Pathological Basis of Oral and Maxillofacial Diseases

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This book is dedicated to the memory of Newell W Johnson for his enormous contribution to Oral and Maxillofacial Pathology.

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Merva Soluk Tekkesin is an Oral and Maxillofacial Pathology Professor at Istanbul University, Türkiye. She completed her dental school training in 2003, her residency in oral and maxillofacial pathology, and her PhD in tumour pathology at the Institute of Oncology, Istanbul University, in 2010. Professor Soluk Tekkesin was an overseas training fellow registered with the General Dental Council (GDC) at King's College London, Guy's Hospital, and the Department of Head and Neck and Oral Pathology in 2009, and she was the first Tier 5 International Training Fellow to complete training in the United Kingdom. She served as the European Councillor of the International Association of Oral and Maxillofacial Pathologists (IAOP) from 2014 to 2020. She is the first digital communication officer of the IAOP, a position she will hold until 2026. Professor Soluk Tekkesin was the secretary of both the Head and Neck Working Group (2010–2014) and the Informatics Working Group (2021–2023) of the Federation of Turkish Pathology Societies in Türkiye. Her main research interests include odontogenic lesions, fibro-osseous lesions, potentially malignant oral disorders, digital pathology and AI. She has numerous high-quality publications and book chapters, including contributions to the fourth and fifth editions of the *WHO Classification of Head and Neck Tumors*. In 2019, she was honoured with the Turkish Academy of Science Outstanding Young Scientist Award in medical sciences.

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Foreword

Teaching methodology in the dental school curriculum continues to evolve as we search for the best ways to educate our students. The traditional curriculum has been heavily weighted with numerous individual basic science courses (anatomy, histology, microbiology, biochemistry, physiology, pathology etc.) during the first years of dental school, which are followed in subsequent years by courses primarily related to direct clinical patient care. Obviously, such an approach is quite logical because it provides students with the critical baseline scientific knowledge necessary to diagnose and treat their patients. However, this type of curriculum sometimes leads to a "disconnect" between the knowledge being learned in various individual courses as well as the application of this knowledge in the clinical arena. In an effort to bridge this gap, many basic science courses now include crossover "enrichment" lectures from clinical faculty members in an effort to demonstrate the clinical relevance of the basic science principles being introduced. Some dental schools today have taken this approach one step further by developing interdisciplinary "systems-based" curricula that attempt to integrate various aspects of the basic and clinical sciences into separate teaching modules based on organ systems (e.g., cardiovascular, gastrointestinal etc.).

Because oral and maxillofacial pathology sits at the crossroads of the basic and clinical sciences, our discipline is ideally suited for incorporation into an integrated approach to dental education. With this ambitious textbook, Drs. S. R. Prabhu, S. Ali Khurram, Omar Kujan and Merva Soluk Tekkesin, in collaboration with a talented international group of contributing authors, have attempted to bridge this gap in recognition of our burgeoning knowledge about oral disease conditions, *Pathological Basis of Oral and Maxillofacial Diseases* presents a broader view of oral pathology, including information on epidemiologic, hereditary, pathophysiologic, immunologic and molecular factors involved in various pathologic processes of the head and neck region. I feel confident that the scope of this book will serve as a valuable resource of information for students, clinicians and teachers alike.

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Preface

In most dental schools, general pathology is traditionally taught as part of the basic medical science curriculum in the initial years of dental training. This is followed in the early years of clinical training by taught courses in oral pathology/oral medicine and oral surgery. Students, particularly undergraduates, find this compartmentalised approach daunting and often miss the relevance of basic pathologic principles in the pathogenesis of diseases affecting the oral and maxillofacial regions. The time gap between general pathology and oral pathology/oral medicine training also leads to some loss of basic pathology knowledge when students enter clinical years. In addition, we have also witnessed widespread advances in the molecular, immunologic and genetic basis of diseases that have enhanced our understanding of the pathogenesis of diseases, including those of the oral and maxillofacial regions. However, there is a lack of this knowledge being adequately compiled and presented in a manner that reaches dental students. *Pathological Basis of Oral and Maxillofacial Diseases* attempts to address this need, integrate pathological principles into oral and maxillofacial diseases and present the knowledge to make the student learning process more meaningful.

This book has 9 sections comprising 35 chapters contributed by over 50 international authors. Section titles include pathology as the foundation of medicine, homeostasis and cellular pathology, defence mechanisms against disease, clinical genetics and developmental pathology, infectious and systemic diseases, disorders of cell and tissue growth, neoplastic diseases of the oral mucosa and salivary glands, diseases of the oral and maxillofacial skeleton and pain disorders. Diagrams, clinical, radiographic and histopathology images and tables supplement the text. Variability in length, style and depth of coverage can be expected in a multiauthor work such as this. However, editors have tried to maintain a coherent approach without unduly restricting chapter contributors, who have been drawn from different parts of the world.

Editors hope the *Pathological Basis of Oral and Maxillofacial Diseases* will enable undergraduate and postgraduate dental students, trainee pathologists and clinicians to grasp the essential features of the pathological basis of diseases and apply that knowledge to diseases of the oral and maxillofacial regions.

July 2024

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Section 1

Pathology as the Foundation of Medicine

1

Introduction to Pathology

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1.1 Introduction

Pathology is the medical speciality concerned with the scientific study of the nature and causes of diseases. It bridges science and medicine and supports every aspect of patient care, from diagnostic testing, treatment and advice to disease prevention. The origin of the term (etymology) 'pathology' is derived from the Greek words 'Pathos' and 'logy', meaning the study of suffering (1). 'Disease' refers to a definable deviation from normal phenotypic observable characteristics evident via patient symptoms and signs (2). The cause of the disease is referred to as its aetiology. One disease entity can have more than one aetiology, and it is also possible that one aetiology can lead to more than one disease. Sometimes, the affix *pathy* indicates a disease state in both physical ailments, such as cardiomyopathy, and psychological conditions, such as psychopathy (3). Each disease develops through physical, chemical and cellular events. This stepwise process of disease development is called its pathogenesis – a Greek word meaning generation of suffering (2). It leads to cellular and tissue function changes. A pathologist is a specialist in pathology who offers diagnosis using observations at the clinical, gross, body fluid, light microscopic, immunophenotypic, ultrastructural, cytogenetic and molecular levels (4). Pathologists diagnose disease by generating a differential diagnosis and then finding the best fit for the clinical presentation, the radiographic appearance and the pathologic (clinical lab and morphologic) findings (2). The presentation of a disease to a clinician is in the form of a human patient with variably specific complaints (symptoms).

1.2 History of Pathology

Pathology has evolved over the years as a distinct discipline. Its roots arise in pre-historic and medieval times. The earliest concept of disease was the religious belief that disease was the outcome of a 'curse from God' or the belief that it had a supernatural cause from the 'evil eye of spirits' (5). The rational approach to disease by methods of observation followed after many decades. Gross features of the disease that were directly visible, either in the living or dead, came first

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to notice, and documentation of the disease began with Egyptian medicine. In the last three centuries BC, the Greeks, heavily influenced by Hippocrates, made lasting contributions to anatomy and pathology (6). Hippocrates (460–370 BC) is traditionally considered 'the father of medicine'. He disassociated disease from religion and magic. He believed in studying patients' symptoms and described methods of diagnosis (6). His collection of writings based on observations of cases called the *Hippocratic Corpus* was the mainstay of learning medicine for over two thousand years. In Rome, Hippocratic teaching was promoted by Cornelius Celsus (53 BC–7 AD) and Claudius Galen (130–200 AD) (6). Celsius was the first to describe the following four cardinal signs of inflammation: rubor, tumour, calor and dolor (6). In addition, Galen postulated humoral theory (Galenic theory). According to this theory, an imbalance of four body fluids – blood, lymph, biliary secretion from the liver and bile, which was believed at that time to be from the spleen – resulted in illness (6).

Human anatomy and gross pathology became popular during the Renaissance (14–17th century). During this period, anatomic dissections were performed in various theatres in ancient parts of Europe. Correlations of clinical manifestations of disease with gross pathological findings at autopsies became the major method of study of pathology until the middle of the 17th century. Before 1668, *Antony van Leeuwenhoek* (1632–1723) (6, 7), a cloth merchant in Holland, invented the first-ever hand-held microscope by grinding the lenses. He recognised male spermatozoa using his microscope and introduced staining using saffron to examine muscle fibres (6, 7). Other prominent individuals of this period who contributed to the development of pathology include *Marcello Malpighi* (1624–1694), *Giovanni B Morgagni* (1682–1771), *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) and *RTH Laennec* (1781–1826) (6–10).

Pathology started developing in the latter half of the 19th century. Rudolf Ludwig Carl Virchow (1821–1902), a German physician and pathologist, is known as 'the father of modern pathology' (8, 9). Virchow was the first to develop a systematic autopsy method based on his knowledge of cellular pathology (10). Virchow is also credited with several fundamental discoveries. His most widely known scientific contribution is his cell theory. Virchow was the first to analyse hair in criminal investigations and made the first forensic report in 1861 (11, 12).

During the 19th century, many other individuals contributed to pathology. They include Louis Pasteur (1822–1895) (13) and G H A Hansen (1841–1912) (14), who were responsible for discovering causative microorganisms for tuberculosis and leprosy, respectively (14). Other prominent individuals who contributed to pathology during this period were Paul Ehrlich (1854–1915) (13), *Christian Gram* (1853–1938), *D L Romanowsky* (1861–1921), *Robert Koch* (1843–1910), *Sir William Leishman* (1865–1926), *Karl Landsteiner* (1863–1943) and *G N Papanicolaou* (1883–1962) (6). In addition, *Joe Hin Tejo* and *Albert Levan* (1956) identified chromosomes and their correct number in humans (6). Other significant milestones in the development of modern pathology include the identification of the Philadelphia chromosome in leukaemia in 1960, the introduction of the in situ hybridisation technique in 1969, the recombinant DNA technique in 1974 and the polymerase chain reaction (PCR) in 1983. In situ hybridisation was invented in 1969 by American biologists (15). Recombinant DNA technology was created in 1974 by Stanley Cohen of Stanford and Herbert Boyer of UCSF (16).

1.3 Study of Pathology

Pathology is best studied in two stages: general pathology and systematic pathology.

1.3.1 General Pathology

General pathology is the foundation of pathology. The broad scientific field seeks to understand the mechanisms of injury to cells and tissues and how to respond to and repair injury. Areas of study include cellular adaptation to injury, necrosis, inflammation, wound healing and neoplasia. General pathology covers basic knowledge that has to be acquired before studying systemic pathology (17).

1.3.2 Systematic Pathology (Systemic Pathology)

Systematic pathology deals with descriptions of diseases affecting organs or organ systems. Some pathologists discuss these diseases under the heading of systemic pathology. In recent years, however, the term systemic has been abandoned by many pathologists because the word 'systemic' refers to a disease that has spread to all body systems. The preferred term for the study of organ-based pathology, therefore, is systematic pathology.

1.4 Specialities and Subspecialties of Pathology

1.4.1 Anatomical Pathology

Anatomical pathology is a medical speciality concerned with diagnosing disease based on the gross, microscopic, chemical, immunologic and molecular examination of organs, tissues and the whole body (autopsy). Anatomic pathology has two subdivisions: histopathology and cytopathology (17).

