1.4.3 Histopathology

Histopathology refers to examining a biopsy or surgical specimen by a pathologist after the specimen has been processed and histological sections have been placed onto glass slides. The tissue specimen obtained from a biopsy or autopsy procedure undergoes five stages of preparation before the slides are viewed by a histopathologist. Steps include formalin fixation, processing, embedding, sectioning, and staining, primarily with hematoxylin and eosin. Different stains and tests may be applied to the specimen or slides when the initial diagnosis is unclear. A frozen section can be examined for immediate diagnosis of soft tissue malignancy during a surgical procedure but is less accurate than the evaluation of paraffin-embedded tissue.

1.4.4 Cytopathology

Cytopathology is the study of abnormal cells from various body sites to determine the cause or nature of the disease. The main applications of cytopathology include screening for the early detection of asymptomatic precancer or cancer, diagnosis of symptomatic cancer, cysts, inflammatory conditions, and various types of infections. It is also used for the detection of recurrence of cancer in those who have been treated for cancer. Different cytopathologic methods include fine-needle aspiration, exfoliative, and abrasive cytology.

1.4.5 Haematopathology

This branch of pathology deals with abnormalities of the blood cells, and their precursors in the bone marrow are investigated to diagnose the different kinds of diseases.

Haematological tests can help diagnose anaemia, infection, haemophilia, blood-clotting disorders, and leukaemia. Common haematological tests include complete blood count, white blood cell count (WBC count), red blood cell count (RBC count), platelet count, haematocrit red cell volume (HCT), haemoglobin concentration (Hb), differential white blood cell count, red blood cell indices, prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR).

1.4.6 Histochemistry

Histochemistry combines biochemistry and histology techniques to study the chemical constitution of cells and tissues. Histochemistry specifically stains constituents of cells and tissues such as mucins, lipids, nucleic acids, amyloid, microorganisms, and other proteins.

1.4.7 Immunohistochemistry (IHC)

This method is used to detect the localisation of antigens, usually proteins, in tissue sections and cells, by the use of antibodies with specificity for an antigen.

1.4.8 Immunofluorescence (IF)

This is a detection technique where the antibodies used in the assay are labelled using fluorescent dyes or fluorescent proteins for detection purposes.

1.4.9 Molecular Pathology

Molecular pathology reveals defects in the chemical structure of molecules in the gnome. Molecular pathology can manifest in disorders such as sickle cell disease, osteogenesis imperfecta, and the development of neoplasms. This technique is commonly used in the diagnosis of cancer and infectious diseases. Common methods include polymerase chain reaction (PCR) and in situ hybridisation (ISH). In the PCR test, minute amounts of nucleic acids can be amplified using oligonucleotide primers specific to the genes being studied. ISH is a technique that allows for the precise localisation of a particular nucleic acid segment within a histologic section. ISH identifies specific genes or their messenger RNA in tissue sections or cell preparations.

1.4.10 Cytogenetics (Clinical Genetics)

This method investigates inherited chromosomal abnormalities in the germ cells or acquired chromosomal abnormalities in somatic cells using molecular biology techniques.

1.4.11 Biochemical Methods

Biochemical techniques refer to assays and procedures that enable investigators to analyse the substances found in living organisms and their chemical reactions. This is a method by which the metabolic disturbances of disease are investigated by assay of various normal and abnormal compounds in the blood, urine, saliva, etc.

1.4.12 Medical Microbiology

Medical microbiology, also known as clinical microbiology, is a subdiscipline dealing with studying microorganisms (parasites, fungi, bacteria, viruses, and prions) capable of infecting and causing human diseases.

1.4.13 Microbial Culture

Microbial culture is one of the primary diagnostic methods in microbiology. Microbial culture is a method of growing a microbial organism to determine what it is, its abundance in the tested sample, or both. The tool is often used to determine the cause of infectious disease by letting the agent multiply in predetermined media in the laboratory. In the case of bacterial infections, the most appropriate antibiotic can be selected by determining the bacteria's sensitivity to various antibacterial agents.

