CHAPTER 7

Dental and Craniofacial Research

CHAPTER OVERVIEW

Research is the process by which new information is obtained and existing tenets are modified. Research involves experimentation and observation, and through this mechanism information is converted to practical application.

Research has enabled advances in diagnosis, disease treatment and management and in the prevention of oral diseases and conditions. Through research, the preventive effects of fluoride for dental caries and specific risk factors for periodontal disease were identified. These findings led to improved interventions and a reduction in the oral disease burden. Ongoing and future research concerning the fundamental mechanisms of oral disease will continue to drive change in dental practice.

Through epidemiological and behavioral research, the dental profession has made advances in understanding the causes and progression of dental disease. Epidemiological research, through national surveys of oral health such as the National Health and Nutrition Examination Survey, has been invaluable in improving the understanding of the extent, distribution, and determinants of most dental diseases and their relationships to general health.

Epidemiological research demonstrates that underserved populations shoulder a disproportionate burden of disease. For example, the death rate from oral cancer for African American males is double that for White males despite only a 20% higher incidence rate of oral cancer among African Americans. This disparity reflects the fact that African Americans have more advanced disease at the time of diagnosis and initiation of treatment. Additional epidemiological research is needed to characterize disease patterns in specific population groups, to understand why diagnoses are not made earlier, to develop new strategies for reaching people who are at risk for oral diseases, and to evaluate treatment outcomes.

Research has shown that behaviors that are under the direct control of the individual can influence the development of many dental conditions. Examples include the relationship between sucrose consumption and caries, poor oral hygiene and periodontal diseases, and smoking and oral cancer. More behavioral research is needed to design effective interventions to deter individuals from harmful personal habits and to promote preventive behaviors.

The transfer of research-based knowledge and technology to practicing dental professionals has lagged behind the expansion of the knowledge base on the etiology of dental diseases and methods of treatment. Hence, there is a need to evaluate and improve the speed and quality of information and technology transferred from the laboratory and other research settings to the public domain.

This chapter discusses the current state of knowledge about nine defined categories of oral diseases and conditions, and identifies research directions for the future with respect to these diseases and conditions.

The chapter is not inclusive of all dental diseases; rather, these disorders are intended to illustrate the directions and challenges for dentistry in the future. The discussions underscore the fundamental importance of research to dentistry's future and demonstrate the value of research to all aspects of dentistry, including:

- Diagnosis, treatment and prevention of oral health problems;
- Education and student training opportunities;
- Adaptation of medical versus surgical models in the treatment of oral disease;
- Identification of the relationships of oral infection to many systemic diseases; and,
- Incorporation of non-dental health care personnel into programs that promote early identification of oral disease.

Progress through research will challenge dentists and students with a need to become familiar with the molecular and genetic basis of oral diseases. This process will help to assure that dentistry continues as a vital and progressive profession.

As the relationships between oral and systemic diseases are clarified, issues will arise about which professionals have the responsibility for diagnosing and managing oral disease and who will pay for treatment. These questions will impact dentistry's future role in the health care system.

I. DENTAL AND CRANIOFACIAL RESEARCH TODAY

THE ROLE OF RESEARCH IN THE IMPROVEMENT OF ORAL HEALTH

Dentistry evolves and is continuously becoming a stronger and more capable health profession because of its commitment to research. The dental profession's recognition of the value of a constantly expanding scientific base is clear. It was largely due to the efforts of the ADA that the National Institute of Dental Research (later to become the National Institute of Dental and Craniofacial Research [NIDCR]) was established in 1948 as one of the first three institutes of the National Institutes of Health. Since then, dental research has contributed to major improvements in the nation's oral health. Approximately $4 billion dollars are saved each year as a result of the nation's investment in dental research (Brown et al, 1994).

The ultimate objective of research is to improve oral health, eliminate health disparities and enhance quality of life. Dental research has led to developments in disease prevention, diagnosis and treatment modalities. During the past century, there has been a shift from an approach based on treatment of disease to prevention of disease. The caries-preventive modalities of fluoride and of dental sealants have had a major impact on the dental health of Americans.

Community water fluoridation, the country's mainstay caries preventive measure, is one of ten top public health achievements of the past century (Centers for Disease Control [CDC], 1999). Uncovering the harmful effects of tobacco use on oral cancer and periodontal diseases has suggested the potential importance of tobacco control programs delivered by the dental profession. The dental office, with patients returning for care on a regular basis, is an ideal location for smoking cessation programs. In the future, members of the dental health care team will become active providers of smoking prevention and smoking cessation programs for dental patients. This will be equivalent to oral hygiene programs that are now standard of care in dental offices.

Dentistry is now among the family of health professions addressing these and other risk factors common to many diseases and conditions that plague our nation. For individuals who have not benefited from the available preventive measures, the development and refinement of restorative materials and equipment, such as the high-speed handpiece and radiography, have enhanced the capacity to manage oral diseases for those who can avail themselves of professional care. An increased understanding of the interdependent role of personal lifestyle behaviors, professional care and community-based programs has demonstrated how oral diseases differ from some other diseases and emphasized the importance of the partnership among these components.

The Research Process

The behavioral and biomedical research process generates new knowledge to promote health and manage diseases and disorders. The research process evolves from a stage focused upon knowledge acquisition to one of knowledge validation. Ultimately, the acquired knowledge needs to be transferred and disseminated effectively, efficiently and in a timely manner to those who will use it. This includes active participation and involvement of the dental profession.

Figure 7.1 demonstrates the research spectrum that parallels this creation and distribution of knowledge. Both behavioral and biomedical research include basic research that pursues the fundamental underlying mechanisms and evolves to applied research and development. At the applied stage, animal studies may be involved, as well as preliminary human studies. Patient and population-oriented studies may include clinical, epidemiological and health services research. Clinical studies include a variety of experimental designs with the design for randomized controlled trials as the gold standard. At this stage of research, efficacy and safety of an intervention or technology are determined. To assess the effectiveness of an intervention demonstration, research projects are undertaken to test the intervention. Education research is also important to determine how best to transfer the research findings into practice, whether it is to be used by patients, clinicians or community programs.

As seen in Figure 7.1, the research process is not unidirectional. As a result of information gathered, further refinement may be necessary before proceeding to the next stage.

Biomedical and behavioral scientists are contributing to an enhanced understanding of the causes, progression and sequelae of diseases and conditions that affect the oral cavity and surrounding tissues. The definition of the role of microbial oral infections—bacterial, viruses, fungi—and their interactions with host immune response and the environment, has suggested ways to prevent diseases and arrest their progression.

The complex nature of the most common oral diseases, dental caries and periodontal diseases, emphasizes the importance of effective biological, behavioral, and environmental approaches for successful prevention and management. Increasingly, investigators are studying viral infections, such as herpes simplex and fungal infections such as candidiasis. Microbial genomes are being completed for several periodontal pathogens, as well as for *Candida albicans* and *Streptococcus mutans*. Researchers are also pursuing studies of normal and abnormal growth and development of teeth, jaws and other craniofacial structures, and are studying conditions such as cleft lip/palate, one of the most common birth defects.

Disabling diseases and conditions such as oral cancers, mouth, face and head injuries, temporomandibular disorders and Sjøgren's syndrome are under investigation. Of particular interest are studies of the associations among oral infections and systemic conditions and diseases. These investigations, which are looking at the relationships among periodontal diseases and diseases and conditions such as diabetes, cardiovascular diseases and low birth weight and/or premature babies, are of considerable interest to the entire health care community.

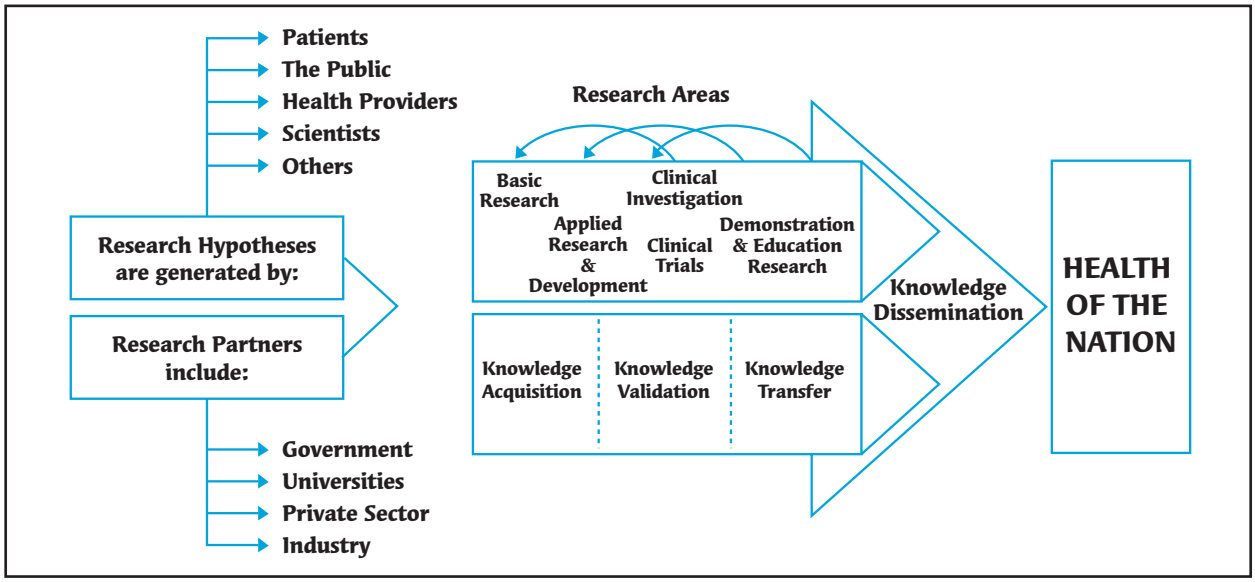
The Dental Research Agenda

During the past 40 years dental research agendas have been developed to highlight those areas that warrant additional study. These agendas include an extensive range of research needs, and vary depending upon the eventual use of the research findings. Also included in these agendas are investigations related to health services delivery and reimbursement, occupational health issues, biomaterials development and testing, disease etiology and pathogenesis as well as prevention, diagnosis and treatment, and studies of health promotion.

The ADA Research Agenda of Importance to the Practicing Dentist (ADA, Council on Scientific Affairs, 2001) emphasizes the practice of dentistry, while other agendas may focus on a subgroup of the population or on a specific disease or condition.

FIGURE 7.1

Biomedical and Behavioral Research Process



Source: Adapted from Biomedical Research Spectrum as conceived by the National Heart, Lung and Blood Institute.

Research agendas also emphasize the need for international collaborative research that develops global approaches aimed at managing oral diseases and conditions. International collaboration is important for many diseases and conditions, such as oral cancer, cleft lip/palate and oral manifestations of HIV infection. The common component of all agendas is a call for more clinical research.

For those oral diseases that have not or cannot be prevented, dental research has enabled development and refinement of techniques and procedures that have improved the management of disease.

Dentistry's science base has supported its evolution and stature as a health profession and has helped the nation improve its overall health. Schools of dentistry have evolved and their curriculum has expanded to cover the essential basic and clinical sciences that comprise the competencies for the initial practice of dentistry.

Growing understanding of the distinctive oral health requirements of special needs populations and low-income populations presents challenges to the research community. As dentistry continues to pursue research that enables providers and the public to have safe and effective disease prevention and management, dentistry's active involvement in health promotion research is required.

Maintaining a strong multi-disciplinary and international research base is critical to the future evolution of dentistry as it continues to work with its partners in the health professions.

Financial Support for Dental Research

Funding for dental research comes from both public and private sources. The primary public agency that supports behavioral and biomedical research is the National Institute of Dental and Craniofacial Research. Dental research support also is provided by other agencies in the Department of Health and Human Services. For example, the Centers for Disease Control and Prevention works with the state and territorial dental directors and academic institutions to support disease prevention and health promotion activities and research. The Agency for Healthcare Research and Quality supports health services research and evidence-based reviews, and the Health Services and Resources Administration and the Indian Health Service provide support for research focusing on access to care and services for underserved populations. Other departments such as the Department of Veterans Affairs, the Department of Defense and the Department of Commerce also conduct and support dental research.

Most publicly funded dental research in the United States is conducted in dental institutions by investigators who come from a wide variety of disciplines. United States investigators located in dental schools also have established collaborations with investigators throughout the world. Industry (i.e., dental product manufacturers, pharmaceutical companies, biotechnology firms and foundations) also provides funding for dental research and development. Much of this support is also for research conducted in dental institutions.

Nevertheless, funding for dental research lags behind that for other diseases and conditions. Greater investments in research are required for dentistry to expand its capacity to promote health, diagnose and manage individual and community risk factors, and enhance functional rehabilitation.

Research Workforce

To ensure the nation's research capacity, a concerted effort is needed to develop and build the dental research workforce. There is a paucity of new investigators entering careers in dental research. The reasons for this situation are complex.

Despite the NIDCR's support, there has been a critical decrease in the number of researchers. Six percent of the NIDCR's budget is devoted to extramural training. Approximately 400 trainees, in 30 centers across the country, receive their training though institutional and individual awards. Training is also available for junior faculty career development. A listing of mechanisms to support research training may be found on the NIDCR website.

A recent Blue Ribbon Panel on Research Training and Career Development in oral health research investigated the dimensions of the problem and proposed several solutions (NIDCR, 2000). The panel expressed serious concern that the research discoveries could be at risk if sufficient numbers of appropriately trained scientists do not enter the workforce. Specifically, the panel found:

- There will continue to be a rise in interdisciplinary studies requiring scientists to acquire a broader mix of skills and ability to work collaboratively;

◆ There will be an expanded phase of functional genomic analyses following an extended period of rapid advances in genetics and genome-based research; and

◆ There will be a greater emphasis on applied research, including domestic and international collaborative, translational, and clinical research; epidemiology; oral health promotion; and health services research.

Barriers to entering a career in research included a lack of candidates with an expressed interest in research, a relative lack of workforce diversity, student debt, and misconceptions about the rewards of a career in research. Lack of a diverse pool of mentors also discourages the consideration of research as a career.

Of great importance to the future of dentistry is the need to promote the clinician scientist who will be able to work in an interdisciplinary environment, to transfer basic findings to the clinical setting (translational research), to design clinical trials, and to undertake health promotion research. All such dental clinician scientists should receive formal training to become a member of a clinical research team.

While this strong emphasis on training may appear to contradict the recent National Research Council report that did not call for expansion of Ph.D. training in the biomedical sciences, this does not apply to dental and craniofacial research. The NIDCR report calls for targeted training.

This chapter includes a discussion of dental biomaterials and summaries of the current status of research for nine selected diseases and conditions:

◆ Dental Caries/Dental Biomaterials;

◆ Periodontal Diseases;

◆ Systemic Diseases;

◆ Cleft Lip, Cleft Palate and Craniofacial Development Disorders;

◆ Malocclusion and Tooth Agenesis;

◆ Oral and Pharyngeal Cancers;

◆ Oral Mucosal and Autoimmune Diseases and Other Infections;

◆ Salivary Gland Diseases; and,

◆ Temporomandibular Disorders.

The following sections provide examples of the many disease-specific research areas and provide a flavor of the breadth of research contributions and needs.

DENTAL CARIES/DENTAL BIOMATERIALS

Despite a remarkable decline in prevalence during the past 20 years, dental caries continues to be a major problem in the United States for adults and children (Kaste et al, 1996; and Winn et al, 1996). Ninety-four percent (94%) of dentate adults have evidence of treated or untreated carious lesions, and 23% have carious lesions on their root surfaces. Furthermore, although 25% of 5-17 year olds have 80% of carious lesions, by age 17, 40% of the population has 80% of carious lesions. Dental caries remains the most prevalent disease of childhood.

The decline in the prevalence of carious lesions has been a result of water fluoridation and fluoride-containing products, such as fluoride dentifrice, varnishes and restorative materials (Burt and Fejerskov, 1996; and Jenkins, 1985). Where one or both of these measures are in place, the prevalence of carious lesions has generally been stabilized.

Dental Caries as an Infectious Disease

The initiation and progression of dental caries are attributable primarily to cariogenic bacteria, especially *Streptococcus mutans* and recently identified *lactobacilli*. Root caries are initiated by the same bacteria as enamel caries and are manifested by loss of mineral in the same way as coronal caries. After the mineral loss, enzymes of bacterial origin degrade proteins on the root surface. Older persons with gingival recession are especially at risk.

As an infectious disease, dental caries is a dynamic multifactorial process that involves one or more tooth tissues (substrate), microorganisms capable of converting dietary components to demineralizing acids, deposits of these microorganisms on the teeth (dental plaque), a sufficient supply and frequency of dietary nutrients (sugars) to shift the chemical equilibrium between the plaque fluid and the tooth to a state of demineralization, and adequate time for significant mineral loss (calcium and phosphate) to occur.

Dental Caries Prevention and Management

Current methods of prevention, detection, and treatment of dental caries are only partially effective. Water fluoridation is only associated with a 30-50% reduction in caries (Burt and Fegerskov, 1996; and Newbrun, 1989).

Management of the disease process can be practically accomplished by reduction in the concentration of cariogenic microorganisms through plaque removal, the use of chemotherapeutic agents (including chlorhexidine and fluoride), and control of the diet (reduced frequency and quantity of sugars and substitution of sugar-free sweeteners).

Conventional restorative dentistry, which removes the carious and surrounding sound tissue to eliminate the disease, weakens the tooth structure, often leading to physical damage later in life. The major drawback of conventional restorative dentistry is that it does not address the underlying causes of the caries.

Lasers have recently been approved for clinical use for the removal of dental caries. Readily accessible caries can be removed by this laser technology and much less sound tissue is removed than is the case with the high-speed drill (Seka et al, 1995). The Er:YAG and the Er:YSSG lasers specifically target the water in carious lesions, explosively ablate the carious tissue, and can ablate surrounding sound tissue to result in a very conservative cavity preparation.

Management of dental caries as an infectious disease is an emerging approach to minimize the risk of restorative over-treatment and under-treatment (because of low diagnostic sensitivity) and to allocate more resources to underserved populations and to those who are at a moderate to high risk for this disease (Anderson et al, 1993; Anusavice, 1997; and Featherstone, 2000).

The caries process can be thought of as a balance between pathologic factors and preventive factors. The pathologic factors include cariogenic bacteria, lack of salivary function, dietary fermentable carbohydrates, and subcomponents of those items, such as highly virulent strains of cariogenic bacteria. The protective factors include fluoride, elimination or reduction of fermentable carbohydrates as a substrate, antibacterial therapy, therapy to inhibit bacterial colonization, and enhancement of salivary flow and function.

Cost-effective methods to prevent dental caries are available (i.e., sealants), but generally are underutilized. A high bacterial challenge does not necessarily progress to dental caries but does require a high level of protection to combat it. Normal salivary function, even supplemented by fluoride, may be insufficient to balance a high bacterial challenge.

Intraoral radiography is a crude detection method, adequate only for inter-proximal lesions at a very advanced state. New methods for detecting caries have recently become or soon will be available:

- Electrical impedance and ultrasound show promise for detecting caries at an early stage or for determining the degree of progression.

- Digital radiography can be used to track lesions over time to assess progression or reversal.

- Optical methods based on fluorescence (using chromophores generated by the bacteria), when effectively utilized, will accurately assess caries in occlusal surfaces (Lussi et al, 1999). Optical coherence tomography may provide two- or three- dimensional images that could become part of the patient's electronic record for insurance purposes and for diagnostic and treatment purposes (Everett et al, 1999).

Synthetic metals, ceramics, polymers, and composites have been used fairly effectively during the past 20 years or more to:

- Restore teeth destroyed or damaged by primary caries and secondary caries;

- Rebuild tooth areas degraded by wear or fracture;

- Seal pits, fissures, and defective margins;

- Improve esthetics; and,

- Release fluoride at variable release rates to inhibit demineralization and enhance remineralization.

These materials are being improved to reduce technique sensitivity, increase survival times, improve esthetic potential, and more effectively release therapeutic agents. Nevertheless, a significant percent of restorations made from these products are replaced because of secondary caries. Other failure causes include: fracture, chipping, cracking, excessive wear, discoloration, pulpal effects and malocclusion. Furthermore, little improvement has occurred in the development of more durable and

less abrasive dental ceramics. The fracture toughness and marginal quality of these prostheses have increased during the past 20 years, but they are still brittle materials that require special precautions. The design of ceramic-based prostheses must be more durable to resist degradation leading to debonding and marginal leakage and to protect against secondary dental caries.