The pathology laboratory receives large whole organs, or parts of organs, removed during surgery. These specimens are examined for size, shape, colour and external abnormalities (gross pathology) (Figure 1.1a). The initial step in reviewing a clinical specimen is confirmation of the identity of the patient and the anatomical site from which the sample was obtained. Next, the clinical team should communicate sufficient clinical data to the pathology team to guide the appropriate diagnostic examination and interpretation of the specimen. After recording these findings, smaller samples are taken for definitive microscopic evaluation. Surgical pathology allows for a definitive diagnosis of the disease. This is usually performed by a

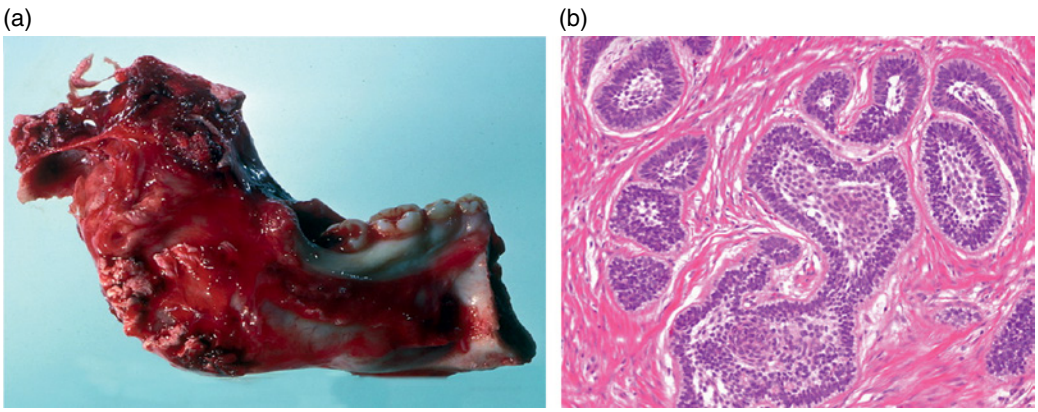

Figure 1.1 Ameloblastoma of the mandible. Gross pathology of a surgical specimen (a) and histopathologic features (b). *Source:* With permission of WebPathology, LLC.

combination of gross (Figure 1.1a) and histopathologic (Figure 1.1b) examinations of the tissue and may involve evaluations of molecular properties of the tissue by immunohistochemistry or other laboratory tests.

1.4.1.1 Histopathology and Cytopathology

Histopathology is a branch of anatomic pathology that involves an examination of tissue from biopsy or surgery under the microscope, often aided by special staining techniques and other associated tests, such as using antibodies to identify different tissue components. Histological tissue sections are processed for microscopic viewing using chemical fixation or frozen sections. Frozen section processing involves freezing the tissue and generating thin frozen slices of the specimen, which are mounted onto glass slides. Before viewing the tissue under a microscope, slides processed by chemical fixation or frozen sections are either stained with chemicals or antibodies to reveal cellular components (17).

Cytopathology (cytology) examines single cells or small groups of cells from scrapings or aspiration of fluid or tissue under the microscope (Figure 1.2). It is not only usually used to aid in diagnosing cancer but also helps diagnose certain infectious diseases and other inflammatory conditions. A common example of a cytology test is the cervical Pap smear.

A brief description of the biopsy and autopsy is in order here.

Biopsy refers to removing cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue. There are many different types of biopsy procedures. The most common styles include (i) incisional biopsy, in which only a sample of tissue is removed; (ii) excisional biopsy, in which an entire lump or suspicious area is removed; and (iii) 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 (FNAB) (17).

An autopsy is a specialised surgical procedure performed by a pathologist. It consists of a thorough examination of a corpse to determine the cause and manner of death and to evaluate any disease or injury that may be present. The principal aim of an autopsy or post-mortem examination is to determine the cause of death, the person's state of health before they die, and whether any medical diagnosis and treatment before death were appropriate (17).

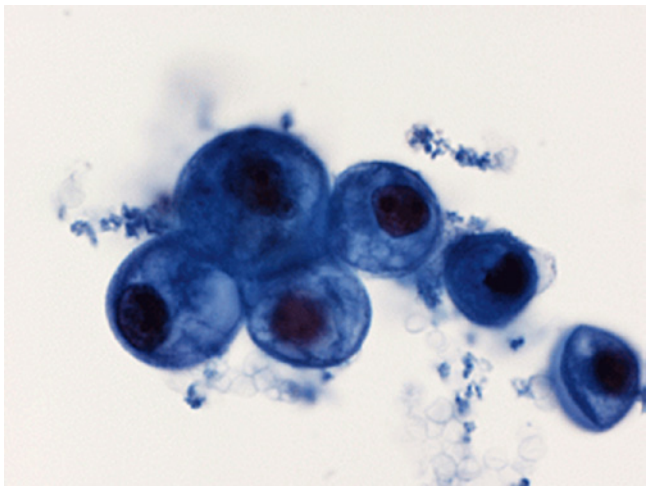

Figure 1.2 Cytological smear showing individual cells.

1.5 Laboratory Medicine (Clinical Pathology)

Laboratory medicine, or clinical pathology, is a medical speciality concerned with diagnosing disease based on the laboratory analysis of bodily fluids, such as blood, urine and tissues, using the tools of chemistry, microbiology, haematology and molecular pathology (17).

1.5.1 Chemical Pathology (Clinical Biochemistry)

Chemical pathology is also known as clinical biochemistry. This subspeciality of clinical pathology includes blood chemistries (e.g. electrolytes, blood gases, lipids, liver and kidney function tests), the study of hormones and diagnosis of endocrine disorders, the study of drugs of abuse and other chemicals (toxicology), measurement of therapeutic medications, blood levels to optimise dosage and chemical analysis of urine for a wide array of diseases, along with other fluids such as cerebrospinal fluid (CSF) and effusions (17).

1.5.2 Hematopathology

Hematopathology (haematology) deals with disorders of the cellular and coagulable components of the blood. Haematology tests such as complete blood count and peripheral blood smear analysis are commonly ordered tests in clinical laboratories. Physicians specialising in this field are referred to as haematologists. Haematologists also diagnose disorders of the bone marrow and lymphatic system (17).

1.5.3 Immunopathology

Immunopathology (immunology) deals with the specific defence mechanisms of the body. Immunopathology consists of adverse reactions generated by the immune response, divided into humoral and cellular (T-cell-mediated) responses. Immunopathology also includes the study of autoimmune diseases, which represent a failure of the normal mechanisms that maintain immunologic homeostasis in response to specific antigens (17).

1.6 Molecular Pathology

Molecular pathology is an emerging discipline of pathology. It can be broadly defined as the testing of nucleic acids within a clinical context. The applications of molecular diagnostics span a range of human disorders, including hereditary, neoplastic and infectious diseases. Many molecular pathology techniques rely on labelled antibodies and nucleic acid probes and are either slide or fluid based. Molecular-based assays are used for specific purposes, such as establishing the basis of an existing disorder (diagnostic testing), determining the presence of a genetic condition when there are no apparent symptoms (predictive testing), carrier testing, assessing a foetus for abnormalities (prenatal testing), detecting cancer-causing genetic mutations and selecting pharmacotherapy. Techniques include PCR, multiplex PCR, DNA microarray, in situ hybridisation, in situ RNA sequencing, molecular profiling of pathogens and analysis of bacterial genes for antibacterial resistance (17).

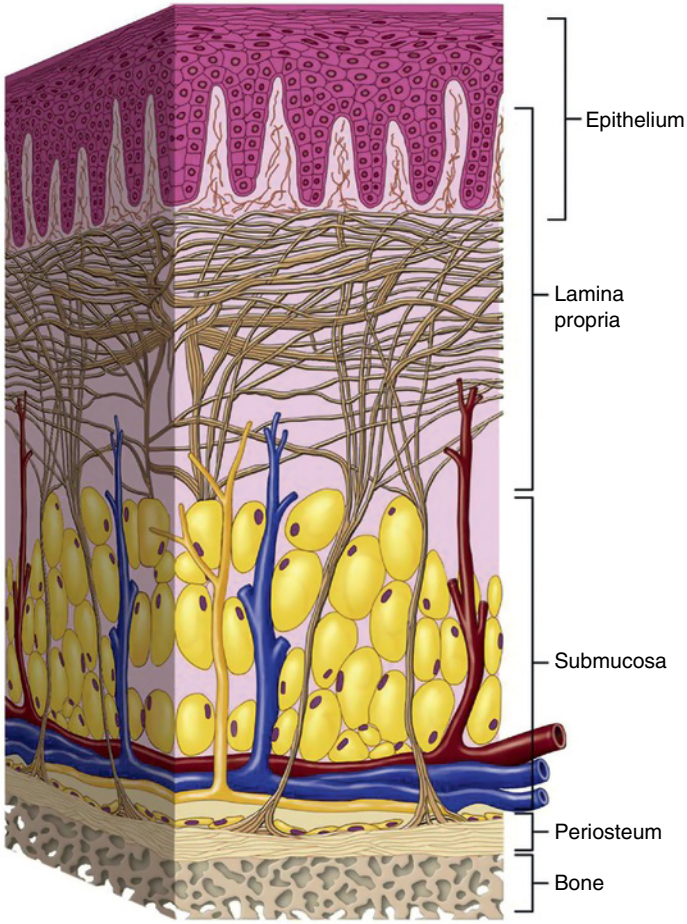

Figure 7.1 Main tissue components of the oral mucosa. *Source:* With permission of Pocket Dentistry.

Table 7.1 Types of oral mucosa (1, 2).

Types of OMM	Histological type of epithelium	Functions	Location (region)
Lining/moveable	Non-keratinised stratified squamous	Flexibility is required for holding water, whistling, blowing air, etc.	Soft palate, buccal, labial and alveolar mucosa, floor of the mouth and vestibular fornix
Masticatory	Keratinised/para keratinised stratified squamous	Support the stress like compressive and shear forces of mastication and abrasion because of hard and sharp food	Attached gingiva, hard palate and tongue dorsum (rigid mucosa)
Specialised	Keratinised/ non-keratinised stratified squamous	Unique feature: lingual papillae (taste buds) have a sensory role, while some have a mechanical purpose	Tongue dorsum

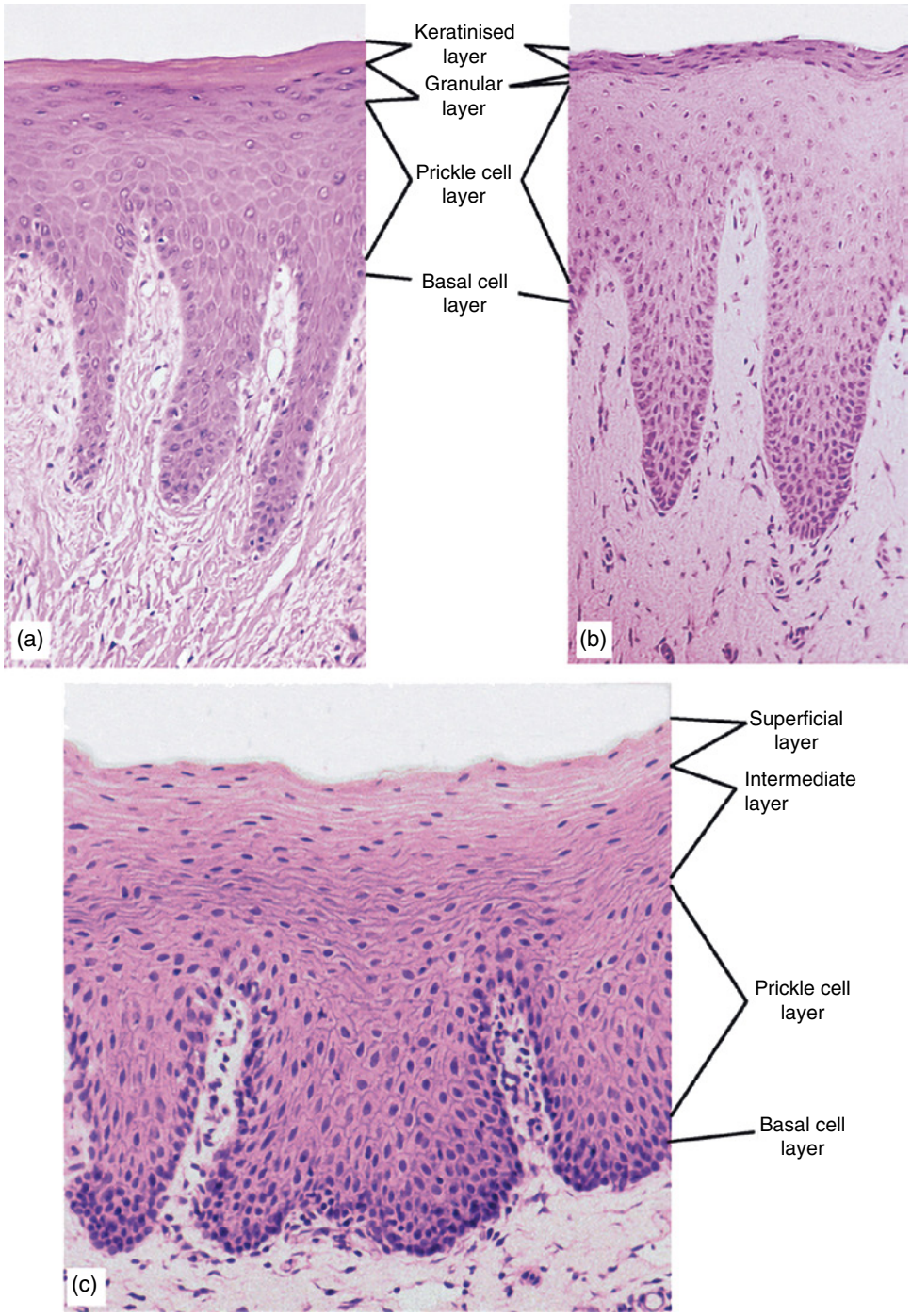

Figure 7.2 Main types of maturation in human oral epithelium. (a) Ortho-keratin in the gingiva shows a narrow, darkly staining granular layer. (b) Para-keratinisation in gingiva shows keratin squames that have retained pyknotic nuclei and a granular layer that contains only a few scattered granules. (c) Non-keratinisation in buccal mucosa shows no clear distinction between cell strata, and nuclei are apparent in the surface layers. Note the difference in thickness, epithelial ridge pattern and maturation patterns. *Source:* With permission of Pocket Dentistry.