1.4.14 Flow Cytometry

This technique is commonly used to diagnose cancers of the blood cells, such as leukaemias.

1.4.15 Electron Microscopy

The standard microscopes used by pathologists are not powerful enough to see the smallest parts that make up a cell. Some diseases can only be diagnosed at this subcellular level

using an electron microscope. Examples include types of kidney disease or aggressive cancers. Electron microscope utilises beams of electrons rather than visible light to magnify the cells in a tissue sample. It can magnify up to 2 million times, whereas the maximum power of a conventional light microscope is only 1 to 2 thousand times.

1.4.16 Forensic Pathology/Autopsy

Forensic pathology is the discipline of pathology concerned with the investigation of deaths where there are medico-legal implications. It is a field of forensic science that involves the application of pathological methods in investigating a crime and of sudden, suspicious, or unexplained deaths. An autopsy examines the dead body to identify the cause of death. This can be for forensic or clinical purposes.

1.4.17 Oral and Maxillofacial Pathology

Oral and maxillofacial pathology (OMFP) refers to the diseases of the oral cavity, jaws, and related structures, including salivary glands, temporomandibular joints, facial muscles, and perioral skin. It is considered to be a speciality of dentistry and pathology.

1.5 Summary

Pathology is concerned with the cause, development, structural, and functional changes, and natural history associated with diseases. It is the foundation for clinical practice, including dentistry. Clinical pathology and diagnostic pathology are two major divisions of pathology. Biopsy and histopathology are the most commonly used diagnostic procedures in dental practice. These procedures are extensively used to diagnose mucosal, jawbone, and salivary gland diseases. Histochemical, immunological, biochemical, and molecular pathology techniques are used for the confirmation of diagnosis of diseases of immunological and neoplastic origin.

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Homeostasis

2

2.1 Introduction

Homeostasis is a state of dynamic equilibrium characterised by steady internal, physical, and chemical conditions maintained by living systems despite changes in the external environment. The term homeostasis is derived from *homeo* (meaning similar) and *stasis* (meaning steady). Disruption of homeostasis causes disease.

2.2 Homeostasis at the Cellular, Tissue, and Organ Levels

At the cellular level, homeostasis is observable in biochemical reactions. Cellular homeostasis relates to the fluid and oxygen levels of the intracellular environment. When the intracellular fluid levels drop, the cell obtains fluid from the surrounding extracellular fluid and the blood. Thus, fluid and oxygen levels are restored within the cell to normal levels.

Homeostasis is involved in every organ system of the body. Some body systems that constantly adjust to normal levels of health include blood sugar, blood pressure, energy, acid levels, oxygen, proteins, temperature, hormones, and electrolytes.

2.3 Regulation and Mechanisms of Homeostasis

Homeostasis is regulated by negative feedback loops and positive feedback loops. Both have the same stimulus components: sensor (also referred to as receptor), control centre, and effector (Fig. 2.1). Negative feedback loops prevent an excessive response to the stimulus, whereas positive feedback loops intensify the response until an endpoint is reached. The sensor collects information from the surroundings and reports further to the control centre. The control centre monitors and processes the received information and conveys a signal to the effector. The effector produces a reaction based on the signal provided by the control centre. Control centres in the brain and other body parts monitor and react to deviations from homeostasis. The effector is an organ, gland, muscle, or another structure that acts on the signal from the control centre to move the variable back toward the set point. A set point is a physiological value around which the normal range fluctuates. As the body works to maintain homeostasis, fluctuations are normal if they do not become too extreme. The normal body temperature range is the spread of values within which such fluctuations are considered insignificant. (E.g. the normal range for an adult is about 36.5–37.5 °C (97.7–99.5 °F).