IMPLANTOLOGY

When teeth are lost and traditional approaches to tooth replacement are not an ideal solution, the replacement of teeth with dental implants now represents a new therapeutic option. Implants are used not only in patients who have lost teeth due to caries and periodontal disease, but are becoming an important part of the restoration of form and function in patients treated for trauma, craniofacial cancers, or other abnormalities.

The evidence base for the survival of the endosseous dental implant is extensive and has been recently reviewed (Cochran, 1996; and Fritz, 1996). Many longitudinal studies exceeding five years in length are in the literature; individual populations have been studied for periods exceeding 15 years. The predictability of endosseous dental implants in fully and partially edentulous patients has been clearly demonstrated in longitudinal studies (Albrektson et al, 1988; Spiekermann et al, 1995; and Buser et al, 1991). Many implant designs and surfaces have shown high success rates (often exceeding 95% in good quality and 85% in poorer quality bone such as the posterior maxilla). While most evidence is available for titanium implants, there is evidence to support the use of hydroxyapatite and titanium plasma sprayed implant surfaces (Cochran, 1996; and Fritz, 1996). As well, there is evidence to support the use of both two-stage and one-stage implant systems (Cochran, 1996; and Buser et al, 1988). Replacement of lost teeth will rely on traditional prosthodontic techniques combined with the application of tooth-sparing dental materials.

DENTAL BIOMATERIALS

Dental biomaterials are incorporated into almost every phase of practice. Diagnostic, restorative and surgical procedures involve biomaterials either as enabling technologies (e.g., resorbable sutures, etchants, NiTi wire) or as definitive replacements for both hard and soft tissues (e.g., calcium phosphate bone cements, silicone-based polymers, ceramics). Advances in clinical practice have often derived from the development of new materials or their co-optation from other fields (e.g., engineering) often nearly coincident with their emergence for non-dental uses.

Dentistry relies on a wide range of materials, including: (1) metals; (2) metallic alloys; (3) cements based on acid-base reactions between metal oxides and either mineral or organic acids as well as products of polymerization reactions; (4) glasses; (5) polycrystalline ceramics; (6) glassy and rubbery polymers (both filled and unfilled) based on acrylic, urethane and epoxy chemistries; (7) amalgam; (8) waxes; (9) textile products; (10) monomers and oligomers of polysulfide, silicone, and vinyl siloxanes; (11) alginates, and (12) gypsum products. Bioactive materials are available, having therapeutic activities ranging from anti-microbial, to promotion of mineralization, to the enhancement of bone formation and maintenance.

Computer-directed materials processing and the collection and manipulation of three-dimensional data sets are today part of dental practice. Dental office CAD/CAM systems allow for single appointment delivery of inlay, onlay and full coverage restorations fabricated from ceramics or resin-based composites. Computer-assisted fabrication systems based in the dental laboratory allow for delivery of prostheses based on titanium or polycrystalline ceramics, such as alumina and zirconia.

PERIODONTAL DISEASES

The human periodontal diseases are a group of inflammatory disorders that affect the supporting tissues of the teeth. Periodontal diseases result from the host response to the bacterial infection of the teeth and subgingival environment. The classification of periodontal diseases was recently modified and now includes eight disease categories (Armitage, 1999). The major disease categories are gingival diseases (plaque-induced and non-plaque-induced), chronic periodontitis, aggressive periodontitis, periodontitis as a manifestation of systemic disease, necrotizing periodontal diseases, abscesses of the periodontium, periodontitis associated with endodontic lesions and developmental or acquired deformities and conditions.

Broadly defined for purposes of disease progression, gingivitis is gingival inflammation without loss of alveolar bone and periodontal ligament, while

periodontitis is gingival inflammation with loss of alveolar bone and periodontal ligament. In some patients inflammatory gingivitis can exist for many years, with only limited amounts of marginal bone loss over decades. In other individuals, gingivitis progresses to periodontitis. At present, the specific events that lead to the transition of gingivitis to periodontitis are not defined, but are likely to involve a qualitative or quantitative shift in the bacterial infection, with activation of inflammatory cascades and production of mediators with catabolic effects.

The currently accepted model for progression of periodontitis consists of periods of disease activity and inactivity. The amount of loss measured on a tooth site is variable and can be dependent on many factors including identifiable risk factors as well as the sensitivity of the technique used for measuring change (Armitage, 1996).

Approximately one dozen species of bacteria, primary Gram-negative anaerobic organisms, have been associated with chronic periodontitis: *Actinobacillus actinomycetemcomitans, Actinomyces naeslundii, Bacteroides forsythus, Campylobacter rectus, Eikenella corrodens, Eubacterium species, Fusobacterium nucleatum, Peptostreptococcus micros, Prevotella intermedia, Porphyromonas gingivalis, Selenomonas sputigena, Streptococcus intermedius* and *Treponema species*.

Among the host inflammatory mediators that have been proposed as important to the pathogenesis of periodontitis are the arachidonic acid metabolite prostaglandin E_2, enzymes known as matrix metalloproteinases (collagenases and other connective tissue-degrading enzymes) and the cytokines interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α) (Schwartz et al, 1997). The prevalence of moderately severe to severe periodontitis is remarkably consistent in different populations throughout the world ranging from 8-12% (Papapanou, 1996). The prevalence of early-onset forms of periodontitis ranges between 0.1% and 0.5% in the United States (Löe and Brown, 1991).

Risk Assessment and Diagnosis

Periodontitis is a multifactorial disease. A number of risk factors for periodontitis have been identified, including cigarette smoking, type 1 and type 2 diabetes, increased age, existing periodontitis, male gender, low socioeconomic status, limited access to dental care, as well as the periodontal pathogens *Porphyromonas gingivalis* and *Bacteroides forsythus*, and an exuberant inflammatory response as evidenced by increased production of inflammatory mediators.

The most important environmental risk factor for periodontitis is cigarette smoking. This finding has emerged within the last ten to fifteen years. A recent report by Tomar and Asma calculated that 41.9% of all cases of periodontitis were attributable to current use of cigarettes, and 10.9% of cases were attributable to former smoking (Tomar and Asma, 2000).

Greater extent and severity of periodontitis have been associated with both type 1 and type 2 diabetes. Recent studies have begun to define the molecular mechanisms that account for this association. The binding of advanced glycation endproducts in the periodontium to their receptor on macrophages, endothelial cells, and other structural cells can induce a hyperinflammatory state. Increased production of proinflammatory cytokines (IL-6, TNF-α) can then contribute to tissue damage (Lalla et al, 1998; and Mealey, 2000).

Today the diagnosis of periodontal disease relies on clinical and standard radiographic techniques and parameters:

- Probing attachment level and bleeding following probing;
- Radiographic analysis of the height of alveolar bone with periapical or bitewing exposures;
- Subtraction radiograph to determine if loss (or gain) of alveolar bone has occurred during a defined interval (limited to research environments because the software and hardware necessary for the subtraction are not commercially available); and,
- Digital radiography.

Diagnostic tests have been developed that identify specific microbial pathogens by use of culture DNA probes or specific cell surface antigens (Zambon et al, 1995). The host response can be assessed by analysis of gingival crevicular fluid, saliva, or blood. These methods have not been widely accepted as a routine part of patient management (Lamster, 1997; and Kaufman and Lamster, 2000).

Treatment and Prevention

Treatment of periodontal diseases focuses on reducing and removing plaque and calculus accu-

mulations, and controlling tissue inflammation. This is achieved in a number of ways:

◆ Plaque removal by the patient, and professional plaque and calculus removal in the dental office;

◆ Use of chemotherapeutic agents (such as essential oils, cetylpyridium chloride, and chlorhexidine) delivered in toothpastes, mouth rinses, and occasionally by oral irrigation devices;

◆ Systemic antibiotics, ideally targeted to susceptible microorganisms, used only for advanced and aggressive disease, or for medically compromised patients;

◆ Local (subgingival) delivery of antibiotics/antimicrobials, including tetracycline HCl incorporated into a polyvinyl acetate carrier, doxycycline HCl incorporated into a thixotropic gel, and chlorhexidine in a gelatin matrix; and,

◆ Host-modulating agents to decrease the inflammatory response (low-dose doxycycline, which has been shown to block the action of matrix metalloproteinases).

The surgical treatment of periodontal disease has focused on the elimination/reduction of excessive probing depths. There is considerable interest in surgical procedures that promote regeneration of lost periodontal tissues:

◆ Placement of barrier membranes to promote regeneration of the surgical wound with cells capable of forming new periodontal tissues (Tatakis et al, 1999);

◆ Allogeneic and xenogeneic bone grafts (Nasr et al, 1999); and,

◆ Xenogeneic enamel matrix proteins that rely on biomimicry to promote regeneration.

In addition, mucogingival surgical procedures are widely used to cover exposed root surfaces and improve esthetics (Wennstrom, 1996).

SYSTEMIC DISEASES

Systemic conditions, such as diabetes, have long been known to affect oral tissues, and oral medicine has focused on the diagnosis and treatment of these oral manifestations of systemic diseases. Recently, however, the results from epidemiologic studies have shown a relationship between severe oral infections, especially periodontal diseases, and other health problems: atherosclerosis, heart attacks, strokes, chronic obstructive pulmonary disease, and premature births. For example, it appears that periodontal disease may increase the risk of dying from a heart attack or having a stroke.

These early findings require confirmation by additional prospective and ultimately intervention studies, and many years of clinical and basic research will be needed to determine whether the association between cardiovascular/cerebrovascular conditions and periodontal disease is actually causative in nature. However, these associations provide the impetus to move the profession of dentistry towards periodontal medicine—a medical model of diagnosis, prevention, and therapy.

New studies are shedding light on how periodontal organisms cause damage beyond the periodontal pocket. These organisms are capable of entering the bloodstream and can target certain organs, such as the liver, major blood vessels, and the placenta, to potentially cause inflammation at distant sites.

Three key organisms that are closely associated with periodontal diseases, *Porphyromonas gingivalis, Treponema denticola,* and *Bacteroides forsythus,* have been implicated in the periodontal infection-systemic disease relationship. They do not colonize easily and require a lush biofilm ecosystem to support adherence, growth, and emergence. They rely mainly on host serum proteins and blood components for sustenance. These organisms have special enzymes and proteins that enable them to trigger mild host inflammation and enhanced gingival crevicular flow to ensure an adequate food and nutrient supply from the serum. These organisms target the liver and activate the hepatic acute phase response. Elevated levels of serum inflammatory mediators and hepatic secretion of acute phase proteins, such as C-reactive protein and haptoglobin, characterize the acute phase response.

Theoretically, over the years, inflammatory mediators and bacteria present in the systemic circulation, even at low levels, cumulatively damage systemic health. Thus, it is the direct systemic action of blood-borne oral bacteria or bacterial products and the chronic inflammation, caused by this hematogenous exposure, which are currently thought to provide a risk to health.

Not everyone gets periodontal diseases, though all are exposed to similar oral pathogens during their lifetime. Some patients never get periodontal diseases, no matter how poor their oral hygiene habits. It now appears that genetic and behavioral characteristics influencing individual inflammatory responses are key predictors of severe periodontal disease (Kornman et al, 1997).

Diabetes and smoking each enhance the inflammatory response to bacterial LPS and impair the ability to fight infection by compromising neutrophil function. An exaggerated inflammatory response results in more tissue destruction clinically seen as severe pocketing and bone loss. This hypothesis does not necessarily negate the potential importance of oral infection as a contributor to systemic diseases, however, it points out that there may be underlying mechanisms not yet identified that may better explain the observed associations between periodontal diseases and other systemic conditions.

Heart Disease and Stroke

Five longitudinal studies have shown that preexistent periodontitis, as determined by direct oral examination, independently confers excess risk for increased morbidity or mortality due to cardiovascular disease. The increased risk ranges from a modest 20% (odds ratio 1:2) to 180% (odds ratio 2:8). Another study demonstrated a dose-response relationship between periodontitis and death caused by myocardial infarction and stroke (Beck et al, 1996). Most of these studies began as cardiovascular disease studies and have controlled for traditional risk factors such as sex, smoking, body mass, serum lipids, exercise, familial history, socioeconomic status, education, and other cardiovascular risk factors. Analyses of the NHANES III data show a strong association between a history of heart attack and increasing periodontitis severity in a dose-response manner: the greater the periodontal disease the greater the risk, with odds ratios greater than five for the most severe periodontal disease groups (Arbes et al, 1999a).

Pregnancy Outcomes

Case-control and prospective human studies suggest that periodontitis is a potential risk factor for premature births, low birth weight, and preeclampsia (Offenbacher et al, 1996; Dasanayake, 1998; and Jeffcoat et al, 2001). Other human studies show no association, but there are supportive data from animal models (Collins et al, 1994b). Preliminary reports of interim findings from larger prospective studies continue to show a significant association between more severe periodontitis and increased incidence of premature delivery. Preliminary reports suggest that periodontal treatments reduce the risk of premature births (Mitchell-Lewis et al, 2001), but these early findings using convenient study populations must be supported by multicenter, placebo-controlled, randomized controlled trials.

Chronic Obstructive Pulmonary Disease and Aspiration Pneumonia

Data from case-control studies and population surveys suggest that periodontal pathogens shed into the saliva can be aspirated via the bronchia to the lung and potentially cause pneumonia, especially in debilitated, infirm, and aged individuals (Joshi et al, 1991). The more severe the periodontal disease status of the patient the greater the apparent risk for aspiration pneumonia. Furthermore, the mature periodontal flora can serve as a habitat for respiratory tract pathogens, especially in hospitalized individuals with dysphagia secondary to stroke (Scannapieco and Mylotte, 1996) and during prolonged intubation. This oral colonization of respiratory pathogens in these compromised individuals appears to increase the risk for pulmonary involvement (Scannapieco, 1999). An association between periodontal diseases and chronic obstructive pulmonary disease has been reported, based upon the NHANES III data set of over 10,000 individuals. Prospective studies on this association are needed.

Diabetes

The preponderance of the data suggest that periodontal diseases are metabolic stressors associated with insulin tolerance, and that periodontal therapy (debridement and systemic antibiotics) can reduce the level of glycosylated hemoglobin—a marker of glycemic control (Grossi et al, 1997). Many epidemiologic studies have confirmed that diabetes is strongly associated with periodontitis, with an odds ratio in the range of 2-3. More recent lines of investigation have clearly demonstrated that periodontal diseases are associated with impaired fasting glucose (Grossi and Genco, 1998; and Taylor et al, 1996),

and an increased demand for insulin, apparently a consequence of insulin resistance (insulin tolerance). The metabolic stress of infection shifts a person with normal glucose tolerance towards a pre-diabetic state of type 2 diabetes. It has been suggested that this metabolic effect is a consequence of systemic LPS, TNF and IL-1, and IL-6, all of which enhance insulin resistance. Experiments are underway to definitively determine whether periodontal therapy reduces the need for insulin in diabetics and reduces the risk for the onset of type 2 diabetes.

Animal Models

Animal models of infections with periodontal pathogens and experimental periodontitis have demonstrated the deleterious effect of infection on atherosclerosis, diabetes, and fetal growth (Collins et al, 1994a; and Lalla et al, 1998). These data not only help establish biological plausibility but also provide important clues regarding the mechanisms of cellular and molecular pathogenesis.

CLEFT LIP, CLEFT PALATE AND CRANIOFACIAL DEVELOPMENTAL DISORDERS

Orofacial clefting is the second most common birth defect (CDC, 1995), and the most frequent of all birth defects affecting the craniofacial region. Only congenital heart defects occur more often.

Oral clefts are classified and distinguished into two major types based on whether the palate only versus the lip or both the lip and palate are involved (Gorlin et al, 1990; OMIM, 2001; and Cohen, 2000). This classification reflects the embryologically distinct events of closure of the lip versus closure of the palate. These two major types of clefting are caused by substantially different genetic and environmental factors, although recent evidence suggests that some overlap in etiology also exists.

◆ *Isolated cleft palate* (CP) is a cleft affecting the palate only, posterior to the incisive foramen. They may affect the soft palate only, or both hard and soft palates. This category includes submucous cleft palate where the cleft affects the musculature of the soft palate but with intact overlying mucosa. Isolated clefts of the palate represent approximately 33% of all clefts.

◆ *Cleft lip with or without cleft palate* (CL/P) are clefts affecting the lip and sometimes also the adjacent maxillary alveolus, or alveolus and palate, typically in the vicinity of the lateral incisor. They may be partial or complete, and unilateral or bilateral. Clefts of the lip, with or without alveolar clefts, represent approximately 17% of all clefts. This condition may occur with cleft palate. Complete lip, alveolar and palate clefts represent approximately 50% of all clefts.

An important distinction is also made depending on whether or not other major or minor physical or mental/neurological anomalies also affect the patient.

◆ *Syndromic clefts* involve the presence of one or more physical and/or mental/neurological patterns of abnormalities in addition to the cleft. The presence of minor anomalies or of major anomalies that might be unrelated to the etiology of the cleft occasionally makes classification uncertain. About 30% of orofacial cleft cases are attributed to the over 350 syndromes recognized to date.

◆ *Nonsyndromic oral clefts* occur without any physical or mental/neurological anomalies. Approximately 70% of oral clefts appear to be nonsyndromic.

Most oral cleft syndromes have a major hereditary cause (Gorlin et al, 1990; and Cohen, 2000). Purely environmental causes are relatively rare, and even these may be affected by genetic differences influencing metabolism of teratogens following maternal and fetal exposures. About 55% of the syndromes associated with syndromic clefting have a monogenic autosomal dominant or recessive or X-linked mode of transmission, 15% involve chromosomal rearrangements, about 5% have primarily an environmental (i.e., teratogenic) etiology, and the cause for the remaining 25% is unknown. The specific gene defects for some of the monogenetic syndromes have been identified, such as three different collagen genes for the three types of Stickler syndrome. Genes for other syndromes, such as van der Woude, have been mapped to a small chromosomal region, and gene identification is expected soon.

The causes of nonsyndromic orofacial clefting involve complex gene-environment interactions (Schutte and Murray, 1999; and Carinci et al, 2000). To date, only a very small number of candidate gene polymorphisms have been evaluated.

These have been selected based on theories about craniofacial development derived from mouse models or genes that metabolize teratogenic or protective dietary nutrients such as folate. These studies have either been consistently negative, inconsistent among studies, or account for a tiny fraction of the heritable risk of nonsyndromic orofacial clefting. It appears that six or more genes probably have major effects on susceptibility, though none of these have been convincingly identified and independently replicated to date (Prescott et al, 2000). Variation at dozens of other genes probably contribute smaller influences on risk. Exposure to smoking, alcohol and certain prescription medicines such as anticonvulsants during pregnancy increases risk (Gorlin et al, 1990; Wyszynski and Beaty, 1996; and Houdayer and Bahuau, 1998) and protective substances in the maternal diet such as folate and multivitamins appear to reduce risk (Loffredo et al, 2001).

However, most studies indicate that inherited variation has the greater overall effect on susceptibility. Furthermore, some of the individual genetic variation important for modifying orofacial clefting risk may occur at genes controlling the metabolism of the teratogenic and dietary factors associated with risk. At present, empirical risk tables are based on epidemiological studies and thus provide only population averages rather than individualized risk assessments, but these still permit genetic counselors to predict the average risk of recurrence of nonsyndromic clefting for different kinds of clefting and reflecting an individual's family history of the disorder. In a small proportion of nonsyndromic families, evidence suggesting a monogenic dominant or X-linked pattern of transmission can be used to further refine risk estimates. The growing list of possible environmental teratogens can also assist in pregnancy counseling to reduce, but not eliminate, risk of having a child with a cleft.

In the United States, approximately 7,000 children are born each year with cleft lip or cleft palate. Estimates of actual incidence vary, but a reasonable range would be between 1 in 750-1000 live births for Whites, with approximately twice this incidence for Native Americans and Asians, and half this incidence for African Americans. Cleft lip with or without cleft palate is about twice as common in males as in females, while the reverse is true for isolated cleft palate.

The total lifetime cost for each year's cohort of children born with oral clefts is estimated at $697 million (CDC, 1995)—about $100,000 per child. This total includes $97 million for medical services, $20 million for non-medical direct costs such as special education, and $599 million for indirect costs of patient work limitations and caregiver costs. These figures do not account for the psychosocial impact of the disease on patients and their families, a component of the disease for which treatment may be insufficient even in developed countries (Turner et al, 1998). The lack of advanced medical services, including surgery, often unavailable in undeveloped countries, contributes to substantial morbidity and mortality and to even greater psychosocial stress on patients living with unrepaired oral clefts. Clearly, there are very strong financial and humanitarian incentives to reduce the frequency of oral clefts both in the United States and worldwide.