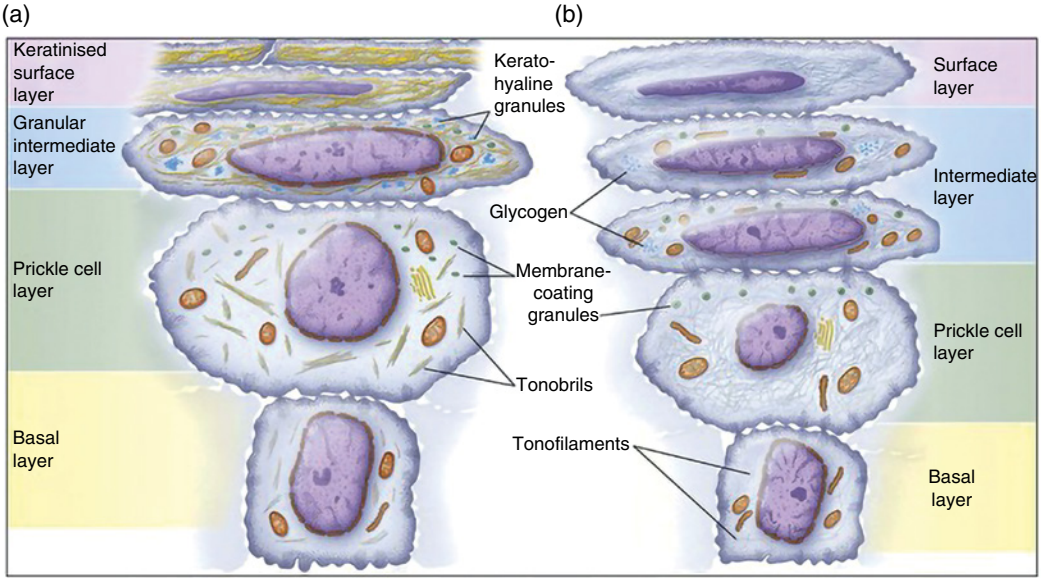

Figure 7.3 Principal structural features of epithelial cells in successive layers. (a) Ortho-keratinised oral epithelium. (b) Non-keratinised oral epithelium. *Source:* Adapted from Squier et al. (6).

anchor the epithelial cells to the underlying connective tissue. Non-serrated cells are stem cells. The stem cells are called slow-cycling cells, and their direct progeny is called the transit-amplifying cells (daughter cells). Stem cells undergo 1–5 cell divisions to form transit-amplifying cells. These next progeny cells migrate laterally and towards the surface, constituting a clone of differentiating cells. These next progeny cells migrate laterally and towards the surface, constituting a clone of differentiating cells. Cells are pushed towards the surface by pressure generated in the underlying proliferation compartment.

Epithelial projections that penetrate the lamina propria of the oral mucosa are known as rete ridges or epithelial ridges. The bottom of the epithelial ridges has a progenitor compartment at two functionally distant subpopulations of cells. One population represents the cells which produce daughter cells and preserve the proliferating potential. The other largest part is constituted by amplifier cells, which undergo subsequent maturation (1). Basal cells along the base of rete ridges contain few cytoplasmic organelles and are the least differentiated cells. They have a high nuclear–cytoplasmic (N:C) ratio. The pattern generation of the oral epithelial cells is the internal function of the epithelium and is not dependent on the underlying connective tissue. Therefore, connective tissue has no role to play in the formation of basal cells (7).

The proliferation and differentiation of oral epithelial cells are controlled by multiple factors, namely autocrine and paracrine factors by keratinocytes, cell-to-cell nutrient transfer, cytokines, growth factors from connective tissue and systemic factors (8, 9).

7.4.1.2 Stratum Spinosum (Prickle Cell Layer)

Stratum spinosum is the first tier of the differentiation compartment. It comprises numerous larger elliptical/spherical (polygonal) cells known as squamous cells arranged in rows (Figures 7.2 and 7.3). The cells in this layer shrink away from each other during routine tissue processing and remain in contact with each other only at the points of intercellular

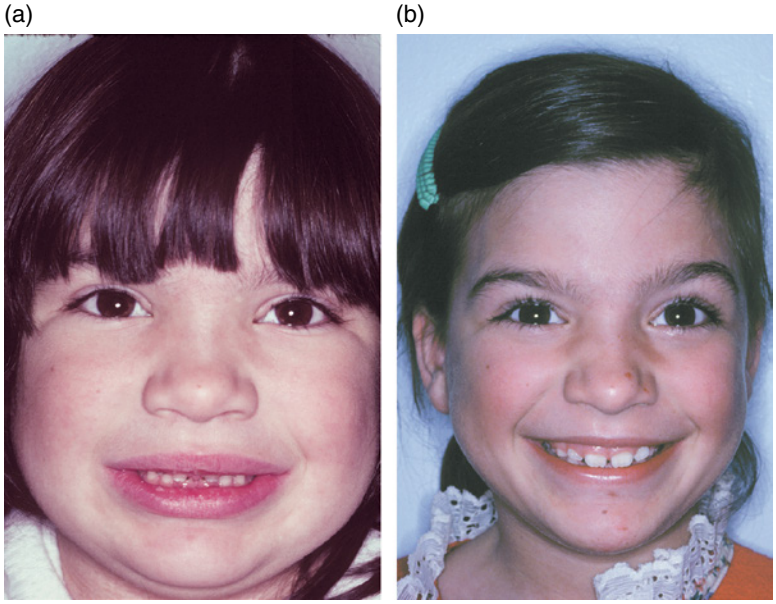

Figure 9.1 (a) The facial appearance of a child with an accumulation of oedema in the setting of hypothyroidism. (b) Same patient after treatment with hormone therapy. *Source:* Reproduced with permission from Elsevier.

Hypothyroidism in children is stratified into congenital thyroid agenesis, which is most likely seen in Down and Turner syndromes, ultimately progressing into cretinism. The annual incidence is ~ 1 in 4000 newborns (19). They typically present with mental and physical retardation, bradycardia, dyspnea, large head, short neck, hypertelorism, flat nasal bridge, loss of facial expression and thick textured skin (18, 20). Puffy face is a characteristic feature of hypothyroidism in children (Figure 9.1).

In contrast, adulthood hypothyroidism is diagnosed more in women, with a prevalence rate of ~5% in the United States of America, out of which ~0.5% of patients present with clinical validation (21, 22). They present with overweight, dysregulated respiratory rate and myxedema (accumulation of subcutaneous polysaccharides), which may evolve into myxedematous crisis, a possibly fatal condition involving multiple organ system failure (23). One of the most reliable tests for hypothyroidism includes circulating TSH, T4 and T3 levels (24). Other supplemental investigations include ultrasound and other imaging modalities with or without radioactive tracer. Treatment involves synthetic thyroid hormones such as levothyroxine (23). Craniofacial features of hypothyroidism are listed in Table 9.2.

9.6.2 Hyperthyroidism

Hyperthyroidism is characterised by increased circulating plasma levels of thyroid hormones due to hyperactivity of the thyroid gland. The aetiology is multifactorial within the exogenous and endogenous realm. The use of a particular class of medications (anti-arrhythmic or potassium channel blockers) and beyond physiologic levels of synthetic thyroid hormone are contributors to Grave's disease, toxic nodular goitre and post-partum thyroiditis (25). The annual incidence of Graves's disease is ~0.5% cases per 1000 people, and goitre constitutes about ~20% of thyrotoxicosis (26).

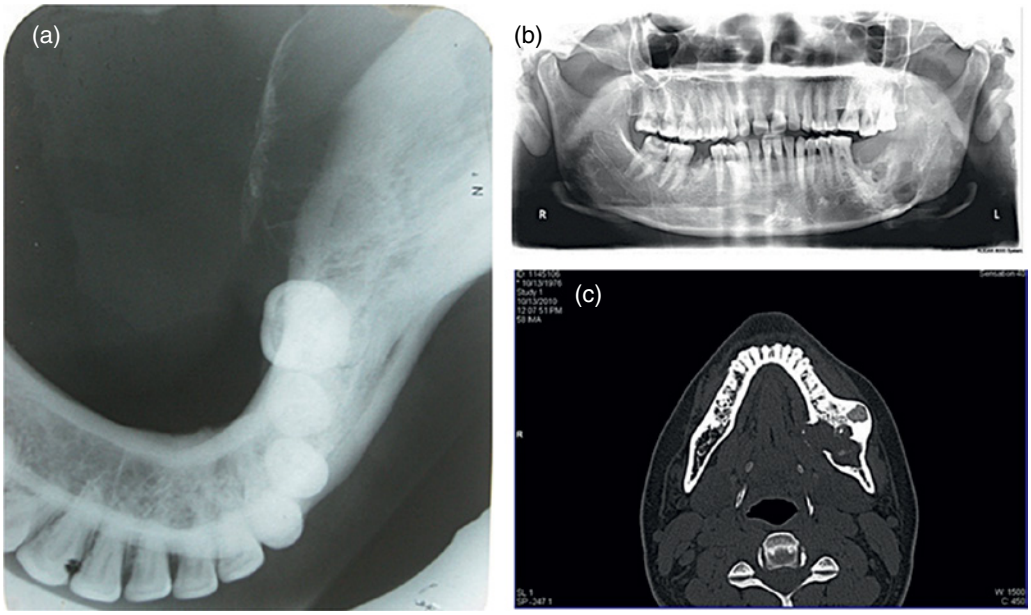

Figure 9.4 (a–c) Occlusal radiograph demonstrating expansion of the lingual cortex, panoramic revealing radiolucencies of the L mandible and CT showing expansile lesion with discontinuity of lingual cortical plate. *Source:* Courtesy of Dr. Preethi Nair.

9.9.1 Hypothalamus Pituitary Adrenal Axis (HPTA)

Like other endocrine organs, cortisol secretion is regulated by the hypothalamus–pituitary–adrenal axis (HPAA). The hypothalamus releases corticotropin-releasing hormone (CRH) to manage diurnal rhythm as an outcome of stress. CRH triggers ACTH stimulation in response to serum cortisol levels via a negative feedback mechanism (44). Cortisol secretion follows a circadian pattern, and the highest serum levels are observed early in the morning (45). Optimal cortisol secretion in 24 hours is ~20 mg; however, cortisol levels increase and are disrupted during infection, neoplasm, surgery and stress (46).

