Shafer • Hine • Levy

Shafer's *Textbook of* Oral Pathology

TENTH EDITION

10th Anniversary Edition

Adaptation Editor
B Sivapathasundharam

ELSEVIER

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Foreword

It is a distinct honor and privilege to have been asked to write a Foreword to the 10th edition of *Shafer's Textbook of Oral Pathology*. More than 50 years ago, during my third year of undergraduate training at the University of Bombay, the first edition of the *Textbook of Oral Pathology* by Shafer, Hine, and Levy was my "bible." It inspired me to take up oral pathology as a career, which I pursued in the early 1970s at the University of Bombay. This first edition remains the most precious book among my collections of books even today. I am delighted that this book has seen nine editions since its first edition and is being revised for the 10th time.

Exponential growth in the knowledge available to dental students today creates considerable challenges in learning clinical skills in dental school clinics. This book is primarily aimed at dental students in India and other neighboring countries, where dental students encounter a wide range of oral diseases in their clinical years of training. Professor B. Sivapathasundharam, with his extensive experience and deep knowledge of the subject matter, has done a commendable job editing the previous five editions. This edition is another excellent example of a job well done. He has retained the principles and style established in the first edition by Professors Shafer, Hine, and Levy in 1958 and added substantial knowledge-based evidence available in the contemporary literature. This updated edition has 26 chapters covering a range of oral diseases. All chapters are well-written by experienced teachers, and clinical, radiographic, and histopathologic images richly supplement the text. Providing a diagrammatic representation of the histopathology of important oral lesions is a welcome idea. This updated edition presents essential knowledge according to the requirements of the standard international curriculum, allowing dental schools to recommend it as a standard text. Elsevier India has done an excellent job as publisher producing a top-quality book.

I have absolutely no doubt that this book will be received favorably worldwide. In the South Asian region, where the oral disease burden is heavy, it will continue to be considered an "encyclopedia" in scope for all undergraduate and postgraduate dental students. Professor Sivapthasundharam and his team of contributors should be congratulated for the 10th edition of *Shafer's Textbook of Oral Pathology*.

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Preface to the Tenth Edition

As the editor of this prestigious *Shafer's Textbook on Oral Pathology* for consecutive six editions, I am delighted to present this comprehensive and meticulously crafted resource to the dental fraternity. This book represents a culmination of collective expertise and extensive research from esteemed contributors in the field of oral pathology, aimed at providing a definitive guide to the intricacies of oral lesions and pathology.

Throughout my career, I have witnessed firsthand the evolving landscape of oral health care and the pivotal role pathology plays in understanding the diagnosis and treatment. This textbook is a testament to our commitment of disseminating knowledge, fostering a deeper understanding of oral diseases, and equipping dental professionals with the necessary tools to deliver ideal patient care.

Each chapter in this textbook is authored by specialists who bring their unique insights and clinical experiences, ensuring that readers receive a comprehensive and up-to-date exploration of oral pathology. From developmental disturbances and neoplasms to infectious diseases, dental caries, and systemic conditions affecting the oral cavity, every aspect is meticulously covered to provide a thorough understanding.

Furthermore, this textbook includes diagrammatic representations that illustrate the histopathological features of key oral lesions, enhancing comprehension and aiding in clinical decision-making. It is my belief that these visuals will serve as valuable educational tools for students and teaching faculty alike.

I am deeply grateful to all the contributors who have dedicated their time and expertise to this project. Their commitment has been instrumental in shaping this textbook into a definitive reference that reflects the latest advancements and best practices in oral pathology.

It is my hope that this textbook will serve as a beacon of knowledge, inspiring curiosity, and fostering excellence in oral health care. May it empower future generations of dental professionals to navigate the complexities of oral pathology with confidence and compassion. Thanks to my wife Dr S. Rohini and my children for sacrificing their family time and helping me out in the making of this book.

B. Sivapathasundharam

Preface to the First Edition

ORAL PATHOLOGY represents the confluence of the basic sciences and clinical dentistry. Since it has no methods of its own, knowledge in this field is acquired through the adaptation of methods and disciplines of those sciences basic to dental practice, such as gross and microscopic anatomy, chemistry, microbiology and physiology, and through information obtained by clinical histories and observation of patients. Through the science of oral pathology, an attempt is made to correlate human biology with the signs and symptoms of human disease. The oral pathologist attempts to understand oral disease so that it can be properly diagnosed and adequately treated.

In this text we have attempted to bring the reader to an understanding of the patient and his problems through applied basic science. We have tried to explain clinical signs and symptoms in the light of known histologic, chemical and physiologic alterations. Where possible, the prognosis of each disease is considered as a reflection of the underlying tissue changes and what we know can be done about them today.

In numerous sections of the text we have attempted to integrate information from many of the basic sciences for adequate diagnosis of oral disease. This approach is a departure from that of the usual textbook of oral pathology, representing an effort to place more emphasis on the physiologic and chemical aspects of oral disease.

The references at the end of each chapter are extensive enough to be of value to those interested in additional reading. Only those papers which constitute good review articles or exceptional discussions or which are of historical importance are included. Because the field of oral pathology is large, much of the bibliographic material has had to be curtailed or omitted. The highlights alone have been stressed. It is our hope that this book will prove to be a stimulus to study as well as a guide for undergraduate and postgraduate students and practitioners of both dentistry and medicine.

The Authors

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My sincere thanks to my colleagues and friends: Ajay Reginald, Anisha Cynthia Sathyasekar, Dulkanti Santhosh Reddy, Einstein T. Bertin, E. Elakeya, Georgia Benitha J, Helen James, Jaideep Mahendra, Jose Joy Idiculla, Karthiga Kannan S., Madhavan Nirmal, Manikandhan R., Pooja PDCH, Pratibha Ramani, Pritam Panja, Ragu Ganesh, Ramakrishnan T., Rajeshwari M.R.C., Sriram G., Sujatha G., Saraswathi Gopal, Saraswathi T.R., Spencer Lilly D., Anna P. Joseph, C. Venugopal, P.K. Rajeesh Mohammad, Sabupaul, Saleem Shaikh, Sivakumar G., Sivaramakrishnan M., Sunil Kumar Kothawar, Twinkle S. Prasad, Vidyarani Bhat, Vasanthi Vinod (former PG student of Prof. Umadevi K. Rao), Gnanambigai Kalaimani, Paavai Ilango, Pavani, Sridhar, Tamilarasan, and Sangeeta Malik from Subharti Dental College, Meerut, for their unstinted support in literature and photograph search, website browsing, proof correction, and data entry.

Special thanks to my former colleagues Manoj Prabhakar and Protyusha Guha Biswas for their help in preparing certain parts of the text, and E. Elakeya, Tutor, Priyadarshini Dental College, for meticulous proofreading. Without their active participation and help, this edition would have been impossible to complete. Thanks to Ms. S. Nivesha for the diagrammatic representation of the selected photomicrographs.

Additionally, I thank my wife Dr. Rohini Sivapathasundharam for her continuous help, support, encouragement, and for sacrificing the personal and family time. I also extend my gratitude to Thiru V. G. Raajendran, Chairman, and Smt. Indira Raajendran, Managing Director, Indira Educational and Charitable Trust, for their constant encouragement and support.

I also thank my former colleagues Dr. Kavitha Bottu, Dr. M. Preethi, Dr. Preethi Sundaraman, Dr. B. Sabari, Dr. Padmapriya, Dr. Karthik K., and Dr. Selvaganesh for their help in updating the text. Thanks to the Elsevier India team, especially Ms. Priyanka Raina Dhar and Mr. Anand K. Jha, for their active contribution and cooperation in publishing this book.

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Agnathia	Since birth No gender predilection	Maxilla/mandible	Partial or complete absence of maxilla or mandible with abnormally positioned ears	N/A	N/A	12
Micrognathia (congenital or acquired)	*Congenital:* Since birth No gender predilection *Acquired*- postnatal, due to disturbance in the TMJ	Maxilla/mandible	Maxilla: Retraction of the middle third of face, mouth breathing Mandible: Severe retrusion of the chin, a steep mandibular angle, and a deficient chin button	N/A	N/A	12
Pierre Robin syndrome	Since birth Equal sex distribution	-	Micrognathia, cleft palate, and glossoptosis Combination of micrognathia and glossoptosis causes severe breathing difficulties Bifid uvula, cleft palate, otitis media, nasal deformities "**Bird face**" appearance, dental and hearing deformities are also noted			12
Macrognathia	Since birth; no gender predilection	Maxilla/mandible	Abnormally large jaws, may be associated with Paget disease, acromegaly, leontiasis ossea			13
Treacher Collins syndrome: Franceschetti syndrome (mandibulofacial dysostosis) Defect in chromosome 5q32–q33.1	Since birth, equal sex distribution		Bird-like or fish-like faces Hypoplasia of facial bones, malar bones, and mandible Macrostomia, high palate, malocclusion of teeth; horizontal fistulas between the angle of the ears and mouth Facial clefts, and other skeletal abnormalities			14
Facial hemihypertrophy	Since birth, no gender predilection	One side of the body	Unilateral macroglossia, enlargement of one side of the body, unilateral increase in the size of dentition in three aspects: crown size, root size and shape, rate of development Velvety, soft, pendulous folds on the affected buccal mucosa		Neurofibromatosis; fibrous dysplasia of jaws	15

Facial hemiatrophy (Parry–Romberg syndrome)	Starts in the 1st decade till 3 years followed by a quiescent stage No gender predilection		Painless cleft near the midline of the face "coup de sabre," atrophy of skin, lips, tongue, muscles, bones, cartilage, soft palate on the affected side, retarded eruption of teeth, incomplete root formation Facial deformity		Posttraumatic fat atrophy Hemifacial macrosomia Goldenhar syndrome	16
Cleft lip and palate **Cleft lip** (CL): Defective fusion of the medial nasal process with the maxillary process **Cleft palate** (CP): Failure of fusion of the palatal shelves	Since birth; CL – male predilection CP – female predilection CL + CP – male predilection	Lips, nostril, hard and soft palate, uvula	Unilateral or bilateral CL, left side common A complete CL extends upward into the nostril Incomplete CL does not involve the nose Often missing lateral incisor CP may involve the hard and soft palates or the soft palate alone Minimal manifestation of CP is a cleft or bifid uvula	Difficulty in eating and drinking, speech and mental trauma		17
van der Woude syndrome (deletion of chromosome band 1q32)	Since birth; no gender predilection	Lip and palate	Cleft lip or palate and lip pits on lower lip, missing teeth, bifid uvula			21
Double lip (congenital or acquired)	Since birth No gender predilection	Lips Common in upper lip	Redundant fold of tissue on the upper lip, "cupid's bow" appearance, unnoticeable at rest Associated with Ascher syndrome	Microscopically, normal structures Abundance of minor salivary glands		22
Miescher–Melkersson–Rosenthal syndrome	No sex predilection	Lips, cheeks	Cheilitis with facial palsy and fissured tongue	Chronic inflammatory granulomatous reaction	Insect bites Sarcoidosis	23
Pigmented cellular nevus (congenital and acquired) **Acquired:** Junctional nevus (high malignant transformation rate) Compound nevus Intradermal nevus Spitz nevus Halo nevus Blue nevus	Anywhere in the oral cavity, palate most common site	Asymptomatic Solitary, flat, or raised lesions	Asymptomatic, solitary, flat or raised lesions Brown, brownish black or black in color	Proliferation of small, ovoid cells (nevus cells) and melanin pigmentation arranged in small, round aggregates (nests/ thèques) either within the epithelium or connective tissue at the junction Based on the type, *i.e.,* junctional, compound, intra-dermal, or blue		24
Peutz–Jeghers syndrome	Since birth Male predilection	Pigmentations in perioral, perinasal areas, fingers, and toes Intraorally buccal mucosa	Multiple, brown patches in skin and all over the mucosa No increase in size or shape History of intestinal polyposis	Deposits of melanin pigments in the basal layer of epithelium	Physiological pigmentations Malnutrition Smokers melanosis Addison disease Postmenopausal pigmentation	28

Continued

Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features/ Clinical Implications	Differential Diagnosis	Page Number
Oral melanotic macule	Any age; female predilection	Commonest – vermillion border of lower lip	Solitary, well-demarcated, uniformly tan to dark-brown, and flat lesion Asymptomatic, round or oval macule with a diameter of 7 mm or smaller Does not grow in size	Increased melanin/ melanocytes in the basal and parabasal layers Elongated rete pegs Melanin incontinence in the connective tissue	Malignant melanoma Pigmented nevus Peutz–Jeghers syndrome	26
Fordyce granules	Since birth; no gender predilection	Bilateral buccal mucosa opposite to the molar teeth	Small yellow spots, separated or as submucosal papules	Heterotopic collection of sebaceous glands		28
Macroglossia (associated with Beckwith–Wiedemann syndrome)	Since birth; no gender predilection	Tongue	Enlargement of tongue	Noisy breathing Drooling, difficulty in eating Open bite Mandibular prognathism		31
Ankyloglossia (tongue tie)	Since birth; male predilection	Ventral surface of the tongue	Tongue fused to the floor of the mouth	Speech defects Anterior open bite Difficulty in swallowing		31
Fissured tongue (scrotal tongue)	Since birth; male predilection	Dorsal surface of the tongue	Multiple grooves, or furrows, on the dorsal surface of the tongue Associated with geographic tongue; may be a component of Miescher–Melkersson–Rosenthal syndrome	Hyperplasia of the rete ridges Loss of filiform papilla; neutrophilic microabscesses		33
Median rhomboid glossitis (central papillary atrophy)	Present since childhood Male predilection	Posterior midline of the dorsum of tongue	Rhomboid – shaped, smooth erythematous mucosa lacking papilla or taste buds	Smooth or nodular surface covered by atrophic stratified squamous epithelium Chronic inflammatory response		33
Benign migratory glossitis (geographic tongue)	Since childhood Female predilection	Anterior two-thirds of the dorsal tongue	Constantly changing pattern of serpiginous white lines surrounding areas of smooth depapillated mucosa	Hyperparakeratosis, spongiosis, acanthosis, and elongation of the epithelial rete ridges Munro abscess	Candidiasis, erythroplakia	34
Lingual thyroid nodule	Since birth, female predilection	Posterior dorsal tongue	Deeply situated nodular mass; smooth surface	Normal thyroid tissue of embryonal type		36
Aplasia	Since birth; no gender predilection		Unilateral or bilateral absence of one or group of salivary glands			39
Hyperplasia of palatal glands	Since birth No gender predilection	Hard palate, junction of hard and soft palate	Small localized swelling Asymptomatic	Normal mucous acini with the usual intermingling of normal ducts		40

Developmental Disturbances of Teeth

Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features/ Clinical Implications	Differential Diagnosis	Page Number
Microdontia (small tooth) Generalized Localized: Single-tooth microdontia	Permanent dentition; female predilection	Affects all teeth Maxillary lateral incisor (**peg lateral**), maxillary third molar common	Teeth are smaller than normal or slightly smaller than normal teeth in larger jaws	No alteration in structure Esthetic compromise	Conical form of supernumerary tooth	41
Macrodontia (big tooth) Single-tooth or localized macrodontia	Permanent dentition No sex predilection	Affects all teeth Rare Seen in hemihypertrophy of face	Teeth are larger than normal or normal teeth in smaller jaws	Esthetic compromise		42
Gemination (double teeth)	Affects deciduous and permanent dentition No sex predilection	Commonly involves maxillary and mandibular incisors	Splitting of a single tooth germ results in incomplete formation of two teeth Two completely/incompletely separated crowns Single root and root canal	Esthetics Problem during endodontic treatment and extraction		42
Twinning	No sex predilection		Equivalent structures produced by splitting of one normal and one supernumerary tooth	May cause crowding		42
Fusion	More common in deciduous dentition No sex predilection	Maxillary anterior region	Union of two adjacent tooth germs Fusion of two teeth completely or union of roots alone Confluent dentin; separate or fused root canals Union of normal and supernumerary tooth with mesiodens or distomolar	Extraction and endodontic treatment is difficult Periodontal problems		42
Concrescence: A type of fusion occurs in roots of adjacent teeth	Permanent dentition No sex predilection	Posterior maxillary region	Fusion of teeth by cementum; resorption of interdental bone; union of roots by excessive cementum deposition	Extraction is difficult		43
Dilaceration (bent tooth)	Permanent dentition No sex predilection	Permanent maxillary incisors Permanent mandibular anteriors	Abnormal curve or bend anywhere along the length of the tooth May affect crown or root Caused by trauma during development	Difficulty in extraction and endodontic treatment		44

Continued

Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features/ Clinical Implications	Differential Diagnosis	Page Number
Talon cusp	Permanent dentition No sex predilection	Maxillary or central incisors commonly involved Also seen in maxillary laterals and canines, mandibular central and lateral incisors	Well-delineated additional cusp in the lingual surface Extends from the cingulum area to half the distance from the CEJ to the incisal edge	Problem in occlusion, causing enamel fracture or exposure of dentin and pulp		44
Dens in dente (dens invaginatus, invaginated odontome)	Permanent dentition No sex predilection	Mostly seen in permanent maxillary lateral incisors Also in central incisors, premolars, canines, and molars	Deep surface invagination of the crown or root Lined by enamel Tendency for pulpal death and periapical pathosis	Misnomer – tooth in tooth Difficulty in endodontic treatment		44
Dens evaginatus (Leong premolar, evaginated odontome)	Permanent dentition No sex predilection	Predominantly involves mandibular premolar; also seen in, mandibular molars, maxillary central, or lateral incisors	Accessory cusp or globule of enamel on the occlusal aspect	Occlusal accommodation Enamel fracture		45
Enamel pearl (enameloma)	Permanent dentition No sex predilection	Roots of maxillary molars, mandibular molars Furcation area	Ectopic formation of enamel in the form of globule Occurs in the cervical third of root	Formed by misplaced ameloblasts		46
Taurodontism (bull-like tooth)	Permanent dentition No sex predilection	Multirooted tooth Second and third molar commonly involved	Enlargement of the body of the tooth at the expense of the root Increased height of the pulp chamber Furcation of roots close to apex Rectangular shape of teeth Crown appears normal	Excess cementum deposition around the periphery of the root Cellular cementum, along entire root or at the apex	Kleinfelter syndrome	46
Supernumerary roots (extra roots)	Deciduous and permanent dentition No sex predilection	Maxillary and mandibular molars, mandibular cuspids and premolars	Development of increased number of roots compared to normal Divergent or small	May pose problem during extraction and endodontic treatment		48
Anodontia (missing tooth-total or partial)	Deciduous and permanent dentition No sex predilection	Any teeth	Total absence of teeth	Common in hereditary ectodermal dysplasia		48
Hypodontia or oligodontia		Lateral incisors may be missing	Lack of development of one or more teeth			49
False/induced anodontia	Any tooth		Missing due to extraction			49
Supernumerary tooth (extra tooth)	Deciduous or permanent dentition Male predilection	Incisors, molars, premolars Mesiodens occurs in between central incisors Paramolar occurs buccal or palatal to molars Distomolar occurs distal to third molar	Excess number of teeth Various forms: Conical, tuberculate, supplemental, odontoma	**Etiology:** Hyperactivity of the dental lamina Multiple impacted supernumerary teeth common in cleidocranial dysplasia, Gardner syndrome		49

