Thus there is an opportunity for infectious agents or their byproducts to penetrate the naked epithelial barrier and initiate an inflammatory response, as happens in gingival disease.

Special cells in the basal layer of the oral mucosa generate replacements for surface cells as they wear out. The painful oral ulcers and oral mucositis that may develop in patients undergoing radiation or chemotherapy for head and neck cancer occur because these cancer-killing agents attack all cells undergoing rapid turnover, whether healthy or cancerous.

The Teeth

The most prominent features of the oral cavity are the teeth. The 20 primary, or deciduous, teeth erupt generally between 6 months and 2 to 3 years of age and are succeeded by the permanent teeth beginning at about age 6. The primary teeth enable infants to eat solid foods, aid speech development, and serve as placeholders for the permanent dentition. Keeping primary teeth healthy is important, not only in sparing an infant pain and disease, but also in preserving the dimensions of the dental arches and lessening the risk of dental caries in the permanent teeth. A period of mixed primary and permanent dentition occurs from about ages 6 to 13. There are 28 to 32 permanent teeth, depending on whether the 4 wisdom teeth (third molars), which are last to erupt, are present. Teeth are anchored in the jaws by the periodontal ligament. This ligament connects the cervix (neck) of the tooth, at the junction between the crown and root, to the gingiva. Below that, the ligament connects the outer layer of the tooth root, the cementum, to the adjacent alveolar bone (the part of the jaw bone that supports the tooth roots).

The evolutionary forces that shaped the human mouth designed an apparatus for optimal food intake. The front four upper and lower incisor teeth are chisel-shaped for biting, cutting, and tearing and exert forces of 30 to 50 pounds. The canines, or cuspids, are larger and stronger and have deeper roots than the incisors; their conical cusps are effective for ripping and tearing. The premolars, or bicuspids, and the molars are designed for heavy grinding and chewing, exerting forces as high as 200-plus pounds. The temporomandibular joint, the most complex synovial joint in the body, equips the human jaw with extraordinary mobility, enabling movements in three dimensions. Its range of motion is controlled by three sets of muscles of mastication—the masseter, temporalis, and pterygoid muscles (Oberg 1994). Chewing reduces food to small particles and mixes it with saliva to form a bolus for swallowing.

The Salivary Glands

Saliva is the mixed product of multiple salivary glands that lie under the mucosa. The three major glands are the paired parotid, submandibular, and sublingual glands. The parotids, near the ears, secrete a watery saliva into the mouth via ducts in the cheeks. The walnut-sized submandibular glands lie in the floor of the mouth and secrete a mucous fluid. The secretions of the almond-shaped sublingual glands, also in the floor of the mouth but near the front, usually join with those of the submandibular glands. Tiny minor salivary glands are scattered within the inner surfaces of the lips, cheeks, and soft and hard palates; these secrete a mucinous saliva directly onto the soft tissue surfaces.

Saliva moistens food and provides mucinous proteins to lubricate the bolus for ease of swallowing. The combined movements of the tongue and cheeks move the bolus to the back of the mouth. Saliva also contains the enzyme amylase, which initiates the digestion of starch. By solubilizing food components and facilitating their interaction with the taste buds on the tongue and palate, saliva also contributes to taste enhancement.

Tissue Protection

The main function of saliva is not—as is commonly believed—to aid digestion, but to protect the integrity of the oral tissues. The moment a baby passes through the birth canal and takes its first breath, microbes begin to take up residence in its mouth. Later, as the teeth erupt, additional bacteria establish colonies on tooth surfaces (Mandel 1989). Nearly 500 species of microbes in all, most of which are not harmful, will colonize the oral cavity (Kroes et al. 1999). The microbes form a biofilm, in which their numbers greatly exceed the number of human inhabitants on Earth.

Millions of years before there were toothbrushes, dental floss, and water irrigators, evolutionary forces generated protective mechanisms to combat potentially harmful microbes. The physical flow of saliva helps to dislodge pathogens (viruses, bacteria, and yeast) from teeth and mucosal surfaces, just as tearing and blinking, sneezing, and coughing and expectorating clear the eye, nose, and throat. Saliva can also cause microbes to clump together so that they can be swallowed before they become firmly attached. Saliva can destroy orally shed infected

white blood cells by virtue of its low salt content: the infected cells—of higher salt content—swell and burst when exposed to fluids of lower salinity (Baron et al. 1999).

Salivary secretions, like tears and other exocrine gland secretions, are rich in antimicrobial components. Certain molecules in saliva, such as lysozyme, lactoferrin, peroxidase, and histatins, can directly kill or inhibit a variety of microbes; the histatins are particularly potent antifungal agents (Xu et al. 1991). Several salivary proteins exhibit antiviral properties, including secretory leukocyte protease inhibitor (SLPI), recently discovered to have the ability to inhibit HIV from invading cells (Shugars and Wahl 1998).

The ability of saliva to limit the growth of pathogens, in some instances even preventing them from establishing a niche in the biofilm community in the first place, is a major determinant of general as well as of oral health. When salivary flow is compromised, the gateway to the body can open wide to local as well as to systemic pathogens.

Barrier and Buffering Properties

Salivary components protect oral tissues in other ways as well. Mucins have unique properties that enable them to concentrate on mucosal surfaces and provide an effective barrier against drying and physical and chemical irritants (Tabak 1995). They act as natural waterproofing, control the permeability of the tissue surfaces, and help limit penetration of potential irritants and toxins in foods and beverages, as well as toxic chemicals and potential carcinogens in tobacco and tobacco smoke and from other sources. This barrier function complements the barrier formed by the oral mucosa itself. The mucosa has a specific permeability coefficient that can change under various conditions of stress, nutritional status, and other challenges.

Saliva contains several effective buffering systems that can help maintain a normal pH when acidic foods and beverages are introduced, thereby protecting oral tissues against acidic attack. When swallowed, these buffers protect the esophagus, helping neutralize the reflux acids of conditions such as heartburn and hiatal hernia (Sarosiek et al. 1996).

Wound Healing

Saliva also contains molecules that nurture and preserve the oral tissues, even helping them to repair and regenerate (Mandel 1989, Tabak 1995, Zelles et al. 1995). Experimental studies have shown that wound healing is significantly enhanced by saliva, in part because of the presence of a potent molecule, epidermal growth factor (EGF) (Zelles et al. 1995). When swallowed, EGF can also protect the tissue surfaces of the esophagus (Sarosiek et al. 1996). Vascular endothelial growth factor (VEGF) has also been identified in saliva. VEGF stimulates blood vessels and may contribute to the remarkable healing capacity of oral tissues (Taichman et al. 1998, Zelles et al. 1995).

Caries Protection

Saliva also guards against dental caries (tooth decay), the disease that has been the greatest threat to teeth. Caries is caused by bacteria that generate acids that attack tooth mineral (see Chapter 3). The buffering systems in saliva, augmented by the neutralizing components urea and ammonium, counter the acid formation. The physical flow of saliva also helps flush out sugars and food particles that are the bacterial food source. Mineral salts in saliva—calcium and phosphate—can remineralize tooth enamel, effectively reversing the decay process. This regenerative function is greatly enhanced by the presence of fluoride in saliva. Finally, saliva forms a film on teeth made up of selectively adsorbed proteins that have a high affinity for tooth mineral. This acquired pellicle is insoluble and limits the diffusion of acids into the teeth and the dissolution of tooth mineral (Lamkin and Oppenheim 1993).

The Immune System

The salivary glands and the oral mucosa, along with the body's other mucosal linings and the lymphatic circulation, constitute a major component of the body's defense system—the mucosal immune system (Mestecky 1987). When the area of the oral mucosa is combined with the areas of the mucosal linings and passageways of the respiratory, gastrointestinal, urinary, and genital tracts, the total represents the largest surface area of the body—nearly 400 square meters, or 200 times larger than the total skin area.

The great majority of infectious diseases affect, or are acquired through, mucosal surfaces. Immune cells that line the mucous membranes throughout the body secrete antibodies targeted to specific disease-causing microbes (Mandel and Ellison 1985). The mucosal immune system works in concert with the bloodborne immune system to detect and dispose of foreign substances and invading microbes.

The two components of the immune system consist of molecules and cells that provide both broad and specific defense mechanisms. In the broad group

are some circulating white blood cells (monocytes and granulocytes) associated with the inflammatory response. These cells migrate to a site of injury or infection and move into damaged tissues manifesting the four signs of inflammation: swelling, heat, redness, and pain. The cells promote an increase in blood flow to begin the healing process, and they recruit other cells able to engulf and dispose of the offending organism.

The specific immune system is associated with two major classes of immune cells: T cells and B cells. T cells react to antigens (proteins associated with microbes or irritants) and can stimulate B cells to make antigen-specific antibodies. These are the Y-shaped molecules called immunoglobulins.

T cells are the instruments of cell-mediated immunity; they are able to detect telltale surface markers on diseased or foreign cells that distinguish them from normal body cells. Some T cells can kill infected cells and cancer cells directly. T cells are also involved in the rejection of organ transplants.

Certain T cells are memory cells, preserving the information from earlier encounters with specific pathogens. Thus they are able to initiate more rapid and effective responses in the event of a repeat encounter with the pathogen. Helper T cells assist in activating killer T and B cells. It is the loss of helper T cells that leads to the many infections that cause illness and death in HIV disease. Still another group of T cells, suppressor T cells, moderates the activities of both B and T lymphocytes.

Activated T cells generate and release cytokines—potent families of proteins, such as the interleukins, that can stimulate immune cells to divide, migrate, attack, and engulf invaders or participate in the inflammatory response. Other cytokines include varieties of tumor necrosis factor and adhesins (proteins that facilitate the binding of immune cells to each other or to blood vessel linings). Feedback mechanisms provide a system of checks and balances to regulate cytokine production.

The immune system interacts with the nervous and endocrine systems. For example, immune cytokines secreted into the brain can induce the fever associated with infection: the high temperature may help destroy the infectious agent. The brain's response to stress also has repercussions for the immune system. The hypothalamus-pituitary-adrenal axis is a major pathway activated in response to stress, which results in the secretion of cortisol, the stress hormone, from the adrenal glands. Cortisol promotes the body's fight-or-flight mechanisms, but via feedback loops, cortisol acts to depress immune reactions.

Much of what we know about the immune system has come from studies of serum factors, but research in the last two decades has generated much new information about mucosal immunity (McGhee and Kiyono 1999). The mucosal immune system can be divided into inductive and effector compartments. The nasal-associated lymphoreticular tissues (NALT) in the nasopharyngeal area (which includes the tonsils) and the gut-associated lymphoreticular tissues (GALT) in gut tissue are inductive regions, where foreign invaders are encountered. If, for example, infectious bacteria are swallowed, they can stimulate immune cells in GALT to circulate T and B cells through the lymph system to various effector sites in the gastrointestinal and upper respiratory tracts and in the salivary and other exocrine glands. The B cells in the gland produce antibodies, designated S-IgA, to which is attached a secretory component (Mestecky and Russell 1997). These antibodies are the dominant type found in saliva, tears, breast milk, and colostrum and in the gastrointestinal and genitourinary tracts.