9.10 Adrenal Dysfunction and Its Oro-facial Manifestations

9.10.1 Adrenal Insufficiency

Addison's adrenal insufficiency (AI) is outlined in primary, secondary and tertiary. Primary AI is chiefly caused by the autoimmune destruction of the adrenal cortex, surgical removal of the adrenal gland and idiopathic infections (47). Secondary AI is most likely due to a pituitary gland tumour leading to suppressing pituitary hormones and the HPA axis. Tertiary AI occurs as a result of persistent administration of extrinsic systemic steroids (48). Chronic use of exogenous steroids has been used by ~2% of adults in the United States, which justifies the rationale for tertiary AI (49). The incidence of AI is observed to be ~1 in 10,000/20,000 newborns (50). ~3 in 10,000 cases are reportedly due to disrupted HPA axis.

women between the ages of 30 and 80 years. Persons of colour may show post-inflammatory melanosis underlying lesions of OLP. Patterns of OLP described include reticular (annular), atrophic/erosive, popular, plaque types and bullous types. Reticular OLP is by far the most common oral presentation. Lesions are widespread and bilateral and present as crisscrossing white lines (Wickham striae) that intersect and create patterns such as a net (reticular) or rings (annular) (Figure 11.24). Lesions of reticular OLP are primarily asymptomatic. Rarely patients may complain of a feeling of roughness and reduced flexibility. Gingival disease is almost always erosive (Figures 11.25 and 11.26), with symptoms including pain, soreness, bleeding, intolerance to spicy and acidic foodstuffs and inability to maintain oral hygiene. Lesions of erosive OLP may extend to involve other oral surfaces. Erosive lesions show fine white striae at the periphery. Erosive gingival lesions may result in desquamation. This presentation is often called a bullous OLP. Dorsum tongue lesions appear as white plaques and patches with fine striae noted at the peripheries. Plaque type mimics oral leukoplakia. Superficial mucoceles may also accompany OLP. Lesions of OLP may need to be differentiated from other conditions such as chronic graft-versus-host disease, lichenoid drug reactions, lichenoid contact metal and hypersensitivity (non-metal dental materials

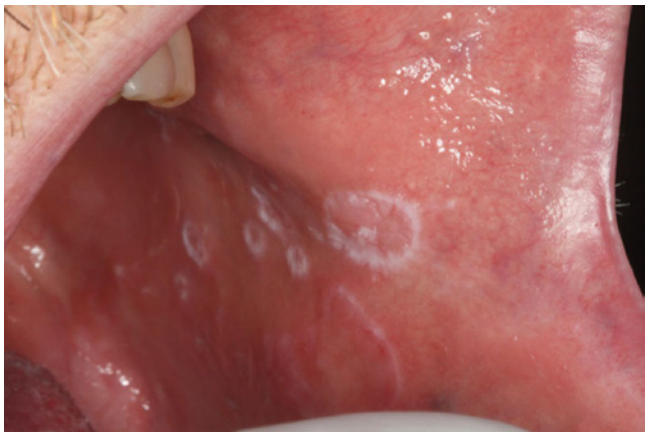

Figure 11.24 Annular lesions of lichen planus on the buccal mucosa.

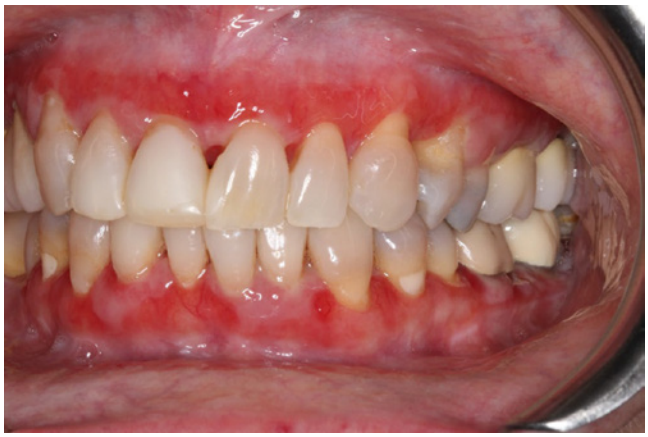

Figure 11.25 Erosive lichen planus on the gingiva.

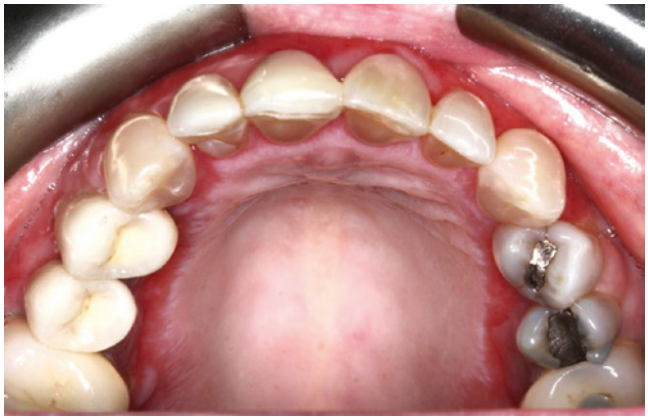

Figure 11.26 Lesions of erosive lichen planus on the palatal gingiva. Note the fine white striae at the periphery of the erosive lesions.

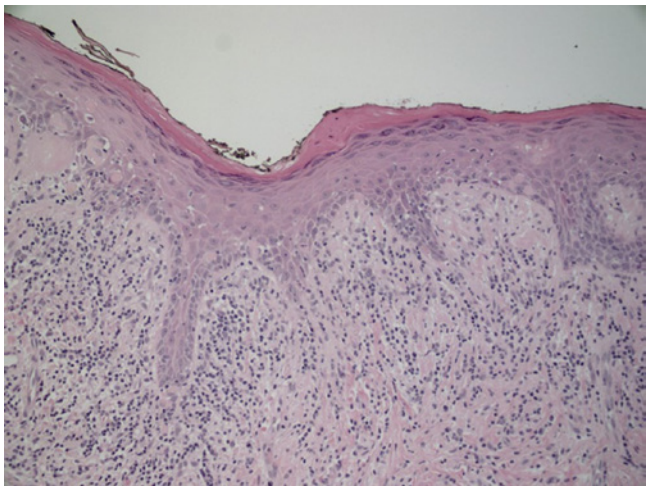

Figure 11.27 Lesions of lichen planus may show hyperkeratosis with variable degree of epithelial hyperplasia. The superficial lamina propria shows chronic inflammation consisting predominantly of lymphocytes.

and artificial flavouring agents) reactions, lupus erythematosus, CUS and MMP. Histopathological features of OLP include hyperkeratosis without a verrucoid surface architecture, variable degree of epithelial hyperplasia (Figure 11.27) saw-tooth-like epithelial rete ridges, liquefaction degeneration of basal cells with colloid/Civatte body formation in the basal layer of epithelium or the superficial lamina propria (Figures 11.28 and 11.29), a band of eosinophilic material at the basement membrane region, a band-like zone of cellular infiltrate consisting of lymphocytes in the superficial lamina propria, and absence of epithelial dysplasia. Direct immunofluorescence studies show a fuzzy fibrinogen band at the basement membrane (Figure 11.30). Management of OLP is directed towards symptomatic lesions. Therapy includes Class I and II potent topical corticosteroids in gel formulations, including fluocinonide, triamcinolone, clobetasol propionate and betamethasone. Other drugs include systemic steroids, hydroxychloroquine, azathioprine, systemic retinoids, phototherapy using psoralen UV A light (PUVA), and calcineurin inhibitors such as cyclosporin,

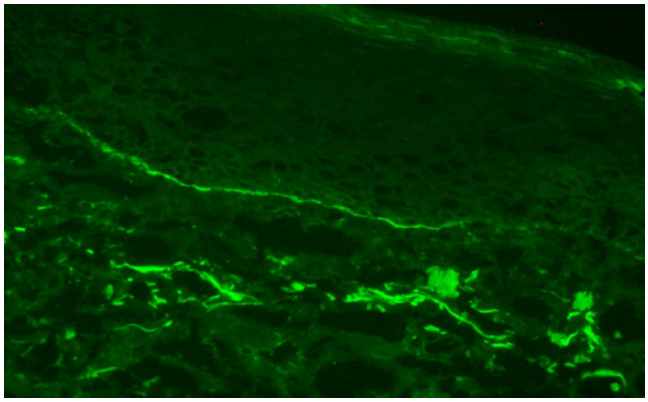

Figure 11.35 Direct immunofluorescence study shows linear deposits of C3 at the basement membrane.

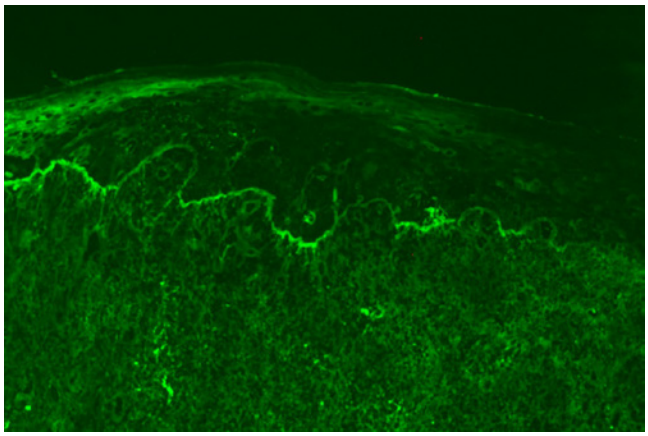

Figure 11.36 Direct immunofluorescence study shows shaggy deposits of fibrinogen at the basement membrane.

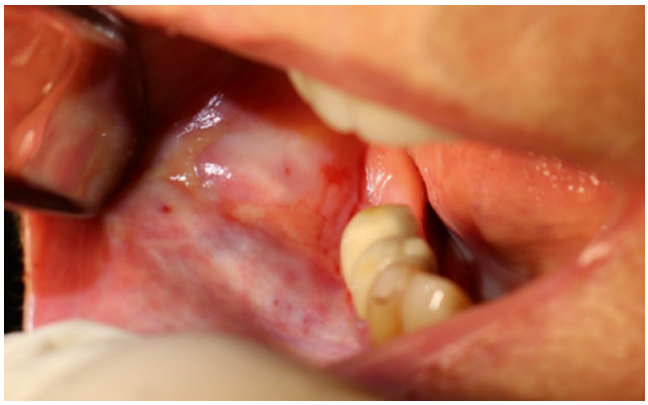

Figure 11.37 Right buccal mucosa shows erosive and ulcerated lesion of chronic ulcerative stomatitis.

Table 12.2 Inflammatory lesions of the oro-facial complex.

Pulpal, periapical, gingival, and periodontal inflammatory conditions	Definition	Causes/risk factors
Pulpitis	Inflammation of the dental pulp	Caries Traumatic exposure of the pulp Fracture of the crown or cusp. Cracked tooth. Thermal or chemical irritation
Chronic hyperplastic pulpitis	Chronic inflammation of the exposed pulp characterised by an overgrowth of granulation tissue often covered by epithelium seen in the open carious (molar) tooth in children	Chronic low-grade irritation
Acute apical periodontitis	Inflammation of the periodontal ligament surrounding the apex of the tooth	Infection, bacterial products, and other irritants
Periapical granuloma	Formation of granulation tissue surrounding the apex of a non-vital tooth arising in response to pulpal necrosis	Bacterial invasion from the pulp. Occlusal trauma from the high spots of restorations. Irritants and inflammatory mediators from the necrotic pulp. Endodontic procedures (iatrogenic)
Dentoalveolar abscess	An odontogenic infection is characterised by the localisation of pus surrounding the roots of involved teeth	Secondary to dental caries, trauma or failed root canal treatment. Bacteria and their toxic products enter the periapical tissues via the apical foramen and induce acute inflammation and pus formation
Condensing osteitis	Focal areas of bone sclerosis associated with apices of teeth.	Low-grade inflammatory stimulus from an inflamed dental pulp
Radicular, lateral radicular and residual cysts	Radicular cyst: a common odontogenic inflammatory cyst located at the apex of a non-vital tooth, also known as a periapical cyst Lateral radicular cyst: a radicular type of cyst located at the lateral surface of a non-vital tooth Residual radicular cyst: a radicular cyst that has persisted after extraction of the causative non-vital tooth	Radicular cyst: caused by the proliferation of odontogenic epithelium in a periapical granuloma due to stimulation derived from chronic inflammation from non-vital pulp Lateral radicular cyst is caused by the proliferation of odontogenic epithelium in the periodontal tissues at the lateral aspect of a non-vital tooth. Stimulation for chronic inflammation is derived from the non-vital tooth Residual radicular cyst is caused by the proliferation of odontogenic epithelium in a radicular cyst that has persisted after extraction due to inadequate curettage. Cystic expansion in all three types of cysts occurs because of the effects of osmotic gradient within the epithelial lining layers and mediators of inflammation