Amelogenesis imperfecta (hereditary brown enamel)	Deciduous and permanent dentition No sex predilection	Generalized, diffused involvement of all teeth	Hereditary structural defect in enamel formation Defect in genes forming enamel Yellowish-brown discoloration, pitting, chipping of enamel **Types:** Hypoplastic, hypomaturation, hypocalcified	Disturbance in differentiation of ameloblasts Defect in enamel matrix formation; improper matrix structure and mineralization; alteration in enamel rod and rod sheath structure		52
Environmental enamel hypoplasia	Either dentition No sex predilection	Generalized or single tooth affected	Caused by environmental factors Nutritional deficiencies, exanthematous fever, congenital syphilis, hypocalcemia, local infection, and fluorosis, etc. Alteration in color and structure of affected teeth	Disturbance in the differentiation of ameloblasts Defect in enamel formation Alteration in enamel rods		53
Molar incisor hypomineralization	Permanent dentition No sex predilection	One or more permanent molars and incisors	White to yellowish-brown opacities in the occlusal/incisal third of affected tooth Hypomineralized, soft, porous enamel resembling discolored chalk	Enamel fracture due to masticatory force leading to dentinal sensitivity Higher incidence of dental caries	Enamel hypoplasia Fluorosis Amelogenesis imperfecta White spot lesion Traumatic hypomineralization	
Turner hypoplasia	Permanent dentition No sex predilection	Single tooth; permanent maxillary incisors, maxillary or mandibular premolar	Mild brownish discoloration of enamel to severe pitting; irregular tooth crown	Bacterial infection in the periapical area due to caries or trauma to the deciduous tooth affects the ameloblastic layer of the developing permanent tooth		48
Dental fluorosis (mottled enamel) Due to overexposure of fluoride in drinking water	Deciduous and permanent dentition No sex predilection	Generalized Bilateral	Mild occasional white flecking or chalky appearance of enamel to severe changes like pitting and brownish discoloration, opaque corroded surface, chipping, or even fracture of enamel	Disturbance of ameloblasts during tooth formation Defective enamel matrix formation		55
Dentinogenesis imperfecta	Deciduous and permanent dentition No sex predilection		Bulbous crowns with restriction in the cervical area, "tulip-shape" teeth Fracturing away of enamel due to hereditary defect in dentin formation Blue-gray opalescent teeth, shell teeth Calcified pulp chamber Shortened roots	Disturbance in dentin formation; irregular dentinal tubules; less in number Areas of uncalcified matrix; degeneration of odontoblasts		57
Dentin dysplasia (rootless tooth)			Normal enamel Atypical dentin Abnormal pulp morphology			58

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Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features/ Clinical Implications	Differential Diagnosis	Page Number
Type I (radicular)	Both dentitions		Normal morphology Amber translucency Teeth extremely mobile; premature exfoliation due to short roots Total obliteration of pulp chamber and root canals in deciduous teeth Crescent-shaped pulpal remnant in permanent teeth Yellowish brown or bluish gray translucency; obliteration of pulp chamber	Blockage of normal dentin formation New dentin forms around obstacles "lava flowing around boulders" appearance Multiple periapical radiolucencies		58
Type II (coronal)	Deciduous dentition and permanent dentition		Normal clinical appearance Abnormally enlarged pulp chamber, "**thistle tube**" appearance	Amorphous and atubular dentin in radicular portion Multiple pulp stones		59
Regional odontodysplasia (ghost teeth)	Deciduous and permanent dentition No sex predilection	Maxillary central and lateral incisors and cuspids often involved	Delay or failure in eruption of teeth Change in shape, defective mineralization Marked reduction in radiodensity – "ghost" appearance	Reduction in the amount of dentin; widening of predentin layer, interglobular dentin, and irregular tubular pattern of dentin Calcified bodies in reduced enamel epithelium around unerupted teeth		59
Eruption sequestrum	Permanent dentition; no sex predilection	Mandibular molars commonly involved	Tiny fragment of bone on the crown of erupting permanent molar, spicule within soft tissue, sequestrates through mucosa and lost Slight soreness in the region	Cork-screw fashion of separation of small bone fragments		61
Impacted teeth	Permanent dentition; no sex predilection	Mandibular and maxillary third molars and maxillary canines are commonly involved	Lack of eruption due to some physical barrier in the path of eruption; crowding, insufficient space	Development of dental caries and odontogenic cyst		62
Embedded tooth			Unerupted due to lack of eruptive force			62
Submerged tooth (ankylosed deciduous tooth)	Any age, usually first two decades of life No sex predilection	Any tooth, primary first molar Lower teeth commonly involved	Cessation of eruption after emergence and fusion of cementum or dentin with alveolar bone	Prevents the eruption of permanent tooth		64

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Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features	Differential Diagnosis	Page Number
Dentigerous cyst (follicular cyst)	Majority in 2nd –3rd decade Male predilection	Mandibular and maxillary third molar and maxillary canine regions	Associated with impacted teeth; enlargement of jaw, facial asymmetry, migration of teeth Cortex intact **Radiographically**, radiolucent area associated with the crown of an unerupted tooth Three radiological variations: central, lateral, and circumferential	Two to four layers of stratified squamous epithelium, resembling reduced enamel epithelium, lining the cystic cavity Absence of rete pegs Loosely arranged fibrous connective tissue wall Presence of odontogenic rests	Odontogenic keratocyst Ameloblastoma **Potential complications:** Development of ameloblastoma, mucoepidermoid carcinoma, or squamous cell carcinoma	70
Eruption cyst (eruption hematoma)	Children younger than 10 years No sex predilection	Alveolar ridge, permanent molars and maxillary incisors	Compressible, soft bluish gingival swelling Considered as soft tissue counterpart of dentigerous cyst	Keratinized stratified squamous epithelium lining the cystic lumen Dense connective tissue with chronic inflammatory cells	Gingival cyst Dentigerous cyst	74
Odontogenic keratocyst (OKC)	Majority in 1st–4th decade; male predilection	Posterior body of the mandible and ascending ramus	Pain, swelling, expansion of bone, drainage, paresthesia of lips and teeth **Radiographically**, unilocular radiolucency with well-defined peripheral rim Occasionally, multilocular radiolucency Expansion is usually antero-posterior rather than buccolingual	Corrugated parakeratinized epithelium Uniform thickness of epithelium ranges from 6 to 8 cells thick Palisading basal layers giving a **"tombstone" or "picket fence"** appearance Thin friable connective tissue wall Daughter/satellite cysts in the connective tissue Aggressive Recurrence common	Ameloblastoma Dentigerous cyst Lateral periodontal cyst	66

Continued

Allergic and Immunologic Diseases of the Oral cavity

Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features	Differential Diagnosis	Page Number
Recurrent aphthous stomatitis (aphthae, canker sores) **Etiology**: Genetics, physical and emotional stress, hemolytic *Streptococcus*, iron, vitamin B_{12} deficiencies, hormonal imbalance, allergic factors	Young adults – middle age Female predilection	Anywhere in the oral cavity except anterior hard palate and gingiva 1. Minor – most common 2. Major – severe form (1–10 number of ulcers, heals by scarring) 3. Recurrent herpetiform ulcers – multiple, clusters of ulcers resembling herpetic lesions in the absence of viruses (up to 100 shallow ulcers) 4. Recurrent ulcer associated with Behçet syndrome				563
Sarcoidosis (Besnier–Boeck–Schaumann disease)	Young and middle-aged adults	Lung, skin, lymph node, salivary glands, spleen bones and mouth	Multisystem granulomatous disease with cutaneous lesions – multiple, raised red patches; erythema nodosum and involvement of lymph nodes and salivary gland Oral – small papular nodules on the lips and in buccal mucosa and palate, bleb-like nodules containing a clear yellowish fluid	Granulomas – nests of epitheloid cells with multinucleated giant cells Inflammatory cell infiltrate with T and B cells; later granulomas transforms into a solid, eosinophilic hyaline masses	Tuberculosis Uveoparotid fever	568
Angioedema (Quincke edema)	Hereditary form – symptomatic in second decade	Lips, chin, eyes, lips, tongue, pharynx, and larynx	Soft, tender, diffuse edematous swelling of rapid onset, single or multiple lesion; perioral or periorbital edema are characteristic allergic edema	Increased neutrophils	Lupus erythematosus Bacterial and viral infections Lymphoproliferative diseases	570
Drug idiosyncrasy (stomatitis medicamentosa)	Any age No sex predilection	Skin and oral cavity	Skin lesions (exfoliative dermatitis), arthralgia, fever, lymphadenopathy, and agranulocytosis Oral cavity shows erythema multiforme lesions	Spongiosis and exocytosis of epithelium Vacuolar changes, individual necrotic epithelial cells Inflammatory cells such as lymphocytes, eosinophils, and neutrophils are seen	Lichenoid drug reactions; lupus erythematosus Pemphigus-like eruptions Vincent infection	571

Contact stomatitis with dermatitis		A localized type of allergic reaction in which a lesion of the skin occurs after repeated contact with the causative agent	Itching, burning sensation at the site of contact Gingival lesion appears soft, spongy, with red attached gingiva Oral lesion may appear as vesicles, erosions, and ulcers	Nonspecific, intra- and intercellular edema of the epithelium along with vesicle formation within the epithelium or at the basement membrane Engorged and dilated blood vessels with infiltrate of lymphocytes and plasma cells are also evident Increased number of eosinophils is a common finding in such allergic lesions		572
Perioral dermatitis	Women with high cosmetic usage		Classically, the lesions present in circumoral areas around the lips as papules or papulopustules lesions with a zone of spared skin immediately adjacent to the vermilion border; pruritus may be evident	Chronic lymphohistiocytic dermatitis or rosacea-like pattern is seen	Sarcoidosis	575
Midline lethal granuloma		The peculiar, localized progressive granulomatous lesion involves destruction of the nose, paranasal sinuses, palate, face, and pharynx	Lesion begin as a superficial ulcer of the palate or nasal septum, eventually spreads from the palate to the inside of the nose and then to the outside The palatal, nasal, and malar bones may become involved, undergo necrosis, and eventually sequestrate Lesions precede by a feeling of stuffiness in the nose Lesion may persist for a month or years Purulent discharge from the eyes and nose; perforating sinus tracts may be noticed Death is usually due to exhaustion or hemorrhage if a large blood vessel becomes eroded	Wide necrosis with infiltration of some inflammatory cells and the formation of occasional new capillaries	Carcinoma Wegener granulomatosis	575
Wegener granulomatosis	Any age, common between 4th to 5th decades Male predilection	Multisystem disease, which commonly involves nose, paranasal air sinuses, lower respiratory tract, gut, joints, nervous system, and kidneys	Strawberry gingivitis – presents as ulcerations, friable granular lesions, or as gingival enlargements; the inflammatory process may start in the interdental papilla and spreads rapidly to the periodontal structure and leads to bone loss and tooth mobility Lesions may range as small ulcerations resembling aphthae to diffuse ulcerative stomatitis	Mixed inflammation around the blood vessels; giant cell necrotizing granulomatous lesions showing vasculitis Pseudoepitheliomatous hyperplasia Subepithelial abscesses	Chronic granulomatous disease	576
Chronic granulomatous disease	Infants and children; male predilection	Lymph nodes, lung, liver, spleen, bone and skin, and face	Eczematous lesions of face, abscesses, septicemia, pneumonia, pericarditis, meningitis, and osteomyelitis Oral – diffuse stomatitis, with or without ulcerations Benign migratory glossitis	Ulcerated lesions exhibit small granulomas with mononuclear histiocytes and multinucleated giant cells Central necrosis with polymorpho-nuclear leukocytes are seen	Wegener granulomatosis	576

Oral Aspects of Metabolic Diseases

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Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features	Differential Diagnosis	Page Number
Amyloidosis An abnormal proteinaceous substance that is deposited between cells in a various clinical disorders		Any organ, most common in kidneys, heart, gastrointestinal tract, liver, and spleen Oral cavity – tongue and gingiva	Type A – secondary amyloid seen in inflammatory, genetic, and syndromes Type B – primary amyloid of immune origin, seen in multiple myeloma and macroglobulinemia Type C – amyloid of aging Macroglossia (plasma cell dyscrasias), xerostomia, and xerophthalmia are seen The affected organs are usually enlarged and the cut surface appears gray with a waxy firm consistency	Hyalinized homogenous material often perivascular in distribution Polarized light – Congo red–stained amyloid shows green birefringence AL (amyloid light) and AA (amyloid associated) can be distinguished histologically	Mucopolysaccharidoses	587
Porphyria Anomalies in the pyrrole metabolism resulting in the pathological elevation of porphyrin concentration	Inborn No sex predilection	Multisystem involvement	Two types: **Erythropoietic porphyria**: Photosensitivity, splenomegaly and increased porphyrin in developing erythrocytes **Hepatic porphyria:** Four subclasses: Acute intermittent porphyria, porphyria variegate, porphyria cutanea tarda, and hereditary coproporphyria **Congenital porphyria:** The deciduous and permanent teeth may show a red or brownish discoloration			588
Mucopolysaccharidoses Abnormal degradation of glycosaminoglycans such as dermatan sulfate, keratan sulfate, heparin sulfate, and chondroitin sulfate	Autosomal recessive except MPS-II, which is X-linked	Multiple organs including brain, liver, spleen, heart, and blood vessels	Progressive disorder Coarse facial features, clouding of the cornea, and mental retardation	Intracellular accumulation of mucopolysaccharide (glycosaminoglycans)	Amyloidosis	589

Mucopolysaccharidoses Hurler syndrome (MPS-I, gargoylism)	Chromosome 4p16.3 First 2 year of life and progresses during early childhood and adolescence and terminates before death or usually before puberty	Multisystem involvement	The head appears large and facial characteristics are quite typical, consisting of prominent forehead, broad saddle nose, and wide nostril, hypertelorism, puffy eyelids with coarse bushy eyebrows, thick lips, large tongue, open mouth, and nasal congestion with noisy breathing; corneal clouding, claw hand, and mentally retarded Oral – broadening of mandible with prominent gonions, a wide intergonial distance, gingival hyperplasia, and spacing of teeth	Intracellular accumulation of mucopolysaccharide "**Hurler cells**" – large cells with metachromatically stained cytoplasm, which is either granular or agranular with crescent-shaped nuclei **Reilly bodies** – metachromatic granules in the cytoplasm of lymphocytes		589
Gaucher disease Lysosomal storage disease, characterized by the deposition of glucocerebroside in the cells of monocyte-macrophage system	Autosomal recessive trait Type I – childhood Type II – infancy Type III – juveniles	Macrophage–monocyte system Skeletal, nervous system, spleen, liver, lymph nodes, and oral cavity	Three clinical forms: Type I: Chronic non-neuropathic form in childhood characterized by hepatosplenomegaly, pancytopenia, and skeletal disease Type II: Progressive neurovisceral involvement and results in death at infancy Type III: Norrbottnian form, progressive CNS involvement; bone – pain and restricted mobility Oral cavity – yellow pigmentation of the oral mucosa and petechiae; tendency to bleed as a result of thrombocytopenia	**Gaucher cells** – round pale cell, measuring between 20 and 80 μm in diameter, containing small eccentric nucleus and "**crumpled silk**" cytoplasm	Niemann–Pick disease Letterer–Siwe disease	591
Niemann–Pick disease (lysosomal accumulation of sphingomyelin)	Autosomal recessive trait Type A – infantile Type B – childhood Type C – perinatal-adult age Common in Ashkenazi Jews	Multi-system involvement	Type A – extensive neurologic involvement, visceral accumulation of sphingomyelin and early death Type B – organomegaly but no nervous system involvement; splenomegaly and hepatomegaly are common Type C – heterogenous, visceral and neurologic manifestations	**Niemann–Pick cells** (foamy lipid-laden cells) enlarged cells with foamy cytoplasm (numerous vacuoles)	Gaucher disease Letterer–Siwe disease	591
Letterer–Siwe disease (Langerhans cell disorder)	Before the age of 3	Skin, spleen, liver, lymph nodes, lungs, gastrointestinal tract, and oral cavity	Skin rashes involving the trunk, scalp, and extremities Rashes are erythematous, purpuric sometimes with ulceration; splenomegaly, hepatomegaly, and lymphadenopathy are seen Oral cavity – either ulcerative or gingival hyperplasia are seen; loosening and premature loss of teeth	Histiocytic proliferation with or without eosinophils; foam cells are not seen; altered histiocytes can be seen	Hand–Schuller–Christian disease Histiocytic lymphoma	592

Continued

Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features	Differential Diagnosis	Page Number
Vitamin D–deficient rickets (failure of endochondral calcification)	Juvenile Seen in urban areas	Bones (epiphyseal and metaphyseal plate) and teeth	Bowing of legs, developmental abnormalities of dentin and enamel Delayed eruption, malalignment of the teeth, and high caries index	Wide predentin zone and interglobular dentin are seen		595
Osteomalacia (adult rickets)	Adulthood Common in postmenopausal women	Flat bones and diaphysis of long bones are affected	Softening and distortion of the skeleton and increased tendency toward fracture Pelvic deformities are seen in multiparous women Oral – severe periodontitis	Nonspecific Bone remodeling with inadequate calcification of bone matrix Cortical bone is thin and osteoid borders are found on the trabeculae	Refractory rickets	595
Vitamin D–resistant rickets (familial hypophosphatemia, refractory rickets, phosphate diabetes)	X-linked dominant defect Mutation in PHEX gene	Skeletal system and teeth	Normocalcemia with high-normal PTH levels Bowing of legs, shortening of stature, continuing osteomalacia, and pseudofractures Muscular weakness and atony are prominent Oral – abnormal cementum, poorly defined lamina dura, and hypocalcified dentin	Teeth – widespread formation of globular, hypocalcified dentin, with clefts and tubular defects in the regions of pulp horn Bone – broad zone called rachitic metaphysis	Osteomalacia	595
Hypophosphatasia-deficiency of enzyme alkaline phosphatase	Autosomal recessive trait Three forms: Infantile, childhood, and adult	Skeletal system, pulmonary, renal gastrointestinal, and teeth	Infantile form – severe rickets, bone abnormalities, hypercalcemia, and failure to thrive Childhood – premature exfoliation of deciduous teeth, increased infection, rachitic rosary, and failure of calvarium to calcify Adult – spontaneous fractures and osseous radiolucencies Oral – loosening and premature loss of deciduous teeth	Long bones – increased width of proliferating cartilage with widening of hypertrophic cell zone and formation of large amounts of osteoid Teeth – absence of cementum	Vitamin D–resistant rickets	596
Scurvy (vitamin C deficiency)	Any age No sex predilection	Intercellular ground substance of bone, dentin, and connective tissue	Oral cavity – interdental and marginal gingivae are bright red with a swollen, smooth, and shiny surface Gingiva in fully developed scurvy – boggy and ulcerated Foul smell due to fusospirochetal stomatitis Loss of bone and loosening of teeth	Osteoblasts fail to form osteoid – wide zone of calcified, but nonossified matrix, called the scorbutic lattice, develops in metaphysis; fragile zone develops; **Trummerfeld zone –** zone of complete disintegration; beneath this zone, **Gerustmark –** made up of connective tissue cells	Water-soluble vitamin deficiencies	599