The uses of the mucosal immune system extend beyond its normal surveillance and defense functions. The tissues can be used as routes for delivery of oral (swallowed) or nasal (inhaled) vaccines, as sites for gene transfer to augment host defenses, and as a means of invoking oral tolerance—the suppression of overactive or inappropriate immune responses that occur in chronic inflammatory and autoimmune diseases (Baum and O'Connell 1995, Hajishengallis and Michalek 1999).

CRANIOFACIAL ORIGINS

The extraordinary successes of research in molecular genetics over the past decade, coupled with the National Institutes of Health's project to map and sequence the human genome, have proved to be a boon in understanding craniofacial development. The use of automated gene-sequencing equipment, the Internet availability of genome databases, and the ability to transfer genes or create "knockout" animals—in which a gene of interest has been eliminated—have greatly facilitated progress. The events that govern the transformation of a fertilized human egg cell into a healthy newborn with all organs and systems in place are being unfolded at the molecular level. Families of master and regulatory genes have been identified, and their role in controlling how the body's general shape and specialized tissues and organs are formed is coming to light.

Early Development

The Three Germ Cell Layers

By the time the face and the mouth are ready to form, the human embryo is in the third week of development. The embryo has evolved from a sphere to an oval two-layered disk with a head-to-tail orientation. The outer layer is the epiblast and will become the ectodermal germ layer. A narrow groove, called the primitive streak, extends from the tail toward the center of the disk, where it ends in a spot surrounding a small depression called the primitive pit. Epiblast cells migrate toward the streak and pit, detach from the surface, and slip downward to form the two additional germ cell layers, the mesoderm and, below that, the endoderm.

The ectodermal layer gives rise to tissues that relate the body to the outside world: the nervous system; the sensory epithelium of the ears, nose, and eyes; skin, hair, nails, salivary glands, tonsils, and tooth enamel; and the pituitary, mammary, and sweat glands. At the head end, the mesodermal layer gives rise to a primitive connective tissue, called mesenchyme, which will interact with the ectoderm to form parts of the head and mouth. The remaining mesoderm develops into the muscle, cartilage, bone, and subcutaneous skin tissue of the rest of the body. The mesoderm is also the origin of the vascular and urogenital systems (except for the bladder), the spleen, and the adrenal cortex. The innermost, endodermal layer provides the linings of the gut, the respiratory system, bladder, liver, pancreas, thyroid and parathyroid glands, and parts of the middle ear.

Neural Tube and Neural Crest

Further migrations and descending movements of cells result in the formation of the notochord, a solid cord of cells along the midline that will become the backbone. The ectoderm above the notochord next thickens to form a neural plate. The sides of the plate curve up and inward to form a neural tube, beginning at the head, with fusion completed by the end of the fourth week. The tail end of the tube will form the spinal cord; the head end differentiates into the three parts of the primitive brain: the forebrain, midbrain, and hindbrain.

What happens next is of central importance to the craniofacial complex: cells that were at the edges of the neural plate break away to form neural crest cells, which migrate to the forebrain area and to the nearby branchial arches, a series of swellings on either side of the embryo, adjacent to the hindbrain. The hindbrain becomes organized into eight rhombomeres, segments of future nerve tissue arranged in an orderly fashion so that the first two rhombomeres innervate branchial arch 1, and so on.

During the formation of the midbrain and hindbrain, cranial neural crest cells migrate into the developing facial areas and differentiate into neuronal and nonneuronal tissues. The neuronal tissues include the clusters of nerve cells (ganglia) that lie adjacent to the spinal cord, parts of the ganglia of four cranial nerves, and two of the meningeal layers of the brain. The nonneuronal tissues include major bones, cartilage, the dentin and cementum of teeth, and the various types of connective tissues of the craniofacial complex, as well as the muscles of the eye. The branchial arches give rise to the bones, cartilage, nerves, muscles, and blood supply of successive segments of the head and neck.

The Face and Mouth

The branchial arches play a key role in the formation of the facial structures. Toward the end of the fourth week of gestation, a primitive mouth appears. This "stomadeum" is flanked by a series of swellings, or prominences, derived from the first pair of branchial arches. A single frontonasal prominence forms the upper border of the stomadeum. On either side of this prominence are two thickened regions of ectoderm—the nasal placodes. At the sides of the stomadeum and below it are pairs of maxillary and mandibular prominences.

In the course of the next 3 weeks, differential growth and movements of the various prominences and fusions of tissues that come together at the midline will sculpt the bridge, crest, sides, and tip of the nose, the upper and lower lips, and the upper and lower jaws (Bhaskar and Orban 1990, Sadler and Langman 1995).

The external merger at the midline of a pair of prominences that helps to form the nose occurs inside the mouth as well, resulting in an intermaxillary segment that will contribute to the formation of the four upper incisors and parts of a small triangular-shaped primary palate and the upper jaw. The bulk of the palate, the secondary palate, forms from shelflike outgrowths of the maxillary prominences. These growths appear in the sixth week, and in the following week fuse along the midline above the tongue. (The tongue appears at approximately 4 weeks, the front two-thirds forming from the first branchial arch, and the posterior third from parts of the second, third, and fourth branchial arches.) The palatal shelves also fuse with the primary palate along a triangular border called the incisive foramen.

This border is considered the line of division among clefting abnormalities. Lateral cleft lip, cleft upper jaw, and clefts between the primary and secondary palates are associated with defects anterior to the incisive foramen. Cleft palate and cleft uvula occur because of defects affecting closure of the palatal shelves posterior to the foramen (Bhaskar and Orban 1990, Sadler and Langman 1995).

The Teeth

Tooth development begins in the sixth week with the appearance of an epithelial band lining the upper and lower jaws. A part of the band develops into a dental lamina, which forms a series of projections into the jaw. These are the tooth buds and correspond to the sites of deciduous teeth. The epithelial tissue of the bud develops into an enamel organ that forms a cap over tissue that is differentiating in the jaw to become the dental papilla. The two structures—the enamel organ, derived from the epithelium, and the dental papilla, derived from neural crest mesenchyme—constitute the tooth germ.

With further development, the tooth germ assumes a bell shape and separates from the oral epithelium. At the same time, the internal epithelial layer of the enamel organ undergoes a series of infoldings that will shape the future crown of the tooth.

Mineralization of the tooth begins at the late bell stage. The first mineralized tissue to form is dentin, which provides the foundation for the deposition of enamel. The differentiation of the odontoblasts (the dentin-producing cells) depends on organizing influences from enamel organ cells. Thus the development of these two different hard tissues is a mutually dependent process.

As dentin is laid down, the odontoblasts move toward the center of the papilla, trailing thin cellular processes, which become embedded in the mineralized matrix. When dentin formation is completed, dentin completely surrounds the pulp, protecting it from injury. The enamel layer of the tooth starts to form soon after the first dentin appears, synthesized by special enamel-forming cells, or ameloblasts, which develop from the enamel organ. The tooth root, and its outer layer of cementum, form only after the crown erupts.

Genetic Controls

Only in the last decade have scientists begun to understand how certain genes and gene families control embryonic development. Their findings have come from detailed studies of species ranging from fruit flies, nematodes, and zebrafish to frog, chick, mouse, and human embryos. In many cases, the simpler organism has been the source of discoveries of genes or developmental processes that are highly conserved in the course of evolution (Alberts et al. 1994).

Research on the fruit fly, for example, has revealed that particular families of genes are responsible for the fundamental head to thorax to tail patterning of the fly's body. Another set of genes determines the back-to-front positioning of organs, and a third set subdivides this general body plan into a series of discrete segments. With further development, yet another family of genes confers a positional memory on the cells within a segment. These "homeotic selector" genes ensure that cells in one part of a particular segment "know" that they are destined to be wings and not legs, or to be eyes and not antennae. In flies the homeotic genes are known as *Hom* genes. Their arrangement on the fly chromosome is ordered with genes at one end of the chromosome specifying the developmental destiny of cells in the most anterior segments of the fly's body and genes at the other end specifying the fate of cells in the most posterior segments.

In the course of evolution, mammals have developed four overlapping sets of positional memory gene clusters homologous to the fly's single *Hom* complex. The four mammalian *Hox* gene families are ordered in a similar anterior-posterior fashion along four different chromosomes. The mammalian genes appear to operate like the *Hom* genes: they code for DNA-binding proteins that control gene expression. The similarity from fly to human is particularly evident when maps of the expression domains of *Hom* genes in anterior segments of the fly embryo are compared to maps of *Hox* gene expression as seen in the rhombomeres and branchial arches of mammals.

Molecular genetic studies of flies and other nonmammalian species show some variation in how and when the basic body patterns and repeating segments are formed. Sometimes the head-to-tail pattern is laid down in the egg cell before fertilization—dictated by egg polarity genes. Although egg polarity genes do not operate in humans, mutations have been found in a human gene homologous to the fly egg polarity gene and account for serious syndromes in which there are defects in anterior organs, such as the pituitary gland and heart.

None of these developmental controls work in isolation. Much remains to be understood about the genetic clock that determines when and where developmental genes act, how they interact, and what

mechanisms are used to sustain as well as terminate their function. The systems that govern programmed cell death are also important: normal development depends as much on the elimination of cells as it does on the orderly movement, proliferation, and differentiation of cells.

When it comes to processes that control the development of particular tissues or organs—bones, skin, or heart—developmental biologists observe that there is often an "organizer," that is, a cell or set of cells that initiates the process. The organizer induces changes in the behavior of neighboring cells through cell-cell interactions, so that these cells develop into the specified type—bone or skin or heart muscle. The interaction with the neighboring cell is often in the form of a signaling molecule, such as a growth factor (e.g., transforming growth factor b, epidermal growth factor, fibroblast growth factor) that attaches to a receptor on the surface membrane of the recipient cell. This interaction is translated to the interior of the cell, where a chain of molecular interactions eventually reaches the cell nucleus to effect gene expression. One of the more startling discoveries of the past decade has been the finding that a series of mutations, each associated with a change in only one nucleotide of the gene for the fibroblast growth factor receptor—a so-called point mutation—accounts for a range of organ defects seen in at least a half dozen craniofacial syndromes. Interestingly, all these syndromes include craniosynostosis, a premature closure of the bones that form the skull.

THE AGING OF CRANIOFACIAL TISSUES

Normal aging describes the developmental processes that begin at conception, continue in childhood, and merge gradually into maturation and senescence. The milestones of development such as the age when children teethe, begin to walk, talk, enter puberty, attain their full height, and so on, are under genetic and hormonal controls, subject to important environmental factors such as nutrition and exercise. Despite the complexity and interrelationships of the variables involved, a reasonably accurate picture of normal age-related changes in the craniofacial complex is emerging (Ship 1999).