S. R. Prabhu, *Textbook of General Pathology for Dental Students*, https://doi.org/10.1007/978-3-031-31244-1_2

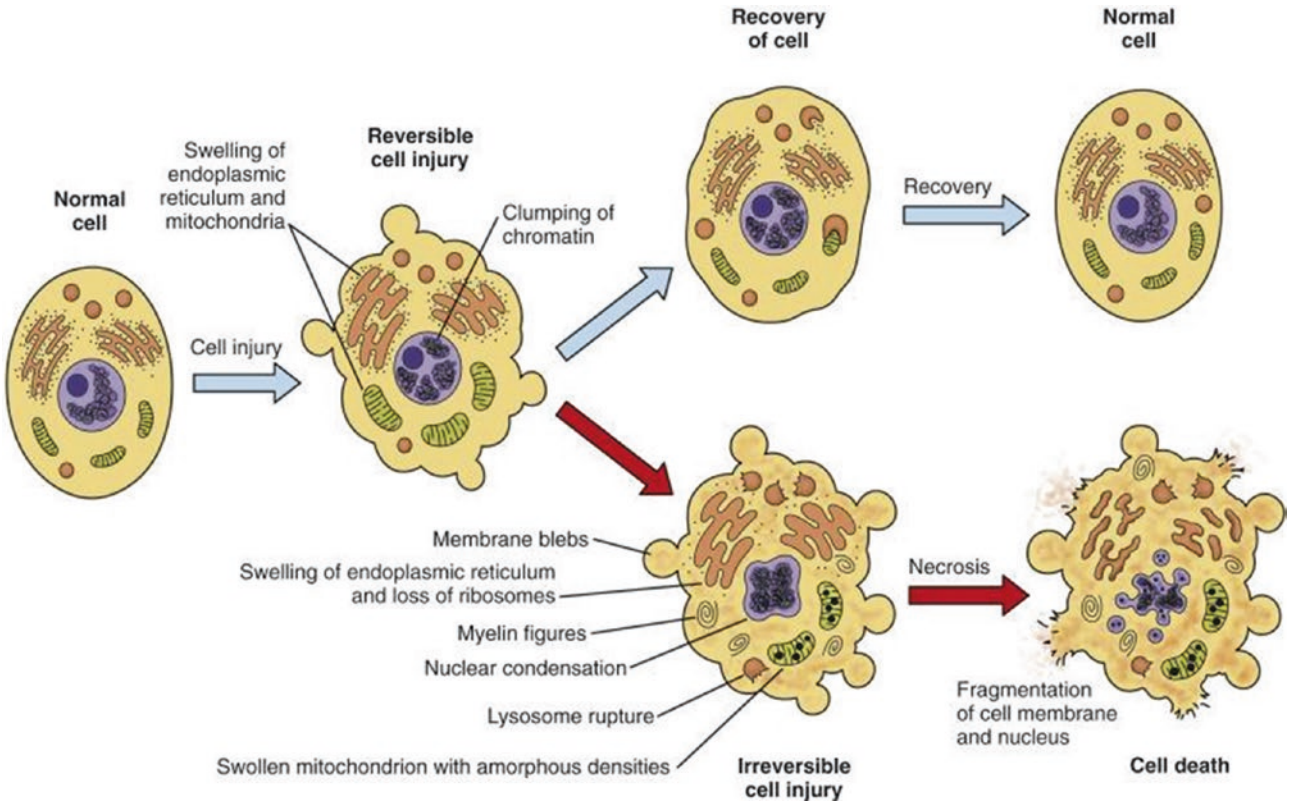

Fig. 5.1 Normal cell and the changes in reversible and irreversible cell injury. (Source: Miller, M. A., & Zachary, J. F. (2017). Mechanisms and Morphology of Cellular Injury, Adaptation, and Death. Pathologic Basis of Veterinary Disease, 2–43. e19. https://doi.org/10.1016/B978-0-323-35775-3.00001-1)

ised by the condensation of chromatin (Fig. 5.1). Karyorrhexis refers to nuclear fragmentation, and karyolysis is marked by the dissolution of the structure of the nucleus and the lysis of chromatin by enzymes such as DNase and RNase. Cytoplasmic enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) are also released from the injured cells. Alcohol liver disease (ALD) is an example.