Disturbances in Hormonal Metabolism

Lesion/Disorder	Age/Sex	Site	Clinical Features	Oral Manifestations/ Histologic Features	Differential Diagnosis	Page Number
Hypopituitarism (pituitary dwarfism)	Before and after puberty	Compression or atrophy of anterior pituitary cells	**Pituitary dwarfism** – diminutive but well-proportioned body, fine, silky sparse hair on the head, wrinkled atrophic skin, and hypogonadism Eruption and shedding of teeth are delayed **Hypopituitarism of adults** – infarction of the pituitary called Simmonds disease Characterized by loss of weight and diminished sexual function Decreased salivary flow rate leading to increased caries activity	The eruption rate and the shedding time of the teeth are delayed The clinical crown appears smaller Dental arch and root appear shorter Overcrowding and malocclusions are seen		604
Hyperpituitarism (gigantism/ acromegaly)	Before epiphyseal closure – gigantism After epiphyseal closure – acromegaly	Adenoma of the anterior lobe of the pituitary	**Gigantism** – general symmetric overgrowth of the body; height of over 8 feet; headache, fatigue, muscle and joint pains are seen Organomegaly and hypertension also seen **Acromegaly** – temporal headaches, photophobia, and reduction in vision Terminal phalanges of hands and feet becomes large, and ribs also increase in size	Gigantism – prognathic mandible, class III malocclusion with interdental spacing **Hypercementosis** is a common finding Acromegaly – lips are thick, enlarged tongue, large mandible resulting in prognathism	Somatotropic adenoma or hyperplasia	604
Hypothyroidism	Infancy – cretinism Child – juvenile myxedema Adults – myxedema	Failure of thyrotropic function of the pituitary gland Atrophy or destruction of the thyroid gland	**Cretinism** – mental defects, retarded somatic growth, generalized edema Base of the skull is shortened; sweat glands are atrophic and hair is sparse **Myxedema** – metabolic rate is lowered, swelling and increased blood protein concentration	Cretinism – mandible underdeveloped and maxilla overdeveloped Juvenile myxedema – enlarged tongue, malocclusion, delayed eruption, and retained deciduous teeth Myxedema – lips, nose, eyelids, and subor-bital tissues are edematous and swollen	Hypopituitarism	605
Hyperthyroidism	Exophthalmic goiter and toxic adenoma	Hyperplasia of the thyroid or benign tumor of thyroid gland	**Exophthalmic goiter** – eye signs and hyperplasia of the thyroid Toxic adenoma – increased basal metabolic rate Tremor, tachycardia, sweating, weight loss, nervousness, and muscle weakness Hypertension and heat tolerance are seen	Surprised or excited facial expression Increased sensitivity to epinephrine	–	605
Primary hyperparathyroidism (osteitis fibrosa cystica) Brown tumor	Common in middle age Female predilection	Adenoma, hyperplasia, or carcinoma of parathyroid gland	Pathologic fracture, urinary tract stone, and giant cell tumor of jaw Skeletal lesions and generalized osteoporosis are common; giant cell tumor or cyst of the jaws, malocclusion, and sudden drifting and spacing of teeth **Radiographically:** Ground-glass appearance and loss of lamina dura	Osteoclastic resorption of the trabeculae of the spongiosa, along the blood vessels of the Haversian system Fibrosis of marrow spaces and plump osteoblasts lining the osteoid Osteoclastomas – later stage	Central giant cell granuloma	605

Continued

Lesion/Disorder	Age/Sex	Site	Clinical Features	Oral Manifestations/ Histologic Features	Differential Diagnosis	Page Number
Secondary hyperparathyroidism	Patients with chronic renal failure	Secondary to other disorders mostly end-stage renal disease	Renal failure and bone disease involving jaws and brown tumors	Loss of lamina dura	Osteitis fibrosa cystica	607
Hypoparathyroidism		Surgical removal or congenital absence of parathyroid gland	Metabolically decreased excretion of calcium Increased neuromuscular excitability, tetany, and carpopedal spasms	Aplasia or hypoplasia of teeth, tetany, stiffness, and cramping Altered tooth eruption pattern, short and blunted roots, enamel hypoplasia, and dentin dysplasia Impacted teeth and partial anodontia Circumoral paresthesia Chronic candidiasis		607
Addison disease (chronic insufficiency of adrenal cortex)		Autoimmune destruction of the adrenal gland	Earlier – lethargy, fatigue, and muscular weakness Feeble heart action, general debility, vomiting, diarrhea, and severe anemia are also seen Irregular menstruation and loss of hair are seen in females Pigmentation in skin and mucous membrane, hypoglycemia, dehydration, hypertension, and postural dizziness	A pale brown to deep chocolate pigmentation spreading over the buccal mucosa from angles of the mouth or developing on the gingiva, tongue, and lips – first evidence of the disease		608
Diabetes mellitus (DM) – disorder of carbohydrate metabolism	Insulin dependent (IDDM) (type I – juvenile onset) Noninsulin–dependent (NIDDM) (type II – adult onset)	Type I – immunologically mediated destruction of pancreatic beta cells Type II – maturity onset diabetes	IDDM – thin body build, extreme thirst, hunger, constant urination, and weight loss Glycosuria, polyuria, polydipsia, weakness, and weight loss Ketoacidosis, microangiopathy, and macroangiopathy are the complications	Dry mouth, persistent gingivitis, multiple carious lesions, periodontal disease, and candidiasis Delayed wound healing and dry socket formation Fulminating periodontitis and periodontal abscess formation Vascular changes have been reported		609
Progeria (Hutchinson–Gilford syndrome)	Autosomal recessive trait LMNA gene Normal at birth; later within first few years of life, the disease becomes manifested	Abnormal lamin A protein called progerin makes nucleus unstable leading to cellular instability	Dwarfism and premature senility Alopecia, pigmented areas of the trunk, atrophic skin, prominent veins, and loss of subcutaneous fat High-pitched squeaky voice and beak-like nose Coxa valga – constant feature Early age – resembles a wizened little old person	Hypoplastic mandible Accelerated formation of irregular secondary dentin Delayed eruption of tooth		610

Regressive Alterations of the Teeth

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Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features	Page Number
Attrition (wearing away of tooth surface)	Middle-aged and older individuals; male predilection	Occlusal, incisal, and proximal surfaces of teeth	From small polished facet on cusp tip or slight flattening of the incisal edge to marked reduction in cusp height or complete flattening of the occlusal surface Complete wearing out of enamel with extrinsic staining of the exposed dentin in severe cases Possible fracture of cusps or restorations	Apposition of reparative secondary dentin within the pulp chamber	611
Abrasion (wearing away due to mechanical means)	Older individuals No sex predilection	Facial surface of crown in cervical areas and exposed surfaces of root Common in premolars and cuspids	Lesions more wide than deep; horizontal cervical notches on teeth in cervical areas in cases of toothbrush trauma, sharply defined margins with a hard, smooth surface Rounded or "V"-shaped notches in the incisal edges of anterior teeth in cases of thread/bobby pins biting	Apposition of reparative secondary dentin within the pulp chamber	612
Erosion (wearing away due to chemical means)	Deciduous and permanent dentitions No sex predilection	Facial surface of maxillary anteriors (dietary sources of acid) more common, palatal surface of maxillary anteriors (regurgitation of gastric secretions)	Shallow spoon shaped-depressions in the cervical portion of crown, cupping of occlusal surface with dentin exposure, increased incisal translucency Wear on nonoccluding surfaces, loss of surface characteristics of enamel in young children, enamel "cuff" in gingival crevice Hypersensitivity	Pulp exposure.	613
Abfraction (due to increased tensile stress in cervical region)	Any age No sex predilection	Single tooth Buccal and labial cervical areas of teeth More common in mandible	Wedge-shaped defect; deep, narrow V-shaped notch in cervical areas; occasionally subgingival lesions More common in individuals with bruxism Hypersensitivity		615
Internal resorption (pink tooth of Mummery)	Any age No sex predilection	Any tooth	Pink-hued area on the crown of affected tooth representing the vascular pulp tissue filling the defect due to loss of dentin, cementum/bone Round/ovoid radiolucency involving the middle portion of the root	Variable degree of resorption of the pulpal surface of dentin Proliferation of pulp tissue to fill the defect Odontoclasts, chronic inflammatory cells	621
External resorption	Any age No sex predilection	Any part on the outside of the tooth From roots to the cementum on the outside	Bowl-shaped areas of resorption on cementum and dentin; can be due to trauma, periapical inflammation, excessive mechanical or occlusal force, reimplantation of teeth, impaction	Inflammation of periodontium Granulation tissue Lymphocytes, plasma cells, and PMNLs	619

Continued

Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features	Page Number
Pulp calcification (Trauma/insult to pulp, local metabolic dysfunction) • True denticles • False denticles • Diffuse calcifications	Any age, more common in older age group No sex predilection	Pulp chamber or root canal of teeth	Mild pulpal neuralgia to severe excruciating pain	Compact degenerative masses of calcified tissue True denticles composed of dentinal tubules	617
Hypercementosis (cementum hyperplasia)	Middle-aged or older individuals No sex predilection	Root area of entire dentition or localized form involving single tooth	Usually asymptomatic Roots appear larger in diameter while extraction Rounding of the apex of tooth Difficulty during extraction Generalized hypercementosis is a feature of Paget disease Extraction is difficult	Excessive deposition of cellular cementum directly over a thin layer of acellular cementum Osteocementum in concentric layers	622

Healing of Oral Wounds

1. Fibrous healing of extraction wound, 668
2. Dry socket, 664

Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features	Differential Diagnosis	Page Number
Fibrous healing of extraction wound (tooth extraction with loss of both the lingual and labial or buccal cortical plates and the periosteum)	Adults No sex predilection	Previous extraction site Usually following a difficult, complicated, or surgical extraction of a tooth	Asymptomatic, found during radiographic examination **Radiographically**, well-circumscribed radiolucent area in the site of a previous extraction	Dense bundles of collagen fibers, occasional fibrocytes, and blood vessels	Residual cyst; granuloma	668
Dry socket (alveolitis sicca dolorosa, localized acute alveolar osteomyelitis, alveolar osteitis)	Adults 40–45 years Common in women and tobacco users due to dislodgement or a disintegration of the clot and the subsequent infection of the exposed bone	Mostly following a painful or difficult extraction Mandible more common, usually seen in mandibular third molars extraction	Starts by the second or third postoperative day and lasts for 7–10 days Extremely painful, radiates to ear, neck Low-grade fever and ipsilateral lymphadenopathy Foul smell and taste due to accumulation of food debris Necrotic exposed bone sequestration of fragments			664

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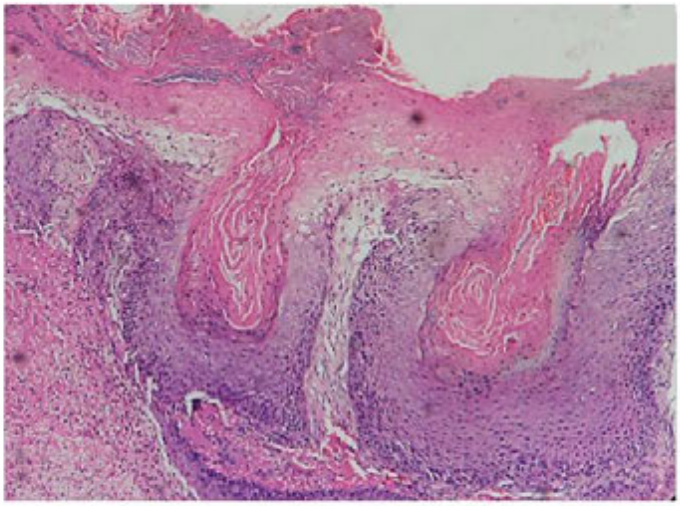
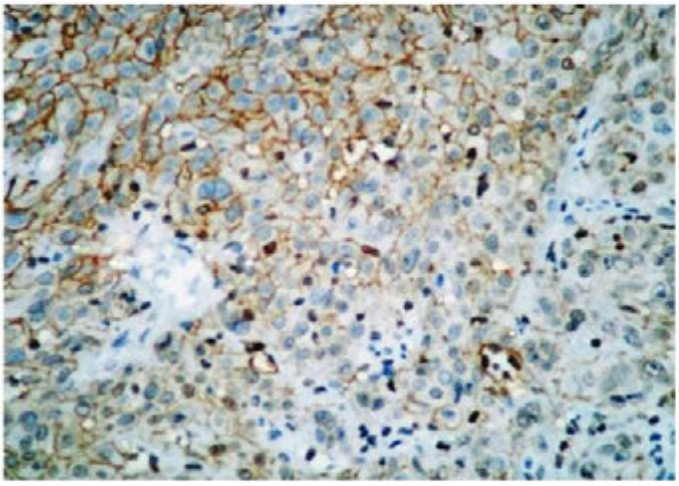
Lesion/Disorder	Age/Sex	Site	Clinical Features	Histologic Features	Differential Diagnosis	Page Number
Traumatic ulcer	Any age No sex predilection	Anywhere in the oral cavity	Solitary, painful lesion with history of trauma	Loss of epithelium, or ulcerations with areas of inflammatory infiltrate in the connective tissue stroma	Aphthous ulcer Herpes infection Behçet syndrome Reiter syndrome	633
Desquamative gingivitis	Middle age Female predilection	Gingiva	Multiple areas ulcers and erythema Gray areas showing necrosis and peeling off	Nonspecific ulcerations or erosions	Pemphigus Pemphigoid Erythema multiforme Herpes infection	408
Necrotizing ulcerative gingivitis	Young adults Equal sex predilection	Gingiva	Erythematous ulceration of the interdental papillae Halitosis Pain Fever and malaise	Ulcerations of the mucosa along with infiltration of inflammatory cells, predominately neutrophils and lymphocytes	Pemphigus Herpes infection	419
Erosive lichen planus (lichen ruber planus) Cell-mediated autoimmune disease	Middle age Female predilection	Buccal mucosa most common followed by tongue, lips, gingival, floor of the mouth and palate	Multiple, erythematous erosion with classic Wickham striae (fine grayish-white lines) Usually bilateral **Malignant transformation** of erosive and atrophic lichen planus: 0.3%–3%	Hyperparakeratosis/hyperorthokeratosis with areas of ulceration Sawtooth-shaped epithelial rete ridges Juxtaepithelial band of inflammatory infiltrate are the characteristic features	Erythroplakia Lichenoid reaction Pemphigus	520
Recurrent aphthous stomatitis (aphthae, canker sores) **Etiology:** Genetics, physical and emotional stress, hemolytic *Streptococcus*, iron, vitamin B_{12} deficiencies, hormonal imbalance, allergic factors	Young adults – middle age Female predilection	Anywhere in the oral cavity except anterior hard palate and gingiva 1. Minor – most common 2. Major – severe form (1–10 numbers of ulcers, heal by scarring) 3. Recurrent herpetiform ulcers – multiple, clusters of ulcers resembling herpetic lesions in the absence of viruses (up to 100 shallow ulcers) 4. Recurrent ulcer associated with Behçet syndrome	Single to few vesicles rupture to form erosions to deep painful ulcers covered by gray membrane Classic, necrotic center with clearly defined raised margin; surrounded by erythematous halo	Not specific Intraepithelial edema and ulcers with fibrinopurulent membrane Occasional colonies of microorganisms The underlying connective tissue shows inflammatory infiltrate Cytology: Characteristic Anitschkow cells (cells with elongated nuclei containing a linear bar of chromatin with radiating process of chromatin extending toward the nuclear membrane)	Herpetic stomatitis Herpangina Erythema multiforme Erosive lichen planus Pemphigoid Pemphigus	563
Behçet syndrome Immune defect (HLA-B51)	Young adults Male predilection	Oral, ocular lesions (uveitis, conjunctivitis), genital lesion and skin lesions Common oral sites – lips, buccal mucosa, tongue, gingiva, palate, uvula, and pharynx	Painful and appears similar to aphthous ulcer Multiplicity and occurrence in soft palate and oropharynx, enables to differentiate between aphthous ulcer	Nonspecific	Recurrent aphthous ulcers Herpetiform lesions Pemphigus	567