Barring major illness or injury, destructive behaviors, or severe or unusual environmental circumstances, the cells, tissues, and fluids of the face and mouth are hardy survivors, eminently durable and functional over a long life span. For any given individual the combination of life experience and lifestyle (including medical and dental history) creates a unique craniofacial portrait, one that inspired George Orwell to remark, "By the age of fifty, a man gets the face he deserves."

The Teeth

One of the more dramatic discoveries in biomedical science in the twentieth century has been the realization that tooth loss is not an inevitable consequence of aging, but the result of disease or injury. Aging does produce a number of other dental changes, however. Teeth change in form and color with age. Wear and attrition alter the biting and chewing surfaces, as do food choices and oral habits. The altered surface structure produces a different pattern of light reflection in older teeth, resulting in some yellowing and a general loss of translucency (Mjor 1986). Fully formed enamel is acellular, hence there is no metabolic activity or turnover as occurs in skin, for example. Dentin and cementum have limited cellular activity. In contrast, tooth pulp and periodontal ligament undergo relatively high levels of tissue turnover.

Tooth surfaces can be eroded by chemical dissolution from fruit acids and from acids from sugars in foods such as soft drinks and candies. This destructive process can occur at any age, resulting in loss of translucency as well as some tissue loss from demineralization (Zero 1996). Countering the erosive forces are the natural components in saliva that help remineralize the enamel surface, a process that is enhanced when fluoride is present (see "Caries Protection" above).

The cementum increases in thickness with age. Gingival recession caused by normal aging exposes the cementum to the oral environment (and is the origin of the expression "long in the tooth"). The exposed cementum can often be worn away mechanically, exposing the underlying dentin, which can then become hypersensitive. Dentin responds through a series of protective changes that work to close off the connections between dentin and nerves in the pulp, reducing transmission of painful stimuli.

The Jaws

The bones of the maxilla and mandible that support the teeth, called the alveolar processes, are, like bone elsewhere in the body, subject to cellular turnover in a coordinated process of bone resorption and

formation. Alveolar bone is well adapted to mechanical stresses, and changes continuously during facial growth, tooth eruption, tooth wear, and tooth loss. This lifelong adaptation makes orthodontic treatments to reposition teeth in adults possible.

Because the primary function of alveolar bone is to support the teeth, the loss of teeth will lead to bone atrophy, making prosthetic replacements difficult. The rate of bone loss is affected by both local disease such as periodontal disease and systemic conditions such as osteoporosis (Bhaskar 1991).

The Oral Mucosa

The oral mucosa appears to age in much the same way as skin does. The oral epithelium thins and becomes less hydrated, increasing vulnerability to injury. The rate of cell division is slower, but the basic cell architecture and patterning of cell types throughout the oral cavity are maintained. It is not certain to what extent these changes are a natural consequence of aging; they may be due to altered protein synthesis or lowered responsiveness to regulatory molecules. They may also be an effect of diminished vascularity, which could limit cellular access to oxygen and nutrients (Mjor 1986).

Overall immune system function deteriorates with age, and it is likely that mucosal immunity does as well. Such a decline could result in an increased risk of transmission of infectious agents across the mucosa and probably contributes to delayed wound healing in oral tissues with aging.

Sensory and Motor Functioning

The high density of sensory nerve endings in the craniofacial tissues and their functional abilities are well-preserved in aging. There may be minor increases in threshold detection levels or in judgments of intensity, but, for the most part, sensory cells can turn over or have a built-in reserve capacity that allows for near-optimal functioning in aging. The exception is olfaction, which declines in both men and women with age. This decrement in smell may lead to some dissatisfaction with how foods taste and increased use of flavor enhancers to compensate. But for most people, the ability to enjoy food is not appreciably diminished as time goes by. Any dramatic change in sensory function—complaints of a continued unpleasant taste or smell or the sudden complete loss of a sensory modality—should be taken seriously as a sign of possible oral or systemic disease or a side effect of medication and not dismissed as a natural by-product of aging.

The distribution of motor fibers in the craniofacial tissues is also abundant and sufficiently fine-tuned to allow for a full range of movement of the tongue, jaws, and oral-facial muscles. There is some loss of muscle tone in aging, along with changes in tongue shape and function in articulating specific speech sounds. Subtle changes may also occur in preparing food for swallowing. As with sensory changes, these developments do not seriously interfere with motor function in healthy older adults.

The Salivary Glands

Studies of normative aging indicate that individuals vary in the quantity of "whole" saliva they produce. Whole saliva consists of the secretions of the various salivary glands plus other oral contents, such as cells shed from the mucosa. These individual patterns are consistent across the life span. In healthy adults, there is no diminution in the production of saliva from the major salivary glands in the course of aging.

This constancy may seem surprising given the morphological changes documented in aging salivary glands. Both the parotid and the submandibular glands lose between 20 and 30 percent of their essential tissue volume in the course of aging. The loss primarily affects the acinar components, the cells that secrete saliva. Increases in the number of ductal cells and in fat, vascular, and connective tissues compensate for this loss, however—evidence of the remarkable functional reserve capacity of the glands, which enables them to maintain a stable salivary output across the life span (Baum 1986).

In contrast, studies of age-related changes in the chemistry of salivary secretions suggest that there are significant reductions in the concentration of mucins from the submandibular gland (Navazesh et al. 1992), which could result in reduced lubrication and contribute to a sensation of mouth dryness. There are also subtle changes in the protective ability of salivary secretory IgA antibody (Smith et al. 1987).

FINDINGS

Natural selection has served *Homo sapiens* well in evolving a craniofacial complex with remarkable functions and abilities to adapt, enabling the organism to meet the challenges of an ever-changing environment. An examination of the various tissues reveals elaborate designs that have evolved to serve the basic needs and functions of a complex mammal as well as those that are uniqely human, such as

speech. The rich distribution of nerves, muscles, and blood vessels in the region as well as extensive endocrine and immune system connections is an indication of the vital role of the craniofacial complex in adaptation and survival over a long life span. In particular,

- Genes controlling the basic patterning and segmental organization of human development, and specifically the craniofacial complex, are highly conserved in nature. Mutated genes affecting human development have counterparts in many simpler organisms.
- There is considerable reserve capacity or redundancy in the cells and tissues of the craniofacial complex, so that if they are properly cared for, the structures should function well over a lifetime.
- The salivary glands and saliva subserve tasting and digestive functions and also participate in the mucosal immune system, a main line of defense against pathogens, irritants, and toxins.
- Salivary components protect and maintain oral tissues through antimicrobial components, buffering agents, and a process by which dental enamel can be remineralized.

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PART TWO

What Is the Status of Oral Health in America?

To begin to answer this question, Chapter 3 guides the reader through a discussion of oral diseases and disorders in such categories as infections, inherited disorders, and neoplasms. Whether or not an individual succumbs to the disease or disorder in question depends on subtle interactions of genetic, environmental, and behavioral variables. Risk factors common to systemic diseases and disorders, such as tobacco use, excessive alcohol use, and inappropriate dietary practices, also contribute to many oral diseases and disorders. As more details on the causes of diseases unfold, specific strategies for disease prevention can be developed.

Chapter 4 describes the magnitude of the problem facing the nation due to oral diseases and disorders. These conditions are prevalent and complex, and they affect individuals across the life span. Although major improvements have been seen nationally for most Americans, disparities exist in some population groups as classified by age, sex, income, and race/ethnicity. National and state-based epidemiologic data presented against the backdrop of demographic and socioeconomic variables provide some information on racial and ethnic minorities, but serious shortcomings exist. The paucity of data at national, state, and local levels extends to other populations, including individuals with disabilities, those with alternate sexual orientation, migrant populations, and the homeless, and limits the capacity to fully document the magnitude of the problem and develop needed programs. The chapter provides a basis for understanding disparities in oral health by presenting available data on dental visits. More work is needed to understand the dimensions of oral health problems in the United States and the reasons for differences among populations.

CHAPTER 3

Diseases and Disorders

As the gateway to the body, the mouth is challenged by a constant barrage of invaders—bacteria, viruses, parasites, fungi. Thus infectious diseases, notably dental caries and periodontal diseases, predominate among the ills that can compromise oral health. Injuries take their toll as well, with the face and head particularly vulnerable to sports injuries, motor vehicle crashes, violence, and abuse. Less common but very serious are oral and pharyngeal cancers, with a 5-year survival rate of hardly better than 50 percent (Kosary et al. 1995). Birth defects and developmental disorders frequently affect the craniofacial complex. These appear most commonly as isolated cases of cleft lip or palate, but clefting or other craniofacial defects can also be part of complex hereditary diseases or syndromes. Additionally, acute and chronic pain can affect the oral-facial region, particularly in and around the temporomandibular (jaw) joint, and accounts for a disproportionate amount of all types of pain that drive individuals to seek health care.

Many systemic diseases such as diabetes, arthritis, osteoporosis, and AIDS, as well as therapies for systemic diseases, can directly or indirectly compromise oral tissues. The World Health Organization's *International Classification of Diseases and Stomatology* currently lists more than 120 specific diseases, distributed in 10 or more classes, that have manifestations in the oral cavity (WHO 1992).

This chapter concentrates on six major oral disease categories: dental and periodontal infections; mucosal disorders; oral and pharyngeal cancers; developmental disorders; injuries; and a sampling of chronic and disabling conditions, including Sjögren's syndrome and oral-facial pain.

DENTAL AND PERIODONTAL INFECTIONS

The most common oral diseases are dental caries and the periodontal diseases. Individuals are vulnerable to dental caries throughout life, with 85 percent of adults aged 18 and older affected. Periodontal diseases are most often seen in maturity, with the majority of adults experiencing some signs and symptoms by the mid-30s. Certain rare forms of periodontal disease affect young people. The major oral health success story of the past half century is that both caries and periodontal diseases can be prevented by a combination of individual, professional, and community measures.

Dental Caries

The word *caries* derives from the Latin for rotten, and many cultures early on posited a tooth worm as the cause of this rottenness. By the twentieth century, caries came to describe the condition of having holes in the teeth—cavities. This description, although not incorrect, is misleading. In actuality, a cavity is a late manifestation of a bacterial infection.

The bacteria colonizing the mouth are known as the *oral flora*. They form a complex community that adheres to tooth surfaces in a gelatinous mat, or *biofilm*, commonly called dental plaque. A cariogenic biofilm at a single tooth site may contain one-half-billion bacteria, of which species of mutans streptococci are critical components. These bacteria are able to ferment sugars and other carbohydrates to form lactic and other acids. Repeated cycles of acid generation can result in the microscopic dissolution of minerals in tooth enamel and the formation of an opaque white or brown spot under the enamel surface (Mandel 1979). Frequency of carbohydrate consumption (Gustafsson et al. 1954), physical

characteristics of food (e.g., stickiness), and timing of food intake (Burt and Ismail 1986) also play a role.