5.6 Cellular Adaptation

Cellular adaptation refers to changes made by a cell in response to adverse or varying environmental changes. The adaptation may be physiologic (normal) or pathologic (abnormal). Physiological adaptations represent tissue responses to normal stimulation by hormones or endogenous chemical mediators. Pathological adaptation means responses in which cells and tissues modulate their size, structure, and function to escape permanent injury. Four types of morphological adaptations include hypertrophy, hyperplasia, atrophy, and metaplasia. Dysplasia means "disordered cellular development." It is not considered a true adaptation, but it often accompanies or precedes metaplasia. (Fig. 5.2).

5.6.1 Hypertrophy

Hypertrophy is an increase in the size of non-dividing cells. Hypertrophy can be physiologic or pathologic and is caused either by increased functional demand or specific hormonal stimulation. This alteration in cell size results from the increased workload that leads to increased protein synthesis, size, and the number of intracellular organelles. These changes result in increased cell size (hypertrophy), leading to increased organ size. A typical example of physiological hypertrophy is muscular hypertrophy in response to a normal stressor such as exercise. Exercise stimulates skeletal and cardiac muscle fibres to increase in diameter and accumulate more structural contractile proteins. Pathologic hypertrophy occurs due to an abnormal stressor. For example, an increase in the size of the heart (hypertrophy) can occur due to aortic stenosis. Aortic stenosis occurs when the orifice of the aortic valve is significantly reduced due to the calcification of a

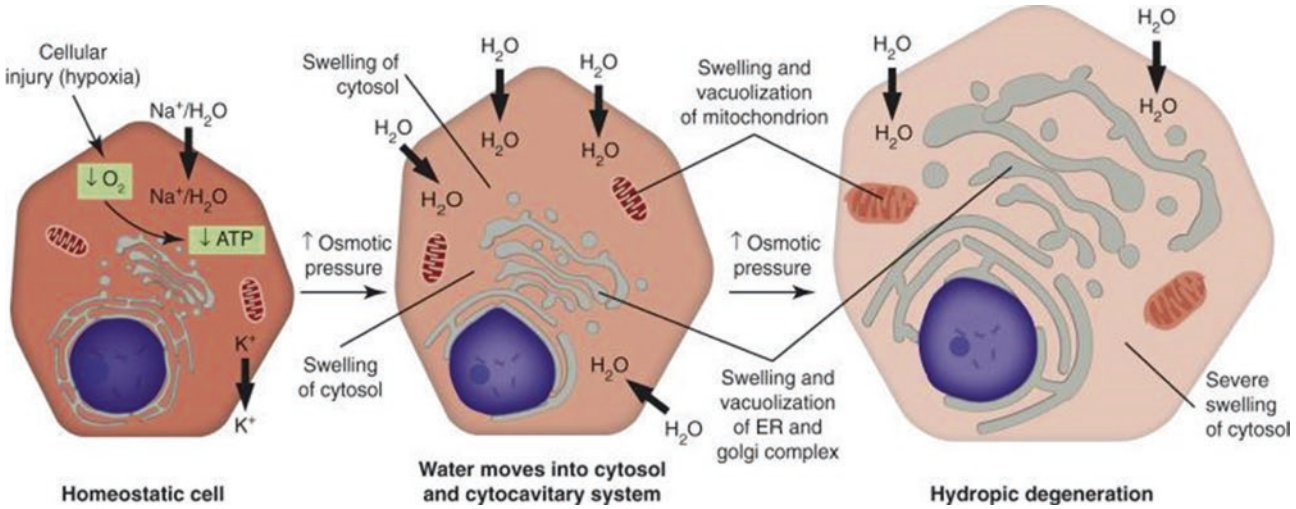

Fig. 5.3 The process of hydropic degeneration (acute cell swelling). (Miller MA, Zachary JF. Mechanisms and Morphology of Cellular Injury, Adaptation, and Death. Pathologic Basis of Veterinary Disease. 2017:2–43.e19. DOI: 10.1016/B978-0-323-35.775-3.00001-1. Epub 2017 Feb 17. PMCID: PMC7171462.)