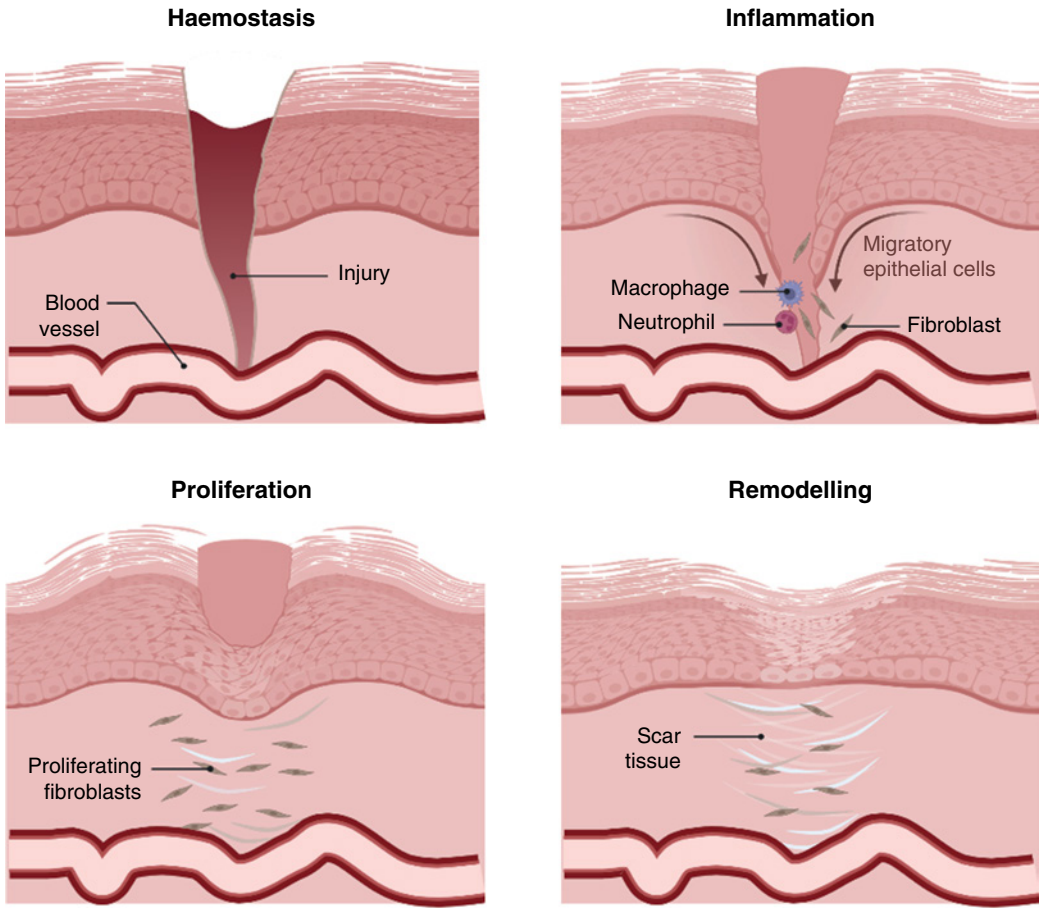

Figure 13.2 Graphical illustration of wound healing in phases: haemostasis, inflammation, proliferation and remodelling. *Source:* BioRender/https://app.biorender.com/biorender-templates2023/figures/all/t-5fa1b1622a60ac00a3d858ec-wound-healing/last accessed on 15 December, 2022.

Wound healing in skin and oral mucosa shares many common cellular and molecular processes, as described above; however, there are also notable differences due to the distinct characteristics and functions of these two tissue types.

A significant difference is the environment. Oral mucosal wounds benefit from a protective mucus layer, which expedites healing and protects against further damage. The mucus layer also aids in maintaining lubrication in the oral cavity. It is known that for skin wound healing, a moist environment results in faster reepithelialisation, angiogenesis and wound maturation (24, 25). In oral mucosa, saliva does not only provide a natural moist environment, it also contains wound healing stimulating growth factors, e.g. epidermal growth factor (EGF), VEGF, fibroblast growth factor (FGF) and histamine (26, 27). Moreover, saliva contains many antimicrobial peptides that eliminate microorganisms, e.g. defensin, histatin, cathelicidin, lysosome, lactoferrin and lactoperoxidase (23, 28). It has been shown that a healthy oral biofilm, with increased antimicrobial peptide expression, improved barrier function in reconstructed human gingiva (29, 30). Furthermore, microbes positively affect wound healing by activating macrophages, dendritic cells and T cells, resulting in stem cell proliferation stimulating cytokines, e.g. TNF-α, IL-6, IL-10 and IL-17 (31, 32).

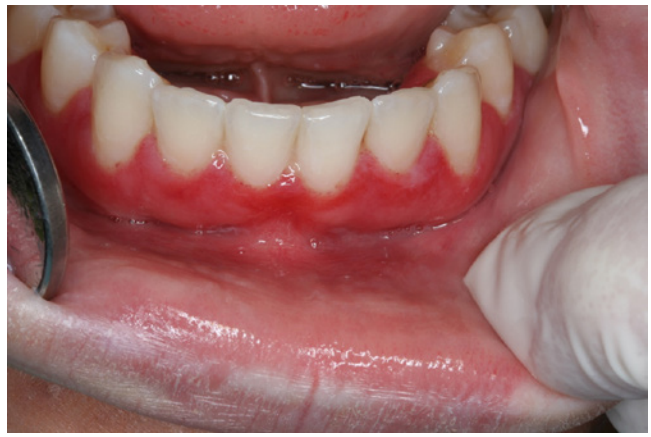

Figure 19.9 Primary herpetic gingivostomatitis presenting as erythema and pain in the gingiva.

19.2.6.4 Management of Primary HSV

The diagnosis is usually based on clinical appearance. Treatment of fever is managed with antipyretics such as acetaminophen. Aspirin is avoided in children. The lesions heal entirely in about 10 days in patients with normal immune status. Immunosuppressed individuals may be treated with antivirals such as acyclovir or valacyclovir.

19.2.6.5 Secondary Herpetic Stomatitis and Herpes Labialis

Recurrence in the form of secondary herpetic stomatitis/herpes labialis is due to the reactivation of the dormant virus in the trigeminal ganglion. The predisposing factors include changes in ambient temperature, immunosuppression, uncontrolled diabetes, stress and following dental treatment (45–51).

19.2.6.6 Clinical Features

Oral lesions occur on the keratinised mucosa of the lips, gingivae and hard palate, initially as grouped vesicles with prodromal symptoms of tingling and pain. The blisters will rupture resulting in grouped ulcerations (Figure 19.10). Herpes labialis shows similar vesicles on the lips (Figure 19.11

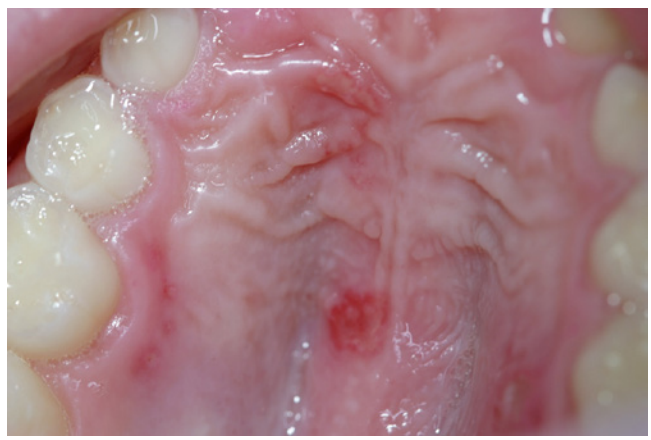

Figure 19.10 Secondary herpes presenting as grouped ulceration on the palate.

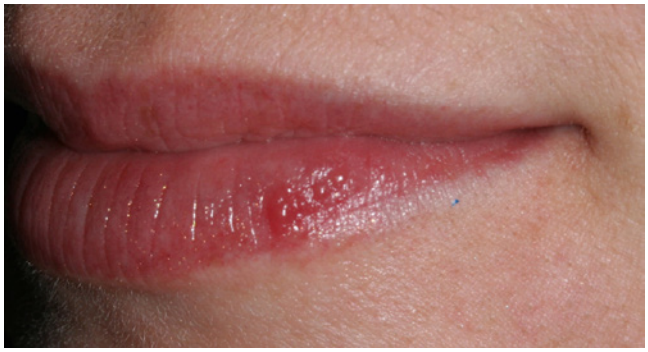

Figure 19.11 Herpes labialis presenting as grouped vesicles on the left lip.

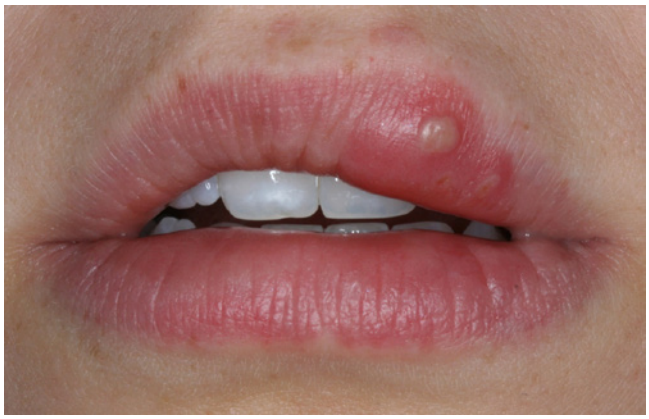

Figure 19.12 Herpes labialis presenting as a bulla and swelling on the left lip.

and Figure 19.12). When the vesicles and ulcerations are weeping, they are highly infectious. Reactivation lesions occur at the same sites in the oral cavity. The diagnosis is established based on clinical features.

19.2.6.7 Management

Most patients usually need no treatment, but if they are immunosuppressed, they require systemic acyclovir therapy. Topical antiviral therapy, such as penciclovir or acyclovir, used during the prodromal period, may be helpful. It is important to note that treatment with acyclovir, either for primary or secondary herpetic lesions, should be initiated within three days of the onset of symptoms.

19.2.7 Herpes Zoster (Varicella Zoster) Infections

Chickenpox is the primary infection caused by the VZV occurring in children as a rule. The patients may present with systemic signs of infection, fever, malaise and lymphadenopathy. The cutaneous lesions are vesiculopapular with pruritus. Oral lesions can occur on the palate and tonsillar pillar.

19.2.7.1 Varicella Zoster (Shingles)

Varicella Zoster, or shingles, occurs mainly in older patients with a history of chicken pox, presenting with lesions on the facial, thoracic or lumbar dermatomes. The oral findings seen in shingles are, characteristically, painful vesicles and bullae rupturing over time, causing ulceration (Figure 19.13). The prodromal features in the oral cavity resemble odontalgia. The unilateral distribution of vesicles, bullae and ulcerations helps diagnose shingles (45–47).

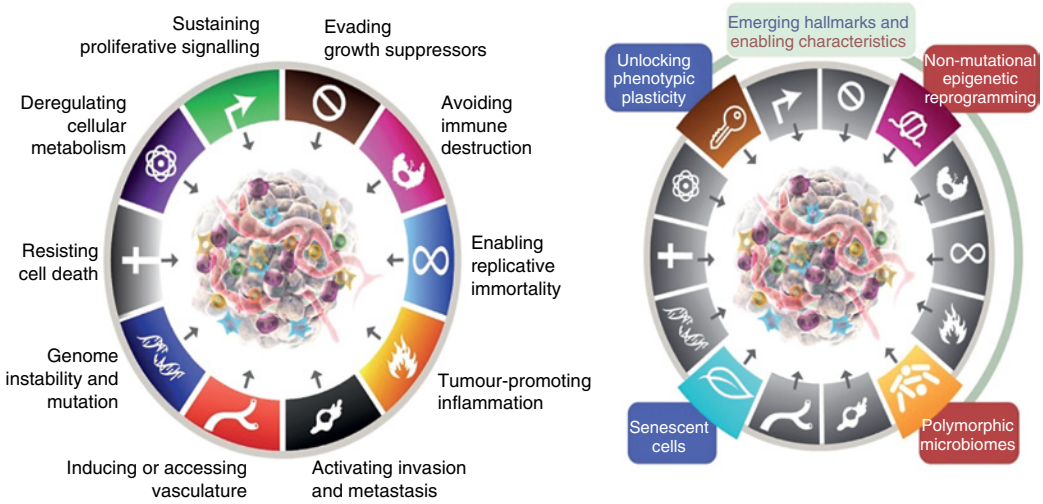

Figure 24.1 Hallmarks of cancer. *Source:* Adapted from Hanahan (2).