The essential role of bacteria in caries initiation was established in landmark experiments in the 1950s. Investigators observed that germ-free animals fed high-sugar diets remained caries-free until the introduction of mutans streptococci (a particular group of bacterial strains having a number of common characteristics, and which adhere tightly to the tooth). Later experiments demonstrated the transmissibility of the bacteria from mother to litter and from caries-infected to uninfected cage-mates (Fitzgerald and Keyes 1960). Species of *Lactobacillus*, *Actinomyces*, and other acid-producing streptococci within the plaque may also contribute to the process (Bowden 1990).

If the caries infection in enamel goes unchecked, the acid dissolution can advance to form a cavity that can extend through the dentin (the component of the tooth located under the enamel) to the pulp tissue, which is rich in nerves and blood vessels. The resulting toothache can be severe and often is accompanied by sensitivity to temperature and sweets. Treatment requires endodontic (root canal) therapy. If untreated, the pulp infection can lead to abscess, destruction of bone, and spread of the infection via the bloodstream.

Dental caries can occur at any age after teeth erupt. Particularly damaging forms can begin early, when developing primary teeth are especially vulnerable. This type of dental caries is called *early childhood caries* (ECC). Some 6 out of 10 children in the United States have one or more decayed or filled primary teeth by age 5 (U.S. Department of Health and Human Services, National Center for Health Statistics 1997). ECC may occur in children who are given pacifying bottles of juice, milk, or formula to drink during the day or overnight. The sugar contents pool around the upper front teeth, mix with cariogenic bacteria, and give rise to rapidly progressing destruction (Ripa 1988). Other risk factors for ECC include arrested development of tooth enamel, chronic illness, altered salivary composition and volume (resulting from the use of certain medications or malnourishment), mouth breathing, and blockage of saliva flow in a bottle-fed infant (Bowen 1998, Seow 1998).

Although there have been continuing reductions in dental caries in permanent teeth among children and adolescents over the past few decades, caries prevalence in the primary dentition may have stabilized or increased slightly in some population groups (Petersson and Bratthall 1996, Rozier 1995). Reductions in caries in permanent teeth also have been proportionately greater on the smooth surfaces rather than on the pit-and-fissure surfaces characteristic of chewing surfaces. The gingival tissues tend to recede over time, exposing the tooth root to cariogenic bacteria that can cause root caries. An important risk factor for root caries in older people is the use of medications that inhibit salivary flow, leading to dry mouth (xerostomia).

Saliva contains components that can directly attack cariogenic bacteria, and it is also rich in calcium and phosphates that help to remineralize tooth enamel. Demineralization of enamel occurs when pH levels fall as a result of acid production by bacteria. It can be reversed at early stages if the local environment can counteract acid production, restoring pH to neutral levels. Remineralization can occur through the replacement of lost mineral (calcium and phosphates) from the stores in saliva. Fluoride in saliva and dental plaque and the buffering capacity of saliva also contribute to this process. Indeed, it is now believed that fluoride exerts its chief caries-preventive effect by facilitating remineralization. Several studies have demonstrated that remineralization results in an increase in tooth hardness and mineral content, rendering the tooth surface more resistant to subsequent acid attack (Larsen 1987, Linton 1996, Retief 1983, Shannon 1978, Vissink et al. 1985, White 1988).

Overt caries lesions develop when there is insufficient time for remineralization between periods of acidogenesis, or when the saliva production is compromised. Over 400 medications list dry mouth as a side effect, notably some antidepressants, antipsychotics, antihistamines, decongestants, antihypertensives, diuretics, and antiparkinsonian drugs (Sreebny et al. 1992). The effects of xerostomia may be particularly severe in cancer patients receiving radiation to the head or neck because the rays can destroy salivary gland tissue rather than simply inhibiting salivary secretion.

The professional application of dental sealants (plastic films coated onto the chewing surfaces of teeth) is an important caries-preventive measure that complements the use of fluorides. The films prevent decay from developing in the pits and fissures of teeth, channels that are often inaccessible to brushing and where fluoride may be less effective.

The rate of caries progression through enamel is relatively slow (Berkey 1988, Ekanayake 1987, Shwartz et al. 1984) and may be slower in patients who have received regular fluoride treatment or who consume fluoridated water (Pitts 1983, Shwartz et al. 1984). Because a large percentage of enamel lesions remain unchanged over periods of 3 to 4 years, and

because progression rates through dentin are comparably slow (Craig et al. 1981, Emslie 1959, Kolehmainen and Rytömaa 1977), the application of infection control and monitoring procedures to assess caries risk status, lesion activity status, evidence of lesion arrest, and evidence of lesion remineralization over extended periods of time is recommended.

Experts believe that the earlier mutans streptococci are acquired in infancy, the higher the caries risk. Most studies indicate that infants are infected before their first birthday, around the time the first incisors emerge. However, one study found the median age of acquisition to be 26 months, coinciding with the emergence of the primary molars (Bowen 1998, Caufield et al. 1993, Seow 1998). DNA fingerprinting has demonstrated that the source of transmission is usually the mother (Caufield et al. 1993).

It is not clear why some individuals are more susceptible and others more resistant to caries. Genetic differences in the structure and biochemistry of enamel proteins and crystals (Slavkin 1988), as well as variations in the quality and quantity of saliva and in immune defense mechanisms are among the factors under study. Analysis of mutans streptococci genomes may also shed light, indicating which species are particularly virulent and which genes contribute to that virulence.

Even the most protective genetic endowment and developmental milieu are unlikely to confer resistance to decay in the absence of positive personal behaviors. These include sound dietary habits and good oral hygiene, including the use of fluorides, and seeking professional care. There are indications, however, that some destructive oral habits are on the rise, such as the use of smokeless (spit) tobacco products by teenage boys. Although the chief concern here lies in the long-term risk for oral cancers, spit tobacco that contains high levels of sugar is also associated with increased levels of decay of both crown and root surfaces (Tomar and Winn 1998).

Periodontal Diseases

Like dental caries, the periodontal diseases are infections caused by bacteria in the biofilm (dental plaque) that forms on oral surfaces. The basic division in the periodontal diseases is between gingivitis, which affects the gums, and periodontitis, which may involve all of the soft tissue and bone supporting the teeth. Gingivitis and milder forms of periodontitis are common in adults. The percentage of individuals with moderate to severe periodontitis, in which the destruction of supporting tissue can cause the tooth to loosen and fall out, increases with age.

Gingivitis

Gingivitis is an inflammation of the gums characterized by a change in color from normal pink to red, with swelling, bleeding, and often sensitivity and tenderness. These changes result from an accumulation of biofilm along the gingival margins and the immune system's inflammatory response to the release of destructive bacterial products. The early changes of gingivitis are reversible with thorough toothbrushing and flossing to reduce plaque. Without adequate oral hygiene, however, these early changes can become more severe, with infiltration of inflammatory cells and establishment of a chronic infection. Biofilm on tooth surfaces opposite the openings of the salivary glands often mineralizes to form calculus or tartar, which is covered by unmineralized biofilm—a combination that can exacerbate local inflammatory responses (Mandel 1995). A gingival infection may persist for months or years, yet never progress to periodontitis.

Gingival inflammation does not appear until the biofilm changes from one composed largely of gram-positive streptococci (which can live with or without oxygen) to one containing gram-negative anaerobes (which cannot live in the presence of oxygen). Numerous attempts have been made to pinpoint which microorganisms in the supragingival (above the gum line) plaque are the culprits in gingivitis. Frequently mentioned organisms include *Fusobacterium nucleatum*, *Veillonella parvula*, and species of *Campylobacter* and *Treponema*. But as Ranney (1989) notes, "The complexity of the results defies any attempt to define a discrete group clearly and consistently associated with gingivitis."

Gingival inflammation may be influenced by steroid hormones, occurring as puberty gingivitis, pregnancy gingivitis, and gingivitis associated with birth control medication or steroid therapy. The presence of steroid hormones in tissues adjacent to biofilm apparently encourages the growth of certain bacteria and triggers an exaggerated response to biofilm accumulation (Caton 1989). Again, thorough oral hygiene can control this response.

Certain prescription drugs can also lead to gingival overgrowth and inflammation. These include the antiepileptic drug phenytoin (Dilantin); cyclosporin, used for immunosuppressive therapy in transplant patients; and various calcium channel blockers used in heart disease. Treatment often requires surgical removal of the excess tissue followed by appropriate personal and professional oral health care.

A form of gingivitis common 50 years ago but relatively rare today is acute necrotizing ulcerative gingivitis, also known as Vincent's infection or trench mouth. This aggressive infection is characterized by destruction of the gingiva between the teeth, spontaneous bleeding, pain, and oral odor. People under extreme stress have an increased susceptibility. Spirochetes and other bacteria have been found in the connective tissue of those affected. An association between smoking and this type of gingivitis is well recognized and was demonstrated as early as 1946 (Pindborg 1947, 1949). This condition has been seen in some HIV-positive patients (Murray 1994). Treatment requires a combination of professional periodontal treatment and antibacterial therapy along with professional smoking cessation assistance as appropriate.

Adult Periodontitis

The most common form of adult periodontitis is described as general and moderately progressing; a second form is described as rapidly progressing and severe, and is often resistant to treatment. The moderately progressive adult form is characterized by a gradual loss of attachment of the periodontal ligament to the gingiva and bone along with loss of the supporting bone. It is most often accompanied by gingivitis (Genco 1990). It is not necessarily preceded by gingivitis, but the gingivitis-related biofilm often seeds the subgingival plaque. The destruction of periodontal ligament and bone results in the formation of a pocket between the tooth and adjacent tissues, which harbors subgingival plaque. The calculus formed in the pocket by inflammatory fluids and minerals in adjacent tissues is especially damaging (Mandel and Gaffar 1986).

The severity of periodontal disease is determined through a series of measurements, including the extent of gingival inflammation and bleeding, the probing depth of the pocket to the point of resistance, the clinical attachment loss of the periodontal ligament measured from a fixed point on the tooth (usually the cemento-enamel junction), and the loss of adjacent alveolar bone as measured by x-ray (Genco 1996). Severity is determined by the rate of disease progression over time and the response of the tissues to treatment.

Adult periodontitis often begins in adolescence but is usually not clinically significant until the mid-30s. Prevalence and severity increase but do not accelerate with age (Beck 1996). One view proposes that destruction occurs at a specific site during a defined period, after which the disease goes into remission (Socransky et al. 1984). The current view is that the disease process may not be continuous but rather progresses in random bursts in which short periods of breakdown of periodontal ligament and bone alternate with periods of quiescence. These episodes occur randomly over time and at random sites in the mouth. Part of the difficulty in determining the pattern of progression reflects variation in the sensitivity of the instruments used to measure the loss of soft tissue and bone. The latest generation of probes finds evidence of both continuous and multiple-burst patterns of loss in different patients and at different times (Jeffcoat and Ready 1991).