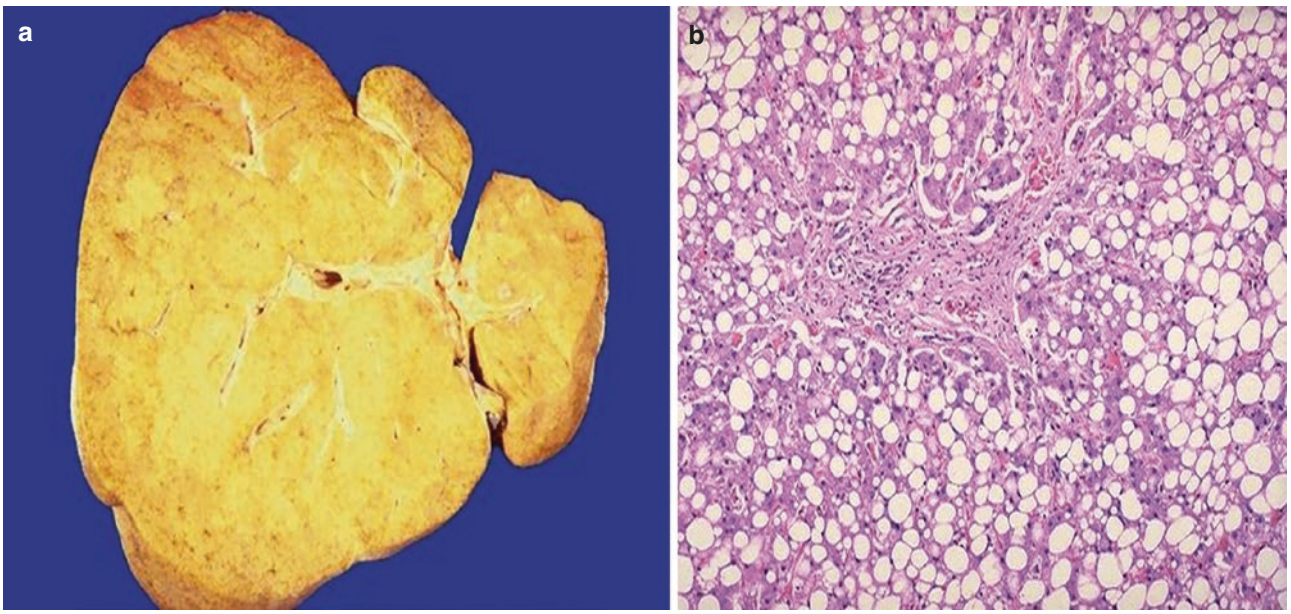

Fig. 5.4 (**a**, **b**) Fatty degeneration (liver). With the progressive accumulation of fat, the liver becomes increasingly yellowish in colour (**a**). Photomicrograph shows hepatic parenchymal cell cytoplasm containing clear vacuoles containing fat of varying sizes (**b**). This change displaces the nucleus towards the periphery giving a signet ring appearance (Source: (**a**) https://webpath.med.utah.edu/LIVEHTML/LIVER004.html).

in other non-fatty tissues, such as the liver, heart, skeletal muscle, and kidneys. The causes of fatty change in the liver include obesity, cirrhosis, diabetes mellitus, alcoholism, starvation, protein-calorie malnutrition, chronic illnesses (e.g. tuberculosis), hypoxia (due to anaemia, cardiac failure), and the use of hepatotoxins. The gross appearance of fatty liver is yellowish due to the deposition of lipids (Fig. 5.4a). Microscopically, many small globular intracytoplasmic clear spaces may be seen to accumulate and displace the nucleus to the periphery (Fig. 5.4b).