Mutations in single genes have been identified for a number of craniofacial developmental disorders that involve structures of the craniofacial complex. Examples include holoprosencephaly-3 (mutations in the sonic hedgehog homolog gene), several types of craniosynostosis (mutations in MSX2, fibrillin-1, or fibroblast growth factor receptor genes), and basal cell nevus syndrome (mutations in the Patched gene) (Gorlin et al, 1990; Cohen, 2000; and Cohen and MacLean, 2000). Most of these syndromes are rare, but in aggregate the group has a substantial impact on human health.

For both syndromic forms of orofacial clefting and for other craniofacial developmental disorders, where specific disease gene mutations have been identified, genetic counseling is both feasible and desirable. Dentists often have an important role to play in both the quick and accurate identification of the syndrome and referral for counseling. For nonsyndromic clefting, it is also important for dental professionals to make referrals for genetic counseling and to help educate the public about the risks of maternal smoking and alcohol consumption and the benefits of prenatal vitamin supplementation and a well-balanced overall diet for disease prevention.

The current standard of care for patients with clefts and other craniofacial developmental disorders is based on the concept of interdisciplinary team care, including significant contributions from many dental specialties. The Parameters for Evaluation and Treatment of Patients with Cleft Lip/Palate or Other Craniofacial Anomalies (American Cleft Palate-Craniofacial Association, 1993), clearly delineates the important role of the dental profession in this field. The malformation affects multiple functional systems, including speech, hear-

ing, dental development, facial growth, facial esthetics, facial animation, occlusion and mastication, and psychosocial development. The dental components to the cleft/craniofacial team represent some of the most significant contributions to total patient rehabilitation, including pediatric dental care, orthodontics, oral and maxillofacial surgery and prosthodontics. In addition, the dental specialists on the cleft/craniofacial team play key roles at almost every age and stage of care of the patient with a cleft. Consequently, they are also uniquely positioned to document and record treatment outcomes, and participate in the clinical research efforts into treatment efficacy and effectiveness.

Research efforts to determine optimal ways to deliver health services to these patients have been hampered by a lack of consensus on minimal standards for documenting outcomes, as well as agreement on which outcomes are relevant indicators of successful treatment in the first place. Current outcomes research has traditionally excluded parent participation in defining treatment success or failure, a serious shortcoming emphasized by the Surgeon General's Conference on Children and Oral Health (Satcher, 2000). Furthermore, evidence for something as basic as the cost-effectiveness of team care is currently lacking, in spite of overwhelming support among care providers, of its appropriateness. Finally, while the large number of centers providing treatment for clefts improves patients' geographical accessibility to care, it simultaneously creates a fractionation of the cleft population thereby reducing the probability of developing patient samples of adequate size to enable valid research. While several recent research initiatives such as the Eurocleft project in Europe (Shaw et al, 2001) and the Craniofacial Outcomes Registry in the United States (http://www.cfregistry.org/) have begun to remedy this problem through significant inter-center collaboration and establishment of common data bases, the lack of collaboration between these various initiatives themselves, continues to limit the benefits of the globalization of this effort.

MALOCCLUSION AND TOOTH AGENESIS

Malocclusion, or faulty intercuspation of the teeth, is usually caused by a moderate variation or distortion of normal growth and development of the teeth or bones of the mandible and maxilla. Usually it occurs without any other dental or medical problems, though occasionally it develops as a symptom of a systemic or syndromic disease. Malocclusion is a continuum from slight irregularity of the bite to severe difficulty with mastication. Abnormal tooth and jaw alignment can affect speech, and in severe cases an abnormal facial appearance may affect the psychological well-being of the individual (Berscheid, 1980).

Although a single specific cause of malocclusion may sometimes be apparent—e.g., trauma, oral habit, dental anomalies of tooth shape or number, or a genetic syndrome—malocclusion is usually the result of a complex interaction among multiple hereditary and environmental factors that influence growth and development. This interaction occurs in, and has an effect on, the craniofacial skeleton, dentition, orofacial neuromusculature, and other soft tissues, including those that border the airway. Although in the past there has been controversy and debate about the relative importance of hereditary versus environmental influences on the etiology of malocclusion, there is evidence of a genetic influence on many aspects of dental and occlusal variation (Mossey, 1999).

Incidence

Estimates of the incidence of malocclusion in the United States vary with the criteria used. The Index of Treatment Need (IOTN) (Brook and Shaw, 1989) relates malocclusion to the need for treatment, using psychosocial and facial considerations, in addition to dental health (traits) to assign five grades of treatment need. One study, using only the dental health (traits) component of the IOTN, estimated the prevalence of malocclusion and orthodontic treatment need in the United States from data in the third National Health and Nutrition Examination Survey (Proffit et al, 1998). This study found that 15% of the population has dental irregularity severe enough to affect both social acceptability and function.

Correction of these severe problems may require major arch expansion or extraction of some teeth. About 20% of the population has deviations from ideal bite relationships. One in 50 of these deviations is severe enough to be disfiguring. Many of these problems are at the limit of treatment by orthodontics alone and may require orthognathic surgery. Another study found sagittal molar asymmetry in 30% of a group of untreated 8-10 year olds and in 23% in a group of untreated 14-15 year olds (Sheats et al, 1998). In the latter group, 12% also showed facial asymmetry and 21% displayed noncoincidence of dental midlines.

Tooth agenesis (missing teeth) and supernumerary teeth (more than the normal number of teeth) are common problems. Tooth agenesis occurs in about 20% of the population, and third molars are by far the most commonly affected teeth. Missing maxillary lateral incisors and mandibular premolars occur at the next highest frequency (Graber, 1978). Most supernumerary teeth are present in the anterior maxillary region (Garvey et al, 1999). Some cases of tooth-number abnormalities occur sporadically (without any family history). However, aside from the common variation of third molars, the pattern often is transmitted through multiple generations of families, indicating that the cause is due to a single gene of major effect. Mutations in key regulatory genes of the homeobox family such as MSX1 and PAX9 have recently been identified as the cause of different forms of hereditary tooth agenesis (Vastardis, 2000; and Stockton et al, 2000).

Treatment

It is likely that there are disparities in access to treatment for malocclusion and tooth agenesis. Just over 30% of White teenagers receive orthodontic treatment in the United States, nearly three times as many as in the Hispanic population and four times as many as in the African American population (Proffit et al, 1998).

Traditional orthodontic approaches to the correction of malocclusions are effective, but new approaches to therapy will continue to appear. For example, a removable appliance-based, computer-assisted treatment modality has been introduced for minor tooth movement in adults. The profession should continue to evaluate the efficacy of new treatment modalities to increase access to ortho-dontic care. Appropriate peer review of studies and claims is required to assure evidence-based treatment.

ORAL AND PHARYNGEAL CANCERS

In 2000, more than 30,000 Americans developed oral and pharyngeal cancers. Almost 8,000 Americans died from this disease (Greenlee et al, 2000). Tongue cancer incidence and mortality are reported to be increasing significantly, especially among young White males (Moore et al, 2000; and Myers et al, 2000). This could be due to increased use of smokeless tobacco, but there have not been increases in rates of cheek, gum and other mouth cancers, which are closely linked to smokeless tobacco use. Increases in tongue cancer have also been observed in the United Kingdom where oral snuff and chewing tobacco are infrequently used (Blot et al, 1996). Oral cancer in young adults appears to be associated with the traditional risk factors of tobacco smoking, drinking alcohol and low consumption of fruit and vegetables, rather than due to any unique or new etiological agent (Mackenzie et al, 2000).

Oral Cancer Etiology

Oral cancer presents a highly complex challenge in terms of understanding its etiology, diagnosis and treatment (Blot et al, 1996; Silverman, 1998; and Winn et al, 1998). A large number of factors influence risk of developing oral and pharyngeal cancers:

◆ *Heavy cigarette smoking and alcohol consumption* are strongly associated with increased risk of oral and pharyngeal cancers (Blot et al, 1996; and La Vecchia et al, 1997). Persons who consume large quantities of both tobacco and alcohol have an estimated 80-fold higher risk of oral and pharyngeal cancers than do people that never used these substances. Cessation of tobacco and alcohol use is associated with a significant reduction of risk after about 5 to 10 years. Dental professionals can be effective in helping people to quit using tobacco by using interventions in dental office settings (Severson et al, 1998; and Crews et al, 1999).

◆ *Diets high in fresh fruits* and possibly some vegetables have been associated with a 50% reduction in risk for oral and pharyngeal cancers, even after adjusting for the effects of tobacco and alcohol (Blot et al, 1996; and La Vecchia et al, 1997).

◆ *Human Papilloma Virus* (HPV) infection has been suggested to increase risk of developing oral cancers. This has led to hope of possible reduction in cancer incidence through use of HPV vaccines now undergoing clinical trials for genital-tract cancers. However, current data suggest that only a relatively small portion of head and neck cancershave major HPV etiological involvement, though additional data are needed to confirm this conclusion (Schwartz et al, 1997; and Franceschi et al, 2000).

◆ *Oral lesions* that may be considered "premalignant" are found in about 2% of the population and

include leukoplakia, erythroplakia, and possibly lichen planus, chronic candidiasis, pemphigus vulgaris and verrucous hyperplasia. Estimates of the chances of progression of these lesions to oral and pharyngeal cancers vary from 6% to 36% over a 10-year period for leukoplakia and erythroplakia (Warnakulasuriya, 2000).

◆ *Inherited susceptibility* influences both chances of becoming addicted to heavy alcohol and tobacco use, and activities of carcinogen-metabolizing genes such as alcohol dehydrogenase (Harty et al, 1997) and glutathione transferase (Park et al, 1999). Although oral cancer does not generally appear to be as heritable as some other forms of cancer, risk has consistently been shown to be elevated in close relatives of oral cancer cases (Jefferies and Foulkes, 2001).

Concern has been raised about possible increased risk associated with use of alcohol-containing mouthwashes, but recent studies indicate risks appear to be relatively small compared to the major risk attributable to high levels of alcohol drinking (Elmore and Horwitz, 1995; and Winn et al, *In Press*).

After adjusting for age, African American males have about a 50% higher incidence of oral and pharyngeal cancers than males of European ancestry (Ries et al, 2000). Five-year survival (relative to the rest of the population of similar age) is 29% for male African Americans and 53% for White males in the United States. The difference in mortality is due primarily to the more advanced stage at which oral cancers are usually detected in African Americans (only 15% at a localized stage when treatment is much more effective, versus 37% for Whites) (Ries et al, 2000).

Other factors that may contribute further to differences in mortality include socioeconomic status and differences in treatment (Arbes et al, 1999b; and Skarsgard et al, 2000). However, only about half of the excess mortality experienced by individuals diagnosed with oral cancer is attributable directly to the cancer itself. For newly diagnosed oral cancer cases, only about 30% of White and 40% of African Americans die from an outcome directly related to their oral cancer within five years. Instead, 30% of newly diagnosed White oral cancer cases and 40% of African American oral cancer cases die due to other causes within five years (Arbes et al, 1999b). This "other" mortality is much higher than expected for average individuals in the population of the same age range, and is due to the fact that most oral cancer cases consume very high amounts of tobacco and alcohol.

Causes of death that are excessive among oral cancer cases include primary cancers of other organs, ischemic heart disease, chronic obstructive lung disease, liver cirrhosis and other tobacco and alcohol-related diseases. This perspective emphasizes that even fully successful treatment of the oral cancer itself by no means restores patients to a normal level of health (Skarsgard et al, 2000).

Diagnosis and Treatment

Oral examinations by dental professionals and education of the public about oral and pharyngeal cancers are important steps to increasing early diagnosis. Early detection and surgical removal of lesions when they are small and localized greatly improve prognosis. Five-year survival rates relative to individuals of similar ages who are not affected by oral cancer are 81% when the tumor is localized, 44% when restricted to the oral region, but only 21% when metastasized to distant locations (Ries et al, 2000). Unfortunately, health professionals perform thorough oral examinations far too infrequently, and only 36% of oral and pharyngeal cancers are diagnosed when the disease is confined to the local area.

There is very sound scientific justification to encourage examinations for these cancers as standard practice, especially for individuals at high risk due to advanced age or heavy use of tobacco and alcohol. Furthermore, there may be benefits to the dental profession in terms of health insurance compensation, which may be strongly justified for the purpose of screening for this serious disease condition, comparable to examinations now routinely performed by physicians for prostate or breast cancer with full insurance compensation.

The American Cancer Society recommends that persons 40 years and older have an oral cancer examination once every 3 years (Smith RA et al, 2000). Unfortunately, in 1992 only 15% of United States adults reported that they had ever had an oral cancer examination, and only 7% of respondents over age 40 had received such an examination in the previous year (Yellowitz et al, 2000).

Standard treatment for oral and pharyngeal cancers depends on the size, location, and histopathological state of the lesions and usually includes surgery and radiation. Interventions for cancers detect-

ed at later stages are highly disfiguring and require post-treatment reconstructive surgery, which greatly reduce the quality of life even when the patient is completely cured of cancer.

ORAL MUCOSAL AND AUTOIMMUNE DISEASES AND OTHER INFECTIONS

Mucosal Diseases

Oral mucosal diseases represent an array of conditions of multiple etiologies and various pathobiologies whose clinical effects range from mildly annoying to life threatening. Included here are the blistering diseases, such as pemphigus vulgaris and pemphigoid; ulcerative diseases, such as aphthous stomatitis and Behcet's disease; and iatrogenic conditions, such as stomatotoxic reactions associated with drug and radiation therapies for cancer.

The overall frequency of these diseases and conditions is high. Aphthous stomatitis affects 20% of the world's population (Woo and Sonis, 1996) and lichen planus affects 1-2% of adults over the age of 50 years (Scully et al, 1998). About 20% of individuals who receive chemotherapy develop painful mucositis of such severity as to require significant intervention or alteration in their cancer treatment plan (Epstein and Schubert, 1999). Among patients with head and neck cancer who are treated with radiation, mucositis is virtually a universal event often resulting in the need for breaks in treatment and hospitalization.

Whereas aphthous stomatitis typically has an age of onset in the first or second decade, lichen planus, pemphigoid and pemphigus vulgaris tend to occur in older populations (Flaitz, 2000). Erythema multiforme is most common in the second decade. Aphthous stomatitis, lichen planus, mucous membrane pemphigoid and pemphigus vulgaris have a gender predilection for females. Erythema multiforme is most common in males.

With the exception of mucosal injury induced by radiation or drug therapy for cancer, virtually all of the oral mucosal diseases are thought to be manifestations of autoimmune processes, although the nature of their etiology is not fully understood (Popovsky and Camisa, 2000). The complexity of the etiopathogenesis of these conditions is illustrated by aphthous stomatitis, which is the most common oral mucosal disease (Barrons, 2001). A number of systemic conditions predispose to the development of aphthous stomatitis. Patients infected with Human Immunodeficiency Virus (HIV), having certain vitamin deficiencies or with quantitative neutrophil disorders, are at risk for the condition. Yet, the majority of patients appear to be genetically predisposed for the condition. Specific HLA types associated with recurrent aphthous stomatitis have not been demonstrated. Similar to lichen planus, aphthous stomatitis appears to be the result of cell-mediated immune injury. Yet, the clinical manifestations of the two conditions are very different.

The blistering diseases, mucous membrane pemphigoid and pemphigus vulgaris, have an autoimmune etiology, and are the consequence of autoantibodies directed at different molecules in the basement membrane zone (pemphigoid) or at desmosomes (pemphigus) (Rye and Webb, 1997). The immunologic complexity of pemphigoid is only now being dissected. Identification of autoantigens has shown that they differ among anatomic sites affected by this disorder. The etiology of pemphigoid remains elusive (Dayan et al, 1999). The fact that oral mucous membrane pemphigoid is a disease of the elderly may suggest the development of abnormal basement membrane antigens to which destructive autoantibodies are produced. Pemphigus vulgaris, in contrast, develops at a younger age (fourth or fifth decade) and has an immunogenetic predisposition. Linkages of the disease to certain genetic regions among large percentages of patients at risk for the condition support this hypothesis.

The explosive onset of erythema multiforme (Laskaris and Satriano, 1993) and its predisposition for young males set this condition apart from other oral blistering diseases. The observation that the disease is often sequelae to Herpes Simplex Virus (HSV) infection or the administration of certain medications suggest a mucosal autoimmune disease directed at aberrant antigens acutely expressed on the oral mucosa.

A major area of controversy surrounds one of the most common mucosal diseases, lichen planus, and focuses on its pre-malignant potential. Strong cases have been made on both sides of the issue (Silverman, 2000; and Eisenberg, 2000). Nonetheless, despite issues with diagnostic criteria, a review of studies in the area leads to the conclusion that patients with some forms of lichen planus are at risk for developing oral cancer. The risk has been reported to range from a frequency of 0.4% to 3.3%. To put this risk in perspective, consider that

the United States population in the age range at risk for oral cancer (ages 50 to 70 years) numbers 51 million. If the estimated frequency of lichen planus is 1%, then among that age group there are 510,000 cases of lichen planus. The expected rate of oral cancer among individuals in that risk group is about 30 cases per 100,000. With a risk of 3.3%, the expected number of oral cancers in the lichen planus group would be five times that (150 cases). Clearly, the issue of lichen planus as a premalignant lesion needs to be better defined and studied. It seems likely that not all forms of lichen planus are at equivalent risk of developing into a malignancy.

Oral mucosal diseases are frequent, symptomatic, and biologically complex. For many of these conditions, current treatment is palliative and/or anti-inflammatory and often unsatisfactory. New molecular biological techniques, the definition of the human genome, and the association between specific genes with effector proteins should lead to a better understanding of the etiology and pathophysiology of these conditions, and ultimately to new therapies.

Other Infections

The mouth is home to a great variety of organisms. Fortunately, the majority of these are not of any serious health consequence. Nevertheless, knowledge about infectious agents and their natural histories is essential for the practicing dentist. Dentists must be able to recognize the oral manifestations of infectious diseases (Lynch, 2000) especially those associated with HIV infection, be aware of the serum tests used to identify hepatitis A, B, and C infections and be aware of the role of the "carrier" (an apparently healthy individual who shows no sign of an infectious disease but is able to transmit the disease to others).

Within the last 20 years, considerable attention has been devoted to the need for universal infection control policies in the dental office. Federal and state regulations have been formulated which can lead to monetary fines and other sanctions if these procedures are not followed.

In recent years, several developments in medicine have further increased the significance of infectious diseases in modern dental practice. These include the widespread use of agents that suppress the immune system, as well as immunosuppressive drugs used to treat patients having organ transplants and other medical problems, reducing immunity and increasing susceptibility to infections. Some of the infections seen in immunocompromised patients were, hitherto, very unlikely to be seen by the dental practitioner.

The most common viral infection identified and treated by dentists is the HSV, and the most common fungal infection is due to *Candida albicans* (Glick and Siegel, 1999). Herpes viruses are characterized by their ability to establish latent infections that can be reactivated, especially in the immunocompromised patient (Oakley et al, 1997). HSV type 1 is responsible for most intraoral infections. In immunocompetent patients, herpetic ulcers are most frequently found on keratinized mucosa (Regezzi and Sciubba, 1989). In contrast, immunosuppressed patients can develop lesions at any intraoral site, with nonkeratinized sites representing half of all sites involved (Woo and Lee, 1997; and Oakley et al, 1997).

Fungal infections have emerged as an increasing problem in patients immunocompromised by disease or treatment. Oropharyngeal candidiasis is perhaps the most frequently encountered fungal infection and constitutes a major cause of morbidity and mortality in immunocompromised patients (Lynch, 1994; and Phelan et al, 1997). In most patients the organism isolated is *Candida albicans* (Odds et al, 1989), but in recent years other *Candida* species such as *Candida glabrata* are increasingly associated with oropharyngeal infection (Coleman et al, 1995). Because of its oral bioavailability and lack of serious side effects, fluconazole is the current drug of choice for fungal infections (Reents et al, 1993). Unfortunately, the widespread long-term use of fluconazole in recent years has lead to the development of resistance of oral isolates to azole drugs and, in some cases, cross-resistance to polyene drugs as well (Rex et al, 1995).

