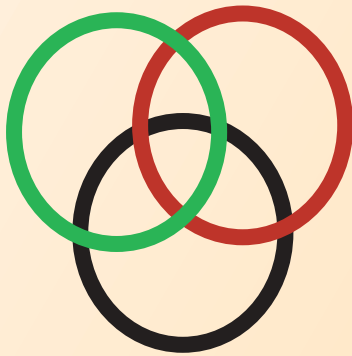


SPECIAL ISSUE

# Compendium

of Continuing Education in Dentistry®



Exploring the Relationship  
Between Oral Health and  
Systemic Health Within the  
African American Population

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# Compendium

Dear Readers:

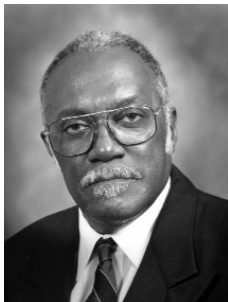
African American dentists have historically focused their attention on improving health by addressing relationships between oral and systemic diseases. In fact, Clifton O. Dummett, Sr., in his recently published book entitled, "NDA II: The Story of America's Second National Dental Association," describes the evolution of African American physicians, dentists, and pharmacists bonding together under one organizational umbrella to enhance the health of African Americans.

The coming together of these health professionals was partially due to discrimination, prejudice, and racism, and resulted in a multidisciplinary approach to health care delivery. Because they were forced to work together, many of their clinical, behavioral, economic, and public health decisions influenced both oral and systemic health outcomes. Many of the patients whom African American health care providers served, and continue to serve, did not have full geographic and economic access to advances in health care. Thus, a multidisciplinary approach by African American health care providers was necessary to navigate through the maze of the health delivery system. Unfortunately many of the same challenges still exist.

This special issue of *The Compendium* includes the proceedings from a December 2000 symposium entitled, "Enhancing the Oral and Systemic Health of the African American Population." The symposium, held at Howard University, was cosponsored by Howard University College of Dentistry, Meharry Medical College School of Dentistry, the National Dental Association Foundation (NDAF), the National Dental Association, Inc. (NDA), the National Institute of Dental and Craniofacial Research (NIDCR), and the Colgate-Palmolive Company. The purpose of the symposium was to discuss how to ensure that African Americans and other underserved populations benefit equitably from research addressing the associations between oral and systemic diseases.

Researchers, educators, clinicians, and students from across the United States gathered to learn about the most current evidence linking oral and systemic diseases, dysfunctions, and disabilities. They also discussed strategies to ensure that African Americans and other underserved populations will be included, from the outset, in all public and private efforts to improve oral and systemic health. Some scientists believe that the approach is new. From years of clinical experiences, however, African American health professionals view this strategy as a "renewed paradigm" at best.

As President of the National Dental Association Foundation, I am very proud to have hosted the symposium. We are grateful to NIDCR and the Colgate-Palmolive Company for joining the NDA/NDAF in cosponsoring the symposium, and very pleased that *The Compendium* has published the proceedings. The symposium was extremely well attended, and the distribution of this edition of *The Compendium* will further the knowledge base about oral and systemic health and oral and systemic diseases. Hopefully, additional partnerships will be established with others who are committed to eliminating the health disparities between diverse populations in the United States and abroad.



Sincerely,

A handwritten signature in black ink, reading "Roosevelt Brown, DDS".

Roosevelt Brown, DDS  
President  
National Dental Association Foundation



# Exploring the Relationship Between Oral Health and Systemic Health Within the African American Population



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# Enhancing Oral and Systemic Health

**Abstract:** Much published research documents continuing racial and ethnic disparities in health, particularly for African Americans, which apply to both oral and systemic diseases. Current research suggests biologically plausible associations between oral and systemic diseases; however, clear cause-and-effect relationships have not been substantiated. Some researchers and health care providers have noted anecdotal associations between oral and systemic health, as well as compounding adverse effects of oral and systemic diseases and dysfunctions. Historically, African American physicians, dentists, and pharmacists have bonded together under one organizational umbrella to combat discrimination, prejudice, and racism directed at them and their patient populations. This coming together has resulted in a more comprehensive clinical, behavioral, economic, and public health decision-making process related to the general health and well-being of their patient populations, such as maximizing health care visits, treatment plans, reimbursements, and oral and systemic health care follow-ups. According to the 1985 Secretary's Task Force Report, the six causes of excess deaths among African Americans were: cardiovascular disease and stroke; cancer; diabetes; cirrhosis; homicide and accidents; and infant mortality. In 1991, HIV/AIDS became the seventh cause of excess deaths. This article summarizes salient information about cardiovascular diseases, diabetes, cancer, and the social and behavioral factors related to oral and systemic health.

...oral health is integral to general health. You cannot be healthy without oral health. Oral health and general health should not be interpreted as separate entities. Oral health is a critical component of health and must be included in the provision of health care and the design of community programs.<sup>1</sup>

The preceding excerpt, taken from the recently published report, "Oral Health in America: A Report of the Surgeon General," details the oral health of the people living in the United States. This report is the first ever on oral health among the many Surgeon General's reports. It describes the broad scope of oral health and its importance to general health and well-being. Oral health means much more than healthy teeth; oral health is integral to general health. Safe and effective disease-prevention measures exist that everyone can adopt to improve oral health and prevent disease, and general health risk factors such as tobacco use and poor dietary practices also affect oral and craniofacial health. These are among the major themes in the Surgeon General's report. The mouth is a mirror of health and disease, the report concludes. This biological mirror can and must be used to promote health

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## Learning Objectives:

After reading this article, the reader should be able to:

- discuss some of the major morbidities and mortalities that disproportionately affect African American and other minority populations.
- list the seven leading causes of "excess deaths" among African Americans.
- summarize the major risk factors for cardiovascular diseases, diabetes, and cancer and discuss how these risk factors may also apply to oral diseases.
- describe some of the barriers to health and health care experienced by African Americans and other minority populations.



and/or to prevent, treat, and/or cure disease, disability, dysfunction, and premature death.

Oral health disparities among select groups of people in the United States include those groups with the poorest oral health status—generally ethnic and racial minority populations, particularly African Americans.<sup>1-5</sup> Ethnic and racial disparities also exist in general or systemic health. In the 1985 federal publication, “Report of the Secretary’s Task Force on Black and Minority Health,” the former Secretary of the US Department of Health and Human Services, Margaret Heckler, writes:

There is a continuing disparity in the burden of death and illness experienced by Black and other minority Americans as compared to our Nation as a whole. That disparity has existed ever since Federal record keeping began more than a generation ago and although our health charts do itemize steady gains in the health of minority Americans, the stubborn disparity remains...an affront to both our ideals and to the ongoing genius of American medicine.<sup>6</sup>

In response to this problem, in December 2000, the National Dental Association Foundation, the National Dental Association, Inc. (NDA), the National Institute of Dental and Craniofacial Research, and the Colgate-Palmolive Company cosponsored a symposium entitled, “Exploring the Relationship Between Oral Health and Systemic Health Within the African American Population.” The symposium addressed oral and systemic health, oral and systemic diseases, dysfunctions and premature deaths, and the relevant behavioral and socioeconomic factors that disproportionally affect the health of African Americans and other underserved populations.<sup>7</sup> This article reviews salient issues on the health status of ethnic and racial populations. It also summarizes several presentations from the symposium that specifically focused on systemic diseases and on the social and behavioral barriers and enablers that influence oral and systemic health. Some of the other presentations at the symposium targeting oral health and diseases are also published in this issue.

“Excess deaths” are additional deaths experienced by African Americans beyond what one

would expect if their death rates were the same as those for the non-Hispanic white population. Excess deaths are one of the measurements that reflect the problem of poorer health status among African Americans. Using data from 1979 to 1981, the analysis of excess deaths reflects 60,000 more deaths among African Americans when compared to the nation as a whole.<sup>6</sup> The causes of excess deaths included heart diseases and stroke, homicide and accidents (unintentional injury), cancer, infant mortality, cirrhosis, and diabetes. The report also chronicled the longstanding problem of the burden of illness suffered by ethnic and racial minority populations. Since the time of the report, acquired immunodeficiency syndrome (AIDS) has become the seventh leading cause of death among African Americans.<sup>8</sup> The Task Force Report focused on four groups: African Americans, Native Americans/Alaskan natives, Hispanics, and Asian/Pacific Islanders. The Task Force, appointed by Secretary Heckler, completed the following assignments: (1) a review of departmental programs to determine how the health problems of minorities [people of color] have been addressed; (2) a careful analysis of the range of health care resources and information available; and (3) a critique of the health status of African Americans, Native Americans, Hispanics, and Asian/Pacific Islanders.

Using previously existing data, the Task Force also focused on several areas including:

- an outreach campaign
- patient education
- delivery and financing of health services
- developing strategies outside the federal sector
- building capacity of the nonfederal sector to address minority health problems
- improving and fully using available sources of data
- a research agenda.

The Task Force reviewed the existing literature, published research, government documents, and epidemiological databases. They conducted interviews and focus groups with health professionals and research scientists both inside and outside of the federal government. Other assessments were undertaken, such as reviews of conference proceedings from minority health symposiums and conferences. Even with the broad-based recommen-



dations from the Task Force, the restructuring of many federal, state, and local public health agencies, and more than a decade of financial support for creative research and intervention programs in both the public and private sectors, racial and ethnic health disparities remain.<sup>9</sup> In fact, since the 1985 Task Force Report, some of the racial and ethnic health disparities are the same or have worsened. While some of the health gap is a result of socioeconomic status, race and ethnic backgrounds remain important in accounting for the disparities. Some of the disparities can be explained by inequalities in the health delivery system, such as differences in accessibility, use, quality of care, or benefit derived.<sup>10-13</sup> Unfortunately, most of these variables can be chronicled by race and ethnicity.<sup>14-17</sup>



**O***ral health means much more than healthy teeth; oral health is integral to general health.*

Regardless of the interventions to close race/ethnic health disparities, the problem remains. In “Eliminating Racial and Ethnic Disparities in Health: Report to Congress FY 1998/1999,” the US Department of Health and Human Services lists the following facts<sup>18</sup>:

- Age-adjusted breast cancer mortality increased 3.9% for black women and declined 15.4% for white women between 1985–1996 (Department of Health and Human Services [DHHS], 1998).
- While the number of tuberculosis (TB) cases among non-Hispanic whites actually decreased 42.9% between 1986–1997, the number of reported TB cases increased 51.1% for Asian Americans and Pacific Islanders, and 30.3% for Hispanics (Centers for Disease Control Tuberculosis Data, July 1998).
- The number of cases of AIDS-opportunistic illnesses from 1991 to September 1998 increased 14% to 34% for non-Hispanic blacks, Hispanics, Asian/Pacific Islanders, and American Indian/Alaskan natives, while the number of cases decreased 18% for non-Hispanic whites. During 1997, the most recent year-end data available, the AIDS case rate was 20.5 per 100,000 for African

Americans, 14.4 per 100,000 for Hispanics, and 2.5 per 100,000 for whites (CDC AIDS Surveillance Report, September 1998).

- Life expectancy gaps between blacks and whites have measured from 6.0 years in 1985 to 6.6 years in 1996b (DHHS, 1998).

- While infant mortality rates among blacks have decreased since 1985, it is still disproportionate. Infant mortality rates decreased by 33.7% for infants of white mothers but only 22.6% for infants of black mothers between 1985 and 1996. The disparity in infant mortality between blacks and whites, as measured by the ratio of infant mortality rates, has, therefore, increased from 2.07 in 1985 to 2.41 in 1996 (DHHS, 1998).

- The same general pattern in infant mortality is seen in American Indians and Alaskan natives in the Indian Health Service’s service areas. From 1985 to 1992, infant mortality among American Indians and Alaskan natives in the Indian Health Service area declined 20.7%, while infant mortality declined 25.8% for the total US white population (Trends in Indian Health, 1997).

- Between 1985 and 1996, age-adjusted heart disease mortality declined 29.1% for white men while declining only 21.9% among black men (DHHS, 1998).

- Between 1996 and 1997, while overall death rates from AIDS declined 32% for whites, death rates declined only 13% for African Americans and 20% for Hispanics.

- Since 1985, age-adjusted firearm injury death rates for black men increased 23.2% compared to only 7.2% for white men (DHHS, 1998).

- African Americans alone made up 57% of new human immunodeficiency virus (HIV) infections reported in 25 states from 1994 to 1997, and represented 45% of all AIDS diagnoses (CDC HIV Surveillance Report, 1997).

- African American and Hispanic women represent less than one quarter of all US women, yet account for 76% of AIDS cases reported among women through 1997 (CDC Surveillance Report).

- 64% of all new HIV infections are among blacks and Hispanics (CDC HIV Surveillance Report, December 1997).

- Prenatal HIV infection among racial and ethnic minorities is also very high. Among children aged 13 years and younger

reported with AIDS from July 1997 through June 1998, 229 (59%) were African American, 22% were Hispanic, 1% were Asian/Pacific Islanders, and less than 1% were Native Americans/Alaskan natives. Nearly all of these cases were a result of mother-to-infant transmission.

Health disparities, diseases, dysfunctions, and premature deaths continue to be recorded based on race and ethnicity, even when other factors are held constant. More aggressive effort must be made if eliminating health disparities is expected.<sup>18</sup>

At the December 2000 NDA/Colgate-Palmolive symposium, Patricia Davidson, MD, a Washington, DC, cardiologist, discussed cardiovascular diseases and the role of oral health by first noting that the age-adjusted mortality rates for African Americans is 205 per 100,000 as compared to 139 per 100,000 for non-Hispanic whites, 107 per 100,000 for Native Americans, 95 per 100,000 for Hispanics, and 78 per 100,000 for Asian Americans.<sup>19</sup> These data indicate higher rates among African Americans as compared to other groups. She also noted that cardiovascular diseases are the leading cause of death for all Americans, except Asian American women.

Arteriosclerosis, the disease process that causes the formation of plaque within the arterial walls, was thought to be the result of accumulation of cholesterol within the artery wall. It is now hypothesized that arteriosclerosis is an inflammatory disease involving complex cellular and molecular responses.<sup>20</sup> Risk factors for arteriosclerosis include oxidation of low-density lipoprotein cholesterol, free-radical formation from cigarette smoking, hypertension, and diabetes.<sup>21</sup> Risk factors that contribute to the preceding diseases are obesity and sedentary lifestyles.<sup>22</sup> Other more recently noted risk factors include elevated homocysteine concentrations and infectious microorganisms such as *Chlamydia pneumoniae*.<sup>23</sup> Diabetes is undoubtedly the deadliest risk factor for cardiovascular diseases and hypertension is the most prevalent. High cholesterol levels are another risk factor for cardiovascular diseases. African American men and women have levels of 46% and 45%, respectively, above the recommended cholesterol level of 200 mg/dL.<sup>24</sup>

Obesity is another risk factor for cardiovascular diseases. Obesity is measured by body mass index (BMI); BMI=kg<sup>2</sup>. Overweight is considered >25 BMI. Using this measure, 68% of African American women and 58% of African American men are overweight. This incidence is higher than other racial/ethnic groups.<sup>25</sup>

Inflammation and coronary risks are important considerations and growing concerns in cardiovascular diseases. C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to tissue injury, inflammation, or infection. High-sensitivity CRP assays are now available.<sup>26</sup> Half of all myocardial infarctions (MIs) occur in patients with normal lipid levels. Other causes of arteriosclerosis have been investigated. Inflammation is hypothesized to play a role in arteriosclerosis development. Proposed markers of inflammation such as high-sensitivity CRP are elevated among men and women who later suffer MIs and strokes. Baseline CRP appears to predict future ischemic events. Aspirin and other drugs and the lipid-lowering agent HMG reductase inhibitors can lower CRP.<sup>27</sup>

Davidson also discussed racial and gender biases in the treatment of cardiovascular diseases, citing several studies that document the inability of physicians to diagnose and appropriately refer patients for revascularization, coronary bypass surgery, and angioplasty based on race and gender.<sup>27-29</sup> She also discussed “the most disturbing study” published in the *New England Journal of Medicine* in 1999.<sup>29</sup> The study involved 720 physicians who were shown videotapes of actors of different races and genders. They presented the same cardiac history and all had positive stress tests. African American women were less likely than all others to be referred for cardiac arteriograms for definitive diagnosis. Physicians must become aware of the high incidence of cardiovascular diseases among all people who live in the United States. They also must become aware of their race and gender biases and improve the prevention, diagnosis, and treatment of cardiovascular diseases. Moïse Desvarieux, MD, PhD, discusses cardiovascular diseases and stroke and their associations with oral diseases in his article on page 34 of this issue.

Juanita Archer, MD, an internist at the

College of Medicine at Howard University, discussed diabetes among African Americans.<sup>30</sup> She noted that almost everyone in the United States has some experience with this disease, either directly or associated with a friend or family member. Diabetes is a group of metabolic diseases based on inadequate insulin secretion and/or abnormal insulin action. The hallmark of diabetes is hyperglycemia, which causes the toxicity that results in neuropathy, nephropathy, cardiovascular diseases, and dermatopathy.

Diabetes is the third leading cause of death among African Americans.<sup>31</sup> In 1990, the age-adjusted rate of hospitalization was 183 per 100,000; 22% higher for African American women than for African American men (150 per 100,000). The hospitalization rate for non-Hispanic white women was 85 per 100,000 and 86 per 100,000 for non-Hispanic white men. In that same year, the age-adjusted rate for diabetic ketoacidosis among African American men with diabetes was 34 per 1,000 compared to 10 per 1,000 for non-Hispanic white men. While the United States has made positive gains over the last generation in improving the health of the people living in this country, all segments of the population have not benefited equally.<sup>32</sup>

Diabetes is commonly classified into two major categories, but there are, in fact, four groups:

1. Type 1—Beta cell destruction is present, usually leading to absolute insulin deficiency.
2. Type 2—This disease may range from predominately insulin-resistant with relative insulin deficiency to a predominately secretory defect with insulin resistance.
3. Other specific types: These include genetic defects of beta cells, genetic defects of insulin action, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced diabetes, viral infections, uncommon forms of immune-mediated diabetes, and other genetic syndromes sometimes associated with diabetes.<sup>33</sup>
4. Gestational diabetes mellitus.<sup>34</sup>

Type 2 diabetes is increasing substantially in the United States and throughout the world, and represents 90% to 95% of all cases of the disease.<sup>34</sup> In the United States 15.7 million people have Type 2 diabetes. It is estimated that 50% of the people who have this disease are unaware that they have it. African Americans

are 1.7 times more likely to have Type 2 diabetes than the general population (2.3 million).<sup>35</sup> Type 2 is the most common type of diabetes seen in African Americans. The incidence of Type 2 diabetes in children and adolescents is also increasing, especially in minority children. Gestational diabetes, another form of Type 2 diabetes, is also very high among African Americans. This is a mild form of diabetes affecting women only during pregnancy.<sup>36</sup>

Archer emphatically states, “Insulin resistance is not diabetes.” It occurs 10 to 15 years before the onset of diabetes and is often unrecognized. Insulin resistance may continue, however, along with diabetes. Nearly 92% of patients with Type 2 diabetes have insulin resistance. A major problem with this disease is that many persons do not learn that they have diabetes until more life-threatening problems occur.<sup>37</sup> For example, heart disease is present in 75% of diabetes-related deaths, resulting in more than 77,000 deaths per year.<sup>36</sup> Diabetes is the leading cause of new cases of blindness in individuals aged 20 to 74. Approximately 200,000 people lose their eyesight as a result of diabetes each year. Diabetes is also the leading cause of end-stage renal disease. In 1995, nearly 27,900 people had this disease. African Americans with diabetes are 2.6 to 5.6 times more likely than non-Hispanic whites to experience end-stage renal disease. Nerve disease and amputation also are major problems associated with diabetes. In fact, diabetes is the leading cause of non-traumatic amputation in the United States—some 57,000 per year. African Americans are 1.5 to 2.5 times more likely to have lower limb amputations.<sup>32</sup>

Improper nutrition and decreased physical activity are major risk factors for diabetes. Although difficult to change, these risks play a major role in the control of the disease. While the exact cause of diabetes is unclear, the disease can be readily controlled by appropriate therapy, proper diet, and exercise.<sup>38</sup> Physical activity is a well-known strategy to improve diabetic health. However, physical activity in the United States is decreasing in all segments of the population.<sup>39</sup>

The dental literature substantiates the association of diabetes and periodontal diseases, yet has not clearly established a cause and effect relationship. George Taylor, DMD,



DrPH, addresses the current research related to these two diseases in his article on page 42 of this issue.

## Cancer

Billy Ballard, DDS, MD, Chairperson, Department of Pathology, Meharry Medical College, discussed cancer among African Americans by first distinguishing the difference between malignant and benign tumors.<sup>40</sup> Cancer refers to all malignant diseases. Benign tumors are neoplasms that grow slowly, are nonmetastasizing, and are usually not life threatening. However, they can be life threatening depending on where they are located. For example, a benign tumor located in the brain or one that secretes some type of hormone can result in premature death. Malignant tumors, on the other hand, are rapidly growing and poorly differentiated. These tumors invade and destroy the surrounding tissue and can spread to additional organs.

Cancer incidence and mortality ratios differ among racial and ethnic groups in the United States. For example, between 1990 and 1996, African Americans had the highest incidence and mortality rates per 100,000 of prostate, breast, lung and bronchus, colon, and rectum cancers.<sup>41</sup> The 5-year survival rates for these cancers among African Americans are the poorest among all racial and ethnic groups. African Americans also have the poorest 5-year cancer survival rates for other sites, such as the esophagus, uterine corpus, stomach, pancreas, and oral cavity. One in every four deaths in the United States is a result of cancer.<sup>42</sup> Approximately 50% of men and 30% of women will develop cancer during their lifetime.

The key factors in reducing cancer rates are prevention and early detection. Risk factors may vary for different types of cancers depending on the body site. Smoking, for example, is a risk factor for cancer of the lungs, mouth, throat, larynx, bladder, and several other organs. These risk factors, however, do not always cause disease. It is important, nonetheless, to know the risk factors and take the appropriate action.<sup>42</sup>

Not all cancers have recommended guidelines for screening and early detection for asymptomatic individuals. Fortunately, tobacco use and alcohol consumption are well-established risk factors for oral cancer.

Screening procedures for oral cancer also are well established.<sup>43</sup> Teresa Perkins, DMD, MMSc, reviews some of the risk factors for oral cancer and discusses the plausible relationship between oral cancer, cirrhosis of the liver, tobacco, and alcohol in her article on page 49 in this issue.

Edwin Nichols, PhD, a psychologist in Washington, DC, has taught medical and dental students for many years.<sup>44</sup> He discussed cultural and social barriers that influence oral and systemic health. The United States consists primarily of people from Europe, Africa, and Asia; Native Americans are the original inhabitants. Some of the people who come from different parts of the world share common ethnic worldviews. Hispanics/Latinos are an example of people who share a common history; to be Hispanic/Latino requires three factors: the forebearers were subjected to colonial Spain, they were forced to speak Spanish, and they were forced to convert to Catholicism. Hispanics/Latinos can be from any racial group, have a variety of surnames, and ethnic identity is not contingent on nationality. This group can include white and Hispanics, black and Hispanics, and Native American and Hispanics, etc.<sup>45</sup>



**M**ore aggressive effort must be made if eliminating health disparities is expected.

Although Nichols did not fully develop the constructs, he described the European culture as another example of a particular ethnic worldview. The ethnic relationship in European culture is subject-object oriented. The highest value for Europeans lies in the object or its acquisition. For Africans, the highest valued group experience is in the relationship.<sup>46</sup> People of African decent see themselves to be of equal worth or value. If a person of African decent is treated less than equal or with disrespect, the relationship has been destroyed. Regardless of the external circumstances (employer/employee, teacher/student, etc), the relationship must be mutually respectful or it will be destroyed. In transmitting knowledge in the European context, one transmits the object or data. The data

are the literature or what the research has reported. However, for other ethnic groups, the object may not be the most important element. A personal relationship must be established to effectively transmit knowledge, particularly about health. To effectively transmit the object or data, a trust relationship must first be established, ie, a patient will likely comply with instructions/treatment if they trust the clinician.

The United States is becoming more and more diverse. Many health care providers will, therefore, have to consider serving a more diverse patient population. These new patient populations will bring their cultural norms with them. Nichols' description indicates that in the Asian culture the highest value is in the cohesiveness of the group. The goal is consensus, not only among individuals, but consensus in "your heart and mind." He says that the word *group*, from the Asian (Chinese) perspective, has two meanings and includes two components—king and sheep. To be a group, there must be a leader and followers. In this scenario, sheep are viewed as conformist animals or followers. Therefore, to respond to patients from this group, providers must seek and receive consensus or approval from local leaders and the local community residents themselves. It is a community decision within the hierarchy of the group. Providers will have to reach out to this group by understanding that a consensus or group discussion will determine the individual decisions concerning oral health care.

In European culture, according to Nichols, pedagogically the individual parts comprise the whole. Things are presented in a linear and sequential pattern—A is followed by B, B is followed by C, C is followed by D, etc. As long as a linear and sequential pattern is used, the parts will equal the whole. For some people, the individual parts do not make the whole. The data or correct information may be provided, but this linear sequential thinking may not be employed; thus a different conclusion may be reached. Medicine is practiced in a linear and sequential form (ie, taking pills in a specific time sequence). There is often noncompliance by some non-Eurocentric groups, because of different cultural or ethnic norms. For example, if the highest value is the relationship, symbolic imagery and rhythm are used. Rhythm means function. If the heart is out of rhythm, it is not

functioning properly, thus taking medicine will not solve the problem.

Disease is viewed as a dysfunction or being out of rhythm. So action or behavior is a sign used to determine disease state. In many non-European cultures, differing from European culture, one looks for rhythms or how an individual is acting. These varying cultural perspectives must be understood if health is to be improved, and if health care is to be effectively delivered. Linear and sequential thinking requires a different set of learning and teaching tools than does holistic thinking. Not good or bad, just different. These different perspectives only become value-laden when they are misunderstood.

Social, behavioral, cultural, and economic factors provide the context for improving oral and systemic health. Matters of discrimination, prejudice, sexism, and racism based on differing worldviews, cultural backgrounds, and experiences will increase as the nation becomes more diverse. If obtaining and maintaining oral and systemic health in the United States are expected, a more holistic public health perspective must be strongly considered. More importantly, the commitment to addressing issues that challenge long-held beliefs, outdated traditions, and systems barriers must be addressed. Oral and systemic health for all are both possible and expected if the United States intends to ensure, among all who live in the country and abroad, a healthy world for the next generation.

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# Nutrition: Impact on Oral and Systemic Health

**Abstract:** Good dietary practices and optimal nutritional status promote growth and tissue development, as well as feature prominently in the prevention of diseases. Malnutrition (particularly protein-energy malnutrition, which invariably involves concurrent deficiencies of the antioxidant micronutrients) promotes salivary gland hypofunction, impaired immunity, and an early shift in the oral microbial ecology toward a preponderance of anaerobic organisms. The immune suppression, which includes impaired cytokine function as well as diminished acute-phase response to infections, impacts negatively on the natural history of inflammatory periodontal diseases. The pathogenesis of oral cancer is influenced by deficiencies of antioxidant nutrients, and there is evidence for diminished DNA methylation, disruption of DNA integrity, and increased DNA damage in folate deficiency.

The interaction of genetics and the environment determines phenotype, development of the individual, and constitutes the foundation for all health and disease.<sup>1</sup> Worldwide, more than 200 million people live in poverty; as many as one third of these individuals are extremely poor.<sup>2</sup> These people generally live in poor sanitary conditions, are invariably malnourished, and suffer from poor health as well as exposure to multiple infections and diseases. Socioeconomic status is a key determinant of health.

In the United States, the burden of diseases, including oral and craniofacial diseases, is borne predominantly by the less privileged racial/ethnic minorities, and this is attributed in part to ignorance and economic deprivation. For example, African Americans, compared with whites who are generally more affluent and better educated, have a significantly higher oral cancer rate and a much poorer 5-year survival rate. Nutrition, along with other aspects of the physical and cultural environments, exerts an important influence on each individual's health status.<sup>1</sup> The term *bionutrition* emphasizes the important interaction between diet, nutrient use, genetics, and the environment, and also underscores the roles of nutrients and other nonnutrient components of foods in health maintenance and disease prevention.<sup>3</sup>

Nutrition is often defined as the sum of the processes by which an individual ingests and uses foods.<sup>3</sup> For maintenance of optimal health, a well-balanced diet consisting of a complex

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mixture of macronutrients (carbohydrates, lipids, and proteins used primarily for energy supply) and micronutrients (vitamins and minerals) is required.<sup>4-6</sup> Also present in foods are unique organic phytochemicals that are linked to promotion of good health, although they are

## Learning Objectives:

After reading this article, the reader should be able to:

- describe possible effects of malnutrition on the endocrine and immune systems.
- discuss the interrelationships between malnutrition, infections, and immunity, as well as their relevance to the oral microbial ecology and the natural history of periodontal diseases.
- demonstrate the concept of gene–nutrient interactions and the potential relevance of these to the pathogenesis of oral cancer.
- discuss how cellular depletion of essential nutrients can result from alcohol and tobacco abuse.



not strict dietary requirements.<sup>5</sup> This article examines the relevance of diet and nutrition to human health, particularly oral health.

### Nutritional Status and Malnutrition

The term *nutritional status* is defined as the condition of health as influenced by the cellular use of nutrients.<sup>7</sup> This is a complex definition, because health status itself modifies the use of nutrients. It is clear that malnutrition is not simply synonymous with dietary deficiencies and excesses. It is rather a generic term for the pathophysiological consequences of the ingestion of inadequate, excessive, or unbalanced amounts of nutrients (primary malnutrition), or the impaired use of ingested nutrients (secondary malnutrition).

The distinction between the two types of malnutrition is often blurred. In the impoverished communities of developing tropical countries, malnutrition is a nonspecific diagnosis reflecting the final outcome of complex interactions between dietary inadequacies, nutrient imbalance, food-borne mycotoxins, and various endemic communicable and parasitic diseases. It is well documented that in these countries, diarrheal diseases, chronic blood loss from hookworm infestation, and the repeated paroxysm of malarial fever can elicit profound deleterious effects on the nutritional status of the individual.<sup>3,7</sup>

### General Effects of Malnutrition

In malnourished humans, concurrent deficiencies of several nutrients are usually encountered. This is best exemplified in the syndrome of protein-energy malnutrition (PEM), a widespread public health problem of children in socioeconomically deprived communities, and fast becoming a serious problem among the rapidly growing elderly population in developed countries.<sup>8</sup> PEM is a mosaic of alterations not only in protein and energy nutriture but also in the balance of essential vitamins and minerals as well as the concurrent effects of infections. Dietary constituents can hinder or promote the development of several chronic diseases, including diabetes, cardiovascular pathologies, cancer, neurological diseases, and inflammatory diseases, among others.<sup>9</sup> PEM often elicits alterations in intermediary metabolism, tissue function, body composition, and immunity.<sup>9,10</sup>

### Nutrition, Growth, and Development

Worldwide, the single most common cause of growth retardation is poverty-related malnutrition.<sup>10,11</sup> An individual's genetic potential for somatic growth and maturation is affected by several environmental factors, and it is known that size at birth is more dependent on maternal nutrition and health, and intrauterine and placental factors, than on the genetic blueprint.<sup>12</sup> Despite having a genetic basis, the ultimate skeletal size is influenced by environmental stimuli such as nutrition and exercise. PEM is known to exert a significant negative effect on the rate and timing of skeletal growth.<sup>13</sup> In ascorbate deficiency, the organic matrix of the bone may be deficient but well mineralized, while in vitamin D deficiency, cartilage proliferation and osteoid deposition may proceed normally but mineralization is impaired. Even the developing brain is subject to structural and metabolic distortions if severe malnutrition occurs during the "critical/vulnerable" periods of brain maturation.<sup>14</sup>

### Gene–Nutrient Interactions and Human Cancers

Cancer is considered a multistep process involving expression of aberrant genes and subject to influence by diet/nutrition through hormonal, paracrine, autocrine, immunological, and metabolic mechanisms that modulate detoxification of carcinogens, cellular proliferation, differentiation, and apoptosis.<sup>3,15</sup> Established dietary causes of cancer include obesity, which is related to high energy intake; aflatoxin ingestion; alcohol abuse; salted fish; and folate deficiency, among others.<sup>3,16,17</sup> For example, folate deficiency, by reducing intracellular S-adenosylmethionine (SAM), can alter cytosine methylation in DNA, leading to inappropriate activation of proto-oncogenes and induction of malignant transformation.<sup>17</sup> Folate is essential for de novo synthesis of purines and thymidine, and, therefore, its deficiency can influence DNA integrity and stability.<sup>16,17</sup>

Nuclear transcription factor kappa B (NF- $\kappa$ B) and activator protein 1, a multisubunit nuclear transcription factor, are implicated in expression of a variety of genes in response to oxidants or changes in cellular redox status, and several antioxidant nutrients (beta ( $\beta$ )-carotene, ascorbate, retinoids,  $\gamma$ -glutamyl-cysteinyl-



glycine, zinc, etc) play a key role in neutralizing the oxidants.<sup>3,17,18</sup> Fruits and vegetables contain large amounts of antioxidant nutrients. Retinoids and carotenoids not only suppress progression of initial cellular events, but may also upregulate gap junctional intercellular communication through increased expression of the connexon 43 gene.<sup>16</sup> Other nutrients suggested to be protective against cancer include vitamin D, calcium, vitamin E, and selenium.<sup>3,16</sup> Diet can also be a major source of cancer inhibitors such as isoflavones, indoles, and terpenoids, among others.<sup>18</sup>

### ***Malnutrition and the Endocrine System***

The neuroendocrine system responds to PEM with increased production/secretion of corticotrophin-releasing factor; adrenocorticotrophic hormone; reverse triiodothyronine; growth hormone; cortisol; and norepinephrine, with decreased secretion of somatomedin-C; luteinizing hormone; follicle-stimulating hormone; insulin; estrogen; and androgen, among others.<sup>15,19</sup> Elevated serum glucocorticoid is considered a major determinant of macrophage dysfunction in PEM.<sup>3,19</sup> Increased release of the glucocorticoids and catecholamines in malnutrition can suppress Th1 function and cause a shift toward a Th2 cytokine pattern, a change that increases susceptibility of the host to infectious pathogens requiring a cell-mediated immune response.<sup>15,19</sup> Hypercortisolism suppresses immunological and inflammatory responses; wound healing; bone matrix formation; collagen synthesis; and mitotic activity of epithelial tissues.<sup>19</sup> Decreased insulin production in malnutrition impairs cellular uptake of ascorbate among other problems.

### ***Malnutrition and Immune System Suppression***

Poor diet and malnutrition impair several parameters of the host's specific and nonspecific defense systems, resulting in increased susceptibility to infections, and the latter in turn intensifies the severity of malnutrition.<sup>20,21</sup> The multifaceted impact of malnutrition on immune function includes abnormalities of the cell-mediated and humoral systems; prominent depression in delayed cutaneous hypersensitivity responses to recall and new antigens; decreased natural killer cell lytic activity in blood mononuclear cells; and marked reduction

in the number of helper CD4+ cells, with less prominent alterations in the number of suppressor T-cells, resulting in a prominently reduced helper/suppressor T-cell ratio. Indeed, what is now clear is that the immunological dysfunctions in severely malnourished African children who are serologically negative for human immunodeficiency virus infection are very similar to those seen in individuals who are seropositive for the infection.<sup>15,20,21</sup> Acute-phase response to infections, which plays a central role in promoting tissue healing, is impaired in the malnourished child,<sup>15,19</sup> and so are the production and functioning of the cytokines.<sup>19,22</sup> Cytokines, a diverse group of polypeptides produced in response to inflammatory stimuli, stimulate/modify immune function and/or initiate profound changes in energy, protein, and micronutrient metabolism.<sup>22</sup>

Malnutrition, especially PEM, not only reduces the quantity of mucus maintained on epithelial surfaces, but also alters the chemical nature of lectins within the mucus.<sup>23</sup> PEM also alters the expression of membrane glycoprotein receptors, which may explain the increased bacterial adherence to respiratory and buccal epithelial cells observed in the disease.<sup>20</sup> Figure 1 summarizes the complex interactions of nutritional status, immune function, and infections. More than three decades ago, Scrimshaw and colleagues<sup>24</sup> published a trailblazing monograph explaining why the malnourished are so vulnerable to various communicable diseases, particularly viral infections. More ominous are relatively recent findings that suggest that malnutrition not only impairs the host's defenses, but may also alter the genotype of the pathogen, and thus, increase its virulence.<sup>25</sup>

### ***Nutrition and Oral Health***

Several studies have noted defective dental development and orofacial skeletal abnormalities in the malnourished.<sup>4,26,27</sup> Hypoplasias of the enamel are linked to periods of malnutrition and/or illness,<sup>26,27</sup> and can be reduced by multinutrient supplementation of the undernourished before enamel formation. While this report focuses primarily on the relevance of good nutrition to the prevention of oral mucosal lesions, particularly oral cancer and inflammatory periodontal diseases, a detailed report by a Federation

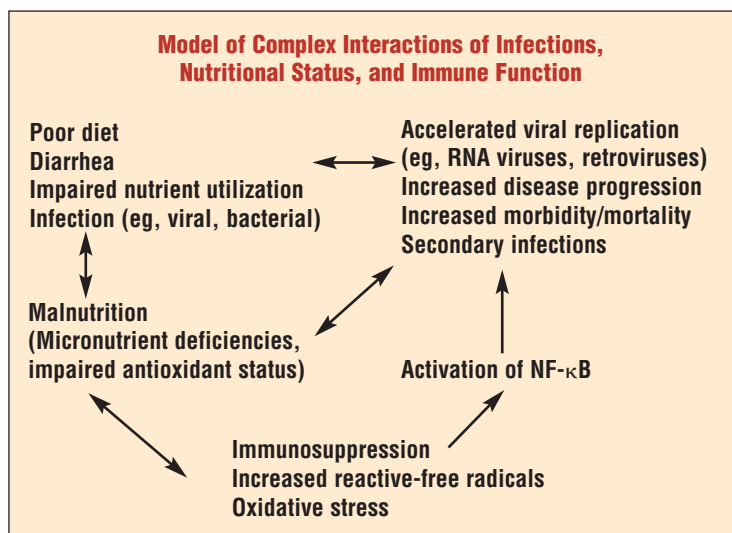
Dentaire Internationale Working Group has examined the effect of diet and nutrition on dental caries.<sup>4</sup>

## Oral Cancer

Oral squamous cell carcinoma (SCC), the main type of oral cancer, exhibits marked ethnic/racial variations in incidence, attributed to differences in specific risk factors, existence of genetic predispositions, and dietary habits and factors.<sup>28</sup> Evidence of defective DNA repair has been shown to underlie some head-and-neck cancers, including SCC.<sup>28</sup> The key risk factors for SCC are tobacco usage (smoking and smokeless) and excessive consumption of alcohol. Both habits pose severe nutritional costs to the host.<sup>3</sup> Alcohol abuse exerts direct toxicity to several organs and elicits malnutrition secondary to dietary deficiencies, maldigestion and malabsorption of nutrients, and impaired hepatic activation or increased degradation of nutrients.<sup>3,16</sup> A review by Enwonwu and Meeks<sup>3</sup> documents deficiencies of selenium, ascorbate, and  $\alpha$ -tocopherol, important scavengers of reactive-free radicals in chronic abusers of alcohol and tobacco. Additionally, low levels of  $\beta$ -carotene (0.14 pmol/10<sup>6</sup> cells) have been reported in exfoliated oral mucosal cells of heavy consumers of alcohol compared with higher levels (2.17 pmol/10<sup>6</sup> cells) in non-drinkers.<sup>29</sup> Alcohol is a folate antagonist, and thus exacerbates deficiency of SAM, which may result in DNA hypomethylation as well as impaired integrity and stability of DNA.<sup>16,17</sup> Conversely, dietary factors and nutritional status influence the metabolism of alcohol.<sup>3</sup>

Generation of hydroxyl radicals is part of the adverse consequences of smoking, and this accounts for increased dietary requirements of vitamin C and other antioxidant micronutrients by smokers.<sup>3</sup> Tobacco chewing, a dietary habit common particularly in Southern Asia, is an important risk factor for oral cancer. The tobacco may be chewed alone or in combination with betel quid constituents such as the areca nut, Piper betle, and slaked lime. Aqueous extracts of betel quid contain genotoxic and cytotoxic substances, as well as others that stimulate cell proliferation.<sup>3</sup>

While malnutrition may play a role in the etiology of SCC, it is often not fully appreciated that the disease intensifies malnutrition in



**Figure 1**—This scheme summarizes the complex interactions among poor dietary intake/malnutrition, infections, and immunity. Impaired nutrient use, for example, can be caused by infections, and both elicit malnutrition. Depletion of the antioxidant nutrient status promotes oxidative stress, which potentiates morbidity and mortality through accelerated disease progression among other factors.

the victim. Oral cancer may seriously limit food intake, and it is believed that complications of starvation/malnutrition, rather than the severity and extent of the cancerous growth, constitute an important cause of death. Tumor-host competition for nutrients and the modes of treatment (chemotherapy, surgery, and/or radiation) are the major causes of malnutrition in cancer patients.<sup>3</sup> Surgical intervention is perhaps the most popular choice of treatment for SCC, and may necessitate removal of segments of the mandible, maxilla, tongue, and other parts of the orofacial structure. Complications may include trismus, as well as difficulties with mastication. Similarly, radiation therapy, through induction of impaired taste perception, diarrhea, and salivary gland hypofunction, will promote malnutrition.

## Malnutrition and Inflammatory Periodontal Diseases

Oral mucosal disruptions, expressed as glossitis, cheilosis, and stomatitis, are commonly seen in the malnourished child.<sup>19</sup> These nonspecific signs constitute some evidence that the structural as well as functional integrity of the oral mucosa is dependent on adequate nutritional status, although we do not rule out the contribution of infections and other environmental factors to the causation of these lesions. While malnutrition may not initiate periodontal diseases, there is substan-

tial evidence for frequent occurrence and rapid progression of severe, destructive periodontal disease in malnourished children.<sup>15,30,31</sup> Like the linings of the gastrointestinal and respiratory tracts, the oral mucosa atrophies in the protein-energy deficient child,<sup>15</sup> and there is compromised salivary gland function.<sup>4,15</sup> The latter limits the availability of anti-infective substances in saliva.

The pathogenesis of periodontal disease can be conveniently divided into the stages of oral microbial colonization, invasion, destruction, and healing.<sup>32</sup> Assessment of the relation between malnutrition, immunity, and periodontal diseases is probably best undertaken within the context of these arbitrary stages. This approach recognizes the possibility that nutrient inadequacies may influence the oral microbial ecology, specific factors/systems involved in the progression of periodontal lesions, and the reparative process.



**W**orldwide, the single most common cause of growth retardation is poverty-related malnutrition.

The stages of colonization of the oral cavity by microorganisms can be placed into major stages. Early colonization of the oral cavity (0 to 6 months of age) is primarily by aerobic/facultative species, including *Streptococcus*, *Actinomyces*, and *Staphylococcus*. Before eruption of teeth, some anaerobic bacterial species can be isolated, including members of the *Veillonella*, *Fusobacterium*, and the nonpigmented *Prevotella* species.<sup>33</sup> Eruption of primary teeth (1 to 3 years) contributes to further bacterial colonization by providing econiches and sites of attachment for oral microorganisms. Here members of the *Capnocytophaga*, *Actinomyces*, and mutans streptococcal species are observed as additions to the aerobic/facultative members, and *Leptotrichia*, *Selenomonas*, *Prevotella*, and *Peptostreptococcus* species are added to the anaerobic flora.

At puberty, hormonal changes may influence the presence of black-pigmented bacteria, in particular *Prevotella intermedia*. The adult flora of nondiseased oral cavities,

*Wolinella* and *Bacteroides forsythus*, appear. The microbial composition of the periodontal flora of children differs from that of adults and the anaerobes that are present increase as periodontal diseases progress. Organisms associated with periodontal diseases in adults and not usually observed in large numbers in children include *P intermedia*, *Porphyromonas gingivalis*, *B forsythus*, *Fusobacterium nucleatum*, *Peptostreptococcus micros*, and in localized juvenile periodontitis, *Actinobacillus actinomycetemcomitans*. Of these, the black-pigmented bacteria, including *P intermedia*, can be used as monitors of early disease activity.

Sawyer et al<sup>34</sup> have carried out studies of oral microflora in well-nourished and malnourished (with PEM) rural Nigerian children. Although their published report provides insufficient details regarding the sampling and microbial identification techniques employed in the study, the data suggest a significantly clear increase in the number and proportion of gram-negative anaerobes in the oral cavities of malnourished children compared with their adequately nourished counterparts. The anaerobes most frequently isolated from the malnourished children in that study were *P gingivalis*, *P intermedia*, *Actinomyces israeli*, *Fusobacterium* spp., and the spirochetes. Our recent studies<sup>35</sup> confirmed increased recovery of *P intermedia* from malnourished Nigerian children compared with samples taken from healthy controls, and the increase was more pronounced in the samples from malnourished children where *Fusobacterium necrophorum* was also isolated. Reasons for the differential overgrowth of potential periodontal pathogens in children with PEM have been reviewed.<sup>15,19,35</sup> Among other factors, increased oral burden of free glucocorticoids in the malnourished<sup>15</sup> not only contributes to the shift in oral microbial flora, but may play a role in the pathogenesis of severe periodontitis seen in the children.<sup>36</sup> Indeed, experimental animal studies indicate that treatment with RU-486, a glucocorticoid receptor antagonist, reduces periodontitis.<sup>37</sup>

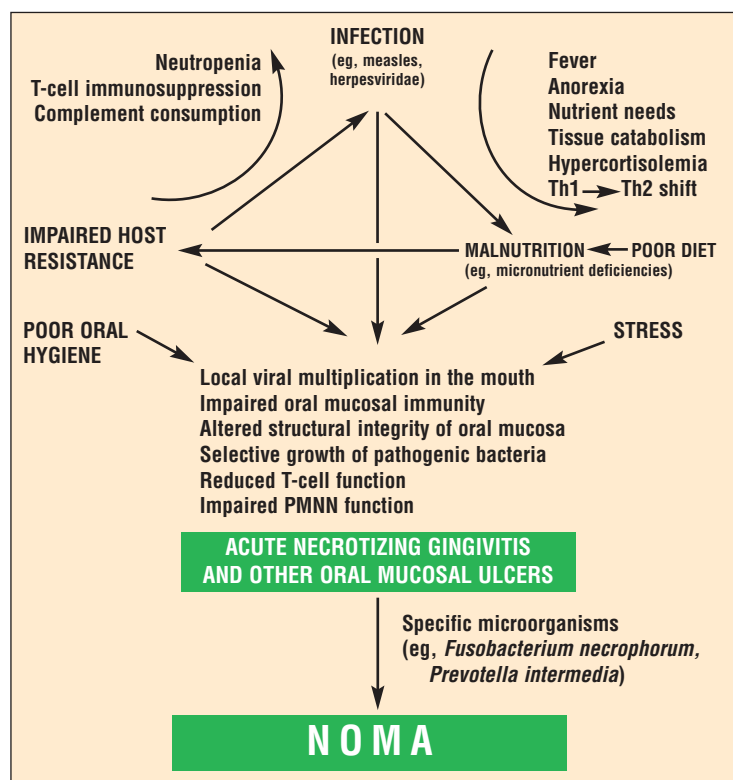
With regard to microbial invasion, tissue destruction, and healing in periodontal disease, the important role of good nutrition and immune competence in their control has been extensively reviewed.<sup>15,19</sup> Phagocytes, particularly the polymorphonuclear neutrophils

(PMNN), constitute the early cellular hallmark of inflammatory response to periodontal pathogens. In individuals with either intrinsic or acquired dysfunction of the PMNN, periodontal tissues are broken down very rapidly, suggesting that the primary role of the PMNN in the human periodontium is protective.<sup>32</sup> Secondary neutropenia is a common finding in the malnourished, and may be due in part to infections.<sup>15</sup> The PMNN shows not only antibacterial effects but also has the potential to damage the periodontium through release of reactive-free radicals and lysosomal enzymes.<sup>19</sup> The balance between the interactions of reactive-free radicals, proteinases, and antiproteinases determines the ability of phagocytic activity to damage the periodontium.<sup>10,19</sup> The inflammatory process, a main feature of periodontal disease, involves complex interactions between cells and potent soluble mediators known as the cytokines. The cytokines enhance recruitment, proliferation, activation, and differentiation of white blood cells, fibroblasts, and osteoblasts, as well as mediating a wide range of metabolic changes, including acute-phase response, which plays a key role in promoting healing of injured tissue. PEM significantly impairs synthesis and functions of the cytokines, as well as the acute-phase response.<sup>19,22</sup> Periodontal disease is episodic, with periods of healing alternating with periods of active tissue destruction.<sup>32</sup> Synthesis of interferon-gamma, transforming growth factor-beta, interleukin-1 receptor antagonist, interleukin-4, and the acute-phase proteins, all factors involved in healing, are compromised in malnutrition.<sup>10,15,22</sup>

Perhaps no orofacial disease exemplifies the complex interactions between malnutrition, infections, and immunity as lucidly as noma, otherwise known as cancrum oris (Figure 2). This gangrenous lesion is now found almost exclusively in malnourished children in third-world countries. Details of its pathogenesis are subjects of recent extensive reports.<sup>30,31,35</sup> Important periods in the lesion development have been suggested. The first is a multifactorial staging period resulting in impaired immune status as a consequence of malnutrition and viral and/or other parasitic infections. During the second phase, oral ulcers (eg, acute necrotizing gingivitis) can result from PEM and viral infections (measles, herpes, etc), and may con-



**Figure 2**—Noma (cancrum oris) in the acute stage in an African child between the ages of 3 and 4, showing a profound destruction of the orofacial structures.



**Figure 3**—Schematic representation of the proposed pathogenesis of noma in malnourished, deprived children.

stitute the portal of entry for the trigger organisms.<sup>31,35</sup> In the final phase, a consortium of microorganisms, including *F necrophorum* and *P intermedia* particularly, infects the ulcers<sup>30,31</sup> (Figure 3).

## Conclusion

Complex interactions exist between nutritional status, infections, and immunity. The most common types of periodontal disease are inflammatory in nature and are elicited by



specific oral pathogens. Inadequate cellular contents of antioxidant nutrients, defective acute-phase response, and compromised innate and acquired immunity all play a role in the severe periodontal disease often encountered in malnourished African children. Therefore, nutrient deficiencies and imbalance, although not initiating periodontal diseases, have the potential to influence the biological gradient and natural history of the lesions. Good nutrition is a useful therapeutic adjunct for delaying and/or mitigating severe inflammatory periodontal destruction, while at the same time promoting healing. Additionally, recent data indicate extensive gene–nutrient interactions, thus raising the strong possibility that diet and nutrition play a key role in the prevention of various cancers, including oral SCC.

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# Impact Factors on Development of Cirrhosis and Subsequent Hepatocellular Carcinoma

**Abstract:** Hepatocellular carcinoma (HCC), on the rise in many countries, is of multifactorial etiology. Its etiological associations differ between populations at high and low risk. Africans and Chinese have the highest incidence of HCC, but other affected groups include African Americans, Japanese, and Native Americans. Chronic infections by hepatitis B and hepatitis C viruses are major risk factors worldwide, although mechanisms through which the infections cause liver cancer are yet to be explained. Other documented risk factors have been postulated and include dietary exposure, cigarette smoking, alcohol consumption, diabetes, oral infection, and oral contraceptive use. In addition, many naturally occurring and synthetic chemicals to which humans are exposed via accidental contamination of food or water are shown to induce liver cancer in experimental animals. Consequently, assessment of possible human liver cancer risk associated with such exposures is complex. Early diagnosis and transplantation are the best treatments presently, although transplantation is not widely available due to donor shortage. Every effort should be directed toward the prevention of HCC, through the treatment and prevention of hepatitis and oral infections, prevention of chronic hepatitis progressing to cirrhosis, and prevention of the cirrhotic liver from developing HCC through chemopreventive modalities. However, at present, very few such studies exist.

## The Cirrhosis–Hepatocellular Carcinoma Link

Hepatocellular carcinoma (HCC) is one of the most common human tumors and its incidence has increased over recent decades in Western countries.<sup>1</sup> However, regardless of the etiology HCC generally develops as a result of the development of liver cirrhosis. Carcinogenesis occurs in three stages: initiation, progression, and promotion, and may be affected not only through exposure to exogenous stimuli but also by genetic and epigenetic influences derived from endogenous factors. In particular, the role of chronic infection with the hepatitis B (HBV) and hepatitis C (HCV) viruses in the etiology of liver cancer is well established. However, other documented risk factors include dietary exposure, cigarette smoking, alcohol consumption, and oral contraceptives. Interactions between some risk factors have been postulated, and are the subject of active research. In this regard, new molecular techniques and identification of biological markers will help in the development of therapeutic interventions. In this article, the current understanding of the factors involved in the development of cirrhosis and subsequent HCC are reviewed.

There is a strong association between

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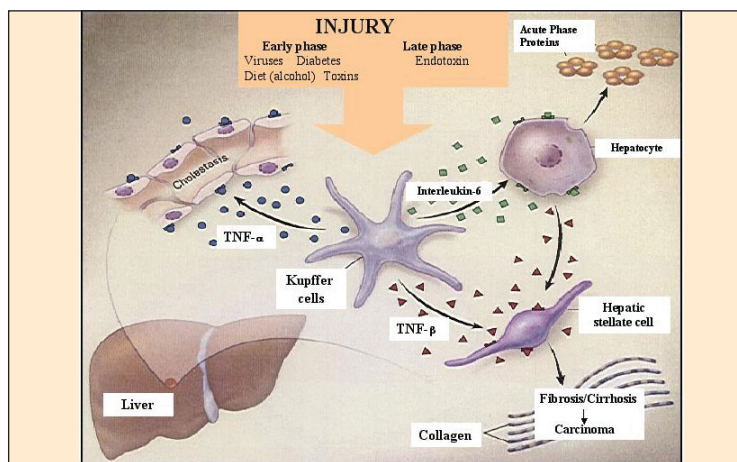
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pathological conditions, such as accumulation of oxidative damage, that cause chronic inflammation, hepatic dysfunction such as fibrosis, cirrhosis, and subsequent HCC.<sup>2</sup> Chronic inflammation usually leads to liver

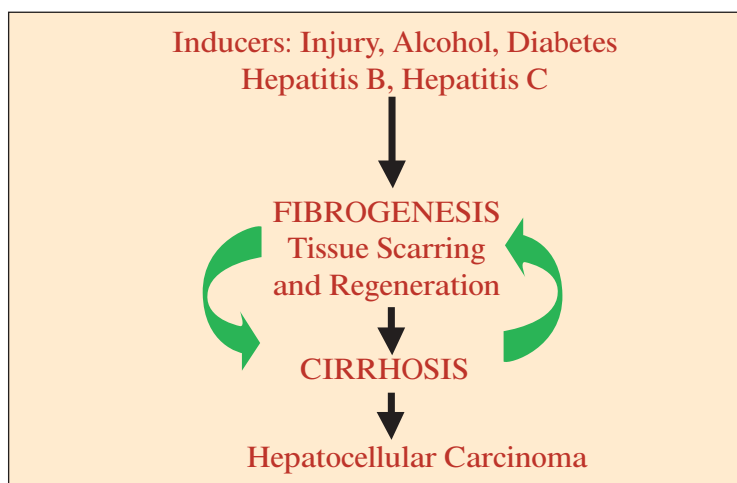
## Learning Objectives:

After reading this article, the reader should be able to:

- discuss the incidence and etiology of hepatocellular carcinoma (HCC).
- identify the risk factors for developing cirrhosis and HCC.
- describe therapeutic modalities successful in treating cirrhotic patients.
- discern and eliminate the disparities among affected patient groups.



**Figure 1**—Liver cell involvement and inflammatory impact on development of carcinoma. In response to an appropriate stimuli in the major cell types (Kupffer, hepatocyte, and hepatic stellate cell) will release specific proinflammatory mediators (TNF- $\alpha$ , IL-6, TNF- $\beta$ ) to initiate an acute inflammatory response, which is a tightly controlled process. In states of chronic inflammation, as is the case of fibrosis/cirrhosis, an imbalance between mediators can result in cellular damage, and this damage can be manifested by the development of liver foci and ultimate carcinoma. Clinical features of chronic liver disease that are mediated by cytokines include cholestasis, fibrosis/cirrhosis, cachexia, and acute-phase protein synthesis. Adapted from Tilg H, Diehl AM: Cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med* 343(20):1467-1476, 2000.



**Figure 2**—Development of hepatocellular carcinoma. Inducers such as alcohol consumption, diabetes, and hepatitis infection can promote hepatic injury, resulting in a cyclic process involving tissue scarring and subsequent tissue regeneration or remodeling, termed fibrogenesis. Eventually fibrosis will progress to cirrhosis with subsequent development of hepatocellular carcinoma. Each of these events is dependent on the type and length of stimulus, cell type, and signal transduction and inflammatory mediators.

cell loss, accompanied by cellular hyperplasia with regeneration of hepatocytes in an attempt to restore liver function (Figure 1).<sup>3</sup> During liver inflammation, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated by Kupffer cells and hepatocytes, as well as by activated leukocytes and neutrophils.<sup>2</sup> ROS and RNS may interact with and modify cellular protein, lipid, and DNA, which can result in altered target-cell

function. Acute oxidative injury may produce selective cell death as well as a compensatory increase in cell proliferation. This oxidative stimuli may promote the formation of newly initiated preneoplastic cells and/or enhance the selective clonal expansion of latent initiated preneoplastic cells. Similarly, sublethal acute oxidative injury may produce unrepaired DNA damage and result in the formation of new mutations and potentially new initiated cells. The continuous action of damaging agents can lead to massive liver fibrosis, which is clinically manifested as cirrhosis.

Liver fibrosis or cirrhosis is characterized by the activation of hepatic stellate cells (Figures 1 and 2), which are involved in the synthesis of matrix proteins and regulating matrix degradation.<sup>4</sup> In the acute phases of liver injury, and as liver fibrosis progresses, there is increased expression of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs).<sup>4</sup> These and other related family members are involved in regulating degradation of both normal and fibrotic liver cell matrix. However, in cirrhosis, liver regeneration is impaired, leading to the irreversible end result of chronic liver disease, which may be the result, in part, of altered gene expression.<sup>5</sup> Hence, chronic inflammation, alteration in liver matrix, and long-term exposure of hepatocytes to either ROS or RNS, combined with liver cell injury-induced hyperplasia, are important factors in degenerative liver diseases, including cirrhosis, and in the induction of HCC.

In low-risk populations, cirrhosis is the most important causal association of HCC. Cirrhosis is often the result of alcohol abuse, but the HCC tumor may complicate all etiological forms of this disease.<sup>6</sup> Hepatocellular cancer is multifactorial in origin, and the pattern of its etiological associations differs between populations at high and low risk. In African and Chinese individuals, who have the highest incidence of HCC, HBV is the most important causal association. Other affected groups include African Americans, Japanese, and Native Americans.<sup>7</sup> African Americans in particular are at increased risk and are more vulnerable to developing HCC because of the poor response to current therapy for chronic hepatitis C.<sup>8</sup> In addition, other potential risk factors for development of cirrhosis and subsequent HCC include age at diagnosis (associat-

ed increase with age), gender (men are at greater risk), place of residence (urban vs rural), sanitary facilities (nonflush toilets in some rural areas), and socioeconomic status and education level. Significant variations exist in the incidence of HCC among different ethnic groups living in the same area and among migrants of the same ethnic groups living in different areas. Furthermore, the age curves of HCC are significantly different in various countries, suggesting variability in exposure to risk factors. The main risk factors for the development of HCC are viral infections (HBV and HCV), alcohol use, and the intake of mycotoxins in some areas of the world.<sup>9,10</sup> In addition to these risk factors, genetic disorders such as hemochromatosis or  $\alpha_1$ -antitrypsin deficiency play a role.<sup>9</sup>

The biological characteristics of HCC vary appreciably in different parts of the world, but especially between regions with either very high or very low incidence of the tumor.<sup>11</sup> Malignant transformation of hepatocytes may occur as a consequence of various etiologies.<sup>9</sup> Although it remains unclear how and in what sequence these factors interact at the molecular level, HCC development includes activation of cellular oncogenes, inactivation of tumor suppressor genes, overexpression of certain growth factors, and possibly telomerase activation. DNA mismatch repair defects may also contribute to the development of HCC.<sup>9</sup> Thus, cirrhosis is considered an efficient promoter of neoplastic transformation because prolonged cell damage is critical in cancer development; however, the molecular mechanism of HCC is largely unknown.

## Risk Factors

### Diet and Lifestyle

Epidemiological data indicate that a large fraction of human disease and cancer are associated with lifestyle and diet (Table 1).<sup>12</sup> In particular, two thirds of cancer cases are associated with 2 lifestyle practices: 35% with diet, and 30% with tobacco use.<sup>13</sup> Because no human diet can be totally free of carcinogens or mutagens, it is necessary to consider the risks associated with environmental and occupational carcinogens<sup>14</sup> and the role of anticarcinogens<sup>15</sup> as they relate to degenerative disease and to liver cancer in particular.

**Table 1—Cirrhosis: Associated Risk Factors**

#### Nonhepatic

Acetaminophen, celiac sprue, heterocyclic amines, immunosuppression and posttransplantation, inherited or acquired muscle disorders, strenuous exercise, and total parenteral nutrition (end-stage liver disease)

#### Hepatic

Nonalcoholic and hepatosteatorosis (fat accumulation), hereditary hemochromatosis, telangiectasia, Wilson's disease: biliary copper excretion and  $\alpha_1$ -antitrypsin deficiency

#### Occupational

Industry (ie, pharmaceutical, plastics, chemicals), health care workers (ie, needle sticks)

#### Chronic Infection

Autoimmune hepatitis, HBV, HCV, schistosoma mansoni and salmonella, transfusion-transmissible virus, gingivitis, and periodontitis

#### Lifestyle (Development of AIDS/HIV)

Homosexual relationships, drug abuse

## Aflatoxin

Aflatoxin ingestion has an etiologic role in high-incidence regions, probably as a genotoxic or epigenetic promoter to HBV-initiated carcinogenesis.<sup>16</sup> The maximal authorized limits of aflatoxin contents in human and animal foodstuffs are very low (few micrograms/kilograms or fractions of micrograms/kilograms).<sup>17</sup> The most important mycotoxins are aflatoxins, which are hepatotoxic and hepatocarcinogenic, and ochratoxins, which are nephrotoxic and nephrocarcinogenic.<sup>17</sup> Mycotoxins are toxic products secreted by microscopic fungi. Humans are exposed to these carcinogens via contaminated products of vegetal origin consumed by humans and cattle, which is therefore a secondary exposure to humans, as well as accidental contamination of food or water.<sup>18</sup> There is a synergistic effect between high aflatoxin B1 (AFB1) exposure and HBV infection in promoting HCC development. AFB1 can induce a p53 gene mutation (p53mt249)—which is critical during the formation of HCC after HBV infection, markedly increase insulinlike growth factor II (IgF-II) transcription, as well as modulate the formation of transcriptional

complexes through enhanced DNA-protein (Sp1 or TBP) and protein-protein (Sp1 and TBP) interactions.<sup>19</sup> Furthermore, experimental AFB1 can induce both nuclear factor-kappa B (NF-κB) and activated protein-1 (AP-1) transcription factors. These studies suggest that certain carcinogen-induced transcription factors may influence viral carcinogenesis to initiate development of HCCs.

## Alcohol

Alcohol or ethanol, which are used interchangeably, remain the most common cause of cirrhosis in the Western world and are associated with increased prevalence of cancer, hypertension, cirrhosis of the liver, and symptomatic neuropathy.<sup>20</sup> Risk factors for severe liver damage in alcoholics or in habitual alcohol consumers include polymorphisms in alcohol-metabolizing enzymes,<sup>21</sup> obesity,<sup>22</sup> hepatotoxin exposure (ie, acetaminophen),<sup>22</sup> and hepatitis infection.<sup>23</sup> Long-term consumption of alcohol can result in numerous liver abnormalities including fatty liver (steatosis), steatohepatitis, cirrhosis, and HCC.<sup>22</sup> Interestingly, only approximately 15% to 20% of consistently heavy drinkers with hepatic steatosis develop clinically important liver disease,<sup>22</sup> which suggests that other host and/or environmental factors may play a role in determining the evolution of alcohol-related liver disease.



**H**epatocellular carcinoma is one of the most common human tumors and its incidence has increased over recent decades in Western countries.

Recent findings suggest that the progression of alcoholic fibrosis may be explained by alteration of the normal hepatic matrix that may be sufficient to promote fibrogenesis and may act as a fixed stimulus that perpetuates fibrogenesis in the absence of ongoing inflammation.<sup>22</sup> Common features of chronic alcoholic liver disease are progressive hypoalbuminemia and a spectrum of liver fibrosis.<sup>24</sup> However, the molecular mechanisms that account for these effects are still controversial.

Studies have shown that ethanol con-

sumption may result in increased oxidative stress with formation of lipid peroxides and free radicals. The importance of radicals in cancer initiation and promotion is presently of great interest. The role of lipid peroxides and free radicals in alcohol-related disease and cancer remains unresolved. The susceptibility of a given tissue to peroxidation is, however, a function of the overall balance between pro-oxidants and antioxidant defense systems.<sup>25</sup> The latter involves both intracellular and extracellular protective factors where nutrients play an important role. Impaired nutritional status of nutrients such as choline, vitamins, and trace elements have been reported in alcoholics.<sup>20,22</sup> Reduced levels of vitamin E have been found in the serum of alcoholics with and without liver disease and in liver biopsies from alcoholics with cirrhosis. Reduced antioxidant capacity has been found in several tissues and may promote the generation of free radicals and lipid peroxides, which may damage cells directly, induce inflammation, and accelerate collagen synthesis,<sup>20,22</sup> with subsequent progress to disease.<sup>22</sup> In contrast, when tumors are experimentally depleted of antioxidants they are more susceptible to cell death.<sup>26</sup> Although paradoxical, further support is provided for how manipulations of the microenvironment are achieved by the tumor for its survival at both early and late phases of carcinogenesis.

## Homocysteine

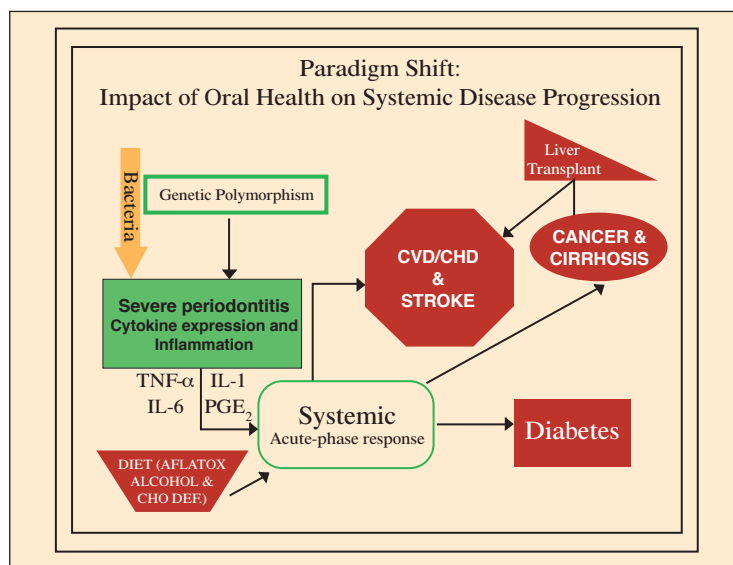
Elevated plasma levels of homocysteine have been shown to interfere with normal cell function in a variety of tissues and organs, such as the vascular wall and the liver.<sup>27</sup> Consequently, the elevated plasma levels of this amino acid found in different pathological or nutritional circumstances may cooperate with other agents, such as ethanol, in the onset of liver fibrosis. Studies show that homocysteine is able to induce the expression and synthesis of the tissue inhibitor of metalloproteinases-1 (TIMP-1) in a variety of cell types ranging from vascular smooth muscle cells to hepatocytes, HepG2 cells, and hepatic stellate cells.<sup>28</sup> In addition, TIMP-1 induction by homocysteine appears to be mediated by its thiol group. In the stellate cell type, homocysteine also stimulated alpha 1(I) procollagen mRNA expression. Additionally,



homocysteine is able to promote AP-1 transcription-factor binding activity, which is critical for TIMP-1 induction. These findings indicate that homocysteine may alter liver extracellular matrix homeostasis, making the liver another physiological target for pathogenesis. However, the molecular mechanisms behind homocysteine effects in the liver are not completely understood.

## Obesity

The rising prevalence of obesity is accompanied with metabolic complications that are under the heading of the “metabolic syndrome.”<sup>29</sup> This syndrome is characterized by a plasma lipid disorder (atherogenic dyslipidemia), elevated blood pressure, plasma glucose, and a prothrombotic state. The clinical consequences of the metabolic syndrome are coronary heart disease and stroke, Type 2 diabetes and its complications, fatty liver, cholesterol gallstones and, possibly, some forms of cancer. Furthermore, obesity is considered a risk factor for cirrhosis.<sup>30</sup> In addition, obesity increases the risk of all stages of alcoholic liver disease, probably reflecting the role of steatosis in the pathogenesis of more advanced disease. Similarities exist between the features of obesity-related and alcohol-induced hepatic pathology, which suggest that a common mechanism may be involved in both disease processes. Autopsy studies suggest that cirrhosis is at least six times more prevalent in obese individuals than in the normal population.<sup>31</sup> In addition, data support a role for endotoxin-mediated, obesity-related liver damage. Specifically, patients who underwent jejunoileal bypass surgery to induce weight loss often experience bacterial overgrowth,<sup>32</sup> with a subsequent increase in systemic levels of gut-derived endotoxins. Inherent immunologic dysfunction is an intrinsic aspect not only of the obese phenotype but also of endotoxin-induced hepatic damage. In particular, hepatic macrophages increase release of the proinflammatory cytokines interleukin-18 (IL-18) and interleukin-12 (IL-12), which have an essential role in host defense against infectious diseases.<sup>30</sup> Furthermore, evidence is accumulating that indicates that obesity is the predominant risk factor for “cryptogenic” cirrhosis—end-stage liver damage—that cannot be attributed to either alcohol use, viral infection, or other established causes of liver



**Figure 3**—Paradigm shift: impact of oral health on systemic disease progression. Bacterial infection and genetic predisposition, due to polymorphisms, are shown to promote severe periodontitis. Cytokine release (TNF- $\alpha$ , IL-1, IL-6, PGE<sub>2</sub>) and dietary factors, including alcohol consumption, nutrient deficiency, and aflatoxin contamination, initiate an inflammatory and acute-phase protein cellular response that can result in systemic disease. Oral health has been linked to several systemic diseases including oral cancer, cardiovascular and coronary heart disease, diabetes, and cirrhosis.

disease.<sup>33</sup> Although there is a strong association between obesity and cirrhosis, the mechanisms promoting obesity-related liver injury remain unknown. Thus, a better understanding of the molecular basis of these relationships is needed to suggest new targets for prevention of hepatic disease and treatment of the associated complications of obesity.

## Systemic Factors Dental Factors

Recent studies have revived the focal-infection theory that links oral and systemic disease (Figure 3). In this prospective study, moderate- to late-stage periodontitis were consistently associated with risk of disease.<sup>34</sup> Therefore, oral cavity infection has been included as a risk factor for systemic disease and an association has been found between the proinflammatory cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) concentration and key markers of inflammation and infection.<sup>34</sup> Thus, there is the considerable possibility for prevention and treatment of infection at the oral level, which could have an impact on chronic systemic diseases.

Dental infection in a cirrhotic patient has been found to be a source of recurrent sepsis. Bacterial infections are frequent complications in patients with cirrhosis, especially in



alcoholics, and a potential source of infection may be dental foci.<sup>35</sup> The associated oral health impact of cirrhosis on periodontal health includes caries and missing teeth. Oral hygiene, dental care, and periodontal parameters are worse, and the number of teeth requiring treatment is higher in alcoholics with or without cirrhosis than in healthy or nonalcoholic patients with cirrhosis. In addition, alcoholics have a lower total number of teeth than patients without alcohol abuse and healthy controls.<sup>36</sup> Therefore, in alcoholics, these dental disorders appear to be caused primarily by bad oral hygiene and poor dental care. Liver transplant recipients also are affected with very poor hygiene (85%), advanced periodontal disease (45%), chronic gingivitis (12%), and excessive bleeding because of liver dysfunction. Thus, the presence of cirrhosis and liver dysfunction may be predisposing factors for dental and periodontal diseases.<sup>36</sup>



**I**n low-risk populations, cirrhosis is the most important causal association of HCC.

### Diabetes

Epidemiologically, there seems to be a correlation between diabetes mellitus, the most common endocrine disease, and hepatitis C, the leading cause of chronic liver disease in the United States.<sup>37</sup> The liver plays an important role in the pathogenesis of diabetes. Importantly, there are a myriad of situations in which the treatment of the diabetic patient is affected by or causes an effect to the liver. Patients with underlying diabetes can present with abnormal liver chemistries, which can represent findings as benign as hepatic steatosis or as severe as cirrhosis of the liver.<sup>37,38</sup> In addition, the medications used to treat diabetes can be potent hepatotoxins, and several primary liver diseases are associated with increased risk of the development of diabetes. Several studies have suggested that patients with diabetes are at increased risk of developing primary liver cancer and perhaps cancers of the biliary tract.<sup>39</sup> It is known that chronic alcoholics and Type 2 diabetics show hyperlipidemia, characterized by hypertriglyceridemia and, in a minor degree, by hypercholesterolemia.

Although the mechanisms underlying the effect of ethanol and carbohydrates on plasma lipids seem to be different, in diabetic subjects chronic alcohol consumption could produce a more severe hyperlipidemia and therefore accelerate atherosclerotic events.<sup>40</sup> Although the mechanisms involved in the association of diabetes and liver cancer needs to be elucidated, in the management of end-stage liver disease, both cirrhosis and orthotopic liver transplantation promote glucose intolerance and diabetes in a number of patients through various mechanisms, including insulin resistance and impaired insulin secretion.<sup>38</sup> These relationships highlight both the importance of the liver as an endocrine organ and the multisystem aspects of the patient with diabetes mellitus. Additional studies are needed to determine whether patients with insulin-dependent diabetes mellitus (IDDM) and those with non-insulin-dependent diabetes mellitus (NIDDM) differ in their risk for primary liver cancer or whether the type of diabetic treatment affects the risk.

### Viral Infections (HBV/HCV/HIV)

Viral hepatitis is an inflammation of the liver caused by one of at least six distinct viruses. The hepatitis A (HAV) and hepatitis E (HEV) viruses are enterically transmitted viruses that produce acute disease only, whereas HBV, HCV, and hepatitis D virus (HDV), are most efficiently transmitted by infected blood, but also can be transmitted by exposure to other infectious bodily fluids.<sup>41</sup> The role of chronic infection with HBV and HCV in the etiology of liver cancer is well established. The attributable risk estimates for liver cancer for each of these hepatotropic viruses vary among countries, but the combined effects of persistent HBV or HCV infections account for well over 80% of liver cancer cases worldwide.<sup>41</sup>

Most patients infected with HBV and HCV go on to develop chronic hepatitis, with approximately 20% developing liver cirrhosis or HCC after 20 years. HCV is a global health problem, with an estimated 170 million people chronically infected.<sup>42</sup> Approximately 70% of patients who contract HCV develop chronic hepatitis C, with 20% to 50% progressing to cirrhosis and 1% to 2% developing HCC within 10 to 20 years. During chronic HCV, there is insidious and progressive liver damage. In late

stages of chronic HCV, liver fibrogenesis is enhanced as a consequence of infection, which contributes to the fibrosis due to scarring and liver regeneration that subsequently leads to cirrhosis (Figure 1). Accumulating evidence indicates that host cellular immune response is involved in the control of viral replication and may also contribute to hepatocellular damage. In particular, a strong CD4+ proliferative and cytokine response to the HCV nonstructural protein 3 has been correlated with viral clearance.<sup>43</sup> Additional biological features include upregulated immune adhesion molecule expression that reflects active recruitment and priming of T-cells in the liver<sup>44</sup> as evidenced by an active CD8+ cytotoxic T lymphocyte response, and elevated messenger RNA (mRNA) levels of both Fas ligand and perforin-granzyme B pathways.<sup>45</sup> Although the pathogenic mechanisms associated with liver disease in acute hepatitis C are not yet elucidated, understanding the pathogenic and molecular mechanisms involved in disease progression, such as the role of B-cell response and the regulation of hepatic stellate cell activation, will allow the design of better therapeutic strategies against HCV infection.

Infection with human immunodeficiency virus (HIV) may further compromise the liver to more damage. Therefore, to assess the HIV infection impact on chronic hepatitis C, the risk factors for liver fibrosis progression must be taken into account, which include alcohol, sex, age at contamination, and duration of HCV infection. HCV is frequently encountered in HIV-infected patients because of common routes of transmission. Previous studies suggested that HIV infection impairs the natural course of chronic hepatitis C, with a more rapid progression to cirrhosis.<sup>46</sup> During HIV infection, a preexisting liver disease superimposed on chronic alcohol consumption may also exacerbate HIV replication and lymphocytic infiltration in the liver because of the ability of HIV glycoprotein 120 (gp120) to stimulate chemokine production by Kupffer cells and stimulate migration of inflammatory leukocytes in the liver.<sup>47</sup>

### ***Altered Gene Expression***

Many tumor cells express numerous mutations and alterations in gene expression. The load of somatic mutations in cancer-related genes in premalignant tissues may become a use-

ful parameter for risk assessment. For the measurement of such mutations, highly sensitive genotypic mutation systems are required that avoid the selection and clonal expansion of cells on the basis of a mutated phenotype. In addition, studies using the newly developed cDNA microarray technology will be useful to identify genes related to clinical phenotypes from cirrhosis to HCC patient tissues. Furthermore, the identification of carcinogens that are responsible for their induction in humans is of great interest because it may suggest measures for therapeutic intervention and disease prevention.

Point mutations in Ras proto-oncogenes and in the p53 tumor suppressor gene are common in many forms of human cancer. The mutability of codons of p53 has been studied with the mycotoxin AFB1 in human hepatocytes. AFB1 can preferentially induce the transversion of guanosine to thymidine (G to T), generating the same mutation that is found in a large fraction of HCC from regions of the world with AFB1-contaminated food. These results support AFB1 as an etiological factor for HCC. Recent studies have clarified a number of genes that characterize HCC and include transcription factors or tissue-specific expression proteins related to cell differentiation or development. The Fas structure and the expression of Fas and Fas ligand have been the focus of current studies because of their role in apoptosis or programmed cell death.<sup>45</sup> Although many HCCs coexpress both Fas and its cognate ligand and a death receptor, it is unclear why these cells do not undergo spontaneous apoptosis. However, Lee and coworkers<sup>48</sup> have shown that expression of soluble Fas and Fas-associated phosphatase-1, along with loss of Fas expression, contribute to resistance to Fas-mediated cell death and may have a role in the pathogenesis of human HCC. Monoallelic loss of the Fas gene has been observed as determined by loss of heterozygosity with intragenic polymorphisms. In addition, these studies can be useful for further clarification of the mechanisms of hepatocarcinogenesis, as well as the diagnosis and the potential treatment of HCC.

Epidemiologically, primary hepatocellular carcinoma (PHC) is associated with chronic HBV infection and other environmental agents and has been thought to be caused by the activation or introduction of an oncogene. Moreover, evidence is accumulating that sug-

**Table 2—Cirrhosis and Hepatocellular Carcinoma-Associated Pathology**

**Phase II enzymes**

Cytochrome P450 2E1

**Autoantibodies**

**Elevated liver enzymes**

Alanine and aspartate aminotransferase, alkaline phosphatase, gamma glutamate transferase

**Hepatitis B antigen (HBsAg) positive**

**Proinflammatory cytokine and growth factors**

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )  
Interleukin family: IL-6, IL-8, IL-12, IL-18  
Chemokines: MCP-1, MIP-1 $\alpha$   
Transforming growth factor  
Colony-stimulating factor (CSF)

**Acute-phase proteins**

Complement: C3, C4, C9  
C-reactive protein

**Oncogene expression**

Ras, p53 mutation  
Genetics, chromosome deletions

gests PHC may be linked through genetic events responsible for the loss of an antioncogene. Human primary liver tumors were tested against a panel of restriction fragment length polymorphisms, and a loss of constitutional heterozygosity for markers on chromosome 4 was demonstrated. Hence an antioncogene may suggest a mechanism for PHC and other cancers related to virus infection.<sup>7</sup>

Recently, beta-catenin ( $\beta$ -catenin) one of the key components of the Wnt signaling pathway, was found to be mutated in about 20% of HCCs.<sup>49</sup> The Wnt signaling pathway is essential for development and organogenesis and it stabilizes  $\beta$ -catenin, which accumulates in the cytoplasm and then upregulates downstream genes.  $\beta$ -catenin downstream transcriptional targets include c-myc and cyclin D1, which are both involved in cell cycle and cell proliferation.<sup>1</sup> The Wnt pathway via  $\beta$ -catenin may be the mechanism associated with early gene alteration events in the genesis of HCC.<sup>49</sup> Hence, the activation of the Wnt signaling pathway by  $\beta$ -catenin mutation may contribute significantly to the

HCC associated with HCV infection. Recently, a relationship has been detected between IgF-II overexpression and gene demethylation in tumors associated with certain hepatocarcinomas, suggesting that alterations of the IgF-II gene may be associated with tumorigenesis.

**Polymorphisms**

The role of polymorphisms has been studied in the development of HCC. Genetic polymorphisms of the carcinogen-metabolizing enzymes cytochrome P450 (CYP450),<sup>50-52</sup> glutathione S-transferase (GST) M1,<sup>52</sup> and N-acetyltransferase (NAT2),<sup>51</sup> as well as p53 polymorphisms, have been studied experimentally as susceptibility markers for HCC development. In particular, the NAT2 is a polymorphic enzyme that is expressed in the liver in a genotype-determined manner and is involved in both activation and inactivation of carcinogens through N-acetylation. Subjects homozygous for NAT2 loss of function alleles were observed among patients with HCC. In addition, the relationship between the slow acetylator NAT2 genotype and HCC risk is more pronounced in patients lacking serum HBV and HCV markers. The additional determination of alleles of the CYP450 2D6 (CYP2D6) gene in the same subjects confirmed previous findings that subjects with two active CYP2D6 genes are at increased risk of developing HCC. Abnormalities in the structure and expression of the tumor-suppressor gene p53 are frequent in HCC cell lines (Table 2). Allelic deletions from chromosome 17p and mutations of the p53 gene have been reported in 50% of primary HCCs from southern Africa. Importantly, four of five mutations detected were G to T substitutions, with clustering at codon 249.<sup>53</sup> This mutation specificity may reflect exposure to a specific carcinogen, with one candidate being aflatoxin B1, which is both a liver-specific carcinogen and a mutagen that induces G to T substitution. Genes p16 and p15 are representative members of cyclin-dependent kinase inhibitors. Moreover, studies suggest that deletions or point mutations in the p16 and p15 genes were not frequent in HCC, but revealed the existence of microsatellite alterations at the 9p21-24 region in HCC.<sup>54</sup> Because the selective expression of p57KIP2 in liver and because p16CDKN2/MTS1/INK4A has been found altered in many primary tumors,

the presence of alterations in either of these genes has been studied in a group of HCCs.<sup>54</sup>

### **Cellular and Environmental Toxicants**

#### **Oxidative Stress Factors**

The production of nitric oxide, a reactive nitrogen species (RNS), occurs in many pathological conditions associated with inflammation and is therefore an important risk factor in organ dysfunction and cancer.<sup>55</sup> In the liver, activated hepatocytes and Kupffer cells, as well as infiltrating polymorphonuclear leukocytes and monocytes, can produce nitric oxide.<sup>55</sup> Furthermore, chronic exposure of hepatocytes to RNS after liver injury and an inflammatory process not only results in both functional morphological alterations but also leads to degenerative liver diseases and eventual HCC.<sup>56</sup> Epidemiological studies have linked human cancers to environmental toxicant exposure, such as arsenic, which has been associated with various diseases and cancers, including liver diseases and HCC.<sup>57</sup> To better understand the molecular mechanisms associated with arsenic toxicity and carcinogenicity, a human cancer cDNA expression microarray was used to profile aberrant gene expression in a 6- to 10-year arsenic-exposed population.<sup>57</sup> The differentially expressed genes included those involved in cell-cycle regulation, apoptosis, DNA damage response, and intermediate filaments. Clearly, identification of the variety of gene expression changes associated with hepatotoxicity and possibly carcinogenesis may play an integral role in elucidating molecular mechanisms as well as developing effective treatments.

#### **Cytokines/Chemokines**

Inflammatory mediators, including cytokines, are associated with the pathology of chronic liver disease. Hepatocytes are generally considered as targets but not producers of these important mediators.<sup>58,59</sup> In addition, invasion of the liver by inflammatory cells may disrupt the normal hepatic extracellular matrix (ECM), which may in itself act as a stimulus for fibrogenesis by altering critical cell-matrix interactions. In particular, the discovery of transitional cells in fibrotic liver tissue, and their relationship to lipocytes, correlates well with studies documenting activation of lipocytes in culture to a fibrogenic phenotype.<sup>60</sup> In the sera of patients with alcoholic liver cirrhosis, increased

IL-6, TNF- $\alpha$ , and IL-8 were detected.<sup>59</sup> Because immunologic dysfunction is intrinsic in hepatic damage, studies have shown an increase in hepatic macrophage release of the proinflammatory compounds IL-12 and IL-18. IL-12 plays an essential role in host defense against infectious diseases, and IL-18, in particular, possesses inflammatory effects by inducing synthesis of the proinflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$  and the chemokines IL-8 and macrophage inflammatory protein 1- $\alpha$  (MIP1- $\alpha$ ).<sup>61</sup> In addition, IL-18 promotes the upregulation of IL-12 receptors that leads to transcription of interferon- $\gamma$  (IFN- $\gamma$ ), the hepatotoxic cytokine, and diminished liver CD4+NK1.1 T-cells.<sup>30</sup>

Chemokines are agents that are highly chemotactic to mononuclear cells and granulocytes. Furthermore, the levels of chemokines in sera and tissue are elevated in patients with alcoholic hepatitis, alcoholic cirrhosis, diseased livers, viral hepatitis, and in experimental models of chronic alcohol intoxication.<sup>47</sup> Furthermore, chemokines are implicated in the pathogenesis of alcoholic liver disease in humans and in experimental models of alcohol intoxication. The major sources of these chemokines are Kupffer cells, which represent more than 80% of tissue macrophages in the body. Kupffer cells are highly responsive to the effects of ethanol, endotoxin, and HIV-1 glycoprotein 120 (gp120). These agents, either independently or in combination, may exacerbate the production of chemokines.<sup>47</sup> Mechanistically, alcohol-induced influx of endotoxin from the gut into the portal circulation is thought to play an important role in the activation of Kupffer cells, which leads to enhanced chemokine release. Although the upregulation of chemokines during alcohol consumption is selective, during the early phase of alcoholic liver disease CXC or alpha-chemokines predominate. The CXC chemokines are a unique family of cytokines for their ability to behave in a disparate manner in the regulation of angiogenesis. CXC chemokines are also associated with neutrophilic infiltration of the liver. However, in the later stage, upregulation of CC or beta-chemokine production and migration of mononuclear cells into the liver are observed, and this may lead to liver cirrhosis. Furthermore, selective upregulation of chemokine synthesis and release may involve differen-



**Table 3—Genotoxic Liver Carcinogens\***

**Food crop mycotoxin contaminants (spoilage mold)**

Aflatoxins B1, G1, and M1; ochratoxin A

**Cyanobacteria (blue-green algae) toxins in polluted drinking water**

Microcystin-LR

**Plant constituents used for foods and medicines**

Cycasin (methylazoxmethanol)

Alkybenzene derivatives

Safrole; estragole; methyleugenol; beta aserone

Pyrrolizidine alkaloids

**Chemicals formed during food processing and cooking**

N-nitroso compounds

Dimethylnitrosamine; N-nitrosopyrrolidine

Heterocyclic amines

IQ; MeIQx; amino acid pyrolysis products

**Drug**

Tamoxifen

\*Adapted from Wogan JM: Impacts of chemicals on liver cancer risk. *Semin Cancer Biol* 10(3):201-210, 2000.

tial modulation of transcription factors required for chemokine gene expression. Increased cytokine release after alcohol consumption may also regulate chemokine secretion in Kupffer cells via paracrine and autocrine mechanisms, and vice versa.

### Growth Factors

Transforming growth factor-betas (TGF- $\beta$ s) are multifunctional polypeptides that have been suggested to influence tumor growth.<sup>62</sup> Because loss of sensitivity to growth inhibition is thought to contribute to the development of neoplasia, transforming growth factor-beta 1 (TGF- $\beta$  1) has been shown to be a potent inhibitor of hepatocyte proliferation in vivo and in cell culture, and also an inducer of fibrogenesis.<sup>63</sup> It is produced by nonparenchymal cells in normal, regenerating, neoplastic, and preneoplastic liver. Both TGF- $\beta$  2 and TGF- $\beta$  3 are also found in liver nonparenchymal cells, and the amounts of their mRNAs increase during liver regeneration. TGF- $\beta$  2 has effects similar to TGF- $\beta$  1. Particular attention has been paid to the TGF- $\beta$  system

and it has been shown that the major three isoforms of TGF- $\beta$  are upregulated both in tumor and stroma cells.<sup>64</sup> In addition, TGF- $\beta$ s play a principal role in intracellular signaling, because they mediate their functions via specific cell-surface receptors (type I ALK5 and type II TGF- $\beta$  receptors).<sup>65</sup> Hepatocyte damage is a signal for macrophage and platelet activation, resulting in the release of TGF- $\beta$  with subsequent overexpression of genes responsible for morphologic and functional changes in Ito cells. TGF- $\beta$ s modulate ECM proteins that are responsible for wound formation and tissue reconstruction.<sup>64</sup> The proper structure of the ECM, particularly the basement membrane and the adjacent interstitial matrix, are essential prerequisites for proper function of tissues. Hence, invasive growth of malignant tumors is associated with a destruction of various matrix structures. Although the significance of TGF- $\beta$  in liver fibrosis is well established, recently a novel factor called connective tissue growth factor, which belongs to a family of factors that regulate fibrogenesis and wound healing, has been shown to play an important role in hepatic fibrosis.<sup>62</sup>

### Chemical Hepatocarcinogens

Chemical hepatocarcinogens are classified into two categories, genotoxic or direct-acting carcinogens. They form covalent adducts with nuclear DNA and induce genetic changes upon cell replication and nongenotoxic or epigenetic carcinogens that act through pathways not involving alterations in DNA structure or genetic damage.<sup>66</sup> Nongenotoxic liver carcinogens stimulate tumor formation by altering cell proliferation relative to cell death and differentiation, with a concomitant increase in the target cell population for transformation. Human exposure to both genotoxic and nongenotoxic liver carcinogens may occur through many routes (Tables 3 and 4) and have been documented as primary liver cancer (PLC) or HCC risk factors.<sup>66</sup> Recent molecular epidemiological studies have shown that low serum retinol levels as well as elevated serum levels of testosterone, neu oncoprotein, and AFB1-albumin adducts also are associated with an increased liver cancer risk. Chronic carriers of HBV and HCV have an increased risk of HCC. The relative and attributable HCC risk of HBV and

HCV carrier status varies in different countries. In addition, a synergistic interaction exists between the two viruses and between chronic HCV infection and AFB1.

Familial aggregation of HCC exists and a major susceptibility gene of HCC has been hypothesized. Patients with some genetic diseases are at an increased risk of HCC. The genetic polymorphisms of CYP450 2E1 and 2D6 and arylamine *N*-acetyltransferase 2 are associated with the development of HCC. A dose-response relationship between aflatoxin exposure and HCC has been observed among chronic HBV carriers who have null genotypes of glutathione *S*-transferase M1 or T1, but not among those who have non-null genotypes. Clearly, gene–environment interactions are involved in the development of HCC in humans.

**Therapeutic Modalities**  
**Chemoprevention/Nutritional Intervention**

In cirrhotic patients with gastrointestinal bleeding, short-term antibiotic prophylaxis significantly increases the percentage of patients free of infection and significantly increases short-term survival rate.<sup>67</sup> In addition, norfloxacin prophylaxis decreases the incidence of bacterial infections in high-risk cirrhotic patients, but may promote the development of quinolone-resistant gram-negative bacteria in stools, and eventually lead to subsequent infections.<sup>68</sup>

Oltipraz and dithiolethiones are an important class of chemopreventive agents that have been shown to inhibit acute hepatotoxicity induced by AFB1,<sup>69,70</sup> whereas indole-3-carbinol (I3C), which is found in cruciferous vegetables, can retard progression of experimental AFB1-induced carcinogenesis at both the initiation and promotion stages.<sup>71</sup> Many patients with liver cirrhosis are in a state of protein and energy malnutrition and require careful nutritional support. Supplementation with branched-chain amino acids alleviates chronic liver failure, improves the protein nutritional state, and subsequently prolongs survival.<sup>72</sup> Coumarin, a naturally occurring dietary compound, is a potent inducer of AFB1-aldehyde reductase, the glutathione *S*-transferase A5 and P1 subunits, and NAD(P) H:quinone oxidoreductase in

**Table 4—Nongenotoxic Liver Carcinogens and Tumor Promoters\***

**Mycotoxins**  
Fumonisin

**Peroxisome proliferators**  
Hypolipidemic drugs  
Phthalates  
Steroids  
Herbicides

**Chlorinated hydrocarbons**  
Organochloride pesticides (ie, DDT, chlordane)  
Polychlorinated biphenyls  
TCDD  
Solvents (ie, chloroform)

**Drug**  
Oxazepam

\*Adapted from Wogan JM: Impacts of chemicals on liver cancer risk. *Semin Cancer Biol* 10(3):201-210, 2000.

the liver.<sup>73</sup> Researchers have postulated that antioxidant vitamins may play a role in preventing cancer because several plausible biological mechanisms exist. Vitamin E supplementation is shown to inhibit hepatic focal lesion growth. Although experimental evidence suggests a protective effect by dietary supplements, supplements are not presently regulated by the US Food and Drug Administration; therefore, final concentrations for supplements can vary tremendously. Therefore, it seems prudent to advocate a diet rich in fruits and vegetables, rather than the consumption of specific antioxidant vitamin supplements, to decrease the risk of developing cancer. Abstinence remains the cornerstone of therapy in patients with alcoholic hepatitis and cirrhosis but, for the first time in nonhuman primates, polyenylphosphatidylcholine (PEPC) was shown to fully prevent alcoholic cirrhosis and is now being tested in a multicenter clinical trial.<sup>22</sup> Nutritional studies investigating the reliability of predicting energy expenditure in cirrhosis and some relevant contributions to the understanding of metabolic consequences of liver transplantation deserve particular attention. Relevant contributions in the field of nutritional intervention and chemoprevention in cirrhosis are surprisingly lacking.

## IFN- $\alpha$

IFN- $\alpha$  has been shown to have antiproliferative effects in the treatment of HCC. This growth-inhibitive effect has been associated with delayed S-phase progression, most likely because of inhibition of the cell cycle dependent induction of Cyclin A with a subsequent decrease in activity of the cyclin-dependent kinases, Cdk2 and Cdc2.<sup>74</sup> The only treatment currently approved for preventing long-term complications of hepatitis C is IFN- $\alpha$ -2a or -2b at 3 MU 3 times a week for 12 months. It is recommended only for patients with chronic, active hepatitis C. However, ribavirin is approved for patients with hepatitis C who have not been treated previously or who have relapsed and must be combined with IFN- $\alpha$ -2b.<sup>75</sup> Although combination treatment is more effective, the ribavirin-IFN- $\alpha$ -2b combination causes hemolytic anemia in most patients, and this can be severe. Caution must also be used because ribavirin is teratogenic and causes sperm defects.<sup>75</sup>

## TGF- $\beta$

TGF- $\beta$  is an important factor in the regulation of liver growth. As an inhibitor of DNA synthesis and an inducer of apoptosis, expression in the resting liver must be well balanced. Several studies have shown that either under- or overexpression appears to cause an increased turnover of hepatocytes and to predispose the liver to hepatocarcinogenesis. Importantly, in HCCs TGF- $\beta$  overexpression has been observed and is associated with loss of TGF- $\beta$  responsiveness that is attributed to a disruption of TGF- $\beta$  signaling.<sup>76</sup> TGF- $\beta$  overexpression is also associated as a late event in tumor development. Although further studies may clarify the mechanisms by which hepatocellular tumors escape TGF- $\beta$  growth control, one mechanism that has been proposed involves mutations in TGF- $\beta$  receptor II or Smad 2 and Smad 4 genes, which are frequently observed in other human cancers.<sup>77</sup>

## Gene Therapy

The use of gene therapy to enhance antitumor immunity has emerged as a promising procedure to treat cancer. Several studies have used an adenovirus delivery system to carry genes directly to the tumor. In particular, animal studies have shown that intratumoral injection of adenovirus carrying the IL-12 gene

(AdCMV-IL12) significantly inhibited tumor growth in a dose-dependent manner.<sup>78</sup> Furthermore, complete regression of the tumor was observed 2 weeks after treatment with 60% long-term survival and showed protection against tumor rechallenge. In experimental carcinogenesis, using the liver carcinogen diethylnitrosoamine (DEN), animals develop multiple hepatic dysplastic nodules. However, intrahepatic artery injection of adenovirus-linked CMV-IL12 (AdCMV-IL12) induced complete tumor regression in 20% of treated animals.<sup>78</sup> The antitumor mechanisms associated with AdCMV-IL12 treatment included activation of natural killer cells with subsequent inhibition of angiogenesis. Thus, these studies suggest that intratumoral or intravascular injection of adenovirus expressing IL-12 can efficiently treat experimental HCC and perhaps even human HCC.



**T***he presence of cirrhosis and liver dysfunction may be predisposing factors for dental and periodontal diseases.*

## Chemotherapy

Advanced inoperable liver tumors have an unfavorable natural course. However, the somatostatin analog octreotide has been shown to have antitumor activity against advanced inoperable HCC and was shown to have significant survival benefits in treated patients.<sup>79</sup> A synthetic analog of vitamin A (acyclic retinoid or 4,5-dehydrogeranyl geranoic acid) have low toxicity and are administered for 12 months with significant survival improvement by the log-rank test.<sup>80</sup> In addition, acyclic retinoids prevent at least the development of second primary tumors after curative treatment of preceding HCC. The mechanism of this cancer chemoprevention is clonal deletion of premalignant and latent malignant cells by the retinoid and in patients with chronic hepatitis C and cirrhosis.<sup>81</sup> Hepatocyte growth factor (HGF) gene therapy transfection into the skeletal muscle can induce high plasma levels of HGF and tyrosine phosphorylation of the cmyc/HGF receptor, HGF-inhibited fibrogenesis and hepatocyte cell death, and resolved fibrosis in

the cirrhotic liver.<sup>76</sup>

Vaccination against hepatitis B interferon-class treatment against hepatitis C in patients with active hepatitis are also effective therapies.<sup>82</sup> Importantly, effective chemoprevention can prevent the progression and incidence of second primary HCC development. Liver transplantation is the method of choice for (1) metabolic disease (infants with inborn errors) and (2) end-stage liver failure where transplantation leads to complete reversal of the metabolic defect. However, laparoscopic hepatectomy is a new approach for HCC that is comparable to conventional surgery with improved resection rates. Benefits include minimal access surgery and acceptable morbidity and mortality (ie, survival from 32 to 52 months). Transarterial chemoembolization (TACE) is a new method with enhanced treatment efficacy,<sup>83-85</sup> but combining liver resection and TACE improves the chances of being disease-free and overall survival.<sup>83</sup>

## Conclusions

Human hepatocarcinogenesis is a multi-stage process with the involvement of a multifactorial etiology. Clinical and molecular medical data have provided considerable molecular and cellular information about liver carcinogenesis including loss of heterozygosity, deletion or inactivation of tumor suppressors, and activation of other candidate genes and transcription factors, as well as factors associated with cell-cycle regulation via cell-signaling pathways, which seem to be mechanistic events in HCC development. Much has been accomplished in various scientific areas, as outlined in this article, to enhance our understanding of the natural history, diagnosis, and treatment of cirrhosis and the subsequent HCC. However, in the next decade it will be imperative for our scientific communities to collaboratively:

- Develop and implement strategies to reduce caries, and periodontal and gingival infection among susceptible populations.
- Initiate research to investigate the oral health–cirrhosis relationship.
- Discern and eliminate the disparities among affected groups.
- Develop effective educational strategies to implement within communities for future eradication.
- Use molecular biology techniques to identify

biological markers and altered gene expression, including additional polymorphisms.

- Elucidate the role of specific cell types involved in liver disease progression.
- Determine the cellular and molecular targets involved in liver disease progression and subsequent pathogenesis.
- Elucidate the signaling pathways and molecules involved in disease progression and pathogenesis.
- Develop new therapies, vaccinations, and chemopreventive interventions based on molecular and cellular targets.
- Develop better animal models to investigate HCC development.
- Elucidate the molecular role(s) of hepatitis C and hepatitis B in mediating disease progression.
- Determine the role of each hepatic cell type as a contributor to disease and cancer progression.

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# Periodontal Disease, Race, and Vascular Disease

**Abstract:** Recently, a number of studies have rekindled the possible hypothesis that oral health has repercussions beyond the oral cavity and is associated with systemic diseases. Interestingly, it is a return to an old theory that chronic infections and inflammation played a crucial role in atherosclerosis. This larger theory was advocated by French physicians, among others, at the beginning of the 20th century. In this article, we will review the epidemiologic evidence pointing to a possible association between oral health and vascular diseases and examine the role of race/ethnicity in the interpretation of this association.

## Association of Acute Infections With Ischemic Stroke

The association of infection with ischemic stroke has been convincingly documented over the years. First, prior acute infections have been consistently shown to increase the risk of vascular diseases. Cerebral infarction is a well-known complication of bacterial endocarditis,<sup>1-4</sup> meningitis,<sup>5,6</sup> and meningovascular syphilis. In 1988, Syrjanen et al<sup>7</sup> reported that preceding infection was an important risk factor for ischemic brain infarction in young and middle-aged adults (less than 50 years old) in Finland. In a conditional logistic regression analysis of their community-based case-control study, prior febrile infection was statistically associated with ischemic stroke (odds ratio [OR] of 14.5). Although they measured antibodies against four bacterial species, in most cases antibodies were directed against one bacterial species, thus excluding nonspecific polyclonal immunostimulation in favor of specific bacterial infection as an explanation for the results.

In another case-control study, Macko et al<sup>8</sup> extended these observations by noting that both febrile and afebrile infections were associated with increased odds of ischemic stroke. This study was significant because a standardized signs- and symptoms-based questionnaire was administered to all participants, allowing for determination of intercurrent inflammatory syndromes and afebrile infections. Both febrile and afebrile infections and, presumably, inflammatory syndromes, were associated with an increased risk of stroke in this study. In an even larger case-control study enrolling nearly 200 case-control pairs, Grau et al<sup>9</sup> also

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reported that the risk of cerebrovascular ischemia was increased in all age groups for patients reporting a preceding infection ( $P < .05$  for patients aged 51 to 60 years and patients aged 61 to 70 years). In a multivariate conditional logistic regression analysis controlling for the effects of previous stroke, hypertension, diabetes mellitus, coronary heart disease (CHD), and current smoking, bacterial infections were independently associated with cerebrovascular ischemia in men (OR 5.75), but the number of women was small (83). Taken together, these studies indicate that as many as one third of patients hospitalized for acute ischemic stroke had a history of recent bacterial infection.

## Learning Objectives:

After reading this article, the reader should be able to:

- discuss the evidence linking acute and chronic infections to vascular disease.
- describe the ethnic variations in periodontal, microbiologic, and clinical parameters in the United States.
- understand the epidemiologic difficulties in assessing the relationship between periodontal infections and vascular disease.

## Chronic Infections and Risk of Cardiovascular and Cerebrovascular Disease

In addition to acute infections, there has been more recent, yet extensive, evidence that chronic infections also are associated with vascular diseases. Since the early reports in 1994, about 20 epidemiologic studies totaling nearly 2,600 cases have linked *Helicobacter pylori* antibody titers with either CHD or stroke. The evidence is even stronger in the case of *Chlamydia pneumoniae*, where most of 17 epidemiologic prospective<sup>10-12</sup> and retrospective<sup>13-26</sup> studies found an OR of at least 2 for the association between *C pneumoniae* and CHD and stroke, with some studies even reporting increasing ORs with increasing antibody titers. In addition, *C pneumoniae* has been detected in plaque samples removed from carotid arteries,<sup>27</sup> and preliminary results of a clinical trial point toward the possible efficacy of roxithromycin, an anti-chlamydial macrolide antibiotic, in reducing the rate of severe recurrent ischemia, myocardial infarction, and death. However, response to antibiotics was not examined according to whether patients were seropositive to chlamydia, leaving open the possibility that some other anti-inflammatory property of the macrolide might be responsible. The final report of the randomized trial of roxithromycin in non-Q-wave coronary syndromes study<sup>28</sup> describes the response of immunoglobulin G (IgG) titers and C-reactive protein (CRP) to macrolide therapy. The IgG titers increased slightly in the placebo group while remaining unchanged in the treatment group. Conversely, CRP levels decreased in both the placebo and treatment groups; however, the decrease was more profound in the treatment group and reached statistical significance.<sup>28</sup> This finding leaves open the possibility that the residual anti-inflammatory properties of the macrolide antibiotic, rather than its anti-infectious properties, might be responsible for the protective effects observed in this study. Studies looking at the relationship between chronic infections and cardiovascular disease “should be large enough for moderate-sized effects to be assessed or refuted reliably.”<sup>29</sup>

Periodontal diseases are among the most common chronic infections that have plagued humans for centuries,<sup>30,31</sup> and yet they are rarely thought of as infections by the medical and nonmedical communities. Nowhere in the body are so many bacteria in contact for so long with

an epithelial surface as in the periodontium, with typically  $10^8$  colony-forming units of bacteria inhabiting a single periodontal pocket. Therefore, it seems plausible that periodontal infections would also be associated with vascular diseases, as a logical extension of the findings relating chronic infections to vascular diseases.

## Periodontal Infections, Atherosclerosis, and Vascular Disease

Poor dental status and chronic dental infection have been consistently associated with vascular diseases, including coronary artery disease and stroke. Syrjanen et al,<sup>7</sup> in a case-control study of 40 patients and controls, found a statistically significant association between periodontal infections and stroke in young and middle-aged men under 50 years of age. Using two elaborate indexes for measuring severity of infection of teeth and periodontium, they reported that poor oral health and cerebral infarction were related in men, independent of the method used to evaluate oral health. However, because of the case-control design, the time line could not be unequivocally established because patients underwent dental exams on average 1 to 4 weeks after the stroke. It is therefore possible that some of the changes might be attributed to the stroke itself.

In another study, Loesche et al,<sup>32</sup> analyzing about 400 Veterans Administration patients in different geriatric groups, showed an increased risk of stroke in patients with both fewer teeth and severe periodontal diseases. Unfortunately, no multivariate analyses were reported. Two additional studies stand out, because of their careful design, as providing some of the more convincing evidence of an association between periodontal infections and stroke. Beck et al<sup>33</sup> used the 2,280 men of the Normative Aging Study in Boston who received a comprehensive dental examination and radiographs at approximately 3-year intervals for 18 years. Using the Framingham Study criteria for stroke, they were able to show, while controlling for the effects of age, smoking, diabetes mellitus, family history, and education, that periodontal diseases, as assessed by bone loss, increased the OR of stroke by 2.8.<sup>34</sup> This OR was larger than the OR for smoking, which was 1.6. Interestingly, it was also larger than the OR toward an outcome of CHD, which was also 1.6. Further, when analyzing mean bone loss as a continuous variable



using a Schei ruler,<sup>35</sup> they were able to describe a gradient between the level of bone loss and the cumulative incidence of CHD and stroke.<sup>33</sup> Unfortunately, the cohort was self-enrolled, not randomly selected, and no adjustments were made for dietary factors. Just as importantly, no women were enrolled and no information on the racial breakup of participants was provided, therefore limiting generalization.



***Studies indicate that as many as one third of patients hospitalized for acute ischemic stroke had a history of recent bacterial infection.***

More convincing preliminary evidence of the potential contribution of dental infections to atherosclerotic growth is provided in a study by Mattila and colleagues.<sup>36</sup> After assessing bone loss in dental radiographs and coronary angiograms by blinded observers, they noted a statistically significant association between dental infections and severe coronary atheromatous plaque, even after adjusting for the effects of age, blood lipids, body mass index, hypertension, smoking, and social class.<sup>36</sup> The adjusted regression coefficient of  $r = 0.34 (+ 0.12)$  ( $P < .001$ ) was of the same magnitude as that of the classic risk factors.<sup>36</sup> Syrjanen et al,<sup>7</sup> in a case-control study involving 40 cases with as many controls, also noted an association between the total dental index and aortocervical atherosclerosis changes ( $P < .01$ ). However, because of their small numbers, they were unable to adequately control for possible confounders, especially smoking. These studies provide preliminary evidence that a relationship between dental infections and atherosclerosis is plausible.

More recently, a case-control study by Grau and colleagues<sup>37</sup> (involving 166 stroke patients with as many age- and sex-matched controls) showed a similarly strong association between periodontal diseases and ischemic stroke (adjusted OR = 2.6) after adjusting for diabetes, socioeconomic status, current smoking, previous stroke, transient ischemic attack, CHD, or peripheral artery disease. The study was significant because they used both the total dental index and

orthopantomography index, computed blindly, and all patients received a cranial computed tomography scan, therefore improving the diagnostic precision of stroke subtype. They also uniquely investigated for sinus infection using a combination of endoscopic exploration of the middle meatus and A-mode sinusal sonography and ascertained for acute inflammatory syndromes within the week before the stroke. Although they did not control for diet, their careful statistical analysis lends credence to the association. In 1999, further indirect evidence of a possible association was provided by Meier et al in a large retrospective study in England.<sup>38</sup> After adjusting for a number of confounders, they found that cases were less likely to have used tetracyclines than controls. Because tetracyclines are concentrated in the gingival crevicular fluid and widely used in periodontal disease, these findings (part of research in progress<sup>39</sup>) are further indirect evidence of a potential association.

More recently, two studies using the National Health and Nutrition Examination Survey (NHANES) dataset reached strikingly different conclusions on the possible association of dental disease and vascular disease. Hujoel et al<sup>40</sup> found a crude positive association between oral infections and CHD; however, the association was not statistically significant after adjustment for traditional risk factors. Importantly, however, their study did not rule out small effects. Using the same dataset, Wu et al<sup>41</sup> looked at periodontitis in relation to stroke as opposed to CHD, and reached strikingly different conclusions. First, they showed a significant association between periodontitis and incident cerebrovascular disease, specifically nonhemorrhagic stroke but not hemorrhagic stroke. Further, they demonstrated significant associations between periodontitis and fatal events of cerebrovascular disease and nonhemorrhagic stroke but not hemorrhagic stroke. These findings also exposed differences between whites and African Americans.

These differing results are evidence of the difficulty of ascertaining a relationship when a risk factor is as ubiquitous as chronic periodontal infections, and when the putative risk is of such small magnitude. Nevertheless, the association, if sustained, would lead to a sig-

nificant contribution to the attributable risk of vascular events because of the common prevalence of periodontal infections.

Based on these studies, a consensus that periodontal infections are associated with vascular disease can be reached. The real question, however, is whether this association is fortuitous, confounded, or the mark of a real causal or explanatory relationship.

### Prevalence of Stroke and Differences by Race

Stroke remains the most disabling of any neurologic disease, as well as one of the leading causes of death in the United States. Yet, cerebral infarction of unknown etiology represents approximately 40% of cases in stroke databanks<sup>42</sup> and the importance of potential precipitants is not well defined.<sup>13</sup> The annual incidence of new strokes in the United States is nearly 700,000, with more than 4 million current stroke survivors alive today.

Stroke prevention is of growing concern particularly in minority populations, where the burden of stroke has been shown to be greater. Stroke is among the major causes of excess mortality among black Americans. Despite the reported decline in stroke mortality, the relative difference among the race–gender subgroups has remained fairly uniform with nearly a twofold increased stroke mortality for black Americans. The few studies regarding stroke incidence, including the Northern Manhattan Stroke Study (NOMASS), have suggested that the excess mortality is probably a reflection of a greater stroke incidence. In contrast with black Americans, Hispanic stroke mortality rates are not well documented, and Hispanics are rarely identified separately in epidemiologic stroke studies. Nevertheless, Hispanics are the fastest growing population subgroup in the United States, and will account for 33% of the population in the United States by 2010.

The reasons for these race–ethnicity disparities in stroke mortality and incidence are not entirely clear. Possible explanations include differences in socioeconomic status, which lead to impaired detection and treatment because of limited access to care, a greater effect and prevalence of behavioral risk factors, and the possible inheritance of other risk factors that increase the genetic susceptibility of stroke. In the NHANES, the stroke mortality risk ratio for black Americans vs white Americans decreased

when adjusted for six well-established risk factors and family income. The National Longitudinal Mortality Study estimated that in men, lower socioeconomic status accounted for 14% to 46% of the excess stroke risk in black Americans, but no association was present for black American women. Studies have indicated a greater prevalence of diabetes among Hispanics and of hypertension among black Americans, as well as other risk factor differences. There are, therefore, wide variations in both the incidence of cerebrovascular disease and the prevalence of conventional risk factors across ethnic groups.

### Prevalence of Periodontal Diseases and Differences by Race

Periodontal diseases destroy the underlying structures of the periodontium.<sup>29,43</sup> As the population of the United States ages, the prevalence of periodontal diseases is bound to increase in the future as more teeth are saved from caries and life expectancy is extended.<sup>29,44-47</sup> Adult periodontitis is rather prevalent, with advanced disease affecting about 10% to 15% of the population worldwide.<sup>48-50</sup> The most comprehensive study of periodontal status in the United States was conducted by the National Institute of Dental and Craniofacial Research (NIDCR) from 1988 to 1991, with a total of 7,447 dentate individuals aged 13 years and older receiving a clinical periodontal assessment.<sup>51</sup> The overall prevalence of severe periodontal disease, as defined by clinical loss of attachment  $\geq 5$  mm, was 35.1% in people aged 55 to 64 years and 41.2% in those aged 65 years and older.



**P**eriodontal diseases are among the most common chronic infections that have plagued humans for centuries... Nowhere in the body are so many bacteria in contact for so long with an epithelial surface as in the periodontium.

Recent epidemiologic studies support the view that differences in both the prevalence and severity of periodontal diseases exist between ethnic groups in the United States. A

1991 national survey of employed adults suggested that the prevalence of periodontal pockets in black Americans was twice that of white Americans (24% vs 13%), a difference that remained constant across age groups, with 39% vs 17% in people aged 55 to 64 years. In that same age group, 90% of black Americans had an average of 10 sites with loss of attachment  $\geq 3$  mm. Furthermore, Beck et al<sup>52</sup> studied 1,000 people aged 65 years and older in North Carolina and found an increased extent and severity of disease in black Americans when compared to white Americans. A similar association was found in Minnesota<sup>53</sup> and Tennessee in 1993.<sup>54</sup> None of these studies provided data on Hispanics. Brown et al,<sup>51</sup> in the only study with comprehensive data on Hispanics, concluded that non-Hispanic white Americans exhibited better periodontal health than both non-Hispanic black Americans and Mexican Americans, who exhibited a slightly higher percentage of sites with loss of attachment  $\geq 5$  mm. No direct comparisons of black Americans and Hispanics were provided.



**T**he annual incidence of new strokes in the United States is nearly 700,000, with more than 4 million current stroke survivors alive today.

Racial differences in the gingival flora have also been detailed. As an important example, *Porphyromonas gingivalis* was found to be significantly associated with black American ethnicity in patients with severe and advanced periodontitis, with both a higher prevalence of affected sites and a higher percentage of isolates in the black American population with advanced periodontitis.<sup>55</sup> Similarly, Beck<sup>56</sup> observed *P. gingivalis* in 39% of older black Americans compared to 9% of age-matched white Americans, with 18.4% of sites vs 3.4% in white Americans harboring the microorganism. These findings are remarkably consistent despite differences in both methodology for bacterial identification and study design between Schenkein and Beck.<sup>55,56</sup> Data also exist suggesting that the antibody response against *Actinobacillus actinomycetemcomitans* is

both more prevalent and of greater magnitude in black Americans compared to white Americans.<sup>57,58</sup> Taken together, these studies indicate that there are significant differences in gingival flora in black Americans and white Americans in the United States. These differences within diagnostic categories remain when the sample sites are matched for pocket depth and mean attachment loss.<sup>55</sup>

### Potential Confounders of an Association Between Periodontal Disease and Vascular Disease

Epidemiologic studies have identified several variables as risk indicators for periodontal diseases.<sup>52,53,59</sup> Convincing evidence has been accumulated for an association between smoking and periodontal disease, with Grossi and coworkers<sup>60</sup> demonstrating a direct and linear dose-response relationship between the number of pack-years and destructive periodontitis.<sup>60,61</sup> There is also mounting evidence of a different periodontal microflora as well as a lesser response to therapy in smokers.<sup>62,63</sup> Similarly, diabetes mellitus was consistently found to be associated with more severe periodontal disease.<sup>60,61,64-66</sup> Age has been consistently implicated, with more periodontal diseases present in older age groups compared with younger age groups,<sup>60,67,68</sup> although the 1996 study by Genco<sup>65</sup> concludes that when oral hygiene status is considered, age is much less of a factor in periodontal disease, and the severity of periodontal disease in older people is more a result of cumulative tissue destruction rather than an intrinsic factor related to age. In most studies,<sup>60,61,69</sup> such as the NIDCR study, gender differences in periodontal measures were observed across age groups, with women exhibiting better periodontal health than men: 21% of men vs 14% of women had loss of attachment  $> 5$  mm and men also demonstrated a higher percentage of sites with severe loss of attachment  $> 5$  mm. The reasons for these gender differences are not clear, but men usually exhibit poorer oral hygiene than women.<sup>70</sup> Studies have also looked at the possible confounding effect of socioeconomic status as related to periodontal disease, with recent studies adjusting for oral hygiene and smoking failing to find an association.<sup>61,71</sup>

The presence of such an array of common risk factors, however, suggests that periodontal

disease and vascular disease may share a common etiologic pathway. It also calls for a careful, meticulous, and systematic appraisal of these factors as potential confounders of this association. The differences at both macrolevels (clinical measurements) and microlevels (periodontal flora) across racial groups raise the possibility that some of the racial differences seen in the incidence of vascular diseases may be partly explained by the varying distribution and characteristics of periodontal disease. Race, therefore, may act as an effect modifier, either through the differences in microflora or through possible differences in immune reaction. Studies incorporating precise and systematic measurement of all these factors, including race, are likely to elucidate the independent contribution of periodontal infections to the occurrence of cardiovascular and cerebrovascular diseases, namely CHD and ischemic stroke.

### Public Health Significance and Potential for Intervention and Reversal

In summary, studies that have looked at stroke and CHD together as outcomes have generally found a stronger association between periodontal diseases and stroke than with CHD. This association has been found in different populations. Because the analysis was often subsequent to the hypothesis, authors were not always able to control for diet, some studies only included men, and most did not provide information on ethnic breakdown. As importantly, none of the larger epidemiologic studies integrated concurrent laboratory workup and evaluation of the periodontal flora, accompanying antibodies, and cytokine levels with the clinical radiographic examination. The dissection of the infection/inflammation components has therefore yet to be done and needs to be undertaken prospectively.

Prospective cohort studies are, in general, less prone to bias and can lead to a direct calculation of relative incidence rates and attributable risks. The largest and best-known prospective studies in the United States have been done in predominantly white populations from Framingham, Massachusetts, and Rochester, Minnesota. Prospective data regarding cardiovascular risks are accumulating from more recent studies that have sampled black American subjects such as the Atherosclerosis Risk in

Communities Study, but these important large studies still lack a significant multiethnic representation drawn from the same community. When subjects of different races/ethnicities are sampled from different communities, unmeasured sociodemographic and health care covariates and variation in sampling may impair the validity of comparisons between the race/ethnic groups. Few prospective studies are able to evaluate the role of stroke risk factors in black Americans and Hispanics living in the same community with similar sources of medical care. There is a clear need for prospective cohort studies of newly identified stroke risk factors in minority communities.



**A**dult periodontitis is rather prevalent, with advanced disease affecting about 10% to 15% of the population worldwide.

The Oral Infections and Vascular Disease Epidemiology Study (INVEST) has been funded by the NIDCR to investigate oral infections as risk factors for ischemic stroke and carotid atherosclerosis. Using the tri-ethnic population of the NOMASS, INVEST represents the first tri-ethnic cohort looking at periodontal diseases and its association with atherosclerosis and vascular events from a clinical, radiologic, microbiologic, and immunologic perspective. Likewise, the Oral Infections and Vascular Risk in Seven Countries Study has been funded to build a standardized multicenter infrastructure capable of testing the hypothesis in multinational clinical trials. Results from these studies should significantly clarify the question of the potential contribution of oral infections to the incidence of atherosclerosis and vascular events, as well as explore racial differences in infectious load and inflammatory response. The importance of clarifying such contributions is not simply academic: periodontal diseases are treatable, making them an important reversible potential risk factor affecting public health.

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# Exploring Interrelationships Between Diabetes and Periodontal Disease in African Americans

**Abstract:** Population-based data on interrelationships between diabetes and periodontal diseases among African Americans are limited. This article is an overview of our knowledge regarding the bidirectional relationship between diabetes and periodontal diseases and a descriptive analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III), focusing on the diabetes–periodontal diseases interrelationship in African Americans. Results of the analysis are consistent with the current body of evidence supporting a bidirectional relationship between diabetes and periodontal diseases and indicate generally poorer periodontal health and glycemic control among African Americans. The results also indicate significantly lower dental care use in dentate African Americans with diabetes than in the US non-Hispanic white population with diabetes.

Both diabetes and periodontal diseases are common chronic diseases in the US population. More than 16 million people in the United States have diabetes<sup>1</sup> and approximately 13% of US adults have moderate or advanced periodontitis.<sup>2</sup>

Diabetes mellitus is a chronic disease characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both, as well as hyperlipidemia and other metabolic abnormalities. The two major types of overt diabetes in the United States are Type 1 (formerly classified as insulin-dependent) and