Most researchers agree that periodontitis results from a mixed infection but that a particular group of gram-negative bacteria are key to the process and markedly increase in the subgingival plaque. The bacteria most frequently cited are *Porphyromonas gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, *Treponema denticola*, and *Actinobacillus actinomycetemcomitans* (Genco 1996). Their role in disease initiation and progression is determined in part by their "virulence factors." These include the ability to colonize subgingival plaque, generate products that can directly injure tissues, and elicit an inflammatory or immune response. The potentially noxious bacterial products include hydrogen sulfide, polyamines, the fatty acids butyrate and propionate, lipopolysaccharide (also known as endotoxin), and a number of destructive enzymes. The interaction of this arsenal with the host response is at the core of periodontal pathology (Genco 1992, Socransky and Haffajee 1991, 1992). Sequencing of the genomes of several key periodontal pathogens is under way and should provide further insight into these pathogens as well as catalyze new treatment approaches.

Delicate Balances. Neutrophils (a type of white blood cell) and antibodies are the major immune defenses against bacterial attack. Neutrophils move to the site of infection, where they engulf bacteria and elaborate antibacterial agents and enzymes to destroy bacteria. Although stimulation of the immune system to attack the offending bacteria is generally protective, immune hyperresponsiveness and hypersensitivity can be counterproductive, leading to the destruction of healthy tissue. Nevertheless, the neutrophil/antibody axis is critical for full protection against periodontal diseases (Genco 1992).

Also important is the release of certain potent molecules called cytokines and prostaglandins, especially prostaglandin E2 (PGE_2) which can contribute to tissue destruction. Cytokines are proteins secreted by immune cells that help regulate immune responses and also affect bone, epithelial,

and connective tissues. Most prominent in periodontal diseases are interleukin 1 (IL-1), tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ). These cytokines mediate the processes of bone resorption and connective tissue destruction.

Susceptibility and Resistance. PGE_2 may play a central role in the tissue destruction that occurs in periodontal diseases. Levels of PGE_2 in periodontal tissue are low or undetectable in health, increase in gingivitis, and rise significantly in periodontitis. Now there is increasing evidence that the level of PGE_2 produced in response to bacterial challenge (especially by endotoxin) can be used as a measure of susceptibility (Offenbacher et al. 1993).

Presumably, the level of PGE_2 production is subject to genetic influence. Studies of identical and fraternal twins, either reared together or apart, provide evidence that genetic factors may indeed influence susceptibility or resistance to the common adult form of periodontitis (Michalowicz 1994). Recently, a commercial test for a genetic marker of susceptibility has been introduced. The marker is associated with increased production of a particular form of interleukin 1β (IL-1β) when stimulated by periodontopathic bacteria (Kornman et al. 1997). Newman (1996) found that nonsmoking adults who are positive for the marker are 6 to 19 times more likely to develop severe periodontitis.

Susceptibility to adult periodontitis has also been explored in relation to a variety of behavioral and demographic variables as well as to the presence of other diseases. One of the strongest behavioral associations is with tobacco use. The risk of alveolar bone loss for heavy smokers is 7 times greater than for those who have not smoked (Grossi et al. 1995). Cigarette smoking also may impair the normal host response in neutralizing infection (Seymour 1991), resulting in the destruction of healthy periodontal tissues adjacent to the site of infection (Lamster 1992). Smokers also have decreased levels of salivary and serum immunoglobulins to *Prevotella intermedia* and *Fusobacterium nucleatum* (Bennet and Reade 1982, Haber 1994) and depressed numbers of helper T cells as well (Costabel et al. 1986). Finally, smoking alters the cells that engulf and dispose of bacteria—neutrophils and other phagocytes—affecting their ability to clear pathogens (Barbour et al. 1997).

Epidemiologic studies have found that such additional factors as increasing age, infrequent dental visits, low education level, low income, co-morbidities, and inclusion in certain racial or ethnic populations are associated with increased prevalence of periodontitis (Page 1995). It is important that epidemiologic studies also take into consideration the fact that tobacco use, oral hygiene, professional prophylaxis, and routine dental care are correlated to socioeconomic status, as are race and ethnicity. Sex is another factor. Males tend to have higher levels of periodontal diseases, presumably because of a history of greater tobacco use and differences in personal care and frequency of dental visits. However, female hormones may play a protective role (as they do in protecting against osteoporosis) (Genco 1996).

Certain systemic diseases heighten susceptibility. Epidemiological studies have confirmed that patients with diabetes mellitus, both type 1 and type 2, are more susceptible to periodontal diseases (Genco 1996). Measures such as the gingival index, pocket depth, and loss of attachment are more severe if the diabetic patients are smokers (Bridges et al. 1996). The likelihood of periodontal disease increases markedly when diabetes is poorly controlled. In contrast, periodontal diseases respond well to therapy and can be managed successfully in patients with well-controlled diabetes. Such therapy can result in improvements in the diabetic condition itself (Mealey 1996) (see Chapter 5).

There is some evidence that osteoporosis may be a risk factor for periodontal disease. More clinical attachment loss and edentulousness have been reported in osteoporotic than in nonosteoporotic women (Jeffcoat and Chestnut 1993). Two studies in 1996 showed that estrogen replacement therapy in postmenopausal women not only gives protection against osteoporosis, but also results in fewer teeth lost to periodontal disease (Grodstein et al. 1996, Jacobs et al. 1996).

The less common rapidly progressive form of adult periodontitis typically affects people in their early 20s and 30s. It is characterized by severe gingival inflammation and rapid loss of connective tissue and bone. Many patients have an inherent defect in neutrophil response to infection. Several systemic diseases have been associated with this form of periodontal disease, including type 1 diabetes, Down syndrome, Papillon-Lefevre syndrome, Chediak-Higashi syndrome, and HIV infection (Caton 1989). Specific bacteria associated with rapidly progressive disease include *Porphyromonas gingivalis*, *Prevotella intermedia*, *Eikenella corrodens*, and *Wolinella recta* (Scheutz et al. 1997). Most recently, mutations in the cathepsin C gene have been associated with the Papillon-Lefevre syndrome (Hart et al. 1999) and how the defect can result in periodontal disease (Toomers et al. 1999).

Refractory Periodontitis. Refractory periodontitis is not a specific form of disease, but refers to cases in which patients continue to exhibit progressive disease at multiple sites despite aggressive mechanical therapy to remove biofilm and calculus, along with the use of antibiotics. Refractory sites exhibit elevated levels of a number of different bacteria, with the dominant species different in different subjects. It is not known whether variations in pathogenicity of the bacteria, defects in the subject's defense systems, or combinations of these factors are responsible for the refractory nature of the disease (Haffajee et al. 1988). The adoption of new diagnostic technology to detect predominant bacterial species, followed by selective antibiotic treatment, may help resolve infection and disease in these patients.

Early-onset Periodontitis

The forms of periodontitis occurring in adolescents and young adults generally involve defects in neutrophil function (Van Dyke et al. 1980). Localized juvenile periodontitis (LJP) mainly affects the first molar and incisor teeth of teenagers and young adults, with rapid destruction of bone but almost no telltale signs of inflammation and very little supragingival plaque or calculus. *Actinobacillus actinomycetemcomitans* has been isolated at 90 to 100 percent of diseased sites in these patients, but is absent or appears in very low frequency in healthy or minimally diseased sites (Socransky and Haffajee 1992). It is possible that the bacteria are transmitted among family members through oral contacts such as kissing or sharing utensils, because the same bacterial strain appears in affected family members. However, evidence of a neutrophil defect argues for a genetic component. Another organism frequently associated with LJP is *Capnocytophaga ochracea.* Neither of these bacteria dominate in the generalized adult form of the disease, where *Porphyromonas gingivalis* is considered of greatest significance (Schenkein and Van Dyke 1994).

Prepubertal periodontitis is rare and can be either general or localized. The generalized form begins with the eruption of the primary teeth and proceeds to involve the permanent teeth. There is severe inflammation, rapid bone loss, tooth mobility, and tooth loss. The localized form of the disease is less aggressive, affecting only some primary teeth. The infection involves many of the organisms associated with periodontitis, but the mix may differ somewhat, with *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *Eikenella corrodens*, and several species of *Capnocytophaga* implicated (Caton 1989). Defects in neutrophil function noted in both forms of the disease (Schenkein and Van Dyke 1994) may explain why patients are highly susceptible to other infections as well (Suzuki 1988).

SELECTED MUCOSAL INFECTIONS AND CONDITIONS

Like the skin, the mucosal lining of the mouth serves to protect the body from injury. This lining is itself subject to a variety of infections and conditions, ranging from benign canker sores to often fatal cancers.

Oral Candidiasis

Chronic hyperplastic candidiasis is a red or white lesion that may be flat or slightly elevated and may adhere to soft or hard tissue surfaces, including dental appliances. It is caused by species of *Candida*, especially *Candida albicans*, the most common fungal pathogen isolated from the oral cavity. Normally, the fungi are present in relatively low numbers in up to 65 percent of healthy children and adults and cause no harm (McCullough et al. 1996). Problems arise when there is a change in oral homeostatis—the normal balance of protective mechanisms and resident oral flora that maintain the health of the oral cavity—so that defense mechanisms are compromised (Scully et al. 1994). Under these circumstances the fungal organisms can overgrow to cause disease. A primary disruption in homeostasis occurs with the use of antibiotics and corticosteroids, which can markedly change the composition of the oral flora. Deficiencies in the immune and endocrine systems are also important. Indeed, the diagnosis of candidiasis in an otherwise seemingly healthy young adult may be the first sign of HIV infection. Other causes of candidiasis include cancer chemotherapy or radiotherapy to the head and neck, xerostomia resulting from radiation to the head and neck, medications, chronic mucosal irritation, certain blood diseases, and other systemic conditions. Also, tobacco use has been identified as a cofactor.

Candidiasis often causes symptoms of burning and soreness as well as sensitivity to acidic and spicy foods. Patients may complain of a foul taste in the mouth. However, it can also be asymptomatic. Genomic analysis of the *Candida albicans* genome is helping investigators identify numerous genes that code for virulence factors, including enzymes that can facilitate adhesion to and penetration of mucous membranes. At the same time, researchers are exploring novel gene technologies to increase production of

a family of native salivary proteins, the histatins, that have known anticandidal and other antimicrobial effects.

The most common form of oral candidiasis is denture stomatitis. It occurs when tissues are traumatized by continued wearing of ill-fitting or inadequately cleaned dental appliances and is described as chronic erythematous candidiasis. Another form, candidal angular cheilosis, occurs in the folds at the angles of the mouth and is closely associated with denture sore mouth (Tyldesley and Field 1995). Other common forms of *Candida* infection are pseudomembranous candidiasis (thrush), which may affect any of the mucosal surfaces, and acute erythematous candidiasis, a red and markedly painful variant commonly seen in AIDS patients.

In most cases, *Candida* infection can be controlled with antifungal medications used locally or systemically. Control is difficult, however, in patients with immune dysfunction, as in AIDS, or other chronic debilitating diseases. Often the organisms become resistant to standard therapy, and aggressive approaches are necessary (Tyldesley and Field 1995). The spread of oral candidiasis to the esophagus or lungs can be life-threatening and is one of the criteria used to define frank AIDS (Samaranayake and Holmstrup 1989).

Herpes Simplex Virus Infections

In any given year, about one-half-million Americans will experience their first encounter with the herpes simplex virus type 1 (HSV-1), the cause of cold sores. That first encounter usually occurs in the oral region and may be so mild as to go unnoticed. But in some people, particularly young children and young adults, infection may take the form of primary herpetic stomatitis, with symptoms of malaise, muscle aches, sore throat, and enlarged and tender lymph nodes, prior to the appearance of the familiar cold sore blisters. These blisters usually show up on the lips, but any of the mucosal surfaces can be affected. Bright-red ulcerated areas and marked gingivitis may also be seen (Tyldesley and Field 1995).

Herpes viruses also cause genital infections, which are transmitted sexually. Both HSV-1 and HSV-2 have been found in oral and genital infections, with HSV-1 predominating in oral areas and HSV-2 in genital areas (Wheeler 1988). Herpes viruses have also been implicated as cofactors in the development of oral cancers. Crowded living conditions can result in greater contact with infected individuals, which aids in transmission of HSV (Whitley 1992).

Normally, the immune system mounts a successful attack on the viruses, with symptoms abating by the time neutralizing antibodies appear in the bloodstream, in about 10 days. However, herpes viruses are notorious for their ability to avoid immune detection by taking refuge in the nervous system, where they can remain latent for years. In oral herpes the virus commonly migrates to the nearby trigeminal ganglion, the cluster of nerve cells whose fibers branch out to the face and mouth. In about 20 to 40 percent of people who are virus-positive, the virus may reactivate, with infectious virus particles moving to the oral cavity to cause recurrent disease (Scott et al. 1997).

The usual site of a recurrent lesion is on or near the lips. Recurrences are rarely severe, and lesions heal in 7 to 10 days without scarring (Higgins et al. 1993). The recurrences may be provoked by a wide range of stimuli, including sunlight, mechanical trauma, and mild fevers such as occur with a cold. Emotional factors may play a role as well.

Oral Human Papillomavirus Infections

There are more than 100 recognized strains of oral human papillomavirus (HPV), a member of the papovavirus family, implicated in a variety of oral lesions (Regezi and Sciubba 1993). Most common are papillomas (warts) found on or around the lips and in the mouth. HPV is found in 80 percent of these oral squamous papillomas (de Villiers 1989). The virus has also been identified in 30 to 40 percent of oral squamous cell carcinomas (Chang et al. 1990) and has been implicated in cervical cancer as well. Whether a cancer or nonmalignant wart develops may depend on which virus is present or on which viral genes are activated.

Oral warts are most often found in children, probably as a result of chewing warts on the hands. In adults, sexual transmission from the anogenital region can occur (Franchesi et al. 1996).

In general, viral warts spontaneously regress after 1 or 2 years. The immune system normally keeps HPV infections under control, as evidenced by the increased prevalence of HPV-associated lesions in HIV-infected patients and others with immunodeficiency.

Recurrent Aphthous Ulcers

Recurrent aphthous ulcers (RAU), also referred to as recurrent aphthous stomatitis, is the technical term for canker sores, the most common and generally

mild oral mucosal disease. Between 5 and 25 percent of the general population is affected, with higher numbers in selected groups, such as health professional students (Axéll et al. 1976, Embil et al. 1975, Ferguson et al. 1984, Kleinman et al. 1991, Ship 1972, Ship et al. 1967).

The disease takes three clinical forms: RAU minor, RAU major, and herpetiform RAU. The minor form accounts for 70 to 87 percent of cases. The sores are small, discrete, shallow ulcers surrounded by a red halo appearing at the front of the mouth or the tongue. The ulcers, which usually last up to 2 weeks, are painful and may make eating or speaking difficult. About half of RAU patients experience recurrences every 1 to 3 months; as many as 30 percent report continuous recurrences (Bagan et al. 1991).

RAU major accounts for 7 to 20 percent of cases and usually appears as 1 to 10 larger coalescent ulcers at a time, which can persist for weeks or months (Bagan et al. 1991). Herpetiform RAU has been reported as occurring in 7 to 10 percent of RAU cases. The ulcers appear in crops of 10 to 100 at a time, concentrating in the back of the mouth and lasting for 7 to 14 days (Bagan et al. 1991, Rennie et al. 1985).

RAU can begin in childhood, but the peak period for onset is the second decade (Lehner 1968). About 50 percent of close relatives of patients with RAU also have the condition (Ship 1965), and a high correlation of RAU has been noted in identical but not fraternal twins. Associations have been found between RAU and specific genetic markers (Scully and Porter 1989).

RAU has also been associated with hypersensitivities to some foods, food dyes, and food preservatives (Woo and Sonis 1996). Nutritional deficiencies—especially in iron, folic acid, various B vitamins, or combinations thereof—have also been reported, and improvements noted with suitable dietary supplements (Nolan et al. 1991).

The two factors that have been found to have the strongest association with RAU are immunologic abnormality, possibly involving autoimmunity, and trauma (Lehner 1968, Ship 1996, Woo and Sonis 1996).

Volunteers with and without a history of RAU were studied for their reaction to the trauma of a needle prick to the inner cheek tissue. No ulcers developed in non-RAU subjects, but nearly half of those prone to canker sores had a recurrence (Wray et al. 1981).

RAU also can occur in a number of systemic diseases, including HIV infection, ulcerative colitis, Crohn's disease, and Behçet's disease (Ship 1996). In general, people who are immunocompromised are more susceptible to RAU, as are people with a variety of blood diseases.

RAU itself does not give rise to other illnesses but is uncomfortable. Symptomatic treatment includes topical analgesics, antibacterial rinses, topical corticosteroids, and a new prescription medication that reduces pain and healing time (Khandwala et al. 1997, Ship 1996).

ORAL AND PHARYNGEAL CANCERS AND PRECANCEROUS LESIONS

In 2000, oral or pharyngeal cancer will be diagnosed in an estimated 30,200 Americans and will cause more than 7,800 deaths (Greenlee et al. 2000). Over 90 percent of these cancers are squamous cell carcinomas—cancers of the epithelial cells. The most common oral sites are on the tongue, the lips, and the floor of the mouth. Oral cancer is the sixth most common cancer in U.S. males and takes a disproportionate toll on minorities; it now ranks as the fourth most common cancer among African American men (Kosary et al. 1995). The prominent role of tobacco use, especially in combination with alcohol, in causing these cancers is a major incentive to develop effective health promotion and disease prevention efforts.

Heightening the Risk

Oral cancer develops as a clone from a single genetically altered cell (Solt 1981). It generally has a long latency period and invariably develops from a precancerous lesion on the oral mucosa, such as a white leukoplakia, or more commonly, a reddish erythroplakia (Mashberg 1978, Shklar 1986). Both kinds of lesions are usually induced by tobacco use alone or in combination with heavy use of alcohol. The development of squamous cell carcinoma from initial erythroplakia lesions has been well demonstrated experimentally. Silverman (1998) reported rates of malignant transformation for leukoplakias of between 0.13 and 17.5 percent. However, there is considerable debate as to the actual malignant potential of the leukoplakia lesion associated with the use of smokeless (spit) tobacco. Meaningful data for determining a specific malignant transformation rate or relative risk of oral cancer due to smokeless tobacco use are difficult to obtain because of the confounding effects of other habits such as concurrent smoking and alcohol consumption and because of the variations in smokeless (spit) products and how they are used.

Another oral precancerous lesion that has received attention is submucous fibrosis. It is commonly seen in India and Southeast Asia and is related to betel nut use (Canniff et al. 1986).

Early epidemiologic studies identified behaviors such as smoking and environmental factors such as exposure to solar radiation and x-rays as causes of intraoral and lip cancers (Pindborg 1977). Researchers then sought experimentally to explain the mechanisms of initiation. In the 1980s and 1990s, investigators exploited the techniques of molecular biology and genetics to probe what was going on deep inside the cell. These studies revealed an abundance of systemic and local factors, including viral and fungal infections, that affect cell behavior. Some factors stimulate cell division and others inhibit it—even to the point of initiating a program of cell "suicide," called apoptosis. How a given cell behaves at any given time in its life cycle is the net result of the signals it receives from neighboring cells and molecules, from circulating factors in the blood or immune system, and from its own internal controls. The following sections provide a brief description of these factors and how they may participate in enhancing the risk for the development of oral cancers.

Tobacco and Alcohol

Tobacco and alcohol are the major risk factors for oral cancers, and their effects have been studied for many years (Rothman and Keller 1972, Decker and Goldstein 1982). Tobacco contains substances that are frankly carcinogenic or act as initiators or promoters of carcinogenesis. Among these are *N*-nitrosonornicotine, 4-nitroquinoline-*N*-oxide, and benzpyrene. The most damaging carcinogens are found in the tars of tobacco smoke, but many forms of smokeless (spit) tobacco, including snuff, have been implicated in the development of mouth cancer (Advisory Committee to the Surgeon General 1986, International Agency for Research on Cancer 1985, Winn 1984). Other habits that have been related to oral cancer include chewing betel nut in the presence of tobacco, as is done primarily in Southeast Asia (Hirayama 1966, Mehta et al. 1981), and, more recently, using marijuana (Donald 1986).

The role of alcohol in oral carcinogenesis has been demonstrated experimentally (Wight and Ogden 1998) and appears to be related to its damaging effect on the liver. Major metabolites of alcohol, such as acetaldehyde—a known carcinogen in animals—may also be important. Alcohol is also thought to act as a solvent that facilitates the penetration of tobacco carcinogens into oral tissues. That observation may partly explain why the combined use of tobacco and alcohol produces a greater risk for oral cancer than use of either substance alone. Indeed, tobacco and alcohol, working in tandem, are thought to account for 75 to 90 percent of all oral and pharyngeal cancers in the United States (Blot et al. 1988).