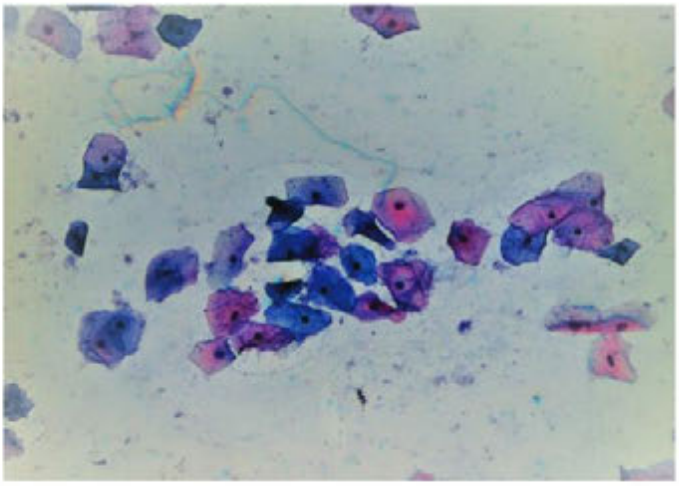
Reiter syndrome Immune defect (HLA-B27)	Young adults Male predilection	Nongonococcal urethritis, arthritis, conjunctivitis and mucocutaneous lesion Common oral sites – buccal mucosa, lips, gingiva, and tongue	Painless, erythematous lesion resembling aphthous ulcers Tongue – geographic tongue	Nonspecific	Recurrent aphthous ulcers Herpetic form lesions Pemphigus	567
Pemphigus vulgaris Immune mediated, circulating antibodies produced against Desmoglein 1 and 3 proteins at the desmosomes	Late adulthood Equal sex predilection	Anywhere in the oral mucosa and skin	Fluid-filled vesicle and bullae Size – few millimeters to centimeters Rupture of bullae – erosion of the mucosa Positive **Nikolsky sign** Intact vesicle and bullae – uncommon – painful, ill defined, erosions of the gingiva, buccal mucosa, and palate Lesions may extend up to the larynx	Intraepithelial vesicle or bullae – suprabasilar split (intraepithelial cleft) Weakened cell junctions – loss of cell adhesion/cohesion; acantholysis – **Tzanck cells** (free lying, round cells with swelling of nuclei and hyperchromatism) Presence of variable number of inflammatory infiltrates Cytology – **positive Tzanck test**	Pemphigoid Erythema multiforme Herpes infection Lichen planus	524
Mucous membrane pemphigoid Immune mediated, antibodies are produced against 2 antigens of hemidesmosomes • BP 180 – transmembrane protein • BP 230 – cytoplasmic protein	Middle age Female predilection	Affects mucous membrane including mouth, oropharynx, conjunctiva, nares, and genitalia **Intraoral sites:** Gingiva most common followed by palate, buccal mucosa, and floor of mouth	Vesicles and bulla are usually thick; on rupture, leaves an area of erosion and ulcer Painful Heals by scarring	Subepithelial vesicle and bulla formation No acantholysis with intact basement membrane Inflammatory infiltrates – lymphocytes and plasma cells Immunofluorescence – positive linear basement membrane zone pattern of IgG, IgA, IgM, and C3	Pemphigus Erosive lichen planus Bullous erythema multiforme	529
Erythema multiforme	Children, young adults Male predilection	Anywhere in the oral cavity, palate, buccal mucosa, and gingiva are the more common site	Oral lesions are nonspecific, appears as papules or vesicles may become eroded or ulcerated and bleed	Ulcerations, intracellular edema, subepithelial vesicle or cleft formation, and chronic inflammatory infiltrate consists of eosinophils, plasma cells, and lymphocytes	ANUG Pemphigus Pemphigoid	533
Chemical burn	Any age No sex predilection	Anywhere in the oral cavity, retromolar area most common site	Painful, superficial ulcer with gray to white fibrin exudate History of direct placement of drug/usage of new dentifrices or oral rinses	Necrotic epithelium, granulation tissue, edema, neutrophilic infiltration	Thermal burn Pemphigus Pemphigoid Candidiasis Allergic reactions	143
Thermal burn May be caused by hot food substances like pizza, or iatrogenic	Not specific	Anywhere in the oral cavity	Same as chemical burn	Same as chemical burn	Same as chemical burn	
Candidiasis	Age age No sex predilection	Anywhere in the oral cavity	Multiple, curdled white scrapable patches on the mucosa Leaves erythematous or bleeding spots on removal	Ulcerated epithelium with presence of fugal hyphae in the superficial surface; few inflammatory cells may be evident in the connective tissue	Thermal burn Chemical burn Pemphigus Pemphigoid	331



• **Fig. 1.7** H&E-stained section of a biopsied case showing Verrucous Carcinoma. *(Courtesy: Dr Manoj Prabhakar, Meenakshi Ammal Dental College and Hospital, Chennai.)*



• **Fig. 1.9** Immunohistochemistry of Epithelial Neoplasm with the Tumor Cells taking up light brown stain. *(Courtesy: Dr J Logeswari, Meenakshi Ammal Dental College, Chennai.)*



• **Fig. 1.8** Papanicolaou (PAP)-stained Cytological Smear of Buccal Mucosa. *(Courtesy: Dr J Logeswari, Meenakshi Ammal Dental College, Chennai.)*

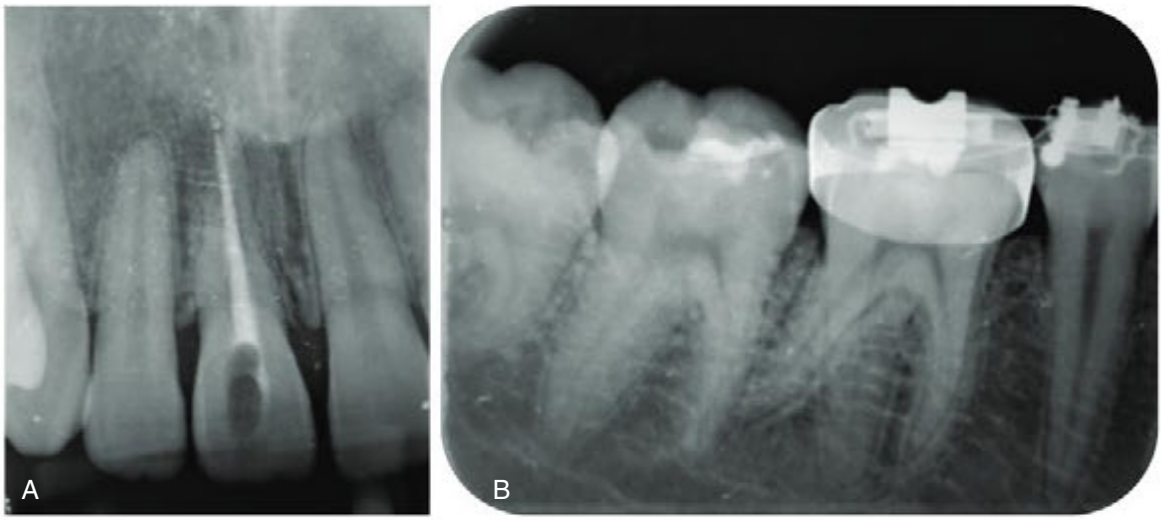
over- or underexpression of the genes in a disease process. It involves identification of antigens (proteins) at the cellular or tissue level by binding an antibody (marker) to the particular site (Figure 1.9). Molecular methods like polymerase chain reaction (PCR), DNA sequencing and hybridization, and microarray technology involving DNA chip are used to detect any mutational changes in tumor-associated oncogenes. Optical innovations like autofluorescence spectroscopy and optical coherence tomography are also add-ons for the molecular technique of diagnosis.

Radiographic Aids

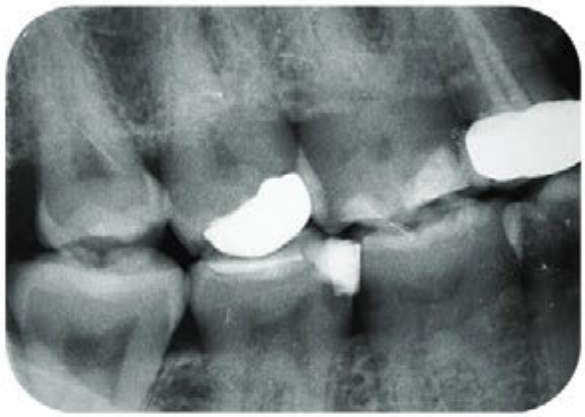
Radiographic pathology, a branch of radiation science, is the field of correlating and diagnosing any abnormality, clinically and radiographically, with suitable and appropriate radiation aids. It has a greater value in identifying an abnormality of the hard tissue, ranging from the detection of caries in a tooth to jaw neoplasms. Wide spectrum of radiographic methods have been implemented based on the site, severity, and extent of the pathology involved. Some of the preliminary investigative radiographic methods that are generally performed are intraoral periapical radiographs for periapical, periradicular, and periodontal pathologies (Figure 1.10); bitewing radiographs to visualize the crown portion of more number of teeth (Figure 1.11); occlusal radiographs for midline, buccal, or palatal orientation of the lesions (Figure 1.12); and panoramic radiographs for all developmental and pathological alterations like cysts and tumors involving the jawbones (Figure 1.13). These alterations can be seen as black or white areas based on the radiodensity of the structures involved. An area in the radiograph that appears black is termed "radiolucent" and that appears white is termed "radiopaque." Some lesions appear both radiolucent and radiopaque and they are termed mixed radiolucent-radiopaque lesions (speckled radiopacity). Based on their radiodensity, some of the jaw lesions give a specific pattern of appearance and these patterns become characteristic of those particular lesions, *e.g.*, soap bubble appearance, honeycomb appearance, sunburst appearance, and cotton wool appearance. Lesion that appears as a single chamber, lobule, or a cavity is generally termed unilocular and those that are divided into multiple small chambers are called multilocular (Figures 1.14 and 1.15). The term "sclerotic border" is often used for long-standing lesions, where there is thin or thick rim of radiopacity depicting the bone formation surrounding the lesion. Advanced imaging techniques like computed tomography (CT), cone beam computed tomography (CBCT), magnetic resonance imaging (MRI), ultrasonography, bone scintigraphy, and positron emission tomography (PET) have made the radiographic process simpler and faster, changing the trend of analogue to digital – a two-dimensional image to a three-dimensional structure.

Stem Cells

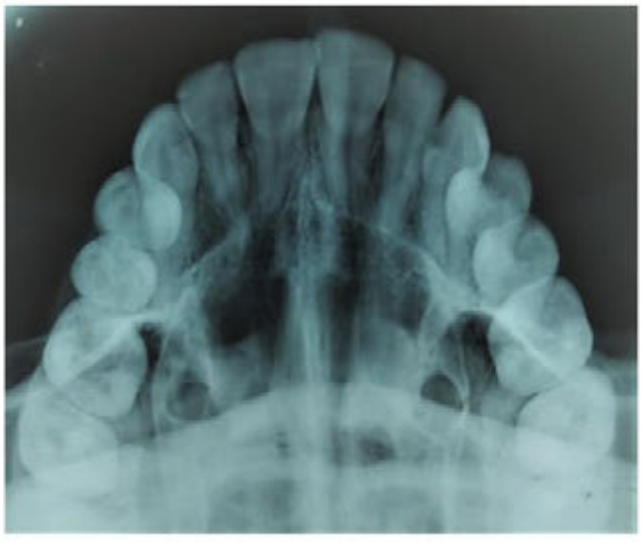
Regenerative medicine, the most emerging field of medical and dental sciences, deals with functional restoration of tissues or organs for the patients suffering from severe injuries or chronic diseases. Stem cells have become the frontline source for regenerative medicine due to its indefinite cell division potential and transdifferentiation. These are unspecialized cells that can develop into any specialized cells, which make up the different types of



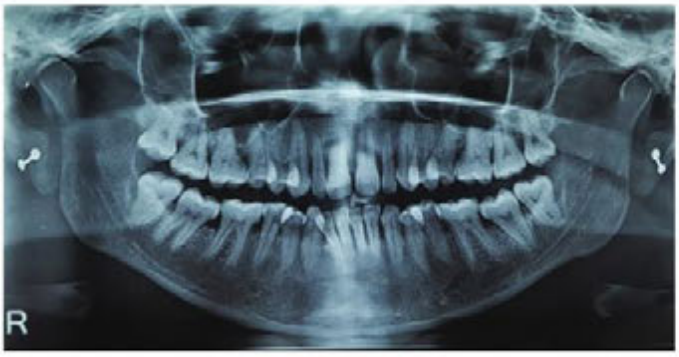
• **Fig. 1.10** Intraoral Periapical Radiograph: **(A)** anterior; **(B)** posterior. *(Courtesy: Dr N Velmurugan, Meenakshi Ammal Dental College, Chennai.)*



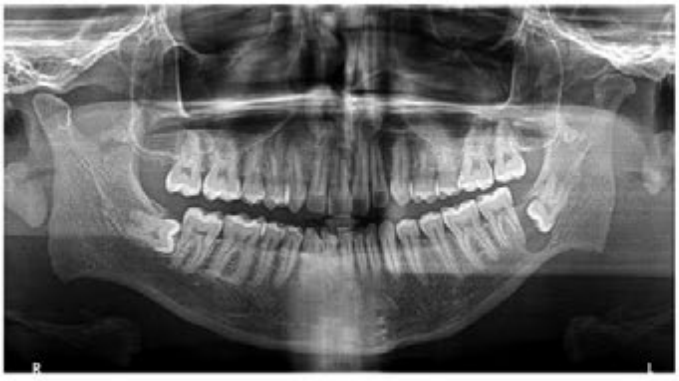
• **Fig. 1.11** Bitewing Radiograph showing Crown Portion of Maxillary and Mandibular Teeth. *(Courtesy: Dr S. Rohini, GRM Dental Clinic, Ambattur, Chennai.)*



• **Fig. 1.12** Occlusal Radiograph of Maxillary Arch showing Dental and Palatal Structures. *(Courtesy: Dr Ragu Ganesh, Meenakshi Ammal Dental College, Chennai.)*

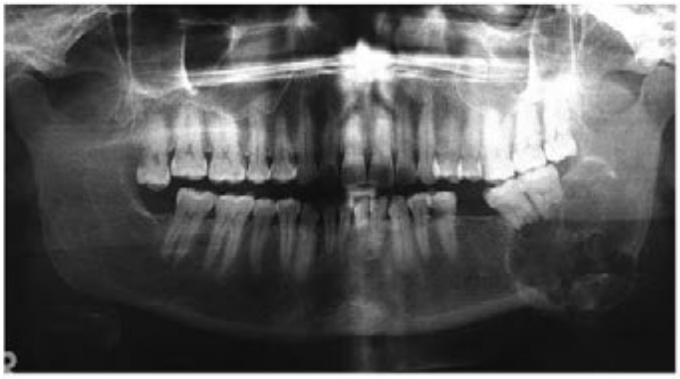


• **Fig. 1.13** Orthopantomograph (OPG) showing Dental and Paradental Structures of Maxillary and Mandibular Arch. *(Courtesy: Dr S. Rohini, GRM Detnal Clinic, Ambattur, Chennai.)*



• **Fig. 1.14** Radiograph showing Unilocular Radiolucency in Posterior Left Mandibular region. *(Courtesy: Professor Dr Eswar Rao, Oral and maxillofacial surgeon, Tirupati.)*

tissues in human body. They have the potential to self-renew and differentiate in order to generate perfect copies of themselves upon division. Based on potency, stem cells can be categorized as totipotent, pluripotent, oligopotent, multipotent, and unipotent. Based on the source of origin, they can be classified as embryonic stem cells and adult stem cells.



• **Fig. 1.15** Radiograph showing Multilocular (Soap-Bubble) Radiolucency in Mandibular Ramus region. *(Courtesy: Dr S. Manivannan, MDS, Kothai Face and Dental Care Centre, Vellore.)*

Repair of pulpal and periodontal lesions of the tooth is a major challenge with the usage of contemporary and classical dental treatment protocol. Although various structures of the tooth (*e.g.*, dentin) have the potential of repair, the capability is often insufficient and limited in restoring the damaged tissues in total. This kind of regeneration and repair is possible with the activation of stem cells and progenitor cells in the dental tissues.

Dental stem cells exhibit potential regenerative capacity and can be incorporated as a therapeutic measure to restore any structural/functional defects. It can be isolated from various sources and can be categorized accordingly, such as dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), stem cells from apical papilla (SCAP), stem cells from gingiva (GSC), periodontal ligament stem cells (PDLSCs), and oral epithelial stem cells (OESCs) (Figure 1.16).

Dental pulp, a connective tissue component encapsulated within the mineralized tooth structure, is an interesting source of adult stem cells with good proliferative potential and regenerative capacity. Dental stem cells derived from pulp and deciduous teeth display mesenchymal stem cell (MSC)–like character such as self-renewal and multilineage differentiation. SHED have a greater extent of differentiation and proliferation compared to DPSCs. PDLSCs are located in the perivascular spaces of periodontal ligament and are also considered as a potential source of MSC. SCAP are obtained from the apical region of the immature permanent tooth during a particular stage of tooth development. Their regenerative potential is superior to DPSCs due to the higher number of adult stem cells present in the dental papilla. Human epithelial tissues contain primitive stem cells that have the potential of self-renewal. Basal layers of the oral mucosa are known to express several stem cell markers that are increasingly being used in the field of cancer recurrence, metastasis, and therapy.

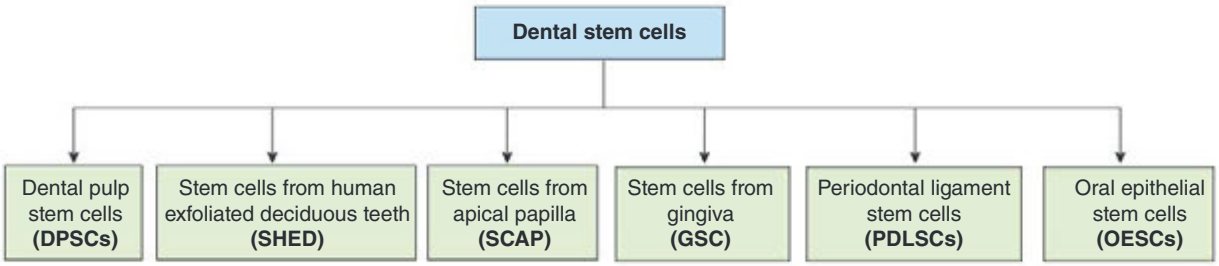
Extraction of MSCs from dental structures is simpler, reliable, and effective when compared to other invasive techniques like bone marrow–derived MSCs. Dental stem cells, which are isolated by such methods, are applied not only in the regeneration of dental structures but also in healing of any oral wounds and ulcers. It has also extended its application in various bone-related diseases and reconstructive surgeries. Preservation of these stem cells is a much essential criterion for its application in various fields. Stem cell banking has gained acceptance in most of the developed countries, with some countries having the provision for tooth banking. Despite the wide application of stem cells in regenerative medicine, certain limitations such as difficulty in isolation and preservation, technique-sensitive laboratory protocols, immune rejection, and lesser clinical (*in vivo*) application have been encountered. Systematic and progressive development efforts are being carried by the researchers to overcome these limitations. Prospective of regenerative medicine by using stem cells focuses on the future vision to enable the medical/dental practitioners to deliver regenerative therapy as a part of their routine practice.