6) Activating invasion and metastasis
7) Reprogramming cellular metabolism
8) Avoiding immune destruction

Enabling characteristics:

1) Genomic instability
2) Tumour-promoting inflammation

Emerging hallmarks and enabling characteristics:

1) Unlocking phenotypic plasticity
2) Senescent cells
3) Epigenetic reprogramming
4) Polymorphic microbiomes

24.3 Sustaining Proliferative Signalling

Proto-oncogenes are a group of genes that cause normal cells to become cancerous when they are mutated (4). They are the first regulatory factors of the cancer biological process. Proto-oncogenes normally function as growth factors, transducers of cellular signals and nuclear transcription factors (Table 24.1) (4). Their function is to control normal cell differentiation and proliferation. Mutations to these genes can activate proto-oncogenes, influence their function and develop into cancer cells, known as oncogenes. It is the oncogenic formation that drives and sustains cell proliferation. It is important to note that proliferation is vital in the formation of mutations and the expansion of clones of cells bearing these mutations (2, 3). Currently, there are 50–60 oncogenes that have been recognised (4).

The genetic alterations that lead to the activation of proto-oncogenes and the development of oncogenes include mechanisms associated with influencing the structure of the encoded protein and those that cause deregulation of protein expression within the proto-oncogene (4).

Table 24.1 Proto-oncogenes with a role in the regulation of cell growth signals.

Role in mitogen signal transduction	Proto-oncogene	Encoded protein	Function of the proto-oncogene product
Growth factor receptors	*ERBB*	Receptor tyrosine-protein kinase	Cell membrane receptor for interleukin
	ERBB2	Receptor tyrosine-protein kinase *ERBB2*	Growth factor receptor
	FMS	Tyrosine-protein kinase transforming protein *fms*	Receptor for *CSF1*
	MET	Tyrosine-protein kinase *Met*	Receptor for *HGF*
	RET	Receptor tyrosine kinase	Receptor for *GDNF*
Growth factors	*SIS*	Platelet-derived growth factor (*PDGF*)	β-Chain for *PDGF*
	HST	Homogentisate solanesyltransferase, chloroplastic	Growth factor for *FGF*
Transduction factors with kinase action	*FGF5*	Fibroblast growth factor 5	Growth factor for fibroblasts
	ABL	Tyrosine-protein kinase *ABL*	Tyrosine kinase
	SRC	Tyrosine-protein kinase *Src*	Tyrosine kinase
	RAS	RAS small GTPase	G-Protein
	SOS	Guanine nucleotide exchange factors	Exchange factor of nucleotide of guanine
	CDK4	Cyclin-dependent kinase four protein	Cyclin-dependent kinase
Nuclear transcription factors	*FOS*	Leucine zipper protein	Transcription factor
	JUN	Activator protein 1	Transcription factor
	MYC	*MYC* transcription factor protein	Transcription factor
	GLI	*GLI* family zinc finger 1	Transcription factor
	TTG	Tissue transglutaminase	Transcription factor
	ERBA	Thyroid hormone receptor alpha	Member of the steroid receptor family
Anti-apoptotic factors	*BCL2*	B-cell lymphoma two protein	Inhibition of apoptosis
Binding to protein p53	*MDM2*	Mouse double minute 2 homolog	Transcriptional regulation

Note. EGF: Epidermal growth factors; CSF1: inducing factor of macrophage-1 colonisation; HGF: hepatocyte growth factor; FGF: fibroblast growth factor; GDNF: glial-derived necrotic factor.
Source: Adapted from (4).

These include:

1) Point mutations of a proto-oncogene, where substitution of a single base by another base is translated by substituting an amino acid in the oncoprotein (e.g. *RAS* oncogene). These alterations often lead to uncontrolled, continuous activity of the mutated protein (4).
2) Chromosomal translocation of a proto-oncogene from a location that cannot be transcribed to an adjacent location where it can be transcribed and produce fusion genes that relay

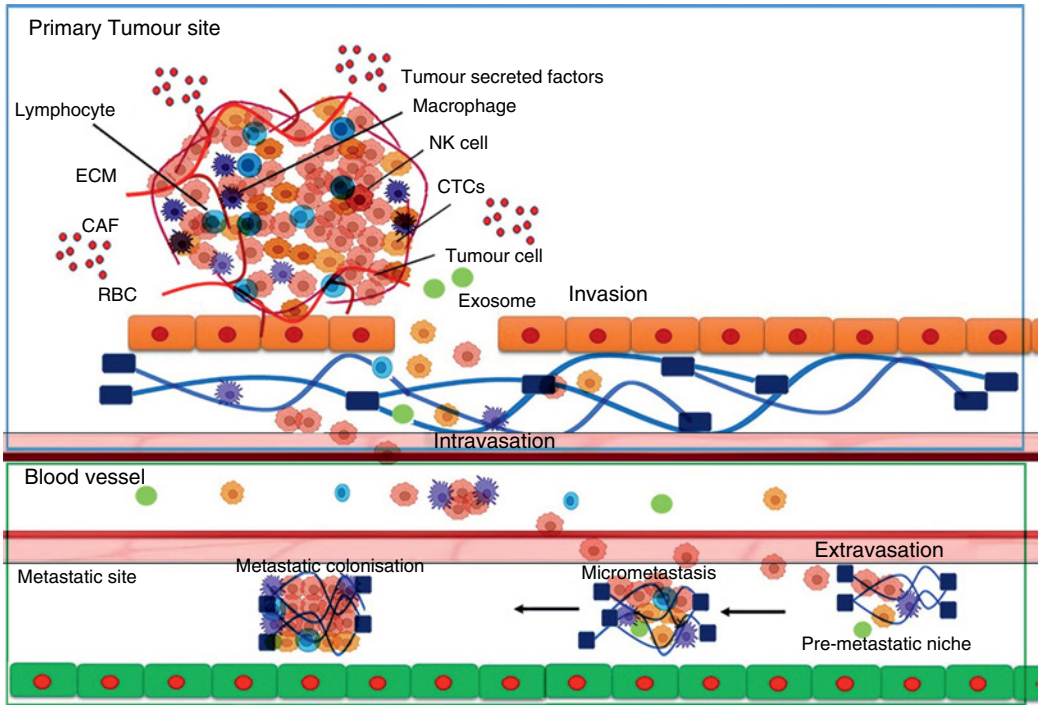

Figure 24.2 Key steps of metastasis. *Source:* Adapted from Sulekha Suresh and Guruvayoorappan (22).

the epithelial–mesenchymal transition (EMT) (22). The EMT program is a spectrum of transitional changes between epithelial and mesenchymal prototypes (23). The loss of E-cadherin and reduced expression of claudin and occludin are key events that trigger EMT initiation and promotion of disruption of apical tight junction between cells (22, 23). Further, the complexity of the stromal component of the tumour microenvironment (neutrophils, cancer-associated fibroblasts and regulatory T cells (Tregs)) disrupts matrix metalloproteinases (*MMPs*), which leads to the loss of basement membrane, which in turn allows direct invasion of tumour cells into the stromal environment (22). For example, studies have shown that interleukin-6 (IL-6) secreted by adipocytes in the stromal microenvironment stimulates breast cancer invasion (24).

Intravasation involves invading disseminated tumour cells through the basement membrane to organs via the lymphatic or blood vasculature. This process is considered a critical rate-limiting step, whereby the number of circulating tumour cells is determined through the mediation of carbohydrates, lipids and proteins (22, 23). For example, the interaction between α2β1 integrin receptor and glycosphingolipids facilitates prostate cancer cells' metastatic properties (22). Further, studies have shown that overexpression of *VEGF* by tumour cells can disrupt the endothelial barrier, facilitating endothelial transmigration (22).

Circulating tumour cells are highly invasive and proliferative, primarily tumour cells. However, primary tumour cells must overcome several barriers to colonise a distant site. It is the interaction between circulating tumour cells and microenvironment components that determine the survival and extravasation ability (23). Most circulating tumour cells die when transported in circulation, primarily due to stress, lack of growth factors and cytokines. It is becoming apparent that neutrophils play an essential role in cell-cluster formation, improving survival chances (22, 25). These complexes have been shown to have increased metastatic potential in breast cancer and are thought to be

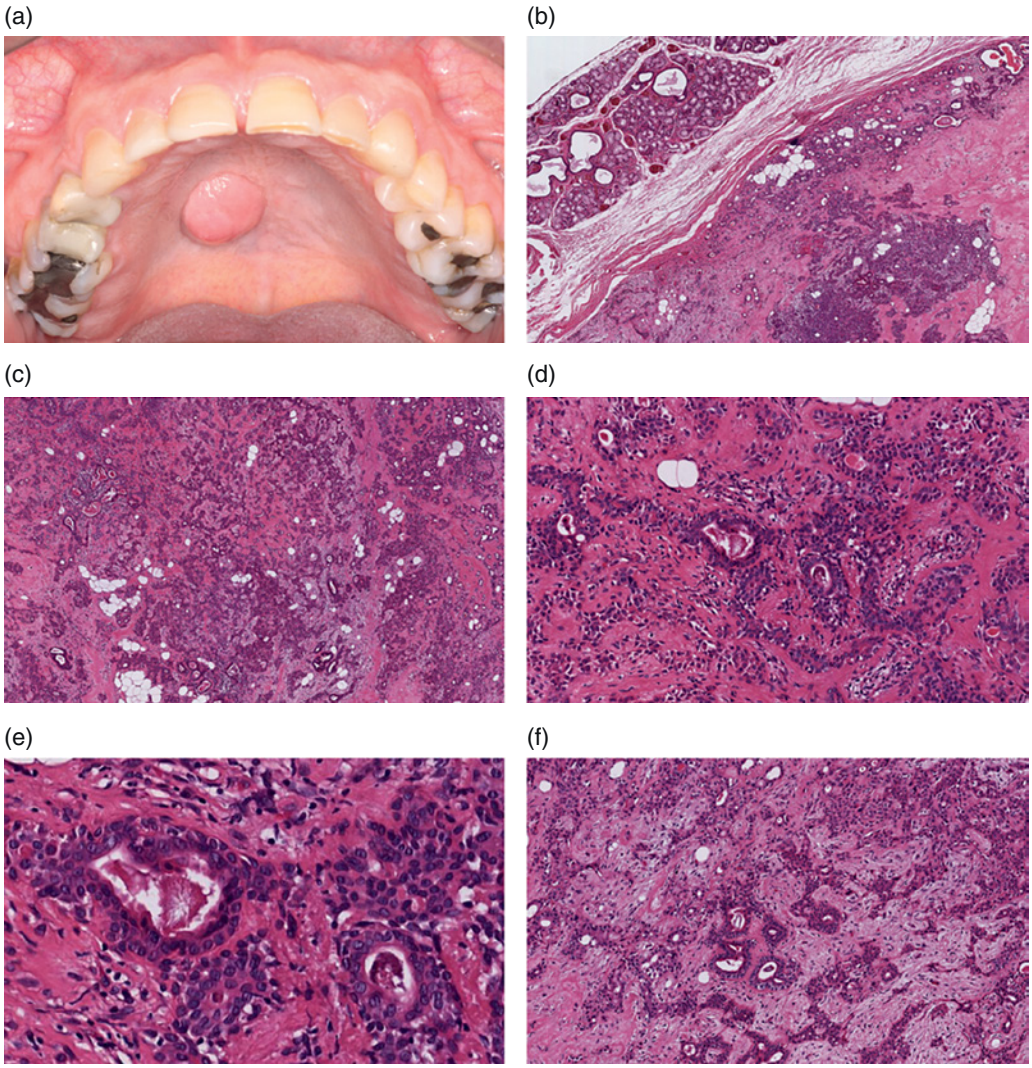

Figure 30.2 Clinical and histopathological aspects of pleomorphic adenoma. (a) Swelling with varying localised colouration on the right hard palate. (b) Well-circumscribed encapsulated lesion associated with a minor salivary gland (hematoxylin and eosin stain, 5×). (c) Tumour proliferation characterised by the proliferation of salivary gland tubules embedded in a fibrous and myxoid stroma (hematoxylin and eosin stain, 10×). (d) Neoplasm composed of salivary gland ducts with a double layer of cells (hematoxylin and eosin stain, 20×). (e) Ducts formed by a double layer of cells, with an outer myoepithelial layer and an inner ductal layer (hematoxylin and eosin stain, 40×). (f) Presence of myxoid matrix with bundles of collagen fibres (hematoxylin and eosin stain, 20×).