Viruses

The role of viruses in causing cancer in animals was established early in the century when Rous showed that a virus, later named the Rous sarcoma virus (RSV), caused tumors in chickens. The issue of whether viruses could cause cancer in humans remained unexplored until the mid-1970s, when Varmus and Bishop showed that RSV had a special gene, which they called *src* (for sarcoma), that could transform the cell it infected into a malignant cell (Bishop et al. 1978). It was an oncogene, or cancer-causing gene. The researchers subsequently, and surprisingly, discovered that *src* was not native to the virus, but had been picked up by some ancestor virus from a chicken cell's own genome, where *src* had presumably played a role in the chicken cell's normal growth and development. Somehow RSV was able to subvert *src* when it infected a chicken cell to cause the cell to divide uncontrollably. Varmus and Bishop called the normal cellular *src* gene a *proto-oncogene*, meaning that it had the potential to be converted to an oncogene. Subsequent research led to the discovery of other viruses that could cause tumors in animals and revealed the presence of proto-oncogenes in birds and mammals. These genes could also be converted to oncogenes, behaving exactly like those carried by cancer viruses. In 1982 an oncogene isolated from a human bladder cancer turned out to be virtually identical to *ras*, the oncogene found in a rat sarcoma virus (Parada et al. 1982).

Viruses that have been implicated in oral cancer include herpes simplex type 1 and human papillomavirus. Epstein-Barr virus, also a herpes virus, is now accepted as an oncogenic virus responsible for Burkitt's lymphoma, occurring primarily in Africa, and nasopharyngeal carcinoma, occurring primarily in China. HPV is a major etiologic agent in cervical cancer (Howley 1991), and has been found in association with oral cancer as well (Sugerman and Shillitoe 1997). HPV DNA sequences have been found in oral precancerous lesions as well as in squamous cell carcinomas (Adler-Storthz et al. 1986, Syrjanen et al. 1988), and experimental evidence has shown that HPV-16 can be an important cofactor in

oral carcinogenesis (Park et al. 1991, 1995). Herpes simplex type 1 antibodies were demonstrated in patients with oral cancer, and herpes was found to induce dysplasia (abnormal cellular changes) in the lips of hamsters when combined with the application of tobacco tar condensate (Park et al. 1986).

More recently, human herpes virus 8, a newly identified member of the herpes virus family, has been found in Kaposi's sarcoma, an otherwise rare cancer occurring in patients with AIDS. These tumors often appear initially within the oral cavity (Epstein and Scully 1992). Other uncommon oral malignant tumors, such as Hodgkin's lymphoma and non-Hodgkin's lymphoma, can also occur in the mouths of AIDS patients.

In addition to viruses, infection with strains of the fungus *Candida albicans* has been linked to the development of oral cancers via the fungal production of nitrosamines, which are known carcinogens.

Genetic Derangements

Of the more than 50 known oncogenes, many have been reported to be present in oral cancer, and multiple oncogenes have been reported in oral and pharyngeal cancer (Spandidos et al. 1985). Some of these are *Bcl*-1, c-*erb*-B2, c-*myc*, *ins*-2, and members of the *ras* family (Berenson et al. 1989, Bos 1989, Riviere et al. 1990, Somers et al. 1990, 1992).

The genetic derangements that can give rise to oral cancer, including many mutations associated with the transformation of proto-oncogenes, have received notable attention (Sidransky 1995, Wong et al. 1996). In some instances a change in a single nucleotide base—a point mutation—in a gene encoding a proto-oncogene is enough to transform it into an oncogene. Cancerous changes may also involve alterations, deletions, and break points in chromosomes that affect the position of genes.

Mutations that disarm the cell's DNA repair mechanisms, as well as mutations in tumor suppressor genes, which inhibit abnormal cell growth, play a major role in cancer development. If an individual inherits or acquires a mutation in one or more tumor-suppressor genes, for example, the loss of this protective mechanism reduces the number of other deleterious changes needed for cancer to develop.

Tumor suppressor genes suspected to be mutated in oral and pharyngeal cancers include those for Rb, p16 (*MTS1*, *CDKN2*, or *IN4a*), and p53. Todd et al. (1995) recently reported a novel oral tumor suppressor gene, named "*deleted in oral cancer-1 (doc-1)*." Of the group of tumor suppressor genes, that coding for p53 is considered of major importance, with mutations in the p53 gene detected in many types of cancer (Greenblatt et al. 1994, Hollstein et al. 1991), including oral and pharyngeal cancer (Langdon and Partridge 1992, Somers et al. 1992). The p53 gene has been called the "guardian of the genome" (Lane 1992) because of its ability to recognize damage to a cell's DNA and stop the process of growth and division until the damage is repaired. If repair is not possible, p53 can trigger apoptosis. Mutations in the p53 gene in oral cancer have been linked to smoking and alcohol use (Brennan et al. 1995).

Loss of Immunosurveillance and Control

The immune system can, as first noted by Paul Ehrlich in 1909, seek and destroy initial clones of transformed cancer cells (Ehrlich 1957). Ehrlich called this process *immunosurveillance*, and it has been confirmed in experimental animals (Burnet 1970, Shklar et al. 1990) and in humans with induced immunosuppression (Penn 1975).

One mechanism of immunosurveillance involves stimulating cytotoxic macrophages and lymphocytes to migrate to the tumor site and release tumor necrosis factors α and β (Shklar and Schwartz 1988). Another mechanism operative in oral cancer appears to be stimulation of Langerhans cells, a special group of immune cells, in the oral mucosa (Schwartz et al. 1985). Other immune cells implicated in tumor rejection are natural killer cells and lymphokine-activated killer cells (Reif 1997).

There is an increased incidence of cancer in patients with AIDS or other immunodeficient conditions or with induced immunosuppression prior to organ transplantation.

In addition, there is evidence that smoking depresses the immune system (Chretien 1978), and this may be one of the ways in which smoking acts as a major risk factor in oral cancer.

Growth Factors

Immune cells are potent generators of growth factors and other molecules that can stimulate other cells to migrate and proliferate. This capacity is important in normal cell growth and turnover, in wound healing, and in coping with infection. Unfortunately, the release of growth factors can contribute to oral cancer by stimulating keratinocyte (oral epithelial cell) proliferation (Aaronson 1991, Issing et al. 1993, Wong 1993). Increased levels of transforming growth factor α (TGF-α) and epidermal growth factor have been found in oral and pharyngeal cancers and therefore could serve as markers for malignancy (Grandis and Tweardy 1993). Nicotine at high doses stimulates

the release of growth hormones, among other endocrine effects (Pomerleau and Pomerleau 1984, Seyler et al. 1984, 1986).

Prevention and Management

Studies of experimental carcinogenesis are elucidating the role of micronutrients in tumor development and progression. Alpha tocopherol (vitamin E) also has been studied as an antioxidant in nutritional approaches to the prevention or control of oral cancer. Antioxidants can trap free radicals, the highly reactive molecules that build up in cells and can damage DNA. The control of oral cancer and precancerous lesions has been demonstrated experimentally using a variety of antioxidant micronutrients, such as retinoids, carotenoids, and glutathione, as well as alpha tocopherol. For example, it was found that alpha tocopherol inhibited tumor development and tumor angiogenesis (blood vessel formation) in hamsters, as well as the expression of TGF-α, a potent angiogenesis stimulator (Shklar and Schwartz 1996). Animal research and tissue culture studies using animal- and human-derived cancer cell lines have shown combinations of micronutrients to be more effective than single micronutrients and to work synergistically. The nutrients not only were able to inhibit experimental carcinogenesis, but also could completely prevent tumor development and cause established squamous cell carcinomas to regress (Shklar and Schwartz 1993). The mechanisms of cancer control by micronutrients are gradually becoming clarified and involve common pathways of activity at the molecular level (Shklar and Schwartz 1994). Clinical studies in humans have shown an inhibitory effect on oral leukoplakia (Benner et al. 1993, Blot et al. 1993, Garewal 1993, Garewal et al. 1990, Hong et al. 1986), suggesting a potential role for nutrients in the overall prevention and management of early oral cancer and precancerous leukoplakia. However, a recommendation to employ such approaches clinically at this time is premature.

DEVELOPMENTAL DISORDERS

The importance of the face as the bearer of identity, character, intelligence, and beauty is universal. Craniofacial birth defects, which can include such manifestations as cleft lip or palate, eyes too closely or widely spaced, deformed ears, eyes mismatched in color, and facial asymmetries, can be devastating to the parents and child affected. Surgery, dental care, psychological counseling, and rehabilitation may help to ameliorate the problems but often at great cost and over many years.

Although each developmental craniofacial disease or syndrome is relatively rare, the number of children affected worldwide is in the millions. In addition, craniofacial defects form a substantial component of many other developmental birth defects, largely because they occur very early in gestation, when many of the same genes that orchestrate the development of the brain, head, face, and mouth are also directing the development of the limbs and many vital internal organs, such as the heart, lungs, and liver.

By about the third week after fertilization, the three germ layers of the embryo—the ectoderm, endoderm, and mesoderm—have formed, as well as the first of four sets of paired swellings—the branchial arches—that appear at the sides of the head end of the embryo. (See Chapter 2 for more details on this process.) Some craniofacial defects result from failure of the arches to complete their morphogenetic development. Other craniofacial defects are the result of the abnormal differentiation of cells derived from the ectoderm and endoderm or from ectomesenchyme cells, which originate in a part of the ectoderm (the neural crest), in interaction with future connective tissue (the mesenchyme).

Craniofacial Anomalies Caused by Altered Branchial Arch Morphogenesis

Cleft Lip/Palate and Cleft Palate

The most common of all craniofacial anomalies—and among the most common of all birth defects—are clefts of the lip with or without cleft palate and cleft palate alone; these occur at a rate of 1 to 2 out of 1,000 births, resulting in over 8,000 affected newborns every year. Cleft lip/palate and cleft palate are distinct conditions with different patterns of inheritance and embryological origins (Lidral et al. 1997, Murray et al. 1997). The male to female ratio of cleft lip/palate is 2:1; the ratio for cleft palate alone is just the reverse, 1:2.

These anomalies result from the failure of the first branchial arches to complete fusion processes (Murray 1995, Robert et al. 1996). Clefting can occur independently or as part of a larger syndrome that may include mental retardation and defects of the heart and other organs. Not all cases of clefting are inherited; a number of teratogens (environmental agents that can cause birth defects) have been implicated, as well as defects in essential nutrients such as

folic acid. Smoking by the mother during pregnancy also increases the risk. It is becoming increasingly evident that most diseases and disorders, not just craniofacial anomalies, result from interactions involving multiple genes and environmental factors.

Infants with clefts have difficulty with vital oral functions such as feeding, breathing, speaking, and swallowing. They are also susceptible to repeated respiratory infections. As these children grow, they must cope with the social consequences of a facial deformity, delayed and altered speech, frequent illness, and repeated surgeries that may persist through late adolescence.

Current molecular epidemiology investigations have examined both syndromic and nonsyndromic (isolated) cleft lip/palate and cleft palate. Linkage studies have identified a number of candidate genes (Lewanda and Jabs 1994), including *MSX1*, *RAR*, an X-linked locus, and the genes for TGF-β3 and TGF-α. The pattern of inheritance in cleft lip/palate and cleft palate suggests that between 2 and 20 genes may be involved, with one gene representing a major component in the development of the cleft. One of the common syndromic forms of cleft lip/palate, the Van der Woude syndrome, is caused by an autosomal dominant form of inheritance at a locus on chromosome 1 (Sander et al. 1995). Future molecular genetic studies will be needed to provide the information necessary for prenatal diagnosis, calculation of risk, and potential gene therapy.

The Treacher Collins Syndrome—Mandibulofacial Dysostosis

Children with the Treacher Collins syndrome have downward-sloping eyelids; depressed cheekbones; a large fishlike mouth; deformed ears with conductive deafness; a small, receding chin and lower jaw; a highly arched or cleft palate; and severe dental malocclusion (Dixon 1996). These defects result from defective cranial neural crest cell differentiation, migration, and proliferation (see Chapter 2). Consequently, the first branchial arch structures are deficient, and all derivative craniofacial components are affected.

The underdeveloped facial structures can contribute to airway blockage and repeated upper respiratory infections, either of which can be fatal. The faulty development of the ears leads to a conductive deafness. The severe facial deformities exacerbate the psychological difficulties these youngsters face.

Investigators have identified the gene involved in an autosomal dominant form of the syndrome (Wise et al. 1997). The function of the gene is not yet known, but its identity will provide opportunities for prenatal diagnosis, gene therapy, and further understanding of craniofacial development.

The Pierre Robin Syndrome

Deficient development of the first-branchial-arch-derived mandibular portion results in the lower jaw's being set far back in relation to the forehead. As a result, the tongue is set back and may obstruct the posterior airway, compromising respiration (Elliott et al. 1995, Tomaski et al. 1995) and, in severe cases, leading to inadequate aeration and failure to thrive. The infant is also at risk for the development of cor pulmonale, an enlargement of the right ventricle of the heart that occurs secondarily to a chronic lung condition. Cleft palate may be another consequence.

The DiGeorge/Velocardiofacial Syndrome

The primary defect in the DiGeorge syndrome results from altered development of the fourth branchial arch and the third and fourth pharyngeal pouches (Goldmuntz and Emanuel 1997). Deficiencies affecting the thymus, parathyroid glands, and the great vessels that derive from these structures result. The facial features are subtle and include a squared-off nasal tip, small mouth, and widely spaced eyes. Similar facial features, along with heart defects, are seen in the velocardiofacial syndrome. Both syndromes are associated with deletions on the long arm of chromosome 22 (22q11) (Gong et al. 1997, Gottlieb et al. 1997). Further characterization of this chromosomal deletion region will provide information on the specific gene(s) affected and its function in craniofacial development.

The thymus defects severely compromise cellular immunity, depriving the body of thymus-derived T cells and paving the way for severe infectious disease. Inadequate or missing parathyroid glands cause severe hypocalcemia (low blood calcium levels) and seizures. The great vessel abnormalities alter cardiac output and lead to compromised circulation to heart tissues.

Cranial Bone and Dental Anomalies

Defects in the timing of developmental events can cause premature fusion of cranial bones. Impairments of tooth development can result from interruptions of the developmental sequence at several different stages.

Craniosynostoses

Some craniofacial anomalies are associated with so-called master genes that orchestrate a program by which the embryo assumes its basic shape. Craniosynostosis, which occurs in approximately 1 out of 3,000 births, is one such anomaly. It results in the premature fusion of the cranial sutures, a dangerous condition that puts pressure on the developing brain. A number of diseases and syndromes, including Crouzon's, Apert's, Boston-type craniosynostosis, Pfeiffer's, and Saethre-Chotzen, share this anomaly, but differ in other features, which can include structural defects such as webbing of the hands and feet as well as mental retardation. Boston-type craniosynostosis has been linked to *MSX2*, one of the master genes. Several of the other syndromes involve point mutations at one or another locus in genes that code for fibroblast growth factor receptors (FGFR 1, 2, and 3) (Howard et al. 1997, Meyers et al. 1996). Collectively, these genes are associated with cell regulation, either through mediating growth factor effects or by serving as transcription factors (Cohen 1997).

Hereditary Hypodontia or Anodontia

Conditions of underdeveloped teeth (hypodontia) or their complete absence (anodontia) have been correlated with specific genes, such as *MSX1* and *LEF1*. The complete absence of teeth alters the bony development of the mandible and maxilla.

Amelogenesis Imperfecta and Dentinogenesis Imperfecta

Amelogenesis imperfecta and dentinogenesis imperfecta are linked to defects in structural genes that code for proteins essential to the development of tooth enamel (amelogenesis imperfecta) or dentin (dentinogenesis imperfecta). The teeth are weak and extremely sensitive to temperature and pressure. The ordinary forces of chewing are painful and can lead to further wear and pain.

The enamel matrix genes include tuftelin, ameloblastin, and amelogenin; researchers have begun to link mutations in these genes with amelogenesis imperfecta. Similarly, genes labeled *DSP* and *DPP* have been characterized for dentin matrix and are associated with the inheritance of dentinogenesis imperfecta.

Craniofacial Defects Secondary to Other Developmental Disorders

A number of genetic diseases occur in which craniofacial defects are secondary to a more generalized structural or biochemical defect.

Osteogenesis Imperfecta

Inherited mutations of collagen genes lead to a number of "brittle bone" diseases characterized by defects in mineralized tissues that form from a collagen-rich matrix. Osteogenesis imperfecta presents a spectrum of deficiencies that includes fragile bones, clear or blue sclera, deafness, loose ligaments, and painful dentinogenesis imperfecta-like changes in the teeth.

Epidermolysis Bullosa—Recessive Dystrophic Type

The gene defect in epidermolysis bullosa—recessive dystrophic type—manifests as blisters or bullae that appear shortly after birth on skin areas following minor trauma. Mutations in keratin genes that contribute to the epithelial cell cytoskeleton have been correlated with this condition.

The oral manifestations include both mucosal bullae and altered teeth. Altered teeth with hypoplastic enamel develop and exhibit an increased susceptibility to caries. Oral bullae develop from even the slightest mucosal trauma. The condition is painful and dangerous because of the constant risk that the bullae will become infected.

Craniofacial Manifestations of Single-Gene Defects

In many craniofacial defects, mutations within a single gene manifest as complex syndromes with varied organ and limb defects as well as facial anomalies.

Ectodermal Dysplasias

The ectodermal dysplasias (EDs) are a family of hereditary diseases first observed by Charles Darwin over a century ago. They involve defects in two or more tissues derived from the ectoderm—skin, hair, teeth, nails, and sweat glands. The ectodermal structures fail to differentiate properly owing to altered epithelial-mesenchymal signaling. A gene, *EDA*, at an X-linked locus has been linked to the syndrome, and ongoing research is aimed at determining the function of the gene and the molecular mechanism of the syndromes (Kere et al. 1996, Zonana et al. 1994).

More recently, investigators have discovered genes linked to autosomal (i.e., non-sex-linked) forms of ED, displaying both dominant and recessive inheritance (Monreal et al. 1999).

Oral manifestations of the ectodermal dysplasias are associated with the teeth. Alterations in tooth development can include hypodontia, anodontia, and conically shaped teeth.

The Waardenburg Syndrome

The Waardenburg syndrome has been subdivided into several types. All involve a variety of abnormalities in the position and appearance of the nose and eyes, with pigment changes that may cause one eye to differ in color from the other. Other signs include deafness, a mildly protruding jaw, cleft lip and palate, and skeletal deformities (Reynolds et al. 1995). The syndrome is inherited in an autosomal dominant manner with complete penetrance and variable expression. Specific genes associated with this syndrome are members of the homeobox family that regulate the transcription of other genes: Waardenburg type 1 with *PAX3*; Waardenburg type 2 with *MITF*, 3q14.1; and Waardenburg type 3 with *PAX3*, 2q35 (Asher et al. 1996).

Cleidocranial Dysplasia

The inheritance of a regulatory gene defect in cleidocranial dysplasia leads to features that include delayed tooth eruption, supernumerary teeth, altered or missing collarbones, short stature, and possible failure of cranial suture closure. The exact mechanism of the associated gene, *CBFA1*, located on chromosome 6, has not been determined but appears to be essential for bone development.

INJURY

The common perception is that injuries are random occurrences that are unpredictable and hence unpreventable. In actuality, experts in the field make the point that there are no basic scientific distinctions between injury and disease (Haddon and Baker 1981). Injuries have been categorized as "intentional" and "unintentional." People identified as being at risk for certain injuries, as well as the causes of those injuries, can be targeted for appropriate prevention strategies. Such an approach is broadly applicable to sports, falls, and motor vehicle injuries (unintentional) as well as to injuries caused by abusive and violent behaviors (intentional).

Injuries are a major public health problem, outranking cancer and heart disease as a leading cause of death in some age groups of the population (Kraus and Robertson 1992). Cranial injuries in particular are a leading cause of mortality. Oral-facial injuries can bring disfigurement and dysfunction, greatly diminishing the quality of life and contributing to social and economic burdens (Reisine et al. 1989).

The leading causes of oral and craniofacial injuries are sports, violence, falls, and motor vehicle collisions (Kraus and Robertson 1992). Oral cavity injuries may also be caused by foreign objects in food (Hyman et al. 1993).

Sports

Craniofacial sports injuries occur not only in contact sports, but also in individual activities such as bicycling, skating, and gymnastics, especially on trampolines. Each sport predisposes its participants to a specific array of extrinsic risk factors (Pinkham and Kohn 1991). These include physical contact, projectiles such as balls and pucks, and the quality of the playing field and equipment. In contact sports the absence of protective equipment such as headguards and mouthguards is a major risk factor. In a recent survey of school-aged children in organized sports, football was the only sport in which the majority of participants used mouthguards and headgear (Nowjack-Raymer and Gift 1996).

There are intrinsic risk factors as well, relating to characteristics of the individual participant. These include age, sex, injury history, body size, aerobic fitness and muscle strength, central motor control, and general mental ability (Taimela et al. 1990).

Falls

Falls are a major cause of trauma to teeth, primarily to incisors. Unlike bone fractures, fractures of the crowns of the teeth do not heal or repair, and affected teeth often have an uncertain prognosis. Problems may develop later due to damage to the pulp.

Motor Vehicle Collisions

The effects of motor vehicle collisions may range from minor and reversible effects to long-term medical, surgical, and rehabilitative consequences. Posttraumatic headaches and chronic oral-facial pain can occur. Neuromuscular and glandular damage may cause short- or long-term problems with chewing, swallowing, and tearing or result in facial tics or paralysis.