Other bacterial infections that occur in the mouth are related to *Treponema pallidum, Mycobacterium tuberculosis* and *Neisseria gonorrhae*. Other viral infections (e.g., human papilloma virus) and fungal diseases (e.g., histoplasmosis, coccidiomycosis and crytococcosis) also manifest in the oral cavity. These "deep" fungal infections have a low incidence, but in some regions of the United States certain fungal infections are epidemic (i.e., histoplasmosis in the Southwestern United States).

SALIVARY GLAND DISEASES

Saliva modulates oral microbial ecosystems, aids in the preparation of the food bolus, lubricates oral tissues, and supports other critical oral functions. The initial phases of dental caries development are reversed in part by saliva, which buffers acids and is supersaturated with calcium and phosphorus. The salivary mucins are a heterogeneous population of glycoproteins that bathe and protect oral soft tissues (Schenkels et al, 1995). Salivary glands are a part of the mucosal immune system.

Salivary Dysfunction

Decreased salivation results in decreased secretion of antimicrobial and antifungal proteins such as salivary IgA, lysozyme, lactoferrin, peroxidases, and histatins (Atkinson and Fox, 1992). Individuals with inadequate salivary function are at risk for rampant dental decay, recurrent mucosal candidiasis and salivary gland infections, esophageal disease, gastric reflux, altered nutritional intake, and a decreased quality of life.

The most pronounced salivary dysfunction occurs in three groups of patients:

◆ Patients with Sjøgren's syndrome, a systemic autoimmune disorder primarily affecting the salivary and lacrimal glands.

Current prevalence estimates for Sjøgren's syndrome, using the European Community criteria, range from 0.6% to 3.3% of the adult population (Dafni et al, 1997; and Thomas et al, 1998), but the diagnostic criteria used in these studies are not accepted universally. International researchers primarily use one of three sets of criteria to select patients for studies (Fox, 1997). This lack of uniformity in patient selection represents a significant barrier to research progress. Diagnostic uncertainty inhibits genetic studies and makes it impossible to compare studies of pathophysiology and therapy.

◆ Patients who have received therapeutic radiation to the head and neck.

Radiation treatment of oral and pharyngeal malignancies typically includes salivary tissue within the field. At doses above 40 Gy, the damage is rapid and irreversible, and the mechanisms for this unfortunate side effect are not understood.

◆ Patients taking medications that interfere with salivary secretory processes, such as signaling pathways. More than 300 medications can cause oral dryness, and certain classes of medications are more likely to inhibit salivation and cause xerostomia. These include sedatives, antipsychotics, antidepressants, antihistamines and certain anti-hypertensive agents. Medi-cations with anticholinergic activity can potentially decrease salivation (Atkinson and Fox, 1992).

Diagnosis, Prevention, and Treatment of Salivary Dysfunction

When evaluating a patient, the dentist should consider the patient's medical, dental, and social histories to identify medications and predisposing conditions. A history of past radiation therapy, both internal and external, is important. The diagnosis of Sjøgren's syndrome is usually established by a complete ophthalmological examination, a minor salivary gland biopsy and tests for serum autoantibodies.

Any patient with salivary gland dysfunction will benefit from an aggressive oral hygiene program that includes the use of topical fluorides (Ripa, 1989). Other prevention strategies could include the use of remineralization dentrifices, which currently are under evaluation in postradiation patients (Papas et al, 1999). Radiation damage to salivary glands can be limited by preradiation planning (conformal and static, multisegmental intensity modulated radiotherapy, IMRT) that spares as much salivary tissue as possible from the radiation field (Eisbruch et al, 1999). The use of pilocarpine and the oxygen radical scavenger amifostine during radiation treatment may decrease damage to glands (Valdez et al, 1993; and Jha et al, 2000). Some investigators are surgically repositioning submandibular salivary glands to the submental space before radiation to maintain gland function (Bohuslavizki et al, 1999).

The availability in the last decade of systemic agents that can stimulate salivary output (secretogogues) has been a major advance in symptomatic management of patients with salivary gland hypofunction (Fox, 1998); however, they have significant side effects that limit their utility and patient acceptance.

TEMPOROMANDIBULAR DISORDERS (TMD)

Temporomandibular disorders (TMD) are characterized by regional signs and symptoms, including pain in the area of the TM joint and/or masticatory muscles, often with limited mandibular range of motion, and/or TM joint sounds (clicking and/or crepitus). Some definitions include a broader range of symptoms, including headaches, earaches, dizziness, and pain in contiguous structures of the head and neck.

Incidence and Causes

The causes of TMD, and why some patients develop chronic, persistent symptoms, are not well understood. The NIH Technology Assessment Conference on Management of TMD recommended the "Parameters of Care for Oral and Maxillofacial Surgery" to help classify patients (NIH, 1996). Some TMD patients may be classified using the International Headache Society's diagnostic classification (Okeson, 1988), and some patients should be evaluated for neurological conditions and for systemic conditions such as fibromyalgia. Furthermore, the American Academy of Orofacial Pain has expanded and modified this classification scheme to include a wider range of orofacial pain and TMD (Okeson 1996).

Research and consensus conferences have not ruled out malocclusions, joint anatomy, and skeletal malformations as significant etiological factors. Attempts to classify or subdivide TMD have relied on groupings of signs and symptoms. A diagnostic classification has been developed for research purposes (Dworkin and Le Resche, 1992); however, its clinical utility and validity as a research tool have not been established. At this time, the most reasonable clinical diagnostic classification appears to be that published by the American Academy of Orofacial Pain.

Cross-sectional studies of TMD indicate that between 40% to 75% of the population experience at least one sign or symptom at any given time; 34% of the population reported having a temporomandibular disorder. Only 4% to 5% of the population is believed to have a clinically significant TMD (Von Korff et al, 1988). Most TMD are self-limiting and resolve with time or palliative care (Okeson, 1996), and studies show a lower prevalence of signs and symptoms associated with TMD at older ages. Clinically serious TMD are infrequent in children. A small percentage of patients develop chronic pain related to their TMD (Kinney et al, 1992). It is not known why some patients progress and others do not.

While epidemiologic studies find slightly higher frequency of signs and symptoms in females than in males, the small differences cannot explain the high proportion of women (7:1) who seek care for TMD (Okeson, 1996). Many individuals with symptoms of TMD do not receive care, and older adults do not tend to seek care. The NIH Technology Assessment Conference on Management of TMD (NIH, 1996) noted that there is no research documenting societal barriers and prejudices that prevent appropriate treatment.

Systemic factors and conditions may play a role in several TMDs. Factors such as degenerative, endo-crine, infectious, metabolic, neoplastic, neurologic, rheumatologic, and vascular disorders, have not been systematically studied. Also the NIH Technology Assessment Conference noted that systemic conditions, such as polymyositis, dermatomyositis, hereditary myopathies and fibromyalgia can affect the masticatory muscles.

Diagnosis and Management

Diagnosis and management of TMDs remain controversial. The NIH Technology Assessment Conference (NIH, 1996) states that, "diagnosis and initiation of treatment should be based on data from physical examination and should include medical and dental history, information about audiological, speech, and swallowing problems, pain and dysfunction. . .Evaluation should encompass examination of orofacial tissues, musculature, and neurological function. . . . Psychosocial assessments should determine the extent to which pain and dysfunction interfere with or diminish the patient's quality of life. However, the consideration of psychosocial factors has the potential for inappropriate use, and it is imperative that such assessments be managed by skilled professionals using validated instruments." It also is important to rule out symptoms that may be due to cancer, various arthritides, neurological diseases and other systemic medical conditions that should be referred to specialists.

Evidence-based guidelines strongly support the use of conservative, noninvasive, and reversible strategies for treating TMD. Current evidence suggests that strategies that permanently modify the occlusion and/or joint structures should be avoided. The guidelines recognize the need for patient education, adequate pain control using pharmacologic and behavioral means, and the possibility of physical therapy and stabilization splints. Surgical approaches may be necessary in a small percentage of patients.

II. DENTAL AND CRANIOFACIAL RESEARCH IN THE FUTURE

Advances in understanding the etiology, pathogenesis, and diagnosis of oral diseases and conditions have led, and will lead to, improved methods of disease management. Dental practice must evolve and broaden to incorporate this knowledge. Furthermore, differences in the burden of oral disease, evident throughout the United States, will challenge the profession to take a leadership role in improving access to care and delivery of dental services.

As noted, the disease-specific discussions illustrate many changes and advances that can be anticipated by the dental profession. But these nine oral disease categories are hardly inclusive of all dentistry.

One topic not addressed in this chapter but discussed elsewhere in the report of the Future of Dentistry is the aging of the population. It should be noted that with fewer severe carious lesions and fewer dental extractions, a continuing decrease in edentulism means that older individuals will retain more teeth, thus increasing risk for periodontal diseases and root caries. These individuals will require more preventive and therapeutic dental care. Conservative management of periodontally involved teeth will be the rule for this segment of the population. General dentists and dental hygienists can be expected to assume most of this increasing responsibility. To adequately treat older patients, who often have concomitant medical problems, it will be essential that dentists become more familiar with geriatric medicine.

FUTURE CHANGES IN DENTAL CARIES RESEARCH/DENTAL BIOMATERIALS RESEARCH

The future of dentistry will require new approaches and new ways of delivering proven methods if the profession is to be successful in further reducing or eradicating dental caries. New thinking in relation to public health dentistry and community dental health measures are needed to address the dental caries problem that occurs in underserved populations.

Dental caries remains a problem for a significant portion of the population, and is the most common disease of childhood. Certain high-risk children and adults suffer from extensive disease. Nevertheless, early identification of at-risk individuals is elusive, and research effort towards this outcome is required.

Approaches to the management of carious lesions in the near future will rely on remineralization. When restoration is required, conservative repair without unnecessary removal of uninvolved tooth structure will be the rule. The shift in restorative dentistry to metal-free restorations is likely to expand with the introduction of improved composite-based materials, and new "smart" biomaterials to provide improved resistance to recurrent caries and wear.

The same bacteria involved in other forms of caries cause early childhood caries, especially among disadvantaged populations, but there are also other causal factors that are not yet fully understood. Future efforts are needed to treat the infection of the mother and/or the caregiver who is the primary infective agent in bacterial transfer to the child. Addressing this aspect in the environment of families and extended families is a major public health issue for the future. The association of increased caries incidence and impaired cognitive development needs further study.

Caries Risk Assessment

Caries management by risk assessment will be essential in the future of dentistry (Anusavice, 2000; and Featherstone, 2000). Risk assessment must be conducted prior to the removal of active caries and the placement of restorations. Future risk assessment strategies will include:

- Analysis of the frequency of cariogenic challenge/diet.

- Assessment of the oral status of caregivers.

- Quantitative determination of cariogenic bacteria with molecular biology tools. Antibodies designed to interact with the surfaces of specific species of cariogenic bacteria have been developed and can be tagged by fluorescent molecules that can be measured photometrically. This technology will enable rapid, chair-side assessment of the level of the bacterial challenge (Krasse, 1988).

- Assessment of the quantity and quality of salivary function.

- Measures of dietary challenge and salivary protective factors.

◆ Assessment of fluoride exposure.

◆ Information management systems to store and evaluate data on the bacterial challenge, salivary status, fluoride exposure, history of caries, and other risk factors, as a basis for planning a rational treatment protocol for the individual patient.

◆ Identification of specific genes or genetic markers that are associated with increased risk for severe, extensive caries.

Dental Caries Prevention and Management

New and improved dental products and antibacterial agents are on the horizon. Products that more effectively deliver fluoride and that provide antibacterial action at the same time will prevent dental caries:

◆ The wider use of sealants in combination with other preventive measures will occur.

◆ Chlorhexidine is currently the only antibacterial agent that effectively kills mutans streptococci. Lactobacilli are resistant to chlorhexidine; thus, other treatments will be necessary to reduce or eliminate them.

◆ Slow-release fluoride products are also likely to become widely utilized.

◆ Antibacterial agents attached to antibodies that react with the surfaces of cariogenic bacteria will likely be developed.

◆ Products will be developed to supplement saliva's function and protective components.

◆ Plant-derived genetically engineered antibodies such as sIgA are currently under development as a tool for inhibiting colonization of specific cariogenic bacteria.

Products incorporating specifically targeted antibacterial agents will become available for use in the dental office and most likely by prescription in the home environment. Such products could also be utilized in targeted community programs for reducing dental caries in populations and for blocking the transfer of infection from the caregiver to the child.

Both positive and negative interactions occur between different species of bacteria inhabiting the same ecosystem. This provides the basis for a novel approach to preventing microbial diseases called "replacement therapy." In this approach, a harmless effector strain is permanently implanted in the host's microflora. Once established, the presence of the effector strain prevents the colonization or outgrowth of a particular pathogen.

To prevent dental caries in the future, replacement therapy will involve construction of an effector strain derived from a clinical *S. mutans* isolate. Recombinant DNA technology will be used to delete the gene encoding lactate dehydrogensome making it entirely deficit in lactic acid production (Hillman et al, 2000). Because of its strong colonization properties, a single application of the effector strain to patients should result in its permanent implantation and development of indigenous, disease-causing *S. mutans* strains over time. Thus, replacement therapy for the prevention of dental caries is an example of biofilm engineering that offers the potential for a highly efficient, cost-effective augmentation of conventional preventive strategies. Attendant concerns are the compatibility of the engineered organism with the normal flora, the ability of the organism to successfully colonize the oral cavity, and the regulatory issues related to safety of the new organism (Mandell, 1996).

There has been considerable interest in the development of a caries vaccine (Smith and Taubman, 1997; and Russell et al, 1999). These studies have considered the importance of humoral immunity in the caries process. Concerns have been raised about the safety of newly introduced vaccines and the relative effectiveness compared to other preventive approaches. Vaccines based on systemic inoculation are unlikely to be approved. Rather, approaches that may be more practical are based on mucosal immunization and production of salivary IgA antibody to mutans streptococci and passive immunization. Furthermore, the use of such a vaccine would likely be limited to high-risk individuals, i.e. patients with persistent xerostomia (Mandell, 1996).

Laboratory studies have shown that specific laser irradiation can alter the surface mineral of the enamel and make it highly resistant to subsequent acid dissolution (Featherstone et al, 1998). Consequently, carbon dioxide lasers with specific laser characteristics designed for this purpose, and potentially Er:YAG and Er:YSSG lasers, could be used to treat specific areas in caries-susceptible individuals to inhibit caries progression. Ideally,

pits and fissures can be treated in this way. When lasers remove early cavities, conditions can then be changed to treat the walls of the cavity preparations, thereby inhibiting secondary caries around restorations (Konishi et al, 1999). Controlled clinical trials are needed to make this technology fully accepted. New lasers with different wavelengths are currently in development that will be even more efficient and effective at removing caries. These lasers can be selective in carious tissue removal, leaving the surrounding tissue intact and much stronger than is the case for a conventional amalgam preparation. Flowable composites can be used to fill these cavity preparations, and better materials will become available for this purpose.

New approaches to remineralization of limited carious lesions represent an important future approach to the clinical management of caries.

The process of tooth remineralization has received significant attention over the past four decades (Koulourides et al, 1961; Silverstone et al, 1981; Larsen et al, 1987; White, 1988; Geiger et al, 1992; and Linton, 1996) although the concept was documented in the early 1900's (Head, 1912). There exists some controversy regarding the extent to which demineralized tissues can be remineralized and the means by which demineralization should be diagnosed in the clinic (Thylstrup and Fejerskov, 1994).

The visual signs of white spots that may disappear or reduce in size may be attributable to wear and polishing of the partially dissolved external surface of an active lesion. However, several studies have demonstrated an increase in hardness and mineral content and reduced subsequent demineralization at the surface of tooth tissues that were remineralized (Shannon and Edmonds, 1978; Retief et al, 1983; Vissink et al, 1985; Larsen and Fejerskov, 1987; White, 1988; and Linton, 1996).

Restorative materials are continually being improved. In the future, they will be able to:

◆ Release antibacterial agents or fluoride on demand. The so-called "actively smart materials" represent a potential approach if they will release sufficient concentrations of therapeutic agents at specific times when they are needed, i.e., when the disease is active.

◆ Be readily placed in very small conservative cav-ity preparations. For temporization of cavitated teeth in individuals at a high risk of caries, "actively smart materials" similar to glass ionomer, but with greater fracture resistance, must be developed to increase the survival times. Highly viscous glass ionomer materials have been used for this purpose, but approximately 20% of these temporary restorations fail over a period of three years when used for the atraumatic restorative treatment technique. Currently, these materials are used primarily in developing countries where electricity and pressurized air and water are not available.

◆ Remain durable and flexible and become an integral part of the tooth.

◆ Stimulate growth of new or reparative dentin.

◆ Be utilized with the increased application of CAD-CAM technology. This will reduce cost and time require for extensive rehabilitation of severely involved dentitions.

Extension of coronal or root caries into the pulpal tissue requires endodontic therapy for the affected tooth. The recent focus on improved instrumentation and use of magnification during endodontic therapy will improve the effectiveness of treatment. The use of lasers in endodontic therapy, including indirect and direct pulp capping, vital pulp amputation and preparation of the root canal system, will see increased emphasis, with attention to specific approaches to clinical application (Matsumoto, 2000). The future will also see new emphasis on treatment of disease processes that affect the periradicular tissues, including persistent apical disease, tooth perforations and fractures, and internal and external resorption. Definition of the importance of growth factors in pulpal repair will likely be an important area of future research, with a focus on clinical application (Roberts-Clark and Smith, 2000). Concern has been raised, however, about delivery of these agents to injured pulp tissue (Tziafas et al, 2000). The potential impact of untreated endodontic disease as a risk factor to certain systemic diseases needs to be explored (Grau et al, 1997).

IMPLANTOLOGY

The use of osseointegrated dental implants will expand in the future. Improved understanding of wound healing associated with implant placement, with a particular emphasis on the implant-bone interface, will be a focus of future research. Relying on both metallurgical and biological science, these studies will lead to improved implant surface coatings. As the demand

for dental implants continues to grow, cost will remain a limiting factor for many people. The challenge for the future is to reduce the cost of this treatment so more patients can benefit from these advances.

In the next 10 years, new approaches to treatment planning and diagnosis will be introduced (e.g., micro-computerized tomography) which will more precisely guide the use of dental implants in regions of the jaws that currently show low success rates. In addition, it is likely that algorithms will be developed to identify patients at risk for implant failure.

DENTAL BIOMATERIALS

Research of importance to the practicing dentist necessarily includes topics associated with dental biomaterials. Advanced materials processing and forming methods have already been introduced into both clinical and dental laboratory settings. It is anticipated that advanced process development will continue. Much focus will remain on the optimization of current materials, minimizing contraindications and broadening use of esthetic materials for posterior restorations. "Actively smart materials" are under development that combines diagnostic, restorative and therapeutic (controlled release) capability. Work continues on improving adhesive chemistries and on mercury-free restorative materials. Increased focus is being given to the development of laboratory tests that validly reproduce clinical behavior. Interest is increasing in promoting systematic evaluation of the technique sensitivity of restorative materials. Biomimetic approaches are being investigated, as are tissue engineering concepts for the development of materials more closely resembling those being replaced. Surface chemistries and topologies of implantable materials are being studied to enhance cellular interactions.

Advanced forming systems, almost all involving some computer control, will (1) broaden the range of currently available materials that can be used in dental practice, (2) improve the precision and automate dental laboratory fabrication, (3) foster development of novel prostheses and craniofacial implants, and (4) provide routes to novel materials. One promising technology undergoing development involves three-dimensional printing of powder/binder combinations followed by sintering to form solid objects from ceramics or alloys (Cima, 1996). One application involves 3-D data sets obtained pre-surgically for use in fabricating custom titanium maxillofacial implants (Hong et al, 2001). This technology also provides a route to structures made of gradient materials, i.e. materials having a gradation of properties such as solubility, elastic moduli, and translucency that may provide novel clinical performance.