30.2.2.3 Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma, characterised by mucous, intermediate and epidermoid cells, sometimes exhibits columnar, clear cell, or oncocytic features (34, 35). Primarily seen in major salivary glands, notably the parotid, it can also occur in minor salivary glands and, rarely, in the sinonasal tract and lungs (34–36). Typically presenting as a painless swelling, palate lesions may be painful with bluish–purplish colouration (34, 37). It is the predominant malignant salivary tumour,

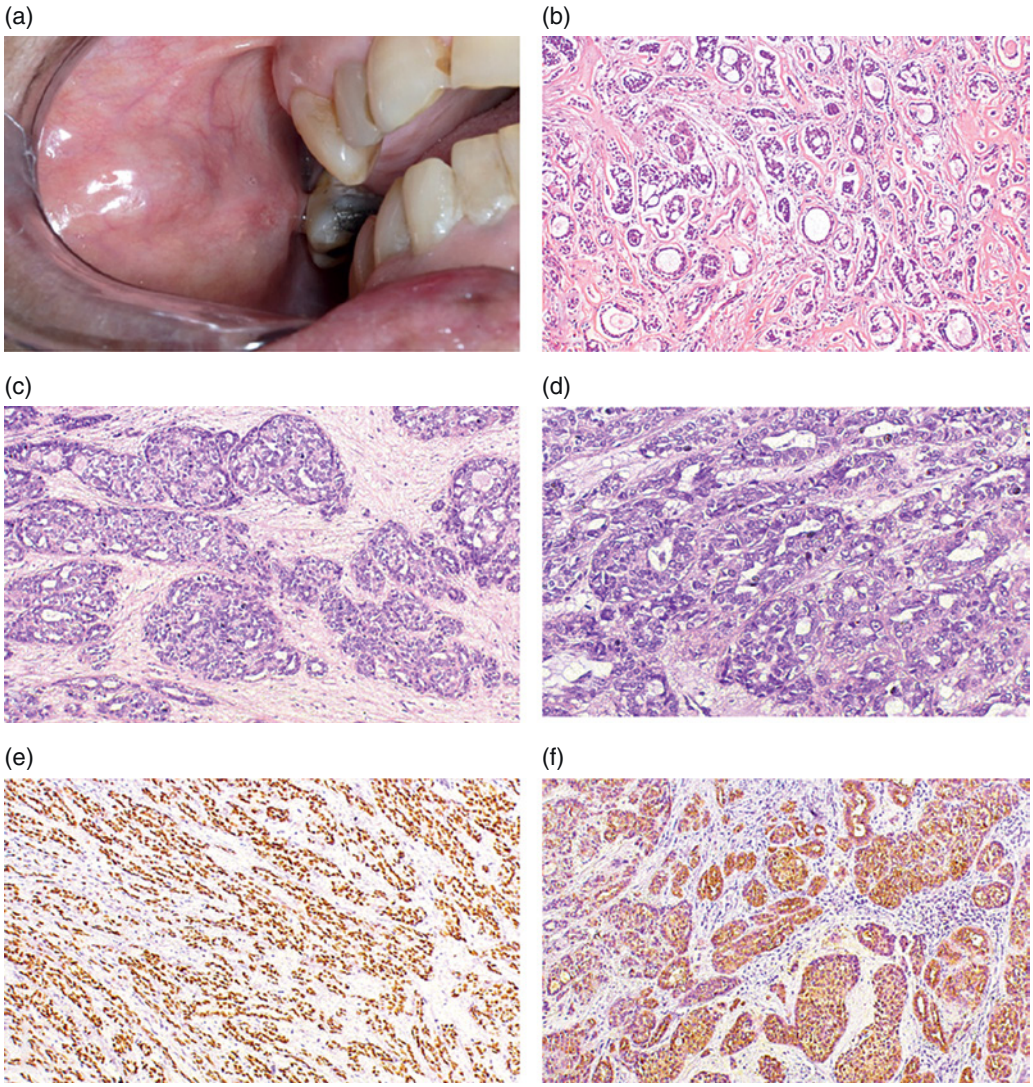

Figure 30.6 Clinical, histopathological and immunohistochemical aspects of polymorphous adenocarcinoma. (a) A bluish swelling in the in the right buccal mucosa. (b) The neoplasm shows a whirling and targetoid arrangement of tumour cells as single columns and tubules (often double-layered) (HE, 10×). (c) The tumour is composed entirely of one type of tumour cells characterised by optic-clearing ground glass-like nuclei with pale chromatin (HE, 20×). (d) The tumour cells are comprised solely of a single variety of tumour cells recognised by nuclei that appear optically clear, resembling a ground glass texture, with light chromatin (HE, 20×). (e) SOX10 positivity in the nuclei of the neoplastic cells (DAB, 20×). (f) S100 diffusely positive in the tumour cells (DAB, 20×).

significant association with these tumours, with pleomorphic adenoma accounting for half of these cases (79, 80). While many salivary tumours seem unaffected by tobacco and alcohol, Warthin's tumour is strongly linked to smoking (81). IgG4-positive plasma cells' prominence in lymphadenomas suggests potential immune involvement (82). Ductal papillomas often emerge in areas like the lower lip, palate and tongue due to oral trauma (83). In contrast, the inverted variant is associated with HPV types 6 and 11 and oral injuries (84). HIV presence also poses a

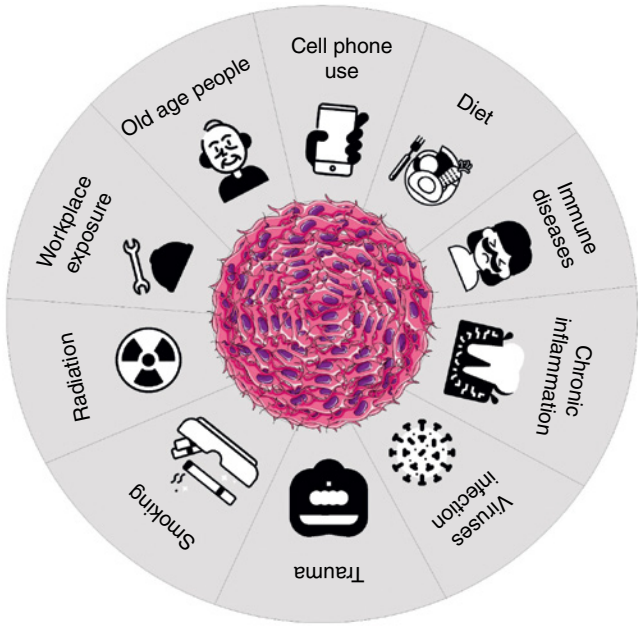

Figure 30.7 Risk factors for salivary gland neoplasm development.

risk for salivary gland cancers, possibly due to a compromised immune system (78–80). Additionally, lymphoepithelial neoplasms have connections to the Epstein–Barr virus (80). Delving into genetics, certain chromosomal shifts, especially around 8q12 and 12q13–15, activate genes like *PLGA1* and *HMGA2*, which are indicative of pleomorphic adenomas and carcinoma ex-pleomorphic adenomas (85, 86).

Ageing, radiation, viruses, genetics and specific occupational risks influence salivary gland malignancies, particularly radiation exposure as seen in atomic bomb survivors and those receiving childhood radiation treatments. Mucoepidermoid carcinoma, notably linked with radiation exposure, is of concern (64, 87). The association between tobacco, alcohol and these malignancies remains debated (65, 88). While the exact role of chronic inflammation in salivary glands is uncertain, autoimmune conditions like Sjögren's syndrome potentially raise non-Hodgkin lymphoma risk, with about 4.3% of cases progressing within 5–10 years (89, 90). Primary squamous cell carcinoma is infrequently observed in salivary glands, setting it apart from other head and neck squamous cell carcinomas, with prior radiation being a chief risk factor for this variant (91, 92). Although major salivary gland melanomas usually arise from metastasis, particularly from the upper face or scalp, there are uncommon instances of melanomas originating solely in the parotid gland. The presence of melanocytes in the parotid's intralobular duct indicates they might initiate these melanomas (93, 94) (Figure 30.7).

30.4 Pathogenesis of Salivary Gland Neoplasms

The pathogenesis of salivary gland tumours is traditionally centred on identifying the originating histologic cell. Reserve cells in adult salivary glands are believed to undergo pathological replication, culminating in the emergence of salivary gland neoplasms (95, 96). Beyond merely identifying the cell of origin, pathologists also focus on cellular differentiation and the spatial configuration of tumour cells during classification. The morphogenic approach,

Three essential elements are needed for cyst formation:

- a source of epithelium
- a stimulus for epithelial proliferation
- a mechanism of growth and bone resorption

The three phases of cyst development:

- Phase of initiation – a source of epithelium and stimulus for proliferation
- Phase of cyst formation – a cyst cavity develops and becomes lined by epithelium
- Phase of growth and enlargement – the cyst enlarges, and growth is accompanied by tissue remodelling and bone resorption

In the case of inflammatory odontogenic cysts, the cyst formation and expansion phases are well-understood (Figure 31.1). However, when it comes to developmental cysts, the underlying mechanisms are less clear, and various theories have been proposed, including aberrant developmental processes, genetic abnormalities and neoplasia.

31.5.2 The Source of the Epithelial Lining

The lining of odontogenic cysts originates from epithelial remnants that persist in the tissues after the completion of tooth formation (Figure 31.2). In most non-odontogenic cysts, the lining derives from remnants of ductal epithelium or epithelial inclusions remaining after fusion of the palatal shelves. Table 31.2 summarises the source and developmental origin of epithelium for each cyst type.

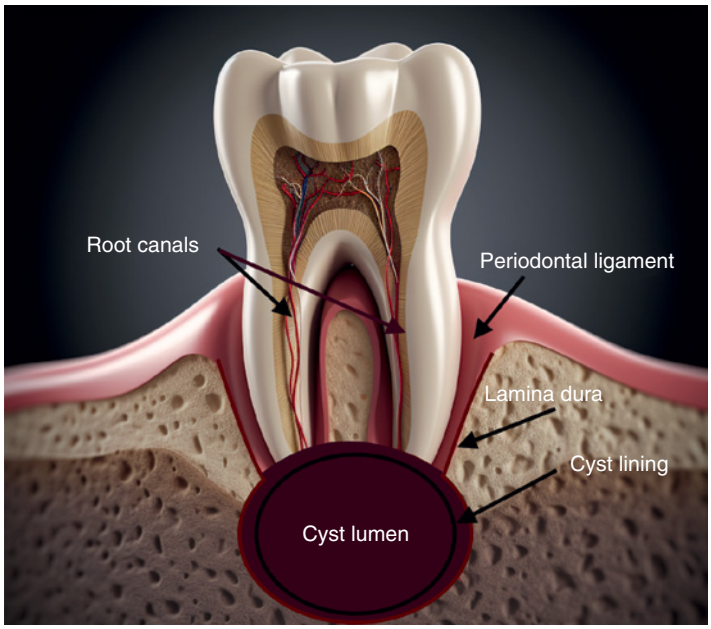

Figure 31.1 A schematic depiction of a radicular cyst. Originating from the Malassez rest cells in the periodontal ligament, the cyst is within the lamina dura. The cyst's corticated boundary seamlessly aligns with the lamina dura.

odontogenic cyst and intraosseous mucoepidermoid carcinoma. These lesions may show similar histology, and distinguishing between them can be difficult, especially on small biopsies. Mucoepidermoid carcinomas often exhibit MAML2 rearrangements, and the detection of these rearrangements assists in distinguishing intraosseous mucoepidermoid carcinoma from glandular odontogenic cysts, as the latter does not display this translocation (30).

While their utility in routine diagnosis is still evolving, these molecular approaches can enhance our understanding and identification of odontogenic lesions.

31.6 An Overview of the Diagnostic Process

An accurate cyst diagnosis can be complex, requiring careful thought and common sense. It is rarely possible to reach a precise diagnosis without careful correlation of the clinical, radiological and histopathological features (Figures 31.3 and 31.4).