Forensic Odontology

Application of dental sciences have become beneficial to the society by its remarkable role in the field of forensic investigation. Forensic identification involves multiple team efforts with cooperation and coordination of law enforcement officials, pathologists, odontologists, anthropologists and other specialists. Forensic odontology is utilized in the area of examination and evaluation of injuries in oral and perioral structures, identification of sexual assault and child abuse cases, age determination, and victim identification in mass disasters. The primary role of a forensic odontologist is to identify the deceased by collecting and comparing both the ante-mortem and post-mortem dental records. Some of the methods like bite mark analysis and lip prints are commonly implemented in crime investigations. Lack of any ante-mortem dental records can be resolved by DNA profiling and reconstructive dental identification methods.

Artificial Intelligence in Pathology

Histopathological diagnosis of the disease involves processing of the tissue specimen and visualization on glass slides after suitable staining under light microscope. This conventional manual method may lead to variations in subjective interpretation and interobserver disagreement at times. Information from various sources are usually combined, analyzed, and integrated by the pathologists in their routine practice. Compiling the information and arriving at a diagnosis for a given condition from a whole slide is a strenuous task for the pathologists as it is time consuming and labor intensive. This has subsequently resulted in the emergence of computational and digitalized methods for making pathological diagnosis.



• **Fig. 1.16** Types of Dental Stem Cells.

Digital pathology refers to scanning or digitizing the glass slide images through the use of computer-based technology. Earlier, a single image was captured and digitized for teaching–learning and to share live slide view for selected cases (telepathology). Later, whole slide imaging (WSI), a process by which the entire glass slide is digitized, has evolved to shift "optical microscopy" to "virtual microscopy." Digitalization of glass slide images and studying the features virtually with the support of computer assisted software has led to the development of a specialized and specific field of study called "computational pathology" (CPATH).

Artificial intelligence (AI) indicates the ability of the computer systems to simulate and perform the actions of human intelligence such as learning and problem solving. Elements of AI, namely machine learning and deep learning, help to evaluate the entire slide and are now the state-of-the-art technique in digital pathology. "Machine learning" identifies or detects pattern from previously stored large and complex datasets, whereas "deep learning" applies multilayered artificial neural networks to analyze specific patterns and images.

Integration of AI is possible at all stages of pathological work process including preanalytic, analytic, and postanalytic phases. Preanalytic phase includes quality assessment of scanned images and paraffin-embedded tissue blocks; analytic phase includes integrated diagnosis along with clinical information and advanced pathological studies like IHC; and postanalytic phase includes final reporting as well as cloud server management.

Application of AI in oral malignancies like oral squamous cell carcinoma and oral epithelial dysplasia using computer-assisted quantitative microscopic method, (*i.e.*, automated segmentation method) helps in observing the architectural variations of epithelial layers as well as in identification of specific features like keratin pearl from *in situ* histological images. In addition to diagnosis making, AI also predicts the outcome and prognosis in terms of risk assessment and recurrence. As majority of pathologists spend valuable time in differentiating benign from malignancy, a set criterion through AI allows the expertise of the pathologists on diagnosing complex cases rather than screening the regular ones.

Despite of its advantages, AI has quite a few challenges in implementation. Digitalization of the available data needs technical support and preliminary investments. The quality of the clinical information is also a prerequisite for application of AI-based methods. Furthermore, evidences on patient-related outcomes are still lacking and are yet to be justified. Meeting the aforementioned requirements, use of AI in digital pathology will certainly assist the pathologists in making a swift diagnosis with greater accuracy.

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2

Developmental Disturbances of Oral and Paraoral Structures

B. SIVAPATHASUNDHARAM

CHAPTER OUTLINE

Craniofacial Anomalies

Craniofacial anomalies (CFA) are a diverse group of deformities caused in the growth of the head and facial bones. The term anomaly means "irregularity" or "different from normal." They may be caused by genetic or environmental factors. These abnormalities are usually congenital (present at birth) and have numerous variations: some are mild; others are severe and cause anatomical and functional derangement.

These abnormalities are caused by more than one factor, which include the following:

- **Combination of genes:** A child may receive a particular combination of gene(s) from one or both parents, or there may be a change in the genes at the time of conception, which results in a CFA.
- **Environmental:** There are no data that show a direct correlation between any specific drug or chemical exposure causing a CFA. However, any prenatal exposure should be evaluated.

Some of the most common types of CFA (Table 2.1), which are important for the dental surgeons, include:

- **Cleft lip and/or cleft palate:** A separation that occurs in the lip or the palate, or both. Cleft lip and cleft palate are the most common CFA seen at birth.
  - ***Cleft lip:*** An abnormality in which the lip does not completely form. The degree of the cleft lip can vary greatly, from mild (notching of the lip) to severe (large opening from the lip up through the nose).
  - ***Cleft palate:*** Occurs when the roof of the mouth does not completely close, leaving a communication into the nasal cavity. The cleft may involve either side of the palate. It can extend from the hard palate to the soft palate and may also include the lip at times.
- **Craniosynostosis:** A condition in which the sutures in the skull of an infant close too early, causing problems with normal brain and skull growth. Premature closure of the sutures may also cause the pressure inside the head to increase and the skull or facial bones to change from a normal to symmetrical appearance.
- **Hemifacial microsomia:** A condition in which the tissues on one side of the face are underdeveloped, affecting primarily the ear, mouth, and jaw. Sometimes, both sides of the face can be affected and may involve the skull as well as the face. Hemifacial microsomia is also known as Goldenhar syndrome, brachial arch syndrome, facio-auriculo-vertebral syndrome, oculo-auriculo-vertebral spectrum, or lateral facial dysplasia.
- **Vascular malformation:** A birthmark or a growth, present at birth, is composed of blood vessels that can cause functional or esthetic problems. Vascular malformations may involve multiple body systems. There are several types of malformations named after the type of blood vessel that is predominantly affected. Vascular malformations include hemangiomas, lymphangiomas, and arteriovenous aneurysms.
- **Deformational (or positional) plagiocephaly:** A misshapen (asymmetrical) shape of the head (cranium) due to repeated pressure to the same area of the head. Plagiocephaly literally means "oblique head" (from the Greek word *plagio* for oblique and *cephale* for head).

TABLE 2.1 Number of Infants with Common Malformations Born Every Year in India

Malformation	Rate Per 10,000	Total Number Per Year
Neural tube defects	36.3	88,935
Talipes equinovarus	14.5	35,525
Polydactyly	11.6	28,420
Hydrocephalus alone	9.5	23,275
Cleft lip with cleft palate (CLP)	9.3	22,786
Congenital heart disease	7.1	17,395
Hypospadias	5.0	12,250
Cleft palate alone (CP)	1.7	4,145

Source: Global registry and database on craniofacial anomalies: Report of a WHO registry on craniofacial anomalies, 2001.

CFA are not lethal but they are disfiguring, and thus cause a tremendous social burden. However, these disorders have an excellent outcome if surgical repair is carried out. Recent information regarding the etiology of CFA provides the means to carry out primary or secondary prevention.

Molecular genetics in dental development

The first sign of tooth development is a local thickening of oral epithelium, which subsequently invaginates into neural crest–derived mesenchyme and forms a tooth bud. This epithelial folding and rapid cell proliferation result result initially as cap, and then the bell stage of tooth morphogenesis. During the bell stage, the dentine producing odontoblasts and enamel secreting ameloblasts differentiate. Tooth development, like the development of all epithelial appendages, is regulated by inductive tissue interactions between the epithelium and mesenchyme.

There is now increasing evidence that a number of different mesenchymal molecules and their receptors act as mediators of the epithelial–mesenchymal interactions during tooth development. Of the bone morphogenetic proteins (BMPs) 2, 4, and 7, mRNAs shift between the epithelium and the mesenchyme in the regulation of tooth morphogenesis. The fibroblast growth factor (FGF) family has also been localized in epithelial and mesenchymal components of the tooth by immunohistochemistry; and in dental mesenchyme, tooth development and shape is regulated by FGF8 and FGF9 via downstream factors MSX1 and PAX9.

Control of tooth development

Homeobox genes have particular implications in tooth development. Muscle-specific homeobox genes Msx-1 and Msx-2 appear to be involved in epithelial mesenchymal interactions, and are implicated in craniofacial development, and in particular, in the initiation of developmental position (Msx-1) and further development (Msx-2) of the tooth buds. Further evidence of the role of Msx-1 comes from gene knockout experiments that result in disruption of tooth morphogenesis among other defects. Pax-9 is also the transcription factor necessary for tooth morphogenesis. BMPs are members of the growth factor family (TGF) and they function in many aspects of craniofacial development with tissue-specific functions. BMPs have been found to have multiple roles not only in bone morphogenesis (BMP 5, for example, induces endochondral osteogenesis *in vivo*), but BMP 7 appears to induce dentinogenesis. Advances in the field of molecular genetics have made great progress in the understanding of a number of dental anomalies with a genetic component.

Congenital Deformations of Head and Neck

These are common, and mostly resolve spontaneously within the first few days of postnatal life. When they do not, further evaluation may be necessary to plan therapeutic interventions that may prevent long-term consequences. Approximately 2% of infants are born with extrinsically caused deformations that usually arise during late fetal life from intrauterine causes. Approximately 30% of deformed infants have two or more deformations. Deformed infants tend to show catch-up growth during the first few postnatal months after release from the intrauterine environment.

Teratogenic Agents

Teratogens are agents that may cause birth defects when present in the fetal environment. Included under such a definition are a wide array of drugs, chemicals, and infectious, physical, and metabolic agents that may adversely affect the intrauterine environment of the developing fetus.

The mechanisms of teratogenesis are selective in terms of the target and effect. Thus, characteristic patterns of abnormalities can be expected to be associated with particular teratogenic agents. However, the extent to which an individual may be adversely affected by exposure to a given teratogen varies widely.

Developmental Disturbances of Jaws

Agnathia

Agnathia is a lethal anomaly characterized by hypoplasia or absence of the mandible with abnormally positioned ears having an autosomal recessive mode of inheritance. More commonly, only a portion of one jaw is missing. In the case of the maxilla, this may be one maxillary process or even the premaxilla. Partial absence of the mandible is even more common. The entire mandible on one side may be missing, or more frequently, only the condyle or the entire ramus, although bilateral agenesis of the condyles and of the rami also has been reported. In cases of unilateral absence of the mandibular ramus, it is not unusual for the ear to be deformed or absent as well. It is probably due to failure of migration of neural crest mesenchyme into the maxillary prominence at the fourth to fifth week of gestation. The prevalence is unknown and less than 10 cases are described so far.

Micrognathia

Micrognathia literally means a small jaw, and either the maxilla or the mandible may be affected. Many cases of apparent micrognathia are not due to an abnormally small jaw in terms of absolute size, but due to an abnormal positioning or an abnormal relation of one jaw to the other or to the skull, which produces the illusion of micrognathia.

True micrognathia may be classified as either congenital or acquired. The etiology of the *congenital* type is unknown, although in many instances it is associated with other congenital abnormalities including congenital heart disease and the Pierre Robin syndrome (*q.v.*). It occasionally follows a hereditary pattern. Micrognathia of the maxilla frequently occurs due to premaxillary deficiency, and patients with this deformity appear to have the middle third of the face retracted. Although it has been suggested that mouth breathing is a cause of maxillary micrognathia, it is more likely that the micrognathia may be one of the predisposing factors in mouth breathing, owing to the associated maldevelopment of the nasal and nasopharyngeal structures.

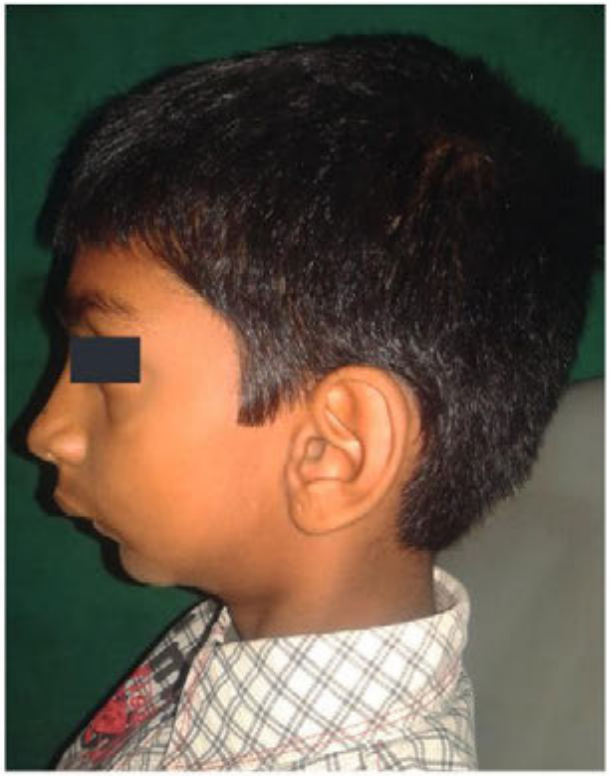
True mandibular micrognathia of the congenital type is often difficult to explain. Some patients clinically appear to have a severe retrusion of the chin but, by actual measurements, the mandible may be found to be within the normal limits of variation. Such cases may be due to a posterior positioning of the mandible with regard to the skull or due to a steep mandibular angle resulting in an apparent retrusion of the jaw. Agenesis of the condyles also results in a true mandibular micrognathia.

The acquired type of micrognathia is of postnatal origin and usually results from a disturbance in the area of the temporomandibular joint. Ankylosis of the joint, for example, may be caused by trauma or by infection of the mastoid, of the middle ear, or of the joint itself. Since the normal growth of the mandible depends to a considerable extent on normally developing condyles as well as on muscle function, it is not difficult to understand how condylar ankylosis may result in a deficient mandible.

The clinical appearance of mandibular micrognathia is characterized by severe retrusion of the chin, a steep mandibular angle, and a deficient chin button (Figure 2.1).

Pierre Robin Syndrome *(Robin Sequence, Pierre Robin Anomalad, Pierre Robin Malformation)*

Pierre Robin malformation is named after the French physician Pierre Robin who reported a case of nonspecific anomalad consisting of glossoptosis (downward displacement or retraction of the tongue



• **Fig. 2.1** Mandibular Micrognathia. *(Courtesy: Dr R.S. Neelakandan, Meenakshi Ammal Dental College, Chennai.)*

toward the pharynx) with cleft palate. It is a congenital defect that presets with a classic triad of micrognathia/retrognathia, glossoptosis, and cleft palate. The affected neonates often suffer airway obstruction and feeding difficulties.

Pierre Robin malformation may occur as an isolated defect, as part of a recognized syndrome (Stickler syndrome, velocardiofacial syndrome, Treacher Collins syndrome, and fetal alcohol syndrome), or as part of a complex of multiple congenital anomalies.

The primary defect in Pierre Robin malformation is the arrested mandibular growth, which in turn prevents the normal descend of the tongue and fusion of palatine shelves, resulting in cleft palate.

The occurrence of micrognathia in Pierre Robin malformation is explained by the following three theories:

- The mechanical theory, which suggests that the *in vitro* constraints limited the mandibular development, which in turn prevents the normal descend of the tongue resulting in failure of fusion of the developing palatine shelves.
- The neurological maturation theory, which states that a delay in the neurological maturation results in the inability of the developing fetus to engage in mandibular exercise that prevents the tongue from descending.
- The dysregulation theory, according to which the motor and regulatory organization of the rhombencephalus is related to a major problem of ontogenesis

Clinical Features. The primary clinical defect of Pierre Robin malformation is the presence of small mandible with an obtuse gonial angle and a posteriorly located condyle (micrognathia), or the jaw size is normal but the mandible is retropositioned with respect to the maxilla (retrognathia), giving the characteristic "bird face" appearance. Because of this, the tongue tends to fall back and obstruct the airway, resulting in serious complications such as breathing and feeding difficulties. In extreme cases, especially when associated with other CFA, bouts of cyanosis, choking spells, and, at times, obstructive sleep apnea syndrome may occur even in the first week of life. Airway obstruction and associated hypoxia carries a high mortality rate.

Most of the patients have cleft palate, which is characteristically without associated cleft lip. Both soft and hard palates are involved and the palatine vault usually takes a "U" or "V" shape.

Other findings include otitis media, hearing loss, nasal deformities, labyrinthitis with equilibrium disturbance, and dental and philtral malformations. Complication of airway obstruction may include infection leading to bronchitis and pneumonia. Rarely, central nervous system defects such as language delay, epilepsy, hypotonia, and hydrocephalus may occur.

Treatment and Prognosis. Treatment of Pierre Robin malformation necessitates a multidisciplinary approach to address the complex features of the disease. The treatment is primarily aimed at preventing the airway obstruction. Obturators for the cleft may be useful in facilitating feeding in milder cases. Children with severe micrognathia may suffer severe respiratory distress and fail to survive. Such patients may require surgical intervention to correct the respiratory obstruction.

Macrognathia

Macrognathia refers to the condition of abnormally large jaws. An increase in size of both jaws is frequently proportional to a generalized increase in size of the entire skeleton, *e.g.*, in pituitary gigantism, acromegaly (Figure 2.2A and B). More commonly only the jaws are affected, but macrognathia may be associated with certain other conditions, such as:

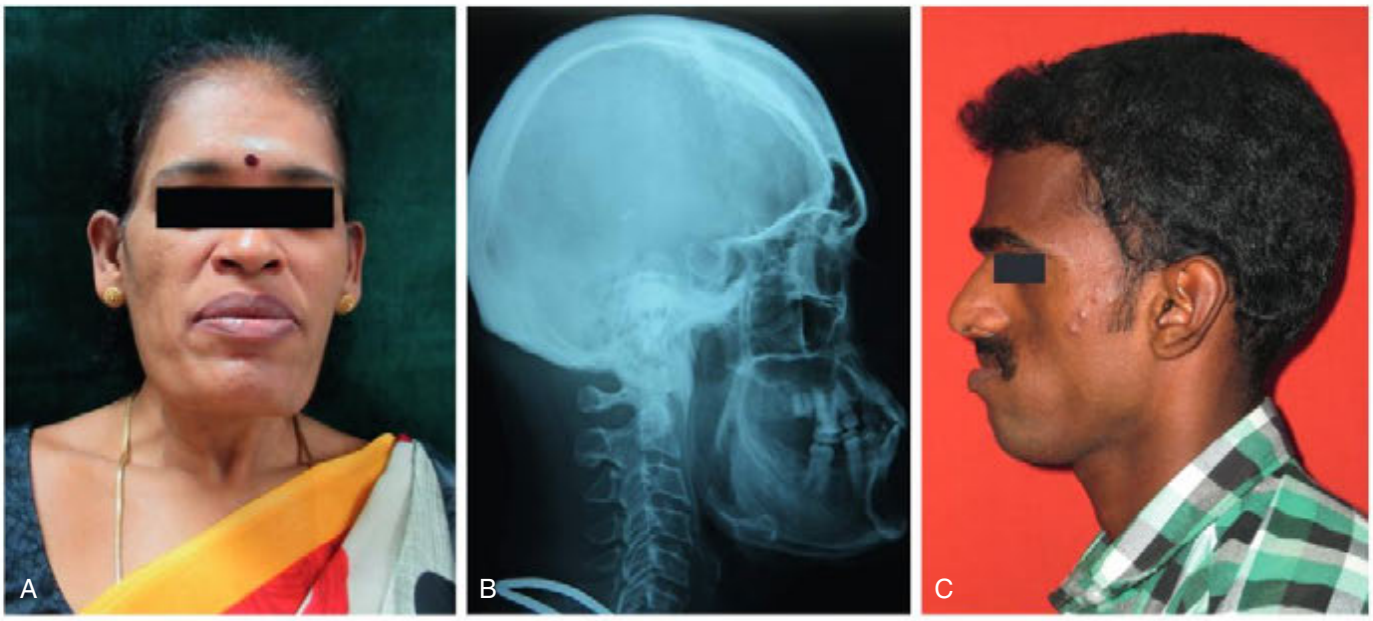
- Paget disease of bone, in which overgrowth of the cranium and maxilla or occasionally the mandible occurs.
- Acromegaly, in which there is progressive enlargement of the mandible owing to hyperpituitarism in the adult.
- Leontiasis ossea, a form of fibrous dysplasia in which there is enlargement of the maxilla.

Cases of mandibular protrusion or prognathism, uncomplicated by any systemic condition, are a rather common clinical occurrence (Figure 2.2C). The etiology of this protrusion is unknown, although some cases follow hereditary patterns. In many instances, the prognathism is due to a disparity in the size of the maxilla in relation to the mandible. In other cases, the mandible is measurably larger than normal. The angle between the ramus and the body also appears to influence the relation of the mandible to the maxilla, as does the actual height of the ramus. Thus, prognathic patients tend to have long rami, which form a less steep angle with the body of the mandible. The length of the ramus, in turn, may be associated with the growth of the condyle. Hence, excessive condylar growth predisposes to mandibular prognathism.

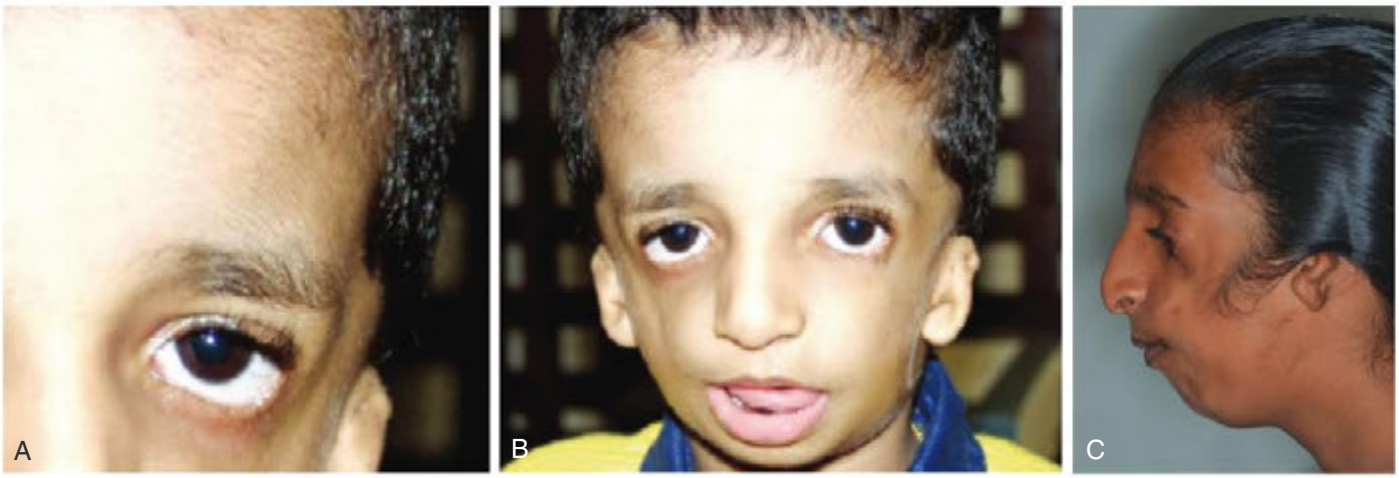
Factors that would influence or tend to favor mandibular prognathism are as follows:

- Increased height of the ramus
- Increased mandibular body length
- Increased gonial angle
- Anterior positioning of the glenoid fossa
- Decreased maxillary length
- Posterior positioning of the maxilla in relation to the cranium
- Prominent chin button
- Varying soft-tissue contours

Surgical correction of such cases is feasible. Ostectomy, or resection of a portion of the mandible to decrease its length, is an established procedure, and the results are usually excellent from both a functional and a cosmetic standpoint.



• **Fig. 2.2** Macrognathia. **(A and B)** Enlarged jaw in patient having acromegaly. **(C)** Mandibular prognathism. *(**A and B,** Courtesy: Dr K. Saraswathi Gopal, Meenakshi Ammal Dental College, Chennai; **C**, Courtesy: Department of Oral surgery, Meenakshi Ammal Dental College, Chennai.)*



• **Fig. 2.3** Mandibulofacial Dysostosis. *(**A and B,** Courtesy: Dr S.M. Balaji, Balaji Dental and Craniofacial Hospital, Chennai; **C,** Courtesy: Department of Oral and maxillofacial surgery, Meenakshi Ammal Dental College, Chennai.)*

Mandibulofacial Dysostosis *(Treacher Collins Syndrome, Franceschetti–Zwahlen–Klein Syndrome)*

Mandibulofacial dysostosis is a genetic disease inherited as an autosomal dominant trait. The earliest report of mandibulofacial dysostosis in the medical literature was by Berry in 1889. But a detailed observation was done by Treacher Collins in 1900, after whom the syndrome has been named.

The gene for mandibulofacial dysostosis was mapped to chromosome 5q31.3–q33.3 designated as TCOF1 (Treacher Collins–Franceschetti 1 gene). Molecular analysis studies showed that insufficiency of TCOF1 causes loss of neural crest cell precursors resulting in reduced number of neural crest cells migrating into developing craniofacial complex.

Although hereditary, majority of the cases do not have a family history and considered due to new mutations.

Clinical Features. The disease has an incidence of 1 in 50,000 births and affects both genders equally. There is a wide variation in the clinical expression and the structures affected are from the first and second pharyngeal arches, associated grooves, and pouches. The following are the important clinical manifestations of mandibulofacial dysostosis:

- Antimongoloid palpebral fissures with a coloboma of the outer portion of the lower eye lids and deficiency of the eyelashes
- Hypoplasia of the facial bones, especially of the malar bones and mandible (Figure 2.3)
- Malformation of the external ear and occasionally of the middle and internal ears
- Macrostomia, high arched palate (sometimes cleft), and abnormal position and malocclusion of the teeth

- Blind fistulas between the angles of the ears and the angles of the mouth
- Atypical hair growth in the form of a tongue-shaped process of the hairline extending toward the cheeks (Figure 2.3C)
- Facial clefts, skeletal deformities, salivary gland pathologies like aplasia/dysplasia of major glands leading to dryness of oral cavity, and high caries activity are also seen

The characteristic faces of the patients have often been described as being "bird-like" or "fish-like." In severely affected patients, because of the hypoplasia of the mandible and the temporomandibular joint, airway obstruction may lead to sleep apnea syndrome and sudden death.

A disease that has been often confused with mandibulofacial dysostosis because of similar clinical features is hemifacial microsomia. However, hemifacial microsomia is sporadic in most of the cases. In addition, as the name implies, hemifacial microsomia is unilateral.

Sleep apnea syndrome is a sleep disorder characterized by frequent episodes of apnea and hypopnea associated with symptoms such as snoring, gasping for breath during sleep, awakening with dry mouth, excessive daytime sleepiness, and cardiovascular morbidity and mortality.

Radiographic Features. The bodies of both malar bones are grossly and symmetrically underdeveloped. There may be agenesis of the malar bones with nonfusion of the zygomatic arches as well as absence of the palatine bones. Cleft palate may be visible on the radiograph. There is usually hypogenesis, and sometimes agenesis of the mandible. The paranasal sinuses are grossly underdeveloped. The auditory ossicles are often absent, and the cochlea and vestibular apparatus may be deficient. The cranial vault is usually normal.

Treatment and Prognosis. The treatment depends on the clinical manifestations and severity of the disease. Management of mandibulofacial dysostosis requires a multidisciplinary approach involving craniofacial surgeons, orthodontists, ophthalmologists, otolaryngologists, and speech pathologists. Severe cases may be treated with tracheostomy at birth to guard the airway and facilitate feeding. Later, multiple surgeries may be required to correct eyelid coloboma, orbital reconstruction and osteotomies. The prognosis of mandibulofacial dysostosis is good and most patients live a normal life span.

Facial Hemihypertrophy

Facial hemihypertrophy is a rare developmental anomaly characterized by asymmetric overgrowth of one or more body parts. It actually represents a hyperplasia of the tissues rather than a hypertrophy. Hemihyperplasia can be an isolated finding, but it also may be associated with a variety of malformation syndromes (Table 2.2). Almost all cases of isolated hemihyperplasia are sporadic.

Anatomic classification of hemihyperplasia is as follows:

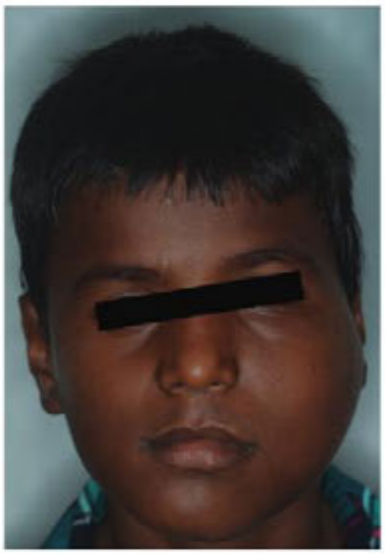
- Complex hemihyperplasia is the involvement of half of the body (at least one arm and one leg); affected parts may be contralateral or ipsilateral.
- Simple hemihyperplasia is the involvement of a single limb.
- Hemifacial hyperplasia is the involvement of one side of the face (Figure 2.4).

Etiology. The cause is unknown, but the condition has been variously ascribed to vascular or lymphatic abnormalities, CNS disturbances, and chromosomal abnormalities.

TABLE 2.2 Malformation Syndromes Associated with Hemihyperplasia

Beckwith–Wiedemann syndrome
Neurofibromatosis
Klippel–Trenaunay–Weber syndrome
Proteus syndrome
McCune–Albright syndrome
Epidermal nevus syndrome
Triploid/diploid mixoploidy
Langer–Giedion syndrome
Multiple exostoses syndrome
Maffucci syndrome
Ollier syndrome
Segmental odontomaxillary dysplasia

Source: H.E. Hoyme et al., 1998.



• **Fig. 2.4** Facial Hemihypertrophy. *(Courtesy: Department of Oral and maxillofacial surgery, Meenakshi Ammal Dental College, Chennai)*

Clinical Features. Patients affected by facial hemihypertrophy exhibit an enlargement, which is confined to one side of the body, unilateral macroglossia and premature development, and eruption as well as an increased size of dentition. Familial occurrence has been reported on a few occasions. Of all reported cases, females are affected somewhat more frequently than males (63% vs 37%). There is an almost equal involvement of the right and left sides.

Oral Manifestations. The dentition of the affected side is abnormal in three aspects; crown size, root size and shape, and rate of development. Not all teeth in the enlarged area are necessarily affected in a similar fashion. There is little information about the effects on the deciduous dentition, but the permanent teeth on the affected side are often enlarged, although not exceeding a 50% increase in size. This enlargement may involve any tooth, but seems to occur most frequently in the cuspid, premolars, and first molar. The roots of the teeth are sometimes proportionately enlarged but may be short.

Characteristically, the permanent teeth on the affected side develop and erupt more rapidly. Coincident to this phenomenon is premature shedding of the deciduous teeth. The bone of the

maxilla and mandible is also enlarged, being wider and thicker, sometimes with an altered trabecular pattern.

The tongue is commonly involved by the hemihypertrophy and may show a bizarre picture of enlargement of lingual papillae in addition to the general unilateral enlargement and contralateral displacement. In addition, the buccal mucosa frequently appears velvety and may seem to hang in soft, pendulous folds on the affected side.

Histologic Features. Tissue examination has been infrequently reported but is generally uninformative. In the cases that have been reported, true muscular hypertrophy was not found.

Treatment and Prognosis. There is no specific treatment for this condition other than attempts at cosmetic repair. Cosmetic surgery is advised after cessation of growth. Effect on life expectancy is not certain, but in some cases patients have lived a normal life span. Periodic abdominal ultrasound/MRI is recommended to rule out tumors.

Differential Diagnosis. There are certain diseases of the jaws, such as neurofibromatosis and fibrous dysplasia of the jaws, which may give the clinical appearance of facial hemihypertrophy, but these can usually be differentiated readily by the lack of effect on tooth size and rate of eruption.

Facial Hemiatrophy *(Parry–Romberg Syndrome, Progressive Hemifacial Atrophy)*

Hemifacial atrophy remains almost as much an enigma today as it was when first reported by Romberg in 1846. Hemifacial atrophy, originally described by Parry and Henoch and Romberg, consists of slowly progressive atrophy of the soft tissues of essentially half the face, which is characterized by progressive wasting of subcutaneous fat, sometimes accompanied by atrophy of skin, cartilage, bone, and muscle. Although the atrophy is usually confined to one side of the face and cranium, it may occasionally spread to the neck and one side of the body and it is accompanied usually by contralateral Jacksonian epilepsy, trigeminal neuralgia, and changes in the eyes and hair. The reported presence of antinuclear antibodies in the serum suggested that the Parry–Romberg syndrome may be a form of localized scleroderma. Hemifacial atrophy is a form of localized scleroderma and supported by its concurrence with scleroderma.

Hemifacial atrophy is a rare condition that occurs sporadically although some familial distribution has been found.

Etiology. The etiology has been the subject of considerable debate, though the following three were considered in the etiology:

1. A cerebral disturbance leading to increased and unregulated activity of sympathetic nervous system, which in turn produces the localized atrophy through its trophic functions conducted by way of sensory trunks of the trigeminal nerve.
2. Extraction of teeth, local trauma, infection, and genetic factors could also be a cause.
3. Disruption of the stapedial artery is attributed to the development of facial deformities.

Clinical Features. Hemifacial atrophy is a syndrome with diverse presentation. The most common early sign is a painless cleft, the "*coup de sabre*," near the midline of the face or forehead. This marks the boundary between normal and atrophic tissue. A bluish hue may appear in the skin overlying atrophic fat.

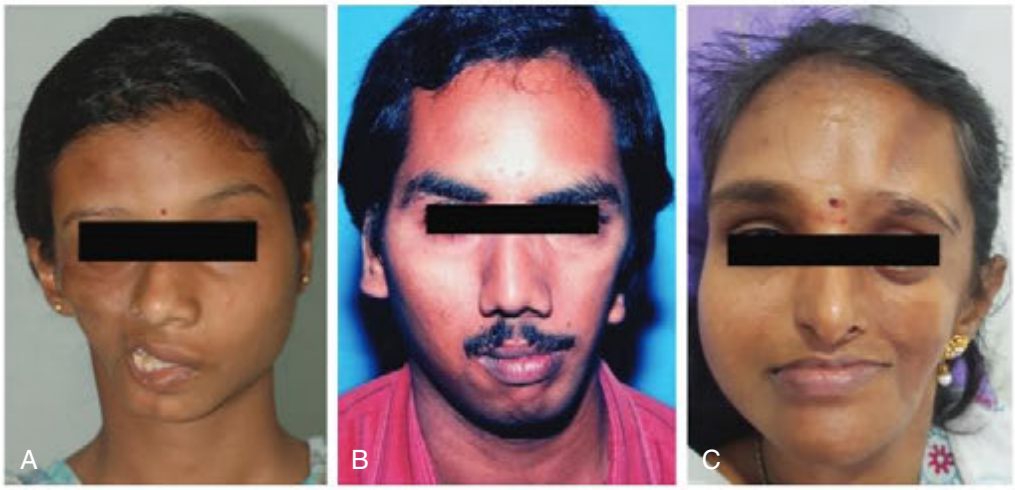
The affected area extends progressively with the atrophy of the skin, subcutaneous tissue, muscles, bones, cartilages, alveolar bone, and soft palate. In addition to facial wasting that may include the ipsilateral salivary glands and hemiatrophy of the tongue, unilateral involvement of the ear, larynx, esophagus, diaphragm, kidney, and brain have been reported.

It starts in the first decade and lasts for about 3 years before it becomes quiescent. The final deformity varies widely, with minimal atrophy in some patients, while in others progressing to marked atrophy.

Neurological disorders are found in 15% of patients, while ocular findings occur in 10%–40%, the most common being enophthalmos.

Rarely, one half of the body may be affected. This condition may be accompanied by pigmentation disorders, vitiligo, pigmented facial nevi, contralateral Jacksonian epilepsy, contralateral trigeminal neuralgia, and ocular complications.

The disease occurs more frequently in women; female-to-male ratio is 3:2. It has a slight predilection for the left side and appears in the first or second decades of life. It progresses over a period of 2 and 10 years, and atrophy appears to follow the distribution of one or more divisions of the trigeminal nerve. The resulting facial flattening may be mistaken for Bell's palsy (Figure 2.5).



• **Fig. 2.5** Facial Hemiatrophy. (***A,*** *Courtesy: Dr Manikandhan, Meenakshi Ammal Dental College, Chennai;* ***B,*** *Courtesy: Dr S. Karthigakannan, Oral Physician, Nagercoil;* ***C,*** *Courtesy: Dr S Rohini, GRM Dental Clinic, Ambattur, Chennai.)*

Oral Manifestations. Dental abnormalities include incomplete root formation, delayed eruption, and severe facial asymmetry, resulting in facial deformation and difficulty in mastication. Hemiatrophy of the lips and the tongue is reported, as are dental effects. Growth of the teeth may be affected just as other tissues are involved. Eruption of teeth on the affected side may also be retarded.

Differential Diagnosis. Posttraumatic fat atrophy, hemifacial microsomia (first and second branchial arch syndrome), Goldenhar syndrome, and partial lipodystrophy are, however, always bilateral.

Treatment and Prognosis. There is no specific treatment for the condition. It has been found that, typically, the disease will be progressive for a period of several years and then remain unchanged for the remainder of the patient's life.

Abnormalities of Dental Arch Relations

In the preceding sections, the conditions discussed are those in which there is an actual or apparent abnormal variation in size of one or both jaws. Of far greater importance than a simple disparity in size is the disparity in relation of one jaw to the other and the difficulties in occlusion and function that result.

A great many different types of malocclusion exist, and many classifications have been evolved in an attempt to unify methods of treatment. The classification of Angle, proposed in 1899, is the most universally known and used, which is as follows:

Class I: Arches in normal mesiodistal relations (Figure 2.6)

Class II: Mandibular arch distal to normal in its relation to the maxillary arch

Division 1: Bilaterally distal, protruding maxillary incisors (Figure 2.7A)

Subdivision: Unilaterally distal, protruding maxillary incisors

Division 2: Bilaterally distal, retruding maxillary incisors (Figure 2.7B)

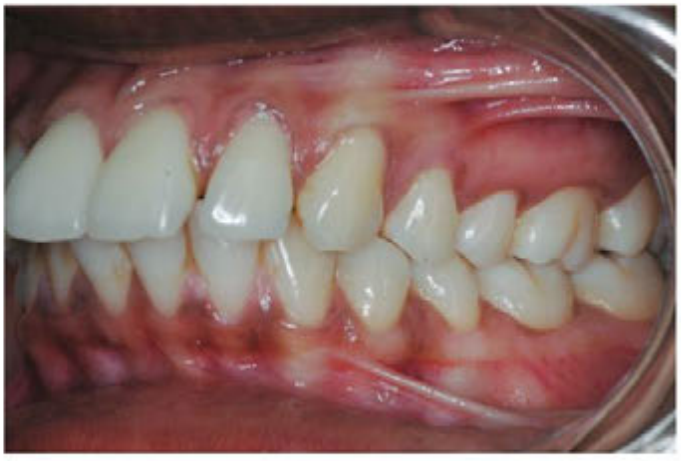
Subdivision: Unilaterally distal, retruding maxillary incisors

Class III: Mandibular arch mesial to normal in its relation to the maxillary arch (Figure 2.8)

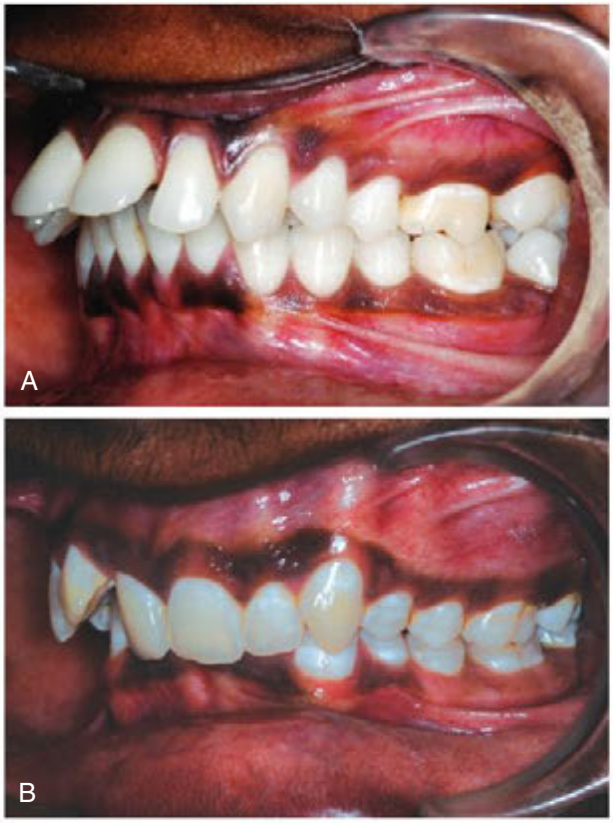
Division: Bilaterally mesial

Subdivision: Unilaterally mesial

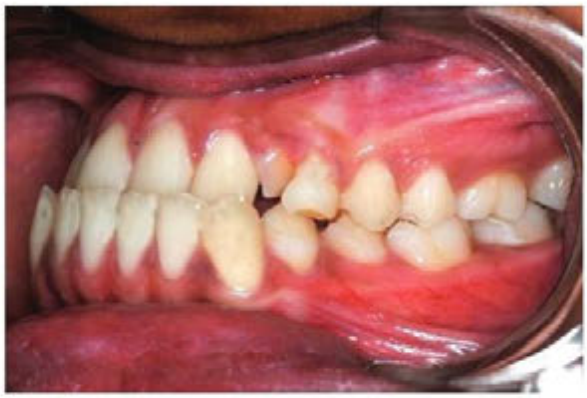
Since these abnormal jaw relations constitute a separate branch of study, no further allusion to this subject is made here.



• **Fig. 2.6** Class I. *(Courtesy: Dr Devaki Saravanan, Meenakshi Ammal Dental College, Chennai.)*



• **Fig. 2.7** Class II, Division 1 (A) and Division 2 (B). *(Courtesy: Dr Devaki Saravanan, Meenakshi Ammal Dental College, Chennai.)*



• **Fig. 2.8** Class III. *(Courtesy: Dr Devaki Saravanan, Meenakshi Ammal Dental College, Chennai.)*

Developmental Disturbances of Lips and Palate

Cleft Lip and Cleft Palate

The term cleft lip and palate is commonly used to represent two types of malformation, *i.e.*, cleft lip with or without cleft palate (CL/P) and cleft palate (CP). Cleft lip and palate are common congenital malformations. The frequency of occurrence of cleft lip, with or without cleft palate, has been computed on a global scale and is estimated to be 1 in every 800 newborn babies. A child is therefore born with a cleft somewhere in the world approximately

every three minutes globally. Accurate data on the frequency of occurrence of these disorders are relevant for implementing strategies aimed at primary prevention and effective management of these disabled children. The reported incidence of clefts of the lip and palate varies from 1 in 500 to 1 in 2500 live births depending on geographic origin, racial and ethnic background, and socioeconomic status. In general, Asian population has the highest frequencies, often at 1 in 500 or higher, with Caucasian population intermediate, and African-derived population the lowest at 1 in 2500.

An understanding of the normal human maxillofacial development is necessary before a discussion of cleft lip and palate. During the fourth week of gestation, the maxillary processes emerge from the first branchial arch on each side and the nasal placodes form from the frontal prominence. By the fifth week, all the primordia for the lip and palate are present. The medial, lateral nasal, and the frontonasal processes are formed from the nasal placodes and the maxillary processes continue to enlarge. During the seventh week the medial nasal, frontonasal, and maxillary processes fuse to form the primary palate, which becomes the medial portion of the upper lip, alveolus and the anterior part of hard palate. When the primary palate is completely formed, the maxillary processes enlarge intraorally to form the palatine processes. During the eighth week of gestation, the palatal shelves fill up the space on both sides of the tongue. During the 9th and 10th weeks, the mandibular arch grows forward and downward allowing the tongue to descend. The palatal shelves transpose horizontally and fuse with each other and with the anterior part of the palate. Palatal fusion occurs anteroposteriorly and the process is completed by 11th to 12th week.

Failure in the fusion of the nasal and maxillary processes leads to the cleft of the primary palate, which can be unilateral or bilateral. The degree of cleft can vary from a slight notch on the lip to complete cleft of the primary palate. Cleft of the secondary palate is medial. It varies from bifid uvula to complete cleft palate up to the incisive foramen. When it is associated with the primary palate, a complete uni- or bilateral cleft lip and palate is formed.

Etiology. It has been clearly established that two separate and distinct entities exist:

- Cleft lip with or without associated cleft palate
- Isolated cleft palate

Heredity is undoubtedly one of the most important factors to be considered in the etiology of these malformations. However, there is increasing evidence that environmental factors are important as well. Slightly less than 40% of the cases of cleft lip with or without cleft palate are genetic in origin, whereas slightly less than 20% of the cases of isolated cleft palate appear to be genetically derived. Most investigations indicate that the inheritance pattern in cleft lip with or without cleft palate is different from that in isolated cleft palate. The mode of transmission of the defect is uncertain. The possible main modes of transmission are either by a single mutant gene, producing a large effect, or by a number of genes (polygenic inheritance), each producing a small effect, which together create this condition. It should be pointed out that cytogenetic studies have failed to reveal visible alterations in chromosomal morphology of the affected individuals.

Bixler has expanded upon this concept and reiterated that there are two forms of clefts. The most common is hereditary, its nature being most probably *polygenic* (determined by several different genes acting together). In other words, when the total genetic liability of an individual reaches a certain minimum level, the threshold for expression is reached and a cleft occurs. Actually, it is presumed that every individual carries some genetic liability for clefting, but if this is less than the threshold level, there is no cleft. When the individual liabilities of two parents are added together in their offspring, a cleft occurs if the threshold value is exceeded. However, even though this is the most common form of cleft, the threshold value is sufficiently high that it is a low-risk type. The second form of cleft is **monogenic** or **syndromic** and is associated with a variety of other congenital anomalies. Since these are monogenic, they are of a high-risk type. Fortunately, the clefting syndromes are rare and probably make up only 5% of all cleft cases, even though there are now over 300 clefting syndromes reported in the literature.

Although there is insufficient evidence that nutritional disturbances cause cleft palates in human beings, abnormal dietary regimens have caused developmental clefts in animals. Cleft palate has been experimentally produced in newborn rats by feeding diets either deficient or excessive in vitamin A to maternal rats during pregnancy. Riboflavin-deficient diets fed to pregnant rats have also produced offspring with a high incidence of cleft palate. The administration of cortisone to pregnant rabbits has induced similar clefts in their young.

It is reported that physiologic, emotional, or traumatic stress may play a significant role in the etiology of human cleft palate, since stress induces increased function of the adrenal cortex and secretion of hydrocortisone.

Other factors that have been suggested as possible causes of cleft palate include:

- A defective vascular supply to the area involved
- A mechanical disturbance in which the size of the tongue may prevent the union of palatine shelves
- Circulating substances, such as alcohol and certain drugs and toxins
- Diabetes
- Maternal infections
- Lack of inherent developmental force

Despite the numerous clinical and experimental investigations, the etiology of cleft palate in the human being is still largely unknown. It must be concluded; however, that heredity is probably the most important single factor.

Alvizi *et al.* hypothesized a 2-hit model in which cleft lip with or without cleft palate penetrance is dependent on a genetic hit (CDH1 [E-cadherin, a member of the cadherin–catenin complex] loss-of-function) and an environmental hit (proinflammatory activation) affects neural crest migration. Impaired neural crest migration results in craniofacial malformations.

Clinical Features. Cleft lip with or without palate is more common in males than in females. Males have also been reported to have more severe defects, whereas the isolated cleft palate is more common in females.

Clefts can be divided into nonsyndromic and syndromic forms. Syndromic forms of clefts include those cases that have additional birth defects like lip pits or other malformations, whereas nonsyndromic clefts are those cases wherein the affected individual has no other physical or developmental anomalies and no recognized maternal environmental exposures. About 70% of cases of cleft lip with or without palate and 50% of isolated cleft palate are nonsyndromic. The remaining syndromic cases can be subdivided into chromosomal anomalies, teratogens, and uncategorized syndromes.

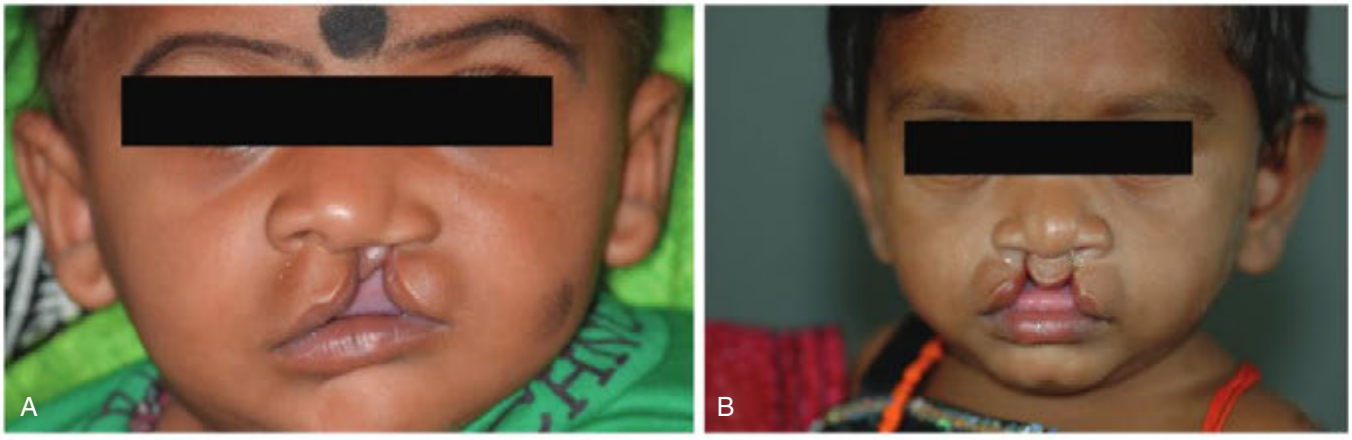
Cleft lip can occur as a unilateral or bilateral anomaly. The line of cleft always starts on the lateral part of the upper lip and continues through the philtrum to the alveolus between the lateral incisor and the canine tooth. The clefting anterior to the incisive foramen (*i.e.*, lip and alveolus) is also defined as a cleft of primary palate. However, rarely median labial cleft occurs. This is due to the deficiency or absence of globular process of the median nasal process. The severity of this clefting ranges from a slight notch at the central portion of the vermilion border to a deficiency of the middle portion of the nose.

Cleft lip may occur with a wide range of severity, from a notch located on the left or right side of the lip to the most severe form, bilateral cleft lip and alveolus that separate the philtrum of the upper lip and premaxilla from the rest of the maxillary arch. When cleft lip continues from the incisive foramen further through the palatal suture in the middle of the palate, a cleft lip with palate (either unilateral or bilateral) is present (Figure 2.9A and B). The cleft line may be interrupted by skin or mucosal bridges, hard (bone) bridges, or both, corresponding to a diagnosis of an **incomplete cleft**. This occurs in unilateral and bilateral cleft lip with cleft palate (CLP).

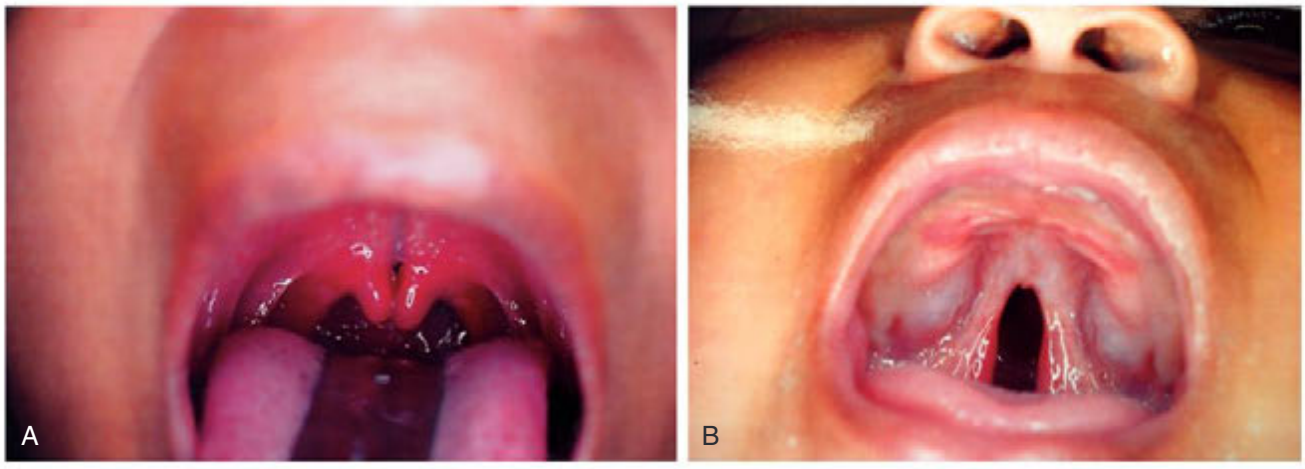
Isolated cleft palate is etiologically and embryologically different from cleft lip with or without cleft palate. Several subtypes of isolated cleft palate can be diagnosed based on severity. The uvula is the place where the minimal form of clefting of the palate is observed (Figure 2.10A). A more severe form is a cleft of the soft palate (Figure 2.10B). A complete cleft palate constitutes a cleft of the hard palate, soft palate, and cleft uvula (Figure 2.11). The clefting posterior to the incisive foramen is defined as a cleft of secondary palate.

A **median maxillary anterior alveolar cleft** is a relatively common defect, occurring in approximately 1% of the population, but this is unrelated to cleft lip or cleft palate (Figure 2.12). This might be due to precocious limitation of the growth of the primary ossification centers on either side of the midline at the primary palate, or to their subsequent failure to fuse. In addition, at least some cases may represent an incomplete manifestation of the median cleft-face syndrome (hypertelorism, median cleft of the premaxilla and palate, and cranium bifidum occultum). This syndrome has no clinical manifestations and is usually detected only on routine intraoral radiographic examination. Very rarely, median mandibular cleft occurs due to the failure of fusion between two mandibular processes (Figure 2.13).

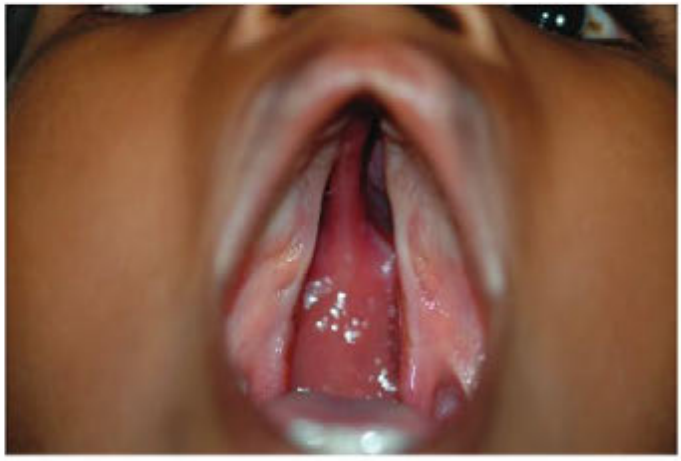
Clinical Significance. Most cases of cleft lip can be surgically repaired with excellent cosmetic and functional results. It is customary to operate before the patient is one month old or when the infant has regained its original birth weight and is still gaining.



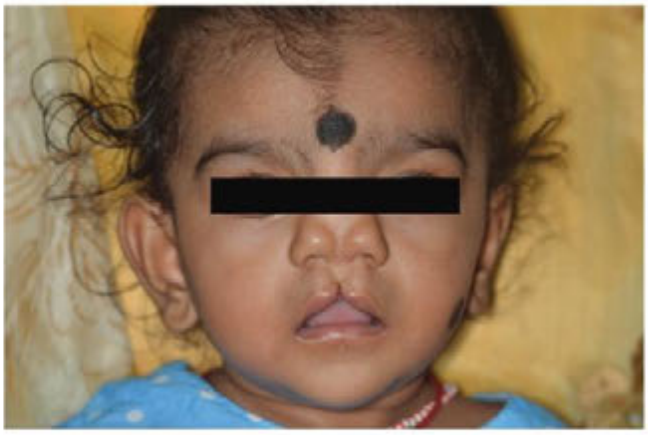
• **Fig. 2.9** Cleft Lip. **(A)** Unilateral and **(B)** bilateral. *(Courtesy: Dr R. Manikandhan, Meenakshi Ammal Dental College, Chennai.)*



• **Fig. 2.10** (A) Cleft Involving the Uvula. (B) Cleft Involving the Soft Palate Only. *(Courtesy: Dr R. Manikandhan, Meenakshi Ammal Dental College, Chennai.)*



• **Fig. 2.11** Cleft Involving Both the Hard and the Soft Palate. *(Courtesy: Dr R. Manikandhan, Meenakshi Ammal Dental College, Chennai.)*

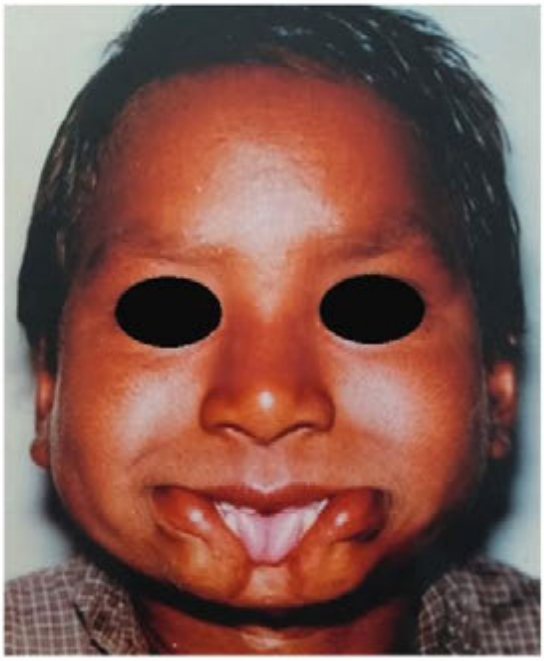


• **Fig. 2.12** Median Maxillary Anterior Alveolar Cleft. *(Courtesy: Department of Oral and maxillofacial surgery, Meenakshi Ammal Dental College, Chennai)*

Both physical and psychological effects of cleft palate on the patient are of considerable concern. Eating and drinking are difficult because of regurgitation of food through the nose. The speech problem is also serious and tends to increase the mental trauma suffered by the patient.

Most individuals with cleft lip, cleft palate, or both require the coordinated care of specialists in many fields of medicine and dentistry, as well as those in speech pathology, otolaryngology, audiology, genetics, nursing, mental health, and social medicine.

Treatment. Treatment of CLP anomalies requires years of specialized care. Although successful treatment of the cosmetic and functional aspects of orofacial cleft anomalies is now possible, it is still challenging, lengthy, costly, and dependent on the skills and experience of a medical team. This especially applies to surgical, dental, and speech therapies. Undoubtedly, closure of the cleft lip is the first major procedure that tremendously changes children's future development and ability to thrive. Variations occur in timing of the first lip surgery; however, the most usual time occurs at approximately 3 months of age. Pediatricians used to strictly follow a rule of "three 10s" as a necessary requirement for identifying the child's status as suitable for surgery (*i.e.*, 10 pounds, 10 mg/L of hemoglobin, and age 10 weeks). Although pediatricians are presently much more flexible, and some surgeons may well justify a neonatal lip closure, the rule of three 10s is still very useful.



• **Fig. 2.13** Cleft in the Midline of the Mandible Exposing the Tongue. *(Courtesy: Dr P. Harikrishnan, Craniofacial Orthodontist & Dental Surgeon, Teeth'N'Jaws Center, Nungambakkam, Chennai.)*

Congenital Lip and Commissural Pits, and Fistulas

Congenital lip pits and fistulas are malformations of the lips, often following a hereditary pattern, that may occur alone or in association with other developmental anomalies such as various oral clefts. In 75%–80% of all cases of congenital labial fistulas, there is an associated cleft lip or cleft palate, or both. The association of pits of the lower lip and cleft lip and/or cleft palate is termed van der Woude syndrome.

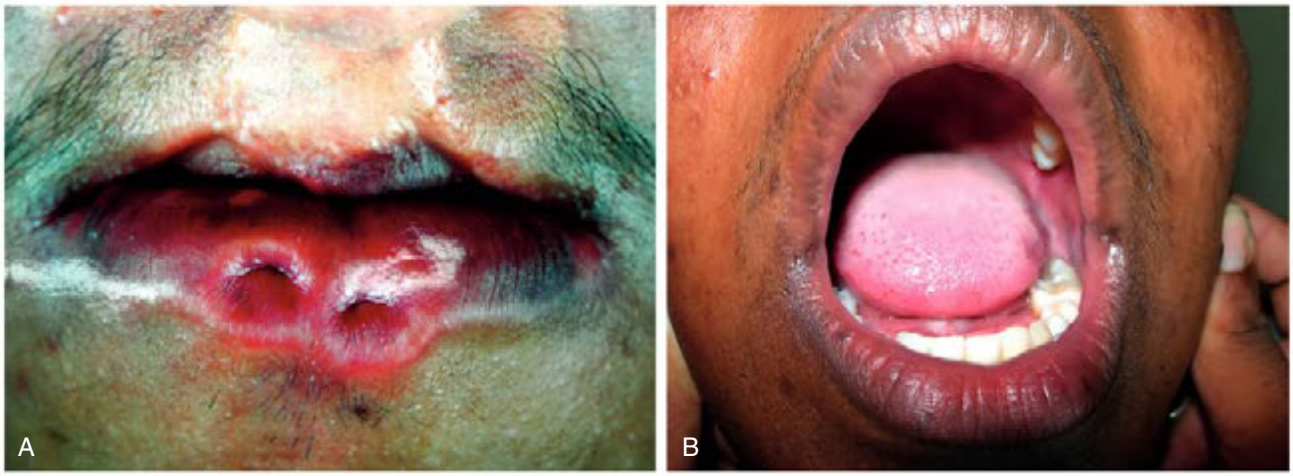
Commissural pits are an entity probably very closely related to lip pits but occur at the lip commissures, lateral to the typical lip pits. It is also frequently hereditary, possibly a dominant trait and may be associated with other congenital defects.

Pathogenesis. Many theories of the formation of congenital lip pits have been offered, but none has been universally accepted. Pits may result from notching of the lip at an early stage of development, with fixation of the tissue at the base of the notch, or from failure of complete union of the embryonic lateral sulci of the lip, which persist and ultimately develop into the typical pits.

Commissural pits are also difficult to explain, but they occur at the site of the horizontal facial cleft and may represent defective development of this embryonic fissure.

Clinical Features. The lip pit or fistula is a unilateral or bilateral depression or pit that occurs on the vermilion surface of either lip but far more commonly on the lower lip (Figure 2.14A). In some cases a sparse mucous secretion may exude from the base of this pit. The lip sometimes appears swollen, accentuating the appearance of the pits.

Commissural pits appear as unilateral or bilateral pits at the corners of the mouth on the vermilion surface (Figure 2.14B). An actual fistula may be present from which fluid may be expressed. Whether this tract, either in lip or commissural fistulas, represents a true duct is not clear. Interestingly, in several cases preauricular pits have been reported in association with commissural pits.



• **Fig. 2.14** (A) Congenital Lip Pits. (B) Congenital Commissural Pits. *(Courtesy: Dr Spencer Lilly, Meenakshi Ammal Dental College, Chennai.)*

Treatment. Surgical excision of these various pits has been recommended but primarily for academic information, since the pits are harmless and seldom manifest complications.

Lateral Soft Palate Fistula

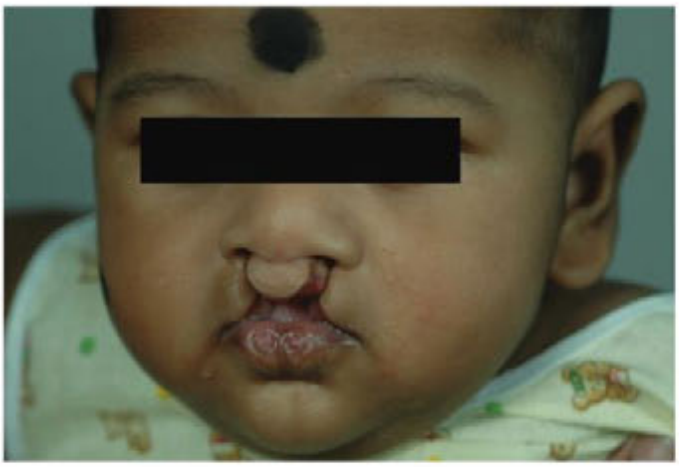
Rarely, fistulas occur on the lateral aspects of the palate and connect the oral cavity and pharyngeal area. Congenital lateral palate fistulas are usually bilateral or unilateral defects of the soft palate resulting from irregularity in development of the second branchial pouch or at times due to infection, either primary or secondary to surgical complications. It is also associated with other anomalies like palatine tonsil aplasia or hypoplasia, preauricular fistulas, and deafness. These fistulas are usually asymptomatic, mostly involving the anterior tonsillar pillar, with its dimension ranging to a maximum of 1 cm. These lesions are not very deleterious and no treatment is necessary.

van der Woude Syndrome *(Cleft Lip Syndrome, Lip Pit Syndrome)*

van der Woude syndrome is an autosomal dominant syndrome typically consisting of a cleft lip or cleft palate and lower lip pits (Figure 2.15). The degree to which individuals carrying the gene are affected is widely variable, even within families. These variable manifestations include lip pits alone, missing teeth or isolated cleft lip, and palate of varying degrees of severity. Other associated anomalies have also been described.

Cleft lip and/or cleft palate may be associated with congenital lower lip sinuses. Bilateral sinuses are relatively more common than unilateral ones, and solitary lower lip sinus unassociated with any other lip or palatal anomalies may occur rarely. Atypical locations of sinuses have been described in the midline, upper lip, and commissures. Prevalence of sinuses in upper lip is extremely rare, and is more commonly seen in females, with majority of cases reported between the first and second decades of life. Asians show an increased prevalence. Usually they present as a pit opening onto a blind sinus ending just beneath the mucosal surface of the lip, with no communication with the oral cavity. The canals are lined by stratified squamous epithelium with the adjacent connective tissue containing numerous mucous secretary glands, whose activity can occasionally be enhanced by mastication.

Treatment for this condition involves complete surgical excision of the sinus tract and surrounding inflamed tissue, if any.



• **Fig. 2.15** Lip Pits with Cleft Lip and Palate. *(Courtesy: Dr Manikandhan, Meenakshi Ammal Dental College, Chennai.)*

Etiology. The most prominent and consistent feature of van der Woude syndrome is orofacial anomalies. They are due to an abnormal fusion of the palate and lips at days 30–50 postconception. The van der Woude syndrome can be caused by deletions in chromosome band **1q32**, and linkage analysis has confirmed this chromosomal locus as the disease gene site. Further studies have raised the possibility that the degree of phenotypic expression of a gene defect at this locus may be influenced by a second modifying gene that has been mapped to chromosome band **17p11**.

Clinical Features. In general, van der Woude syndrome affects about 1 in 100,000–200,000 people. About 1%–2% of patients with cleft lip or palate have van der Woude syndrome. The van der Woude syndrome affects both genders equally and no difference among them has been reported. The severity of the van der Woude syndrome varies widely, even within families. About 25% of individuals with the van der Woude syndrome have no findings or minimal ones, such as missing teeth or trivial indentations in the lower lips. Others have severe clefting of the lip or palate. The hallmark of the van der Woude syndrome is the association of cleft lip and/or palate with distinctive lower lip pits. This combination is seen in about 70% of those who are overtly affected but in less than half of those who carry the gene. The cleft lip and palate may take any degree of severity and may be unilateral or

bilateral. Hypernasal voice and cleft or bifid uvula are clues to this diagnosis. It is also possible that a bifid uvula is an isolated finding in certain individuals with the van der Woude syndrome. The lower lip pits seen in this syndrome are fairly distinctive.

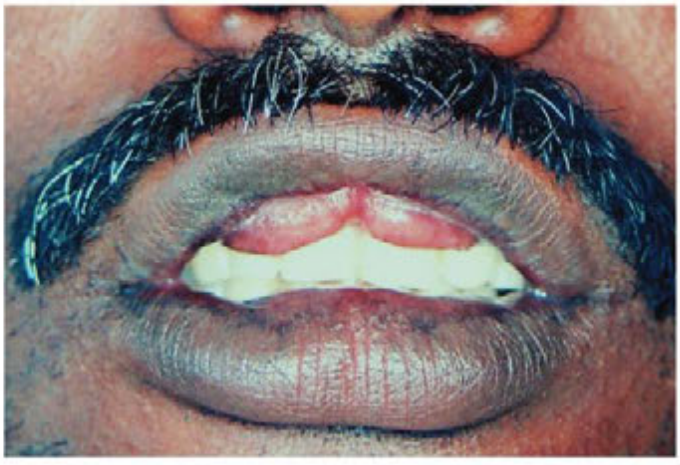
The pits are usually medial, on the vermilion portion of the lower lip. They tend to be cantered on small elevations in infancy, but are simple depressions in adults. These pits are often associated with accessory salivary glands that empty into the pits, sometimes leading to embarrassing visible discharge. Occasionally lip pits may be the only manifestation of the syndrome. Affected individuals may have maxillary hypodontia, missing maxillary incisors or missing premolars. Again, this may be the only manifestation of the syndrome. Although infrequently reported, other oral manifestations include syngnathia (congenital adhesion of the jaws); narrow, high, arched palate; and ankyloglossia (short glossal frenulum or tongue tie).

Extraoral Manifestations. The reported incidence of extraoral manifestations is rare but includes limb anomalies, popliteal webs, and brain abnormalities. Accessory nipples and congenital heart defects have also been reported.

Treatment. Along with a thorough orofacial examination, a thorough general physical examination helps to determine if there are other associated anomalies of the cardiovascular system, genitourinary system, limbs, or other organ systems. Examination and genetic counseling by a pediatric geneticist (dysmorphologist) is suggested for families that may be affected by the van der Woude syndrome. This should include an examination of as many potentially affected family members (probands) as possible. Surgical repair of the cleft lip and palate or other anomalies may be required, when planning surgical intervention, imaging studies of affected areas, such as CT scanning of the oropharynx, may be appropriate. Even among those less severely affected, surgical excision of lip pits is often performed, either to alleviate discomfort or for cosmetic reasons.

Double Lip

Double lip is an anomaly characterized by a fold of excess tissue on the inner mucosal aspect of the lip (Figure 2.16). It may be congenital or acquired as a result of trauma. Congenital type is thought to be due to the persistence of the sulcus between the pars glabrosa and the pars villosa.



• **Fig. 2.16** Double Lip. *(Courtesy: Dr S. Karthigakannan, Oral Physician, Nagercoil.)*

Clinical Features. This redundant mass of tissue usually occurs on the upper lip, although the lower lip, and on rare occasions, both upper and lower lips are involved. When the upper lip is tensed, the double lip resembles a "cupid's bow." The double lip usually cannot be seen when the lips are at rest and becomes visible when the individual smiles. There is no information available regarding the familial, sex, or racial predilection. Occasionally, it occurs in random association with other oral anomalies.

The occurrence of acquired double lip in association with blepharochalasis and nontoxic thyroid goiter is known as **Ascher syndrome**. The etiology for this condition is not known, but an autosomal inheritance with variable expressivity has been suggested as the cause. Blepharochalasis is drooping of the tissue between the eyebrow and the edge of the upper eyelid so that it hangs loosely over the margin of the lid and may be severe enough to cause interference with vision. It is caused by the relaxation of the supra tarsal fold as a result of atrophy and thinning of the skin of the eyelid. In these cases, the eye and the lip abnormalities usually develop abruptly. Many cases exhibit only the lip and eyelid involvement, and thyroid enlargement may appear after several years.

Treatment. No treatment is necessary except for cosmetic purposes or function involving speech and mastication. The excess tissue is easily excised surgically.

Cheilitis Glandularis *(Actinic Cheilitis)*

Cheilitis glandularis is a clinical diagnosis that refers to an uncommon and poorly understood inflammatory disorder of the lip. The condition is characterized by progressive enlargement and eversion of the lower lip that results in obliteration of the mucosal–vermilion interface. With externalization and chronic exposure, the delicate labial mucous membrane is secondarily altered by environmental influences, leading to erosion, ulceration, and crusting. Most significantly, susceptibility to actinic damage is increased. Therefore, cheilitis glandularis can be considered a potential predisposing factor for the development of actinic cheilitis and squamous cell carcinoma.

Etiology. Cheilitis glandularis is an unusual clinical manifestation of cheilitis that evolves in response to one or more diverse sources of chronic irritation. Lip enlargement is attributable to inflammation, hyperemia, edema, and fibrosis. Surface keratosis, erosion, and crusting develop as a consequent to long-standing actinic exposure, unusual repeated manipulations that include self-inflicted biting or other factitial trauma, excessive wetting from compulsive licking, drying (sometimes associated with mouth breathing, atopy, eczema, and asthma), and any other repeated stimulus that could serve as a chronic aggravating factor.

Clinical Features. Cheilitis glandularis is a chronic progressive condition. Patients typically present for diagnostic consultation within 3–12 months of onset. Complaints vary according to the nature and the degree of pain, the enlargement and the loss of elasticity of the lip, and the extent of evident surface change. Asymptomatic lip swelling initially occurs with clear viscous secretion expressible from dilated ductal openings on the mucosal surface. Some patients report periods of relative quiescence interrupted by transient or persistent painful episodes associated with suppurative discharge. A burning discomfort or a sensation of rawness referable to the vermilion border may be reported. This is associated with atrophy, speckled leukoplakic change, erosion, or frank ulceration with crusting (Figure 2.17). Cheilitis glandularis affects the lower lip almost exclusively. In more suppurative cases, application of gentle pressure can elicit mucopurulent exudate. Prolonged