Direct resin-based composites, in particular, will continue to be improved. Active research efforts are underway, targeting decreased polymerization shrinkage. Decreased polymerization shrinkage is important for reducing stresses at the material-tooth interface that lead to gap formation and degradation of material-tooth bonding. Ring-opening monomers and certain epoxy systems that can expand during polymerization are being developed or investigated for dental use (Guggenberger et al, 1998; and Tilbrook et al, 2000). Improved filler phases, bonding agents and toughened polymer matrixes are being investigated to improve wear and structural behavior and add remineralizing capability (Antonucci et al, 1991; Stansbury and Antonucci, 1992; Skrtic et al, 1996; Schumacher et al, 1997; Stansbury and Antonucci, 1999; and Xu et al, 2000). Novel posterior restorative materials are being developed, including mercury-free, condensable silver fillings and esthetic interpenetrating-phase composites (non-shrinking), based on the resin infiltration of porous, three-dimensional ceramic skeletons (Dariel et al, 1995; Eichmiller et al, 1996; Giordano et al, 1997; Kelly and Antonucci, 1997; and Sabrosa et al, 1999). "Wear-kind" ceramics are increasingly conceivable, as more information becomes available regarding intraoral damage mechanisms and microstructure-property relationships. Research efforts continue to be expended on broadening the use of titanium in fixed prosthodontics, particularly with respect to improving the interface with fired porcelains (Könönen and Kivilahti, 2001).

Many academicians recognize the need for a more robust evidence base to guide clinical decisions involving comparisons among materials and the rational development of clinical indications for new materials (Laskin, 2000). Investigations are being called for to identify the relative technique sensitivity of restorative systems with respect to clinical outcomes. Research is anticipated in the development of *in vitro* test methodologies predictive of clinical behavior to evaluate dental biomaterials and assist in standard test development. Additional work is anticipated in standardized protocol development for clinical evaluations of dental biomaterials in

both university-based and private practice-based settings. This interest derives from dissatisfaction with the validity of surrogate data from laboratory testing and the limited comparability (e.g., in meta-analysis) of too large a percentage of published dental clinical trials (Kelly, 1999; and Palmer and Sendi, 1999). Rather than focusing on component material properties, dental prostheses are being evaluated as engineered structures for purposes of design evaluation and improvement (Kelly et al, 1995; and Goetzen and Anusavice, 2001).

Improving and directing the interaction of cells and cellular processes with implanted materials remains a research focus to both enhance the clinical application of titanium dental implants and to induce the rapid restoration of normal tissue architecture in repaired hard and soft tissues (Hallab et al, 2001; and Ogawa et al, 2000). The development and microstructure of tissues continues to be studied with the hope that biological processes can be mimicked in the fabrication of biomimetic prosthetic materials (Marshall et al, 2001; White et al, 2001; Kamat et al, 2000; and Kirkham et al, 2000). Scaffold materials are receiving much attention in tissue engineering research as initial carriers of cells, growth factors and molecular species designed to direct and enhance defect repair, especially in bone (Ma and Choi, 2001; Loty et al, 2000; Reddi, 2000; and de Bruijn et al, 1999). Tissue engineering approaches may also provide clinicians with the capability to restore salivary gland tissues and function (Baum et al, 1999).

FUTURE CHANGES IN PERIODONTAL DISEASES RESEARCH

Periodontal Disease Risk Assessment and Diagnosis

The diagnosis of periodontal disease will continue to evolve over the next 10 years. Clinicians will begin to identify individuals who are at risk for active periodontal diseases using genetic tests and biologic tests that identify specific microorganisms in subgingival plaque and/or inflammatory mediators in gingival fluid and/or saliva. In addition, digital radiography will be used more in periodontal diagnosis, and practical systems will be introduced to perform subtraction radiography in the dental office.

Attention is focusing on ways to identify patients at risk for advanced forms of periodontitis. One such approach is the recent report of a periodontitis-associated genotype that has been linked to elevated production of proinflammatory cytokines IL-1α, IL-1β, TNF-α (Kornman et al, 1997). Future research will form an improved definition of genetic, environmental, and microbial risk factors for periodontitis that will lead to development of a profile for patients at risk for advanced disease.

Digital radiography has been introduced for clinical use, and its application is likely to increase because it reduces radiation exposure and facilitates storage of diagnostic information. It can be anticipated that subtraction radiography will be introduced as part of patient management, but may be limited to specialized treatment centers.

The use of laboratory tests (microbial challenge, host response) has been intensely studied, and it is possible that this area of investigation will see renewed interest because of the growing body of evidence linking periodontal diseases and various systemic diseases. These tests will likely be formatted in a user-friendly style, utilizing saliva or blood to measure a parameter reflective of the patient, rather than a particular tooth. Research in this area will be linked to studies of the relationship of periodontal diseases and cardiovascular disease, cerebrovascular disease, pre-term low birth weight babies, and diabetes mellitus. The effect of periodontal treatment as a means of reducing the risk for these medical disorders will also be explored.

The identification of the genetic basis for syndromic and nonsyndromic rapidly progressive forms of periodontal disease offers to dramatically improve our understanding of basic mechanisms that account for destruction of the supporting tissues of the teeth. As an example, a specific mutation on chromosome 11q14 associated with the gene encoding of the enzyme cathepsin C was detected in a consanguineous family with prepubertal periodontitis (Hart et al, 2000). These studies will become an important part of periodontal disease research, in tandem with the general emphasis on using information about variations in the human genome, and the protein products of those genes, to explain human diseases.

Periodontal Disease Management

The improved understanding of the pathogenesis of the periodontal diseases should lead to new and improved treatments. Antimicrobial approaches have focused on local delivery of antimicrobials/ antibiotics

into the gingival crevice. The use of systemic antibiotics will be reserved for the most aggressive forms of disease, and also may be employed as part of periodontal therapy for patients with certain systemic diseases that have been linked to periodontitis. Considerable research effort has focused on the use of newer anti-inflammatory agents for treatment of periodontitis. While systemically delivered agents have been used in both animal and human studies, topical delivery of these agents (mouth rinses, toothpastes) seems the most logical approach for the future. In addition, recent understanding of the specific events in the pathogenesis of periodontal disease will lead to highly specific and novel therapies. For example, IL-1 receptor antagonists may be employed as anti-inflammatory agents (Graves et al, 1998), and, in the case of diabetes-associated periodontitis, blockade of the receptor for advanced glycation endproducts (Lalla et al, 2000) may be selectively utilized in affected patients.

Advances in treatment of periodontitis will focus on procedures to induce regeneration of lost periodontal tissues. Among the specific mediators being studied for application in periodontal therapy are recombinant bone morphogenetic proteins and combinations of growth factors. The success of these therapies will depend on the identification of the appropriate biological mediator and the appropriate delivery system.

FUTURE CHANGES IN SYSTEMIC DISEASES RESEARCH

Although there are a few negative findings (Hujoel et al, 2000), the evidence in support of a link between periodontal and systemic diseases continues to mount. Oral infections are suspected to be a risk factor for certain systemic diseases (that is, cardiovascular disease, cerebrovascular disease, aspiration pneumonia) and for pre-term low birth weight babies.

As supportive research evidence becomes available, dentists will need to provide more intense management of patients' oral infections. Increased communication by dentists with other health care professionals can be expected.

However, without intervention studies demonstrating a systemic therapeutic benefit from periodontal therapy, there is no concrete evidence to justify a change in oral health care policy or current standards of care. New studies in progress have the potential to alter this position rapidly. Evidence suggests that poor oral health may be as detrimental to general health as other risk factors, such as smoking or high cholesterol levels.

As the relationship of oral infection and certain systemic diseases is further defined, dentists will be expected to be active participants in the management of patients with certain systemic diseases, and to broadly consider how medical management of patients will influence dental health and dental care. For example, longitudinal medical studies have demonstrated that good glycemic control limits the onset and prevalence of complications from diabetes mellitus. Consequently, an important part of managing periodontal diseases in these patients is the medical management of the patient. When indicated, dentists should be checking hemoglobin A1c. Periodontal diseases are the sixth complication of diabetes mellitus. Since dentists may see patients more regularly than physicians, dentists should be screening for diabetes mellitus in their patients who are at risk.

If, in the near future, multicentered, randomized, controlled clinical trials confirm that periodontal disease causes systemic conditions, several issues will confront the dental profession:

◆ Studies will need to be conducted to determine the effectiveness of screening patients in the dental office for certain diseases with obvious ramifications for the oral cavity (i.e. diabetes mellitus). Furthermore, the effectiveness of screening for oral disease by physicians and other non-dental health care workers should be assessed. If effective, these programs will enhance the oral health and general health status of patients.

◆ There will be a growing appreciation by the public and physicians that dentistry can no longer be considered solely a luxury, elective health care. Recent polls indicate that 85% of the public is already aware of the fact that poor oral health can worsen general health.

◆ The recognition of the medical necessity for periodontal care will increase the perceived importance of dental services, and the demand for dental services will increase. Thus, the larger problems are the perception among health care professionals, the nature and system by which health care is delivered, and access and utilization.

◆ Research findings providing a clear demonstration of the medical necessity for periodontal care among

pregnant women would undoubtedly lead to a rapid and profound increase in the priority of dental services in such high-risk populations.

◆ This view of the future has profound implications for the dental profession—from education to practice to public policy—that will require considerable planning and redirection.

FUTURE CHANGES IN CLEFT LIP, CLEFT PALATE AND CRANIOFACIAL DEVELOPMENTAL DISORDERS RESEARCH

Given the many new developments in studies of the etiology and treatment of oral clefts and craniofacial developmental disorders, and the pivotal role played by dental specialists on the cleft/craniofacial team, the dental profession will have opportunities in the future to make significant contributions to research. Training dentists in the benefits and conduct of epidemiological, basic science, social science and clinical trial research will enable them to participate more fully in these areas. Current research efforts are pointing the way to promising directions, especially in the areas of etiology/prevention and outcomes.

Etiology and Prevention

◆ Family studies have for many years demonstrated that inherited genetic variation has a very large effect on risk of nonsyndromic oral clefts, and this is the basis of current genetic counseling based on averages obtained from population studies. The challenge for the future is to identify the specific genes and DNA polymorphisms that influence risk. This will move us towards an era of "individualized medicine" where risk of orofacial clefting can be much more accurately predicted based on the "genetic blueprint" of the parents. The human genome project has now produced the tools and knowledge in the form of millions of single nucleotide polymorphisms (SNPs, pronounced "snips") which will enable this line of research to move forward at a greatly accelerated pace.

◆ Further studies of teratogens and potentially protective dietary factors such as vitamins and folate are needed to better understand the role of environmental factors in both nonsyndromic and some forms of syndromic orofacial clefting. Continued development of biomarkers to more reliably measure subjects' nutrition rather than relying solely on self-reports from questionnaires will benefit this area of research. Since gene-environment interactions are presumed to be common and important, these studies will also benefit from the incorporation of large scale SNP-mapping into the design.

◆ Animal models of spontaneous and teratogen-induced clefting have yielded candidate biological mechanisms and candidate genes for evaluation in humans (Diehl and Erickson, 1997). These models warrant further exploration using modern genomic techniques that have very substantial promise to quickly identify a number of specific genes that have major effects on risk of orofacial clefting and craniofacial developmental disorders.

◆ Studies in animals and of human inter-racial marriages have clearly demonstrated that the maternal genotype has a very important effect on risk of nonsyndromic orofacial clefting. Future research in humans should more thoroughly evaluate the maternal genotype in addition to that of the fetus in determining risk of this birth defect.

◆ Continued efforts should target the identification of additional gene mutations involved in currently unresolved syndromic forms of orofacial clefting and craniofacial developmental disorders. Basic research should also work towards obtaining a better understanding of the molecular pathways that are disrupted by mutations at these genes.

The very high overall genetic component of susceptibility to these birth defects, combined with the evermore powerful tools of human and animal genetics, promise to reveal their basic causes with continued investment. However, the nature of clinical research requires very long-term commitments of major resources for patient recruitment and evaluation, laboratory assays, and data management and statistical analysis. Because of the complex nature of these diseases, multiple independent studies of large collections of subjects and their families or appropriate control groups will be needed to provide the statistical power necessary for making definitive findings. Groups around the world currently focused on this research effort will need continued support for many years to achieve major success. Clinical trials of new means of prevention for some disorders such as nonsyndromic oral clefts will also be very expensive and worthwhile, but it must be recognized that these efforts are likely to be years

away from producing strategies that will completely prevent clefts, so treatment will continue to be necessary for the foreseeable future.

Treatments and Outcomes

Given the complexity of the genetic contributions to clefting, and the long time-frame before prevention is a reality, immediate research goals must also address the issues of access to care, delivery of care, quality of care, and outcome of care. Some recent research and initiatives have begun to address these issues and can be used as guidelines for planning future directions.

◆ The 1992 Eurocleft project was one of the first attempts to comprehensively compare treatment outcomes from different centers, each with widely differing treatment protocols. Using multidisciplinary outcome measures and strict research methodology, these studies not only demonstrated the fact that outcomes can vary considerably based on the particular treatment approach used, but also that well-planned retrospective use of standardized treatment records can allow for valid research approaches.

◆ A 2000 survey of 201 cleft palate centers in Europe indicated that there were 194 different primary surgical protocols. With the likelihood that the dental protocols used by different centers vary as much or more, the need for clinical trials and outcome studies to establish the efficacy and effectiveness of various treatment approaches is obvious. Few randomized control trials have been carried out in the cleft/craniofacial field, and these are essential in order to objectively determine the relative merits of different treatment methods.

◆ The lack of standardized recording and reporting results of treatment has led to several recent initiatives having the potential to greatly facilitate future outcomes research. For example, the Craniofacial Outcomes Registry is an attempt to establish standard outcome measures for all aspects of cleft care, and to provide a centralized repository where individual cleft/craniofacial centers can register patients online and then subsequently submit treatment information and out-come measures. The dental profession has the potential for making significant contributions to this effort, both in terms of participation in the establishment of valid and reliable outcome measures, and also through submission of properly recorded and analyzed patient data. The range of outcome measures in areas of importance to dentistry include assessments of pre-surgical orthopedic treatment, pediatric dental management, alveolar bone grafting, orthodontic and orthopedic management, orthognathic surgical results, and dental implants in the bone-grafted cleft alveolar ridge, among others.

◆ An extension of the 1992 Eurocleft study has set up a network of nearly all cleft/craniofacial teams in Europe to establish standards for recording and reporting treatment outcomes in many areas of cleft care with the aim of improving effectiveness and efficiency. Dental specialists have played a major role in the creation of this organization. As with the Craniofacial Outcomes Registry, the Eurocleft Project has the potential for providing collective information on cleft/craniofacial treatment outcomes which will enable more productive future research efforts to identify the most effective treatment regimes.

◆ Advances in fields such as gene therapy and tissue bioengineering will eventually revolutionize the treatment of orofacial clefts and craniofacial developmental disorders (Lorenz et al, 2000). These long-term research efforts need to receive ongoing support in order to achieve their potential. Encouraging interdisciplinary interactions between experts working on these "futuristic" approaches and dental professionals experienced in applying today's best treatment methods will also enhance progress.

As a result of these developments, the potential future impact of the dental profession on improvements in the treatment and research of orofacial clefts and craniofacial developmental disorders is significant. Since many of the projects moving towards globalization of the research effort are still early in planning stages, dental professionals have a great opportunity to shape these efforts to ensure that dental concerns in cleft/craniofacial care are properly addressed. Appropriate training of dental scientists in the execution of valid and reliable outcome studies and randomized control trials will facilitate the development and use of evidence-based treatment decisions by future cleft/craniofacial teams. Future research of a high caliber should finally allow for the scientifically-based elimination of treatment methods which fail to produce outcomes and benefits necessary to justify their continued use.

Additionally, research agendas aimed at evaluating the efficacy, cost-effectiveness, and benefits of team care will need to be designed such that patients with orofacial clefts and craniofacial developmental disorders continue to be treated in interdisciplinary centers by care-providers with focal interest in, and high-volume experience with, problems unique to this group of patients. Finally, there is also a need for the development of outcome measures which incorporate the potentially more meaningful issues of patient/parent expectations, satisfaction, and quality of life evaluations (e.g., orofacial aesthetics, speech and non-speech functions, and self image) which may be greater indices of successful treatment than other more traditional data.

FUTURE CHANGES IN MALOCCLUSION AND TOOTH AGENESIS RESEARCH

Research on human genetic variation that influences the development of the craniofacial complex may be one way to bridge the gap between developmental biology and the study of clinical variation. It has been shown that certain craniofacial types have tendencies towards certain types of malocclusion–for example, dolichocephalic/leptoprosopic craniofacial types are associated with Class II malocclusion (Enlow and Hans, 1996).

Understanding the genetic basis for malocclusion represents one of the major challenges for the future. Furthermore, there is a need to understand the contribution of genetic versus environmental contributions to malocclusion. Genetic linkage analysis is a powerful approach for identifying genes that have a major effect on familial skeletal Class II or Class III malocclusion and familial forms of tooth agenesis and supernumerary teeth.

Research using both cell and tissue culture and animal models will greatly increase our knowledge of the process of cellular control, suture biology, genetic factors, and the interaction of environmental factors with genetic susceptibility. A major task will be to apply the increasing knowledge of craniofacial developmental biology (Thesleff, 1998) to research on malocclusion and agenesis in humans. Investigators must also evaluate epigenetic factors that may activate expression of regulatory genes and influence postnatal growth (Carlson, 1999).

Future diagnoses for some of these disorders will include the analysis of genetic polymorphisms associated with specific growth and development tendencies and/or the ability of the craniofacies to respond to epigenetic signals.

Research is needed to capitalize on potential benefits of three-dimensional imaging of both hard and soft tissue, digital radiography, and imaging without ionizing radiation (e.g., magnetic resonance imaging).

Relatively new techniques for treatment of malocclusion, such as osteodistraction and implant/ onplant-based anchorage, arise from basic research in biomaterials/bioengineering/biomimetics. In the future, a combination of biological and biomechanical signals may direct growth and development where it is needed.

With this consideration, increased understanding of the various morphogenetic signaling pathways that regulate development of the craniofacies should allow manipulation of the proliferation, patterning, and differentiation of tissue in order to treat malocclusion due to skeletal discrepancies. Furthermore, it should be advantageous to induce tooth development in areas of tooth agenesis (Nuckolls et al, 1999). As more is learned about cell biology and tooth movement, the effect of different biomechanics may be studied and applied to clinical practice (Gu et al, 1999).

Research on factors that may contribute to external apical root resorption associated with orthodontic movement of teeth, including genetic factors (Harris et al, 1997), may help decrease the incidence of this unwanted side effect.

Nanotechnology and materials science may lead to ways to generate biomechanical forces in a more controlled and biologically appropriate manner. Joint conferences between academic and industry communities could be of benefit.

Scientific evaluation of the clinical outcomes following application of different protocols, techniques, and appliances to treat malocclusions is needed. Retrospective/prospective investigations (Johnston, 1998a,b) or randomized clinical trials (Ghafari et al, 1998) may be employed. The power of these investigations will increase with better communication and interactions among centers pursuing these studies. Furthermore, advances in bioinformatics may im-prove the reliability of predicting treatment outcomes.

While treatment of major malocclusions will remain in the domain of the orthodontic specialist, general practitioners will have an expanding role in the early diagnosis of malocclusions and early, interventional therapy. The specialist will utilize new three-dimensional imaging techniques and conservative tooth movement approaches utilizing computer-guided pro-

jection of desired outcomes to affect tooth movement. New techniques that cross specialty barriers (e.g., oseointegrated implants used for anchorage, distraction osteogenesis) will be utilized to achieve optimum results in particularly challenging cases.

FUTURE CHANGES IN ORAL AND PHARYNGEAL CANCERS RESEARCH

A number of new diagnostic approaches will facilitate an expanded role for dental practitioners in identifying the risk for oral cancer, and the early diagnosis of oral cancerous lesions. A recently introduced brush biopsy-computerized cytological identification system has shown promise for diagnosis of epithelial cancers without the need for a surgical biopsy. In the future, new saliva-based diagnostic approaches based on the improved understanding of the genetic basis of oral cancer will become available for clinical application.

Clinicians will be able to use algorithms to identify persons at greater risk for development of malignancy. These algorithms will combine the effects of environmental and genetic risk factors. Other diagnostic procedures, including quantitation of nuclear DNA, may be used to identify the prognosis and predict the clinical outcome of patients with intraoral epithelial dysplastic lesions.

Chemoprevention research is aimed at reversing the growth of advanced premalignant lesions using retinoic acid derivatives and other substances (Geyer et al, 1998). This approach may also help prevent new primary cancers in patients who already have oral and pharyngeal cancers and may increase the effectiveness of methods aimed at treating the primary cancers themselves. Additional basic research and clinical trials are needed to evaluate promising chemoprevention approaches more rapidly and effectively. Since such individuals are at very substantially elevated risk of developing oral cancer, they could be prioritized for frequent oral examinations for early cancer detection and for smoking and alcohol cessation intervention programs (Prochazka, 2000).

Advances in the understanding of the molecular basis for progression, angiogenesis, invasion, and metastasis of oral cancers (Califano et al, 2000; Grandis et al, 2000; Hanzawa et al, 2000; Nitta et al, 2000; and Smith BD et al, 2000) is especially important for developing new methods to detect these tumors and new treatments to halt their growth and metastisis.

Future research should focus on the following challenges and opportunities:

◆ Continued research on promising improvements in the detection and diagnosis of oral mucosal lesions, including cancers, using molecular tools:

- Staining with toluidine blue to focus attention on lesions progressing toward malignancy (Ephros and Mashberg, 1999; and Kerawala et al, 2000).

- A neural network computational approach using an oral brush biopsy and computerized cytological detection of abnormalities to facilitate detection of dysplasia and carcinoma (Sciubba, 1999).

- Molecular assays such as those based on mitochondrial DNA mutations to provide highly sensitive and non-invasive early oral cancer detection (Fliss et al, 2000).

- Following-up on a very exciting recent development regarding the use of abnormal DNA content (tetraploidy or aneuploidy) to assess the risk of cancer development from oralleukoplakias (Sudbø et al, 2001). A carcinoma developed in only 3% of normal diploid lesions, versus 60% of tetraploid and 84% of aneuploid lesions during a mean follow-up period of over eight years.

◆ New treatment approaches using gene therapy combined with chemotherapies (Khuri et al, 2000), immunotherapy (Chikamatsu et al, 1999) and approaches directed at reducing invasiveness (Simon et al, 1999).

◆ Investigating ways to reduce oral cancer patients' excess morbidity and mortality from causes other than due to oral cancer itself, mostly due to the patients' high levels of alcohol and tobacco use.

◆ Developing more effective methods to educate dental professionals about oral cancer risk factors and to encourage high quality and frequent oral examinations for early cancer detection (Yellowitz et al, 2000).

◆ Research should also investigate optimal and cost effective ways to inform both health professionals and the general public about the great value of decreasing high-risk behaviors such as smoking and alcohol drinking and increasing consumption of fruits and vegetables.

◆ Improving methods based on molecular and genetic assessments, in combination with alcohol, tobacco and dietary risk-factor profiles, to more accurately predict which common non-malignant oral lesions present the most significant danger to the patients (Warnakulasuriya, 2000).

◆ New advances in biomaterials and biomimetics to provide improved tools for tissue reconstruction, reducing the impact of treatment on patients' quality of life.

◆ Increasing knowledge of how inherited susceptibility and gene-environment interactions influence cancer risk. The potential for advances in this area has been greatly enhanced by the human genome project's discovery of several million human single nucleotide polymorphisms and strategies to relate these genes to disease risk (Chakravarti, 2001; and Peltonen and McKusick, 2001). In addition to greatly facilitating the identification of genes most strongly associated with oral cancer risk, these tools will also usher in an exciting new era of individualized risk assessment and therapy. Treatments will be custom-tailored to each person's genotype, with potentially great improvements in effectiveness.

◆ Continued research aiming at better understanding of the processes of tumor initiation, progression and metastasis at the cellular and molecular levels. These efforts will be greatly accelerated by new and powerful tools such as microarrays capable of assessing very large numbers of genes and/or proteins simultaneously, and laser capture microdissection that promises to extend resolution to the level of single cells.

FUTURE CHANGES IN ORAL MUCOSAL AND AUTOIMMUNE DISEASES/OTHER INFECTIONS RESEARCH

The oral cavity can be the site of infections that cause disorders other than dental caries and periodontal diseases. Most of these bacterial diseases (e.g., *Mycobacterium tuberculosis* and tuberculosis, *Treponema pallidium* and syphillis, *Neisseria gonorrhoeae* and gonorrhea) and viral diseases (e.g., human papilloma virus) are rare in the oral cavity. Other infections are more common (e.g., *Candida albicans*, herpes simplex virus 1).

Diagnosis and chemotherapeutic management of these infections will become a regular part of dental practice as more dental patients are older and taking more medication. The resulting reduction in salivary flow will result in an increased incidence of fungal, viral and less common bacterial infections.

With the identification of specific risk factors for oral diseases, and the clear understanding that many oral diseases are multifactorial, risk analysis for these infections will be considered as part of treatment planning for at-risk patients. Computer-based algorithms will be created, patients' variables will be entered, and a measure of risk for future diseases will be determined. Such risk determinants can guide the clinician in preventive strategies or treatment decisions.

A bacterial cause of aphthous stomatitis has been suspected for years, but evidence was limited to studies in which bacteria were identified by conventional culture. The use of polymerase chain reaction techniques has made it possible to study the potential relationship of bacteria to aphthous stomatitis at the molecular level. Evidence supports a frequent association between *Helicobacter pylori* and aphthous stomatitis. If true, this finding might suggest a reason why clinicians have long reported the response of canker sores to treatment with tetracycline, as well as suggesting new approaches to treatment (Birek et al, 1999).

Descriptive and immunohistochemical microscopic studies have done much to define components of the cellular and humoral immune system that participate in oral blistering diseases and aphthous stomatitis. Elements of the immune system are active in the mucosa during periods of disease, but the identification of the precipitating antigen that triggers the reaction has been elusive (Dabelsteen, 1998).

Relationships between mouth conditions and specific HLA types have been identified between HLA-Te22 antigen and antinuclear antibody in Chinese patients with lichen planus (Sun et al, 2000). With the identification of the human genome, it can be anticipated that genetic associations and risk definitions for many of the diseases of the oral mucosa will be possible. A challenge facing researchers is to differentiate casual or coincidental associations from those that are of etiologic or clinical significance.

The clinical changes associated with pemphigoid are the consequence of antibody deposition at the junction of the epithelium and the underlying connective tissue. Recently, researchers identified the presence of a unique integrin that functions as the antigenic driver of the disease and shows a genetic link to the expressed integrin (Kumari et al, 2001). This type of discovery may lead to identification of at-risk individuals and populations, and for developing genetic

manipulation to reduce the likelihood of the disease.

Recent research has suggested a possible association between aphthous and herpes virus type 6 (HHV-6). Specific HHV-6 IgM was detected in a significant percentage of patients with aphthous stomatitis. Also, high levels of anti-HHV-6 antibody were found in patients with lichen planus (Ghodratnama et al, 1999). The dissimilarity of the two conditions notwithstanding, the finding points to the need for additional studies to define the role of the virus in both conditions.

Thalidomide is now available for treating major aphthous stomatitis, especially that associated with HIV infection (Jacobson, 2000). Data from a series of studies suggested that a cytokine, tumor necrosis factor-alpha (TNF-α), was a critical mechanistic driver of the development of these large, persistent, and highly symptomatic ulcers. Consequently, compounds that were effective inhibitors of TNF-α may prove to be an effective therapy.

There may be a relationship between lichen planus and oral cancer. While the World Health Organization defines oral lichen planus as a premalignant lesion, it has been argued that only those lesions demonstrating dysplasia are truly premalignant. A simple quantitative comparison between the number of individuals with lichen planus and the number with oral cancer intuitively seems to negate the hypothesis that all cases of oral lichen planus are premalignant. The use of increasingly sophisticated techniques, such as microsatellite analysis in which oral lichen planus was evaluated for loss of heterozygosity, are needed to ultimately resolve this issue (Zhang et al, 1997).

One of the recent advances that may aid in the faster diagnosis of oral HSV infection in immunocompromised patients involves in situ hybridization of cytobrush smears using an automated smear apparatus (Kobayashi et al, 1998). New treatment and prevention modalities that are targeted to immunocompromised patients are also emerging. Low dose interferon alpha administered orally has been successfully used to treat both animal and human oral herpetic disease (Scalvenzi and Ceddia, 2000). In addition, certain advances have been made in the vaccine development arena with the most notable being the potentially protective immunity generated with a vaccine based on the use of attenuated *Salmonella typhimurium* as an expression vector of HSV antigens (Karem et al, 1997).

Dentists will need to recognize infectious diseases or immunocompromised states that show oral manifestations. Various diagnostic tests have already been developed which can assist the dentist in determining, chair-side, the presence of an herpetic or a monilial infection. At present, these tests do not seem to be in widespread use (Laga et al, 1993; and Contreras et al, 1996). It is expected that there will be more chair-side tests developed that will permit a dentist to make a definitive diagnosis of an opportunistic infection, treat the infection and encourage the dentist to arrange for an early referral for definitive care by a medical specialist.

Furthermore, the greatest future threat to patients will, in all likelihood, come from newly emerging infectious diseases. As illustrated by the HIV pandemic (Casiglia and Woo, 2000), a new human pathogen indirectly led to the dramatic increase in previously recognized oral infection (*Candida albicans*), as well as the occurrence of previously unrecognized oral pathology, including hairy leukoplakia (due to the Epstein-Barr virus), linear gingival erythema and necrotizing ulcerative periodontitis. The successful identification and management by dentists of these emerging infections will, as illustrated in the past, depend upon close collaboration between infectious disease specialists and dental health care professionals.

There will be continuing developments and better understanding of infectious disease control policies. Research will no doubt lead to the availability of new vaccines (Cho, 2000) similar to the Hepatitis B vaccine now widely accepted by the dental profession. There will be a more complete understanding of the precautionary measures that can be taken to reduce the infectious disease hazards of patients and members of the dental team in the dental environment.

FUTURE CHANGES IN SALIVARY GLAND DISEASES RESEARCH

The testing and introduction of secretogogues with longer duration of action and fewer side effects will occur in the near future. The development of controlled-release formulations of these agents also can be anticipated. Furthermore, improved anti-inflammatory and immune-mediating agents are expected, in the near future, that will be therapeutic for Sjøgren's syndrome and other salivary gland inflammatory conditions. Examples include thalidomide derivatives that have immunomodulating activity without the devastating teratogenic side effects, and new tolerance-inducing regimens that may markedly reduce the incidence and severity of autoimmune conditions. Both cytokine and anti-cytokine therapies are

being evaluated in clinical trials.

Better criteria for defining Sjøgren's syndrome and other autoimmune conditions should enable the development of agents that block or reverse critical mechanisms of the pathophysiology and that have fewer serious side effects than current therapeutics. These include gene therapy to salivary glands using the major salivary ducts to deliver relevant molecules directly to the affected site (Baum and O'Connell, 1999). This approach enables the delivery of proteins to the salivary glands and also to the oral cavity through the salivary secretions and to the systemic circulation by an endocrine route.

Better animal models of Sjøgren's syndrome are needed. Non-Obese Diabetic (NOD) mice develop severe diabetes, which is a confounding factor in studies with these animals. Strains of NOD mice that lack severe diabetes have been reported, but these animals have not been studied extensively (Robinson et al, 1998).

If the critical autoantigen can be identified, several strategies could be utilized to prevent or halt the autoimmune exocrine destruction. Autologous salivary tissues harvested from the individual, expanded *ex vivo*, and then re-implanted in an appropriate matrix, is used to induce regrowth and repair (Baum and Mooney, 2000). Tissue could be harvested prior to a course of head and neck radiotherapy and then placed back into an individual after radiation and a healing period.

Tissue engineering could create an implantable fully functional salivary gland using allogeneic tissues (Baum and Mooney, 2000). This would have application in cases where there has been complete loss of salivary function from disease or therapy. The basic principles for production of an "artificial salivary gland" have been detailed, and initial experimental work has begun.

Advances in detailing the human genome will have a major impact on studies of the genetics of salivary gland diseases and their treatment. With full definition of the proteome, it will be possible to recognize individual genetic variations responsible for responses to treatments.

FUTURE CHANGES IN TEMPOROMANDIBULAR DISORDERS (TMD) RESEARCH

The current emphasis on conservative and non-invasive therapies for TMJ disorders clearly suggests that with appropriate training all dentists can treat affected patients, with referral indicated only for the most recalcitrant cases. Further research emphasis on orofacial pain will promote the use of new imaging techniques for improved patient management.

The NIH Technology Assessment Conference (NIH, 1996) recommended future approaches to research on treatment:

- "Medical management" model rather than a "dental treatment" model.
- Interdisciplinary teams to manage the patient.
- Randomized controlled clinical trials to determine the safety and efficacy of treatments.
- Repair and regeneration of living tissue using tissue engineering and biomimetic approaches.
- Biocompatability of materials used in implants.
- Multidisciplinary collaborations.

Information related to TMD is available on the NIDCR home page and on the TMJ Association Website. However, many practitioners are inadequately trained to manage TMD. This was the conclusion from the Third Educational Conference to Develop the Curriculum in Temporomandibular Disorders and Orofacial Pain. It is estimated that at least 13 million patients seek care for chronic orofacial pain annually. There is a need for increased emphasis on predoctoral courses in orofacial pain and for significant increases in dentists completing advanced training devoted to this area.

Private industry has been involved in practice management, marketing, and the development of diagnostic and treatment instruments and devices for TMD. There have been concerns about whether testing of new diagnostic and treatment products have been adequate. Until more is known about the pathophysiology of the various TMDs, it is unlikely that progress will be made in the development of valid and reliable preventive/diagnostic and diagnostic interventions and cost-effective treatment. There is need for industry/university collaboration.

Since many TMD involve pathophysiologies similar to conditions affecting other muscles and joints of the body, the knowledge gained from research on the basic mechanisms of these diseases will likely be applicable to TMD and the studies of TMD will shed light on other musculoskeletal conditions. Currently, the primary source of funding for TMD

research is the NIDCR, which has significantly increased its support of TMD research in the past decade. Recently a TMD Interagency Working Group has been established to increase the scope of activities related to TMD. This group includes many institutes and offices of the NIH, the Food and Drug Administration, the Agency for Health Care Research and Quality, the Health Care Financing Administration, and the Department of Defense. This multidisciplinary effort should promote a focused clinical and research agenda for TMD.

III. PATHWAYS AND STRATEGIES FOR DENTAL AND CRANIOFACIAL RESEARCH IN THE FUTURE

This chapter has described selected research efforts underway that hold much promise for oral health and the future of dentistry in the United States. The research points to four key issues and strategies.

First, while the prevalence of dental caries and periodontal diseases may be changing for the entire population, these disorders are still common among segments of the population, especially those who are economically disadvantaged, and particularly racial and ethnic minorities. Within the next decade, the dental profession and the United States health care delivery system should make primary dental treatment available to these underserved populations.

Second, if a causal relationship can be established between dental infections and severe, life-threatening medical conditions, primary physicians may become active in diagnosing oral diseases and in referring their patients for dental care. Thus, dental and medical professionals should take a team approach to the prevention and management of dental diseases to limit their impact on overall patient health.

Third, within the next 10 to 20 years, research will lead to new biological therapies for use by dental practitioners. Additionally, advances in molecular diagnostic and imaging technology will likely enhance and facilitate the detection and monitoring of dental diseases. Thus, the dentist of the future will require a degree of facility with, and an understanding of, fundamental biology in order to provide optimum patient care as novel treatments become available for dental caries, periodontal diseases, and other oral disorders.

Fourth, researchers have seen an increasing frequency of significant age-associated oral conditions. These include salivary gland hypofunction, mucosal lesions, and related tissue discomfort, dysphagia, and chronic orofacial pain. Additionally, many medical therapies have significant effects on oral tissues and functions, ranging from conventional pharmaceuticals that cause dry mouth to extensive mucosal lesions in persons receiving cyctotoxic chemotherapy, to mucosal candidiasis in immunosuppressed patients. Dental practitioners will require more advanced training in managing age- and pharmaceutical-associated oral problems.

To establish a pathway toward achieving the vision articulated at the outset of this discussion, the following strategies are suggested:

ECONOMICS

The dental profession should consider:

- Exploring, in association with public and private health care delivery agencies, plans by which routine primary dental care can be provided to economically disadvantaged individuals.

- Advocating for third party medical insurance coverage for oral health care for selected patients.

- Supporting the concept of medical insurance benefits for medically necessary dental care as defined by the Institute of Medicine in 1999.

DISEASE PATTERNS

The dental profession should consider:

- Coordinating programs whereby resources and services are better provided to underserved populations.

- Promoting the concept of evidence-based research as the predominant knowledge base that defines dental training and the practice of dentistry. Dental schools should serve as models for the evidence-based practice of dentistry by requiring outcomes assessment for dental care.

◆ Developing a general classification scheme for all dental/oral diseases and disorders.

◆ Exploring the potential impact of advances on dental education and dental practice that are leading to effective nonsurgical therapies for dental caries and most forms of periodontal diseases.

SCIENTIFIC DEVELOPMENT/TECHNOLOGY

The critically important transfer of research-based knowledge and technology to practicing dental professionals has lagged behind the expansion of the knowledge base for the etiology of dental diseases and methods of treatment. There is a need to evaluate and improve the speed and quality of information and technology transferred from the laboratory and other research settings to the public domain.

Considering the importance of the NIDCR to the development of the profession, dental education and therapy for dental disease, the dental profession should consider:

◆ Maintaining support for the NIDCR as a separate institute within NIH.

◆ Accelerating the transfer of knowledge about systemic disease and oral disease to the dental school curriculum through the process of accreditation and working with the NIDCR and the American Dental Education Association (ADEA). The new developments in healthcare, including molecular biology, genetics and bioengineering, must be an important part of the dental school curriculum.

◆ Creating national clinical research networks that link treatment approaches and treatment outcomes in private practice settings. These networks, which exist for medical care, will enable large-scale evaluations of treatment protocols.

◆ Working with local and state dental societies to strongly support the need to increase resources available for dental research.

◆ Promoting the use of laboratory tests to diagnose oral disease. These tests include genetic tests, blood tests, salivary and gingival crevicular fluid analyses, and microbial tests. There is a need to link diagnostic tests with therapeutic strategies.

◆ Working closely with the NIDCR, ADEA, the American Association for Dental Research (AADR), and dental schools to establish links for information and technology transfer for health care providers. This network will provide current information on the knowledge base related to the practice of dentistry.

◆ Increasing translational and clinical research activities that adopt the new science into the practice of dentistry to improve oral health and the delivery of dental care.

◆ Establishing educational guidelines regarding the pathogenesis of different oral diseases. Promote these guidelines for adoption in the dental school curriculum, and by other fields such as general internal medicine, geriatrics, genetics, and information technology.

◆ Urging the NIH/NIDCR to increase the percent of its budget devoted to clinical research concerning the diagnosis, prevention and treatment of oral diseases. The percent of the NIDCR budget devoted to clinical research is now below that of other institutes.

◆ Continuing to support research funded by the NIDCR, corporate sponsors and foundations on issues of infection control in the dental office, including water line infections and percutaneous injuries.

WORKFORCE

Oral and craniofacial research efforts have been remarkably successful in promoting oral health and reducing the prevalence of oral disease. This effort is in danger of losing momentum due to the shortage of individuals who are pursuing careers in academics and dental research. The dental profession should consider taking an active role in developing the teachers and researchers of the future. This effort should include incentives for those who pursue these career choices. Furthermore, the dental profession should support the need to increase support for research training of dental students and recent dental graduates. Workforce for clinical research will be derived from dental academic institutions and dental practitioners.

Dental specialties should take an active role in promoting the development of dentists who wish to pursue a career in academics and research. Financial incentives should be established and mentoring pro-

grams should be instituted.

Finally, the dental profession should begin to educate medical practitioners and other non-dental health care workers on the causes and identification of dental disease, and on the need for appropriate referral. In turn, the dental profession will need to explore the dental office as a site for screening of systemic diseases with implications for oral disease.

References

Albrektsson T, Dahl E, Enbom L, Engevall S, Engquist B, Eriksson AR et al. Osseointegrated oral implants: A Swedish multicenter study of 8139 consecutively inserted Nobelpharma implants. J Periodontol 1988 May;59:287-96.

American Cleft Palate-Craniofacial Association. Parameters for evaluation and treatment of patients with cleft lip/palate or other craniofacial anomalies. Pittsburgh: American Cleft Palate-Craniofacial Association;1993.

American Dental Association, Council on Scientific Affairs. 2001 ADA research agenda. J Am Dent Assoc 2001;132(4):535-37.

Anderson MH, Bales DJ, Omnell K-A. Modern management of dental caries: the cutting edge is not the dental burr. J Amer Dent Assoc 1993;124:37-44.

Antonucci JM, Fowler BO, Venz S. Filler systems based on calcium metaphosphates. Dent Mater 1991;7:124-129.

Anusavice KJ. Efficacy of nonsurgical management of the initial caries lesion. J. Dent. Ed. 1997; 61:895-905.

Anusavice KJ. Need for early detection of caries lesions: a United States perspective. In: Stookey GK, ed. Early detection of dental caries II. Indiana Conference 1999. Indianapolis: Indiana University Press; 2000.

Arbes SJ Jr, Slade GD, Beck JD. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. J Dent Res 1999a;78:1777-82.

Arbes SJ Jr, Olshan AF, Caplan DJ, Schoenbach VJ, Slade GD, Symons MJ. Factors contributing to the poorer survival of black Americans diagnosed with oral cancer (United States). Cancer Causes Control 1999b; 10:513-23.

Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1-6.

Armitage GC. Periodontal diseases: diagnosis. Ann Periodontol 1996;1:37-215.

Atkinson JC, Fox PC. Salivary gland dysfunction. Clin Geriatr Med 1992;8:499-511.

Barrons RW. Treatment strategies for recurrent oral aphthous ulcers. Am J Health Syst Pharm 2001;58:41-50.

Baum BJ, Wang S, Cukierman E, Delporte C, Kagami H, Marmary Y et al. Re-engineering the functions of a terminally differentiated epithelial cell in vivo. Ann NY Acad Sci. 1999 Jun 18; 875:294-300.

Baum BJ, Mooney DJ. The impact of tissue engineering on dentistry. J Am Dent Assoc 2000;131:309-18.

Baum BJ, O'Connell BC. In vivo gene transfer to salivary glands. Crit Rev Oral Biol Med 1999;10:276-83.

Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodont 1996 Oct;67:1123-1137.

Berscheid E. An overview of the psychological effects of physical attractiveness. In: Lucker GW, Ribbens KA, McNamara JA, eds. Psychological aspects of facial form: craniofacial growth series 11. Ann Arbor: The University of Michigan Press; 1980.

Birek C, Granghi R, McNeil K, Singer D, Ficarro G, Bowden G. Detection of Helicobacter pylori in oral aphthous ulcers. J Oral Pathol Med 1999;28:197-203.

Blot WJ, McLaughlin JK, Devesa SS, Fraumeni JFJr. Cancers of the oral cavity and pharynx. In: Schottenfeld D and Fraumeni JFJr., eds. Cancer epidemiology and prevention, 2nd Edition. New York: Oxford University Press; 1996.

Bohuslavizki KH, Klutmann S, Brenner W, Kroger S, Buchert R, Bleckmann C et al. Radioprotection of salivary glands by amifostine in high-dose radioiodine treatment. Results of a double-blinded, placebo-controlled study in patients with differentiated thyroid cancer. Strahlenther Onkol 1999;175:6-12.

Brook PH, Shaw WC. The development of an index for orthodontic treatment priority. Eur J Orthod 1989;11:309-332.

Brown LJ, Beazoglou TF, Heffley D. Estimated savings in dental expenditures from 1979 through 1989. Pub Health Rep 1994 March-April;9:195-203.

Burt BA, Fejerskov O. Water fluoridation. In: Fejerskov O, Ekstrand J, Burt BA, eds. Flouride in dentistry. Copenhagen: Munksgaard International Publishers; 1996.

Buser D, Schroeder A, Sutter F, Lang N. The new concept of ITI hollow-cylinder and hollow-screw implants: Part 2. Clinical aspects, indications and early clinical results. Int J Oral Maxillofac Implants 1988;3:173-81.

Buser D, Weber H-P, Bragger U, Balsiger C. Tissue integration of one-stage ITI implants: 3-year results of a longitudinal study with hollow-cylinder and hollow-screw implants. Int J Oral Maxillofac Implants 1991;6:405-12.

Califano J, Westra WH, Meininger G, Corio R, Koch WM, Sidransky D. Genetic progression and clonal relation ship of recurrent premalignant head and neck lesions. Clin Cancer Res 2000;6:347-52.

Carinci F, Pezzetti F, Scapoli L, Martinelli M, Carinci P, Tognon M. Genetics of nonsyndromic cleft lip and palate: a review of international studies and data regarding the Italian population. Cleft Palate Craniofac J 2000;37:33-40.

Carlson DS. Growth modification: from molecules to mandibles. In: McNamara JA, Ed. Growth modification: what works, what doesn't, and why? Craniofacial Growth Series 35. Ann Arbor: University of Michigan Press; 1999.

Casiglia JW, Woo S. Oral manifestations of HIV infection. Clin Dermatol 2000;18:541-51.

Centers for Disease Control. Achievements in public health, 1900-1999. Fluoridation of drinking water to prevent caries. Morbidity and Mortality Weekly Report (MMWR) 1999;48(41):933-40.

Centers for Disease Control. Economic costs of birth defects and cerebral palsy-United States, 1992. MMWR 1995;44:694-99.

Chakravarti A. Single nucleotide polymorphisms...to a future of genetic medicine. Nature 2001;409:822-23.

Chikamatsu K, Reichert TE, Kashii Y, Saito T, Kawashiri S, Yamamoto E, Whiteside TL. Immunotherapy with effector cells and IL-2 of lymph node metastases of human squamous-cell carcinoma of the head and neck established in nude mice. Int J Cancer 1999;82: 532-37.

Cho MW. Assessment of HIV vaccine development: past, present, and future. Adv Pharmacol 2000;49:263-314.

Cima MJ. Solid free form fabrication methods and ceramic components. In: VE Henkes, GY Onoda, WM Carty, eds. Science of whitewares. Westerville, OH: The American Ceramic Society; 1996.

Cochran D. Implant therapy I. Ann Periodontol 1996;1:707-90.

Cohen MMJr. Etiology and pathogenesis of orofacial clefting. Oral and Maxillofacial Surgery Clinics of North America 2000;112:379-97.

Cohen MMJr., MacLean RE, Eds. Craniosynostosis: diagnosis, evaluation and management. Second Edition. New York: Oxford University Press; 2000.

Coleman DC, Bennett DE, Gallagher PJ. Oral Candidiasis and HIV infection: anti-fungal drug resistance and changes in Candida population dynamics. In: Greenspan JS, Greenspan D, eds. Oral manifestations of HIV infection. Chicago: Quintessence; 1995.

Collins JG, Smith MA, Arnold RR, Offenbacher S. Effects of Escherichia coli and Porphyromonas gingivalis lipopolysaccharide on pregnancy outcome in the golden hamster. Infect Immun 1994a;62:4652-55.

Collins JG, Windley HW III, Arnold RR, Offenbacher S. Effects of Porphyromonas gingivalis infection on inflammatory mediator response and pregnancy outcome in the hamster. Infect Immun 1994b Oct;62:4356-61.

Contreras I, San-Millan R, Agustin-Barrasa A, Ponton J, Quindos G. Utility of Albicans ID plate for rapid identification of Candida Albicans in clinical samples. Rapid identification of Candida Albicans. Mycopathologica 1996;136:17-20.

Crews KM, Gordy FM, Penton-Eklund N, Curran AE, Clay JR. Tobacco cessation: a practical dental service. Gen Dent 1999;47:476-83.

Dabelsteen E. Molecular biological aspects of acquired bullous diseases. Crit Rev Oral Biol Med 1998;9:162-78.

Dafni UG, Tzioufas AG, Staikos P, Skopouli FN, Moutsopoulos HM. Prevalence of Sjogren's syndrome in a closed rural community. Ann Rheum Dis 1997;56:521-525.

Dariel MP, Admon U, Lashmore DS, Ratzker M, Giuseppetti A, Eichmiller FC. A silver-tin alternative to dental amalgams. J Mater Res 1995;10:505-11.

Dasanayake A. Poor periodontal health of the pregnant woman is a risk factor for low birth weight. Ann Periodontol 1998;3:206-12.

Dayan S, Simmons RK, Ahmed AR. Contemporary issues in the diagnosis of oral pemphigoid: a selective review of the literature. Oral Surg, Oral Med, Oral Pathol, Oral Radiol, Endond 1999;88:424-30.

de Bruijn JD, van den Brink I, Mendes S, Dekker R, Bovell YP, van Blitterswijk CA. Bone induction by implants coated with cultured osteogenic bone marrow cells. Adv Dent Res 1999;13:74-81.

Diehl SR, Erickson RP. Genome scan for teratogen-induced clefting susceptibility loci in the mouse: evidence of both allelic and locus heterogeneity distinguishing cleft lip and cleft palate. Proc Natl Acad Sci USA 1997 May 13;94:5231-36.

Dworkin SF, Le Resche L. Research diagnostic criteria for tem poromandibular disorders: review, criteria, examination, specification, critique. J Craniomandibular Disorders, Facial and Oral Pain 1992;6:302-55.

Eichmiller FC, Marjenhoff WA, Dariel MP, Lashmore DS. Direct metallic amalgam alternative: a research update. J Maryland Dent Assoc 1996;39:139-41.

Eisbruch A, Dawson LA, Kim HM, Bradford CR, Terrell JE, Chepeha DB et al. Conformal and intensity modulated irradiation of head and neck cancer: the potential for improved target irradiation, salivary gland function, and quality of life. Acta Otorhinolaryngol Belg 1999;53:271-275.

Eisenberg E. Oral lichen planus: a benign lesion. J Oral Maxillofac Surg 2000;58:1278-85.

Elmore JG, Horwitz RI. Oral cancer and mouthwash use: evaluation of the epidemiologic evidence. Otolaryngol Head Neck Surg 1995;113:253-61.

Enlow DH, Hans MG. Essentials of facial growth. Philadelphia: WB Sanders Co; 1996.

Ephros H, Mashberg A. Toluidine blue--viewpoints. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:526-29.

Epstein JB, Schubert MM. Oral mucositis in myelosuppressive cancer therapy. Oral Surg, Oral Med, Oral Pathol, Oral Radiol, Endod 1999;88:273-76.

Everett MJ, Colston BW, Sathyam US. Da Silva LB, Fried D, Featherstone JDB. Non-invasive diagnosis of early caries with polarization sensitive optical tomography (PS-OCT). In: Featherstone JDB, Rechmann P, Fried D, eds. Lasers in Dentistry V. Bellingham WA: Proceedings of SPIE 3593; 1999.

Featherstone JD. Innovative methods for early caries intervention. In: Stookey GK, ed. Early detection of dental caries II. Indiana Conference 1999. Indianapolis: Indiana University Press; 2000.

Featherstone JD, Barrett-Vespone NA, Fried D, Kantorowitz, Seka W. CO2 laser inhibitor of artificial caries-like lesion progression in dental ena J Dent Res. 1998;77:1397-403.

Flaitz CM. Differential diagnosis of oral mucosal lesions in children and adolescents. Adv Dermatol 2000;16:39-78.

Fliss MS, Usadel H, Caballero OL, Wu L, Buta MR, Eleff SM et al. Facile detection of mitochondrial DNA mutations in tumors and bodily fluids. Science 2000;287:2017-19.

Fox PC. Acquired salivary dysfunction. Drugs and radiation. Ann NY Acad Sci 1998;842:132-37.

Fox RI. Sjogren's syndrome. Controversies and progress. Clin Lab Med 1997;17:431-44.

Franceschi S, Munoz N, Snijders PJ. How strong and how wide is the link between HPV and oropharyngeal cancer? Lancet 2000;356:871-72.

Fritz, ME. Implant therapy II. Ann Periodontol 1996;1:796-815.

Garvey MT, Barry HJ, Blake M. Supernumerary teeth-an overview of classification, diagnosis and management. J Can Dent Assoc 1999;65:612-16.

Geiger AM, Gorelick L, Gwinnett AJ, Benson BJ. Reducing white spot lesions in orthodontics population with fluoride rinsing. Amer J Orthod Dentofac Orthop 1992;101:403-07.

Geyer C, Papadimitrakopoulou V, Hong WK. Chemoprevention in head and neck cancer: basic science and clinical application. Semin Radiat Oncol 1998;8:292-301.

Ghafari J, King GJ, Tulloch JF. Early treatment of class II, division 1 malocclusion--comparison of alternative treatment modalities. Clin Orthod Res 1998;1:107-17.

Ghodratnama F, Wray D, Bagg J. Detection of serum antibodies against cytomegalovirus, varicella zoster virus and herpes virus 6 in patients with recurrent aphthous stomatitis. J Oral Pathol Med 1999;28:12-15.

Giordano R, Lee S, Pober R, Sabrosa C. Flexural strength of a resin infused ceramic matrix. J Dent Res 1997;76(Spec Iss):137 (Abstract No. 989).

Glick M, Siegel MA. Viral and fungal infections of the oral cavity in immunocompromised patients. Infect Dis Clin North Am 1999;13:817-31.

Goetzen N, Anusavice KJ. Design optimization of all-ceramic bridges via FEM and CARES. J Dent Res 2001;80 (Spec Iss):57 (Abstract No. 175).

Gorlin RJ, Cohen MM, Levin LS. Syndromes of the head and neck. New York: Oxford University Press; 1990.

Graber LW. Congenital absence of teeth: a review with emphasis on inheritance patterns. J Am Dent Assoc 1978;96:266-75.

Grandis JR, Drenning SD, Zeng Q, Watkins SC, Melhem MF, Endo S et al. Constitutive activation of Stat3 signaling abrogates apoptosis in squamous cell carcinogenesis in vivo. Proc Natl Acad Sci 2000;97:4227-32.

Grau AJ, Buggle F, Ziegler C. Association between acute cerebrovascular ischemic and chronic and recurrent infection. Stroke 1997;28:1724-29.

Graves DT, Delima AJ, Assuma R. Interleukin-1 and tumor necrosis factor antagonists inhibit the progression of inflammatory cell infiltration toward alveolar bone in experimental periodontitis. J Periodontol 1998; 69:1419-25.

Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin 2000;50:7-33.

Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. Ann Periodontol 1998 Jul:3(1):51-61.

Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG et al. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. J Periodontol 1997 Aug;69:713-19.

Gu G, Lemery SA, King GJ. Effect of appliance reactivation after decay of initial activation on osteoclasts, tooth movement, and root resorption. Angle Orthodontist 1999;69:515-22.

Guggenberger R, May R, Stefan KP. New trends in glass-ionomer chemistry. Biomaterials 1998;19:479-83.

Hallab NJ, Bundy KJ, O'Connor K, Moses RL, Jacobs JJ. Evaluation of metallic and polymeric biomaterial sur face energy and surface roughness characteristics for directed cell adhesion. Tissue Eng 2001;7:55-71.

Hanzawa M, Shindoh M, Higashino F, Yasuda M, Inoue N, Hida K et al. Hepatocyte growth factor upregulates E1AF that induces oral squamous cell carcinoma cell invasion by activating matrix metalloproteinase genes. Carcinogenesis 2000 Jun;21:1079-85.

Harris EF, Kineret SE, Tolley EA. A heritable component for external apical root resorption in patients treated orthodontically. Am J Orthod Dentofac Orthop 1997; 111:301-09.

Hart TC, Hart PS, Michalec MD, Zhang Y, Marazita ML, Cooper M et al. Localization of a gene for prepubertal periodontitis to chromosome 11q14 and identification of a cathepsin C gene mutation. J Medical Genetics 2000;37:81-82.

Harty LC, Caporaso NE, Hayes RB, Winn DM, Bravo-Otero E, Blot WJ et al. Alcohol dehydrogenase 3 genotype and risk of oral cavity and pharyngeal cancers. J Natl Cancer Inst 1997;89:1698-1705.

Head JA. A study of saliva and its action on tooth enamel in reference to its hardening and softening. J. Am. Med. Assoc. 1912;59:2118-22.

Hillman JD, Brooks TA, Michalek SM, Harmon CC, Snoep SL, van Der Weijden CC. Construction and characterization of an effector strain of Streptococcus mutans for replacement therapy of dental caries. Infect Immun 2000;68:543-49.

Hong S-B, Eliaz N, Leisk GG, Sachs EM, Latanison RM, Allen SM. A new Ti-5Ag alloy for customized prostheses by three-dimensional printing (3DPTM). J Dent Res 2001 Mar;80:860-863.

Houdayer C, Bahuau M. Orofacial cleft defects: inference from nature and nurture. Ann Genet 1998;41:89-117.

Hujoel PP, Drangsholt MT, Spiekerman C, DeRouen TA. Periodontal disease and risk of coronary heart disease. J Am Med Assoc 2000;284:1406-10.

Jacobson JM. Thalidomide: a remarkable comeback. Expert Opin Pharmacother 2000;1:849-63.

Jeffcoat MK, Geors NC, Reedy MS, Clives ST, Goldenberg RL, Hauth, JC. Periodontal infection and pre-term birth. J Am Med Assoc 2001;132:875-80.

Jefferies S, Foulkes WD. Genetic mechanisms in squamous cell carcinoma of the head and neck. Oral Oncol 2001;37:115-26.

Jenkins GN. Recent changes in dental caries. Br Med J 1985;291:1297-98.

Jha N, Seikaly H, McGaw T, Coulter L. Submandibular salivary gland transfer prevents radiation-induced xerostomia. Int J Radiat Oncol Biol Phys 2000;46:7-11.

Johnston LE Jr. Let them eat cake: the struggle between form and substance in orthodontic clinical investigation. Clin Orthod Res 1998a;1:88-93.

Johnston LE Jr. A comparative analysis of class II treatments: a retrospective/prospective alternative. Clin Orthod Res 1998b;1:142-46.

Joshi N, O'Bryan T, Appelbaum PC. Pleuropulmonary infections caused by *Eikenella corrodens*. Rev Infect Dis 1991 Nov-Dec;13:1207-12.

Kamat S, Su X, Ballarini R, Heuer AH. Structural basis for the fracture toughness of the shell of the conch Strombus gigas. Nature 2000;405:1036-40.

Karem KL, Bowen J, Kuklin N, Rouse BT. Protective immunity against HSV type 1 following oral administration of recombinant Salmonella typhimurium vaccine strains expressing HSV antigens. J Gen Virol, 1997; 78(2):427.

Kaste LM, Selwitz RH, Oldakowski RJ, Brunelle JA, Winn DM, Brown LJ. Coronal caries in the primary and permanent dentition of children and adolescents 1-17 years of age: United States, 1988-1991. J Dent Res 1996;75:631-41.

Kaufman E, Lamster, I.B. Analysis of saliva for periodontal diagnosis: a review. J Clin Periodont 2000;27:53-465.

Kelly JR. Approaching clinical relevance in failure testing of restorations. J Prosthet Dent 1999;81:652-61.

Kelly JR, Antonucci JM. Processing and properties of interpenetrating-phase composites. Amer Chem Soc Polymer Preprints 1997;38:125-26.

Kelly JR, Tesk JA, Sorensen JA. Failure of all-ceramic fixed partial dentures *in vitro* and *in vivo*: analysis and modeling. J Dent Res 1995;74:1253-58.

Kerawala CJ, Beale V, Reed M, Martin IC. The role of vital tissue staining in the marginal control of oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2000;9:32-35.

Khuri FR, Nemunaitis J, Ganly I, Arseneau J, Tannock IF, Romel L et al. A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer. Nat Med 2000;6:879-85.

Kinney RK, Gatchel RJ, Ellis E, Holt C. Major psychological dis orders in chronic TMD patients: implications for successful management. J Am Dent Assoc 1992;123:49-54.

Kirkham J, Zhang J, Brookes SJ, Shore RC, Wood SR, Smith SA et al. Evidence for charge domains on developing enamel crystal surfaces. J Dent Res 2000 Dec;79:1934-47.

Könönen M, Kivilahti J. Fusing of dental ceramics to titanium. J Dent Res 2001;80:848-54.

Kobayashi TK, Ueda M, Nishino T, Terasaki S, Kameyama T. Brush cytology of herpes simplex virus infection in oral mucosa: use of the ThinPrep processor. Diagnostic cytopathol,1998;18(1):71.

Konishi N, Fried D, Staninec M, Featherstone JD. Artificial caries removal and inhibition of artificial secondary caries by pulsed CO2 laser irradiation. Am J Dent 1999 Oct;12:213-16.

Kornman KS. Microbiology and the etiology of periodontal diseases. In: Wilson TG, Kornman KS, eds. Fundamentals of Periodontics. Chicago: Quintessence Publishing Company; 1996.

Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. J Clin Periodontol 1997 Jan;24:72-77.

Koulourides T, Cento H, Pigman W. Rehardening of softened enamel surfaces of human teeth by solution of calcium phosphates. Nature 1961;189:226-27.

Krasse B. Biological factors as indicators of future caries. In. Dent J 1988;38:219-25.

Kumari S, Bhol KC, Simmons RK, Razzaque MS, Letko E, Foster CS et al. Identification of ocular cicatricial pemphigoid antibody binding site(s) in human beta 4 integrin. Invest Ophthamol Vis Sci 2001;42:379-85.

La Vecchia C, Tavani A, Franceschi S, Levi F, Corrao G, Negri E. Epidemiology and prevention of oral cancer. Oral Oncol 1997;33:302-12.

Laga EA, Toth BB, Roston KV, Tanand JJ. Evaluation of a rapid enzyme-linked immunoassay for the diagnosis of herpes simplex virus in cancer patients with oral lesions. Oral Surg Oral Med Oral Pathol 1993;75:168-72.

Lalla E, Lamster IB, Feit M, Huang l, Spessot a, Qu W et al. Blockade of RAGE suppresses periodontitis-associated bone loss in diabetic mice. J Clin Invest 2000;105:1117-24,.

Lalla E, Lamster IB, Feit MH, Schmidt AM. A murine model of accelerated periodontal disease in diabetes. J Periodontol Res 1998;33:387-99.

Lamster IB. Evaluation of components of gingival crevicular fluid as diagnostic tests. Ann Periodontol 1997;2:123-37.

Larsen MJ, Fejerskov O. Chemical and structural challenges in remineralization of dental enamel lesions. Scand J Dent Res 1987;97:285-96.

Laskaris G, Satriano RA. Drug-induced blistering oral lesions. Clin Dermatol 1993;11:545-50.

Laskin DM. Finding the evidence for evidence-based dentistry. J Am Coll Dent 2000;67:7-10.

Linton JL. Quantitative measurements of remineralization of incipient caries. Am J Orthod Dentofac Orthop 1996;110:590-97.

Löe H, Brown LJ. Early-onset periodontitis in the United States of America. J Periodontol 1991;62:608-10.

Loffredo LC, Souza JM, Freitas JA, Mossey PA. Oral clefts and vitamin supplementation. Cleft Palate Craniofacial J 2001;38:76-83.

Lorenz HP, Hedrick MH, Chang J, Mehrara BJ, Longaker MT. The impact of biomolecular medicine and tissue engineering on plastic surgery in the 21st century. Plast Reconstr Surg 2000;105:2467-81.

Loty C, Sautier JM, Boulekbache H, Kokubo T, Kim HM, Forest N. In vitro bone formation on a bone-like apatite layer prepared by a biomimetic process on a bioactive glass-ceramic. J Biomed Mater Res 2000;49:423-34.

Lussi A, Imwinkelried S, Pitts NB, Longbottom C, Reich E. Performance and reproducibility of a laser fluorescence system for the detection of occlusal caries in vitro. Caries Res 1999;33:261-66.

Lynch DP. Oral candidiasis: history, classification and clinical presentation. Oral Surg Oral Med Oral Pathol 1994,78:189.

Lynch DP. Oral viral infections. Clin Dermatol 2000;18:619-28.

Ma PX, Choi JW. Biodegradable polymer scaffolds with well-defined interconnected spherical pore network. Tissue Eng 2001;7:23-33.

Mackenzie J, Ah-See K, Thakker N, Sloan P, Maran AG, Birch J, Macfarlane GJ. Increasing incidence of oral cancer amongst young persons: what is the aetiology? Oral Oncol 2000;36:387-89.

Mandell ID. Caries prevention: current strategies, new directions. J Amer Dent Assoc 1996;127:1477-88.

Marshall GW Jr, Balooch M, Gallagher RR, Gansky SA, Marshall SJ. Mechanical properties of the dentinoenamel junction: AFM studies of nanohardness, elastic modulus, and fracture. J Biomed Mater Res 2001;54:87-95.

Matsumoto K. Lasers in Endodontics. Dent Clin North Am 2000;44:889-906.

Mealey B. Position paper: diabetes and periodontal diseases. J Periodontol 2000;71:664-78.

Mitchell-Lewis D, Engebretson SP, Chen J, Lamster IB, Papapanou PN. Periodontal infections and pre-term labor: early findings from a cohort of young minority women in New York. Eur J Oral Sci 2001;109:34-39.

Moore SR, Johnson NW, Pierce AM, Wilson DF. The epidemiology of tongue cancer: a review of global incidence. Oral Dis 2000;6:75-84.

Mossey PA. The heritability of malocclusion: part 2. The influence of genetics in malocclusion. Br J Orthod 1999;26:195-203.

Myers JN, Elkins T, Roberts D, Byers RM. Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes. Otolaryngol Head Neck Surg 2000;122:44-51.

Nasr HF, Aichelmann-Reidy ME, Yukna RA. Bone and bone substitutes. Periodontol 2000. 1999;19:74-86.

National Institute of Dental and Craniofacial Research. Research opportunities and investigator competencies in the 21st century. report of the Blue Ribbon Panel on Research Training and Career Development to Meet Scientific Opportunities of the 21st Century. Washington DC: U.S. Department of Health and Human Services, Public Health Service; 2000 January.

National Institutes of Health. Management of temporo mandibular disorders. National Institutes of Health Technology Assessment Conference Statement. J Am Dent Assoc 1996 Nov;127:1595-606.

Newbrun E (1989) Effectiveness of water fluoridation. J Public Health Dent 1989;49:279-89.

Nitta T, Sugihara K, Tsuyama S, Murata F. Immunohistochemical study of MUC1 mucin in premalignant oral lesions and oral squamous cell carcinoma: association with disease progression, mode of invasion, and lymph node metastasis. Cancer 2000;88:245-54.

Nuckolls GH, Shum L, Slavkin HC. Progress towards under standing craniofacial malformations. Cleft Palate Craniofac J 1999;36:12-26.

Oakley C, Epstein JB, Sherlock CH. Reactivation of oral herpes simplex virus; implications for clinical management of herpes simplex virus recurrence during radiotherapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endodont 1997;84:272.

Odds FC, Kibbler CC, Walker E, Bhamra A, Prentice HG, Noone P. Carriage of Candida species and C albicans biotypes in patients undergoing chemotherapy or bone marrow transplantation for haematological disease. J Clin Pathol 1989 Dec;42(12):1259-66.

Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G et al. Periodontal disease as a possible risk factor for preterm low birthweight. J Periodont 1996 Oct;67:1103-13.

Ogawa T, Ozawa S, Shih JH, Ryu KH, Sukotjo C, Yang JM, Nishimura I. Biomechanical evaluation of osseous implants having different surface topographies in rats. J Dent Res 2000;79:1857-63.

Okeson JP. Long-term treatment of disk-interference disorders of the temporomandibular joint with anterior repositioning occlusal splints. J Prosthet Dent 1988;60:611-16.

Okeson JP, de Kanter RJ. Temporomandibular disorders in the medical practice. J Fam Pract 1996;43:347-56.
OMIM™(Online Mendelian Inheritance in Man), Johns Hopkins University, Baltimore, MD. MIM Number: 119530 and 119540, 2001. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/.
Page RC. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. Ann eriodontol 1998;3:108-20.
Palmer AJ, Sendi PP. Meta-analysis in oral health care. Oral Surg, Oral Med, Oral Path, Oral Radiol Endod 1999;87:135-41.
Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol 1996;1:1-36.
Papas A, Russell D, Singh M, Stack K, Kent R, Triol C et al . Double blind clinical trial of a remineralizing dentifrice in the prevention of caries in a radiation therapy population. Gerodontology 1999;16:2-10.
Park JY, Schantz SP, Stern JC, Kaur T, Lazarus P. Association between glutathione S-transferase pi genetic polymorphisms and oral cancer risk. Pharmacogenetics 1999;9:497-504.
Peltonen L, McKusick VA. Dissecting human diseases in the ostgenomic era. Science 2001;291:1224-29.
Phelan JA, Begg MD, Lamster IB, Gorman J, Mitchell-Lewis D, Bucklan R et al.. Oral candidiasis in HIV infection: predictive value and comparison of findings in injecting drug users and homosexual men. J Oral Pathol Med 1997;26:237.
Popovsky JL, Camisa C. New and emerging therapies for diseases of the oral cavity. Dermatol Clin 2000;18: 113-25.
Prescott NJ, Lees MM, Winter RM, Malcolm S. Identification of susceptibility loci for nonsyndromic cleft lip with or without cleft palate in a two stage genome scan of affected sib-pairs. Hum Genet 2000;106:345-50.
Prochazka AV. New developments in smoking cessation. Chest 2000;117:169S-175S.
Proffit WR, Fields Jr HW, Moray LJ. Prevalence of malocclusion and orthodontic treatment need in the United States: estimates from the NHANES III survey. Int J Adult Orthod Orthognath Surg 1998;13:97-106.
Reddi AH. Morphogenesis and tissue engineering of bone and cartilage: inductive signals, stem cells, and biomimetic biomaterials. Tissue Eng 2000;6:351-59.
Reents S, Goodwin SD, Singh V. Antifungal prophylaxis in immunocompromised hosts. Ann Pharmacother 1993;27:53.
Regezzi JA, Sciubba JJ, eds. Oral pathology: clinical-pathologic correlations. Philadelphia: WB Saunders Co; 1989.
Retief DH, Bradley EL, Holbrook M, Switzer P. Enamel fluoride uptake, distribution and retention from topical fluoride agents. Caries Res 1983;17:44-51.
Rex JH, Rinaldi MG, Pfaller MA. Resistance of candida species to fluconazole. Antimicrob Agents Chemother 1995;39:1.
Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. Cancer 2000;88:2398-2424.
Ripa LW. Review of the anticaries effectiveness of professionally applied and self-applied topical fluoride gels. J Public Health Dent 1989;49:297-309.
Roberts-Clark DJ, Smith AJ. Angiogenic growth factors in human dentine matrix. Arch Oral Biol 2000;45:1013-16.
Robinson CP, Yamachika S, Bounous DI, Brayer J, Jonsson R, Holmdahl R et al. A novel NOD-derived murine model of primary Sjøgren's syndrome. Arthritis Rheum 1998;41:150-56.
Russel MW, Hajishengallis G, Childers NK, Michalek SM. Secretory immunity in defense against cariogenic mutans streptococci. Caries Res 1999;33:4-15.
Rye B, Webb JM. Autoimmune bullous diseases. Am Fam Phys 1997;55:2709-18.
Sabrosa C, Pober R, Kittipibul P, Giordano R. Flexural strength of glass and resin infiltrated ceramic matrices. J Dent Res 1999;78(Spec Iss):204 (Abstract No. 46).
Satcher DS. Oral health in America: a report of the Surgeon General. Public Health Rep 2000;115:489-90.
Scalvenzi M, Ceddia C. Research in simple blind with natural interferon alpha at low dosage in subjects affected by herpes genitalis and labialis. Clin Ter 2000;151(1 Suppl 1):13-18.
Scannapieco FA, Mylotte JM. Relationships between periodontal disease and bacterial pneumonia. J Periodontol 1996 Oct;67(10 Suppl):1114-22.
Scannapieco FA. Role of oral bacteria in respiratory infection. J Periodontol 1999:70:793-802.
Schenkels LC, Veerman ECI, Nieuw Amerongen AV. Biochemical composition of human saliva in relation to other mucosal fluids. Crit Rev Oral Biol Med 1995;6:161-75.
Schumacher GE, Antonucci JM, Bennett PS, Code JE. N-phenyliminodiacetic acid as an etchant/primer for dentin bonding. J Dent Res 1997 ;76:602-09.
Schutte BC, Murray JC. The many faces and factors of orofacial clefts Hum Mol Genet 1999;8(10):1853-59.
Schwartz Z, Goultschin J, Dean DD, Boyan BD. Mechanisms of alveolar bone destruction in periodontitis. Periodontol 2000. 1997 Jun;14:158-72.
Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. J Natl Cancer Inst 1998;90:1626-36.
Sciubba JJ. Improving detection of precancerous and cancerous oral lesions. Computer-assisted analysis of the oral brush biopsy. United States Collaborative OralCDx Study Group. J Am Dent Assoc 1999;130:1445-57.
Scully C, Begli M, Ferreiro MC, Ficarra G, Gill Y, Griffiths M et al. Update on oral lichen planus. Crit Rev Oral Biol Med 1998;9:86-122.
Seka W, Fried D, Featherstone JD, Borzillary SF. Light deposition in dental hard tissue and simulated thermal response. J Dent Res 1995;74:1086-92.
Severson HH, Andrews JA, Lichtenstein E, Gordon JS, Barckley M.F. Using the hygiene visit to deliver a tobacco cessation program: results of a randomized clinical trial. J Am Dent Assoc 1998;129:993-99.
Shannon IL, Edmonds FL. Effect of fluoride concentration on rehardening of enamel by a saliva substitute. Int Dent J 1978;28:421-26.
Shaw WC, Semb G, Nelson P, Brattstrom V, Molsted K, Prahl-Andersen B, Gundlach KK. The Eurocleft Project 1996-2000: overview. J Maxillofac Surg 2001;29:131-140.
Sheats RD, McGorray SP, Musmar Q, Wheeler TT, King GJ. Prevalence of orthodontic asymmetries. Sem Orthod 1998;4:138-45.
Silverman S Jr. Oral lichen planus: a potentially premalignant lesion. J Oral Maxillofac Surg 2000;58:1286-88.
Silverman S.Jr, ed. Oral Cancer. Fourth Edition. London: C. Decker Inc; 1998.
Silverstone LM, Wefel JS, Zimmerman BF, Clarkson BH, Featherstone MJ. Remineralization of natural and artificial lesions in human dental enamel in vitro. Caries Res 1981;15:138-57.

Simon C, Hicks MJ, Nemechek AJ, Mehta R, O'Malley BW Jr, Goepfert H. PD 098059, an inhibitor of ERK1 activation, attenuates the in vivo invasiveness of head and neck squamous cell carcinoma. Br J Cancer 1999;80:1412-19.

Skarsgard DP, Groome PA, Mackillop WJ, Zhou S, Rothwell D, Dixon PF. Cancers of the upper aerodigestive tract in Ontario, Canada, and the United States. Cancer 2000;88:1728-38.

Skrtic D, Antonucci JM, Eanes ED. Improved properties of amorphous calcium phosphate fillers in remineralizing resin composites. Dent Mater 1996;12:295-301.

Smith DJ, Taubman MA. Vaccines against dental caries infection. In: Levine MM, Woodrow GC, Kaper JB, Cobon GS, eds. New generation vaccines. New York: Dekker; 1997.

Smith BD, Smith GL, Carter D, Sasaki CT, Haffty BG. Prognostic significance of vascular endothelial growth factor protein levels in oral and oropharyngeal squamous cell carcinoma. J Clin Oncol 2000;18:2046-52.

Smith RA, Mettlin CJ, Davis KJ, Eyre H. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin 2000;50:34-49.

Spickermann H, Jansen V, Richter EJ. A 10- year follow-up study of IMZ and TPS implants in the edentulous mandible using bar-retained overdentures. Int J Oral Maxillofac Implants 1995;10:231-43.

Stansbury JW, Antonucci JM. Evaluation of methylene lactone monomers in dental resins. Dent Mater 1992;8:270-73.

Stansbury JW, Antonucci JM. Dimethacrylate monomers with varied fluorine contents and distributions. Dent Mater 1999;15:166-73.

Stockton DW, Das P, Goldenberg M, D'Souza RN, Patel PI. Mutation of PAX9 is associated with oligodontia. Nat Genet 2000 Jan;24(1);18-19.

Sudbø J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A. DNA content as a prognostic marker in patients with oral leukoplakia. N Engl J Med 2001;344:1270-78.

Sun A, Wu YC, Wang JT, Lia BY, Chiang CP. Association of HLA-te22 antigen with antinuclear antibodies in Chinese patients with erosive oral lichen planus. Proc Natl Sci Counc Repub China B 2000;24:63-69.

Tatakis DN, Promsudthi A, Wikesjo UME. Devices for periodontol regeneration. Periodontol 2000 1999;19:59-73.

Taylor GW, Burt BA, Becker MP, Benco RJ, Shlossman M, Knowler WC et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin dependent diabetes mellitus. J Periodontol 1996 Oct;67:1085-93.

Thesleff I. The genetic basis of normal and abnormal craniofacial development. Acta Odontol Scand 1998;56:321-25.

Thomas E, Hay EM, Hajeer A, Silman AJ. Sjogren's syndrome: a community-based study of prevalence and impact. Br J Rheumatol 1998;37:1069-76.

Thylstrup A, Fejerskov O. Clinical and pathological features of dental caries. In: Fejerskov O, ed. Textbook of Clinical Cariology. Copenhagen: Munksgaard International Publishers; 1994.

Tilbrook DA, Clarke RL, Howle NE, Braden. Photocurable epoxy-polyol matrices for use in dental composites I. Biomater 2000;21:1743-53.

Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. J Periodontol 2000;71:743-51.

Turner SR, Rumsey N, Sandy JR. Psychological aspects of cleft lip and palate. Eur J Orthod 1998 ;20:407-15.

Tziafas D, Smith AJ, Lesot H. Designing new treatment strategies in vital pulp therapy. J Dent 2000;28:77-92.

Valdez IH, Wolff A, Atkinson JC, Macynski AA, Fox PC. Use of pilocarpine during head and neck radiation therapy to reduce xerostomia and salivary dysfunction. Cancer 1993;71:1848-51.

Vastardis H. The genetics of human tooth agenesis: new discoveries for understanding dental anomalies. Am J Orthod Dentofacial Orthop 2000;117:650-56.

Von Korff M, Dworkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints. Pain 1988;32-173-83.

Vissink A, Gravenmade EJ, Gelhard TBFU, Panders AK, Franken MH. Rehardening properties of mucin and CMC-containing substitutes on softened human enamel. Caries Res 1985;19:212-18.

Warnakulasuriya S. Lack of molecular markers to predict malignant potential of oral precancer. J Pathol 2000;190:407-09.

Wennstrom JL. Mucogingival therapy. Ann Periodontol 1996;1:671-701.

White DJ. Reactivity of fluoride dentifrices with artificial caries. II. Effects on subsurface lesions, F uptake, surface hardening, and remineralization. Caries Res 1988;22(1):27-36.

White SN, Luo W, Paine ML, Fong H, Sarikaya M, Snead ML. Biological organization of hydroxyapatite crystallites into a fibrous continuum toughens and controls anisoptropy in human enamel. J Dent Res 2001;80:321-26.

Winn DM, Brunelle JA, Selwitz RH, Kaste LM, Oldakowski RJ, Kingman A. Coronal and root caries in the dentition f adults in the United States, 1988-1991. J Dent Res 1996;75:642-51.

Winn DM, Diehl SR, Horowitz AM, Gutkind S, Sandberg AL, Kleinman DV. Scientific progress in understanding oral and pharyngeal cancers. J Am Dent Assoc 1998;129:713-18.

Winn DM, Diehl SR, Brown LM, Harty L, Otero EB, Fraumein JF.Jr., Kleinman DV. Hayes RB. Mouthwash in the etiology of oral cancer in Puerto Rico. Cancer Causes and Control 11 In Press.

Woo SB, Lee SF. Oral recrudescent herpes simplex virus infection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:239.

Woo SB, Sonis ST. Recurrent aphthous ulcers: a review of diagnosis and treatment. J Am Dent Assoc 1996;127:1202-13.

Wyszynski DF, Beaty TH. Review of the role of potential teratogens in the origin of human nonsyndromic oral clefts. Teratology 1996;53:309-17.

Xu HH, Smith DT, Schumacher GE, Eichmiller FC. Whisker-reinforced dental core buildup composites: effect of filler level on mechanical properties. J Biomed Mater Res 2000;52:812-18.

Yellowitz JA, Horowitz AM, Drury TF, Goodman HS. Survey of United States dentists' knowledge and opinions about oral pharyngeal cancer. J Am Dent Assoc 2000;131:653-61.

Zambon JJ, Haraszthy VI. The laboratory diagnosis of periodontol infections. Periodontol 2000. 1995 Feb;7: 69-82.

Zhang L, Michelsen C, Cheng X, Zeng T, Priddy R, Rosin MP. Molecular analysis of oral lichen planus. A premalignant lesion? Am J Pathol 1997;151:323-27.