The most common clinical presentation is a swelling of the jaw. Still, many cysts are discovered by chance during radiological examination for other reasons, such as orthodontic

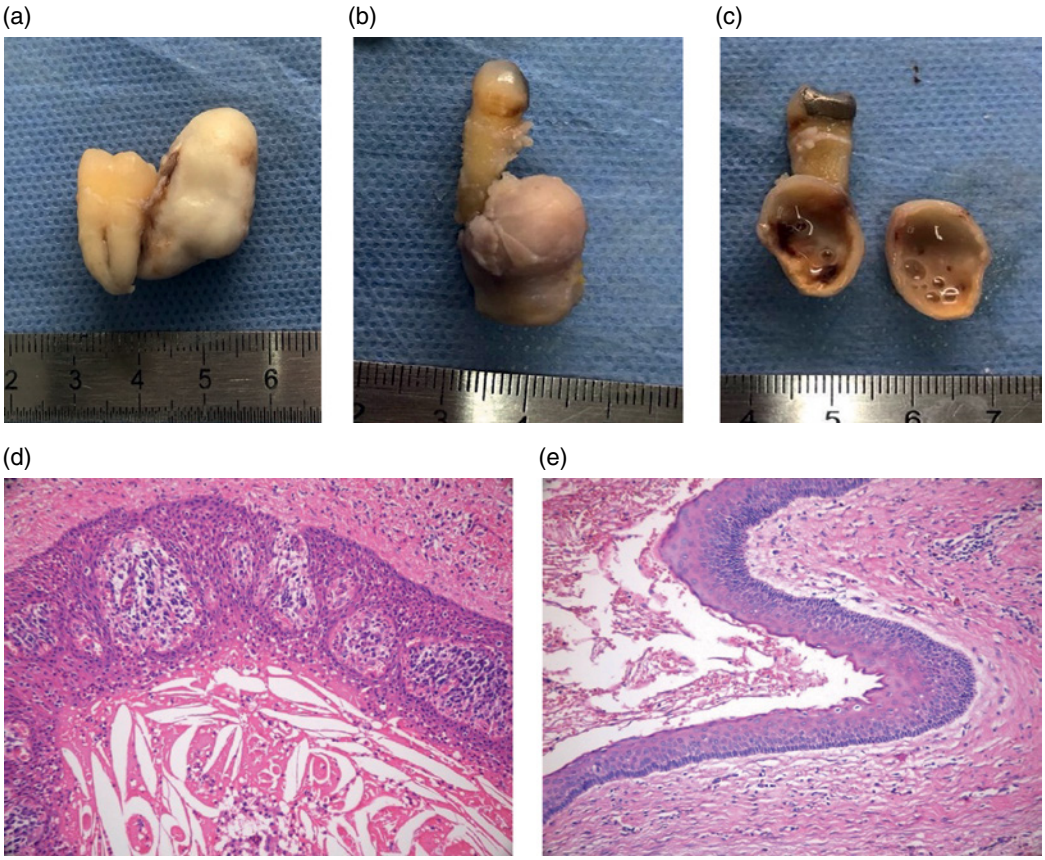

Figure 31.3 Gross and histopathological samples of odontogenic cysts. (a,b) Cystic structures in the form of a sac can attach to different regions of the teeth. (c) a cavity filled with liquid or semi-liquid material or gas can be seen in the cut surface. (d) A classic lining of an inflammatory cyst shows proliferating epithelium forming arcading anastomoses with each other and cholesterol clefts (H&E × 100). (e) If there is no inflammation, the lining epithelium can be diagnostic; here, the classic palisading in the basal layer and parakeratosis on the surface are observed for odontogenic keratocyst (H&E × 100).

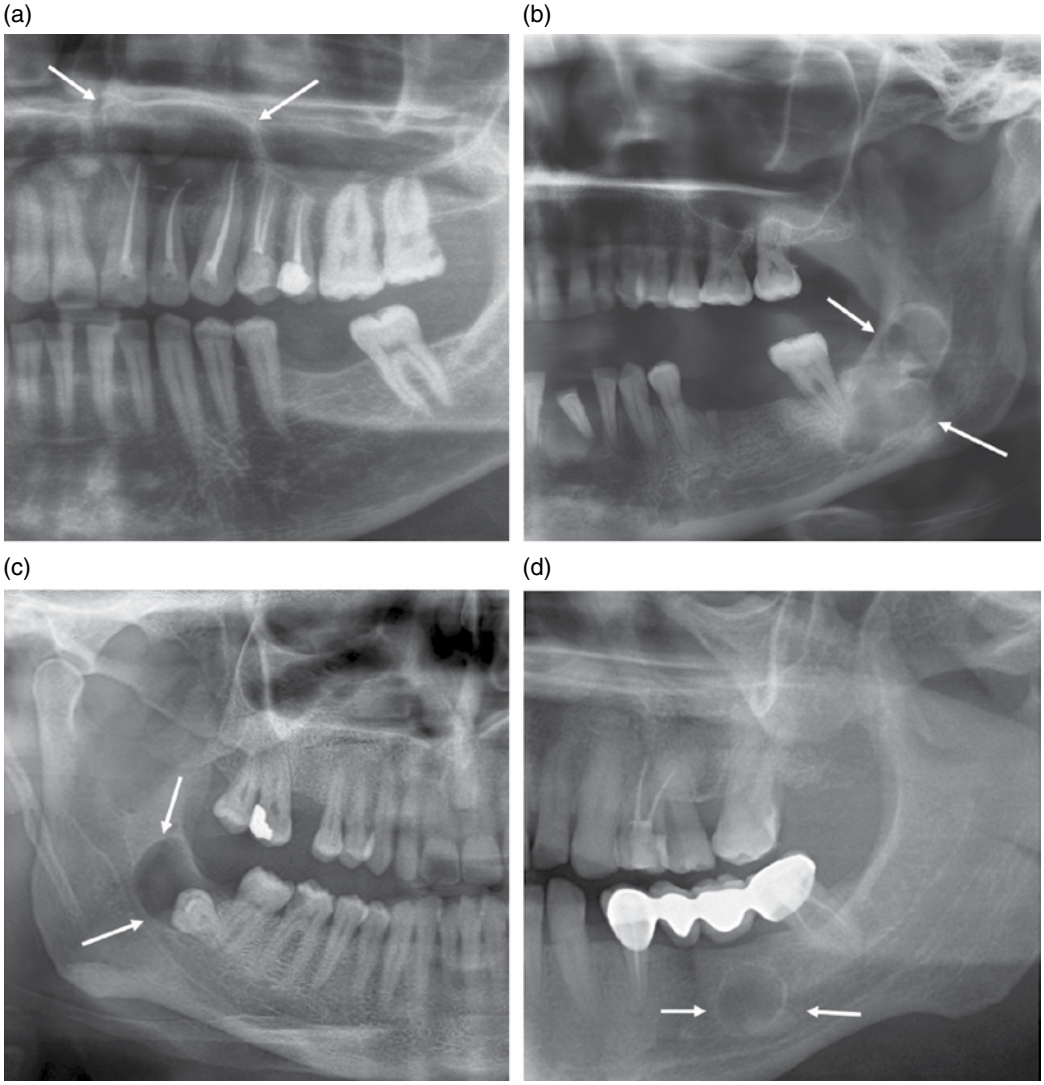

Figure 31.4 Cropped panoramic X-rays show different cyst features important for differential diagnosis. (a) A radiolucent lesion with well-defined borders accompanying non-vital teeth is most likely suggestive of a *Radicular cyst*. (b) The multilocular radiolucent lesion, due to its location and growth in the anterio-posterior direction, is characteristic of an *Odontogenic Keratocyst*. (c) The first consideration should be a Dentigerous Cyst in a radiolucent lesion surrounding the embedded tooth and attached at the enamel-cementum junction. (d) Other developmental cysts are also considered in an edentulous area, along with a Residual Cyst. (Arrows indicate the lesions.)

assessment or following trauma. One of the main diagnostic clues is the relationship of the cyst to the teeth, but most cysts also have characteristic demographic features and locations within the jaws. These are summarised in Table 31.3. Typically, for example, a radicular cyst is found in adults in the anterior maxilla and presents as a round radiolucency at the apex of the tooth root. In contrast, a dentigerous cyst is more often seen in adolescents in the third molar region and surrounds the crown of an unerupted tooth. However, these common features are not specific, and an accurate diagnosis can rarely be made based on clinical or radiological features alone (Table 31.4).

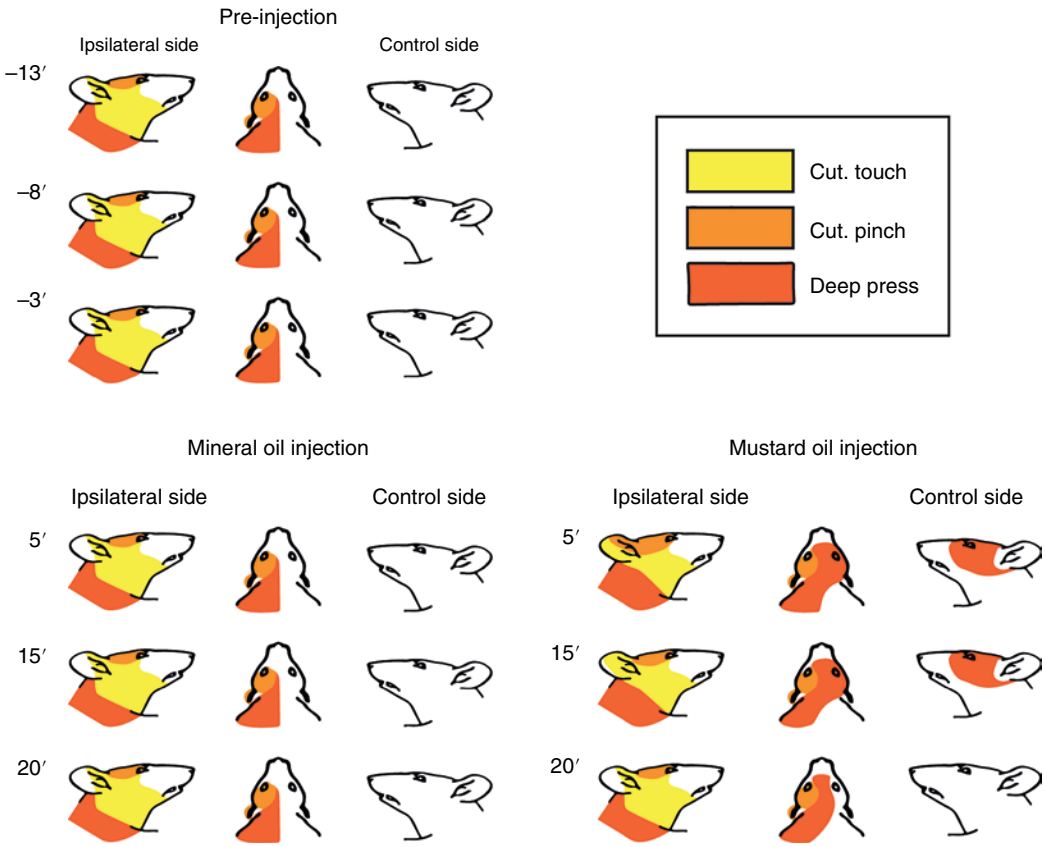

Figure 34.5 Trigeminal central sensitisation reflected through extensive mechanoreceptive field expansion induced by injection of the inflammatory irritant mustard oil into a masticatory muscle. The neuron manifesting this parameter of central sensitisation was recorded in the trigeminal subnucleus caudalis and was a wide dynamic range neuron since it could be activated by both innocuous tactile stimulation and noxious pinch stimulation of the posterior facial skin; it could also be activated by strong pressure stimulation of cervical deep tissues. In the control condition (prior to injection), the mechanoreceptive field was limited to the ipsilateral side and was stable for several minutes and did not change when the vehicle for mustard oil (mineral oil) was injected; however, within 5 minutes of the inflammatory irritant mustard oil injection, the mechanoreceptive field expanded to 143%, 187% and 140%, for pinch, touch and deep pressure stimuli, respectively, encompassing both the ipsilateral and contralateral facial and cervical regions. *Source:* Adapted from Sessle (3).

cannabinoid receptors (e.g. cannabinoid type 2) and glutamatergic receptors (e.g. NMDA). Nociceptive afferent endings (i.e. nociceptors) express one or more cell membrane receptors that can respond to the mediators (3, 48). Most of these mediators and associated receptor processes are excitatory, but some of the released mediators (e.g. GABA, cannabinoids and opioids) may depress the excitability of the nociceptive afferent endings.

The changes in excitability are not localised to the trigeminal nociceptive afferent endings in the damaged or inflamed tissue, but the mediators can spread beyond the region of injury or inflammation to modulate the excitability of other nociceptive afferent endings; thus even undamaged afferents may also be sensitised and send abnormal ectopic afferent inputs to the TBSNC (3, 11, 39). Furthermore, in the case of a nerve injury, some of the undamaged afferents may continue to innervate their peripheral receptive fields, but some may sprout locally to innervate fields left vacant by the injury. This leads to the newly sprouted afferent nerve endings sending signals to the TBSNC with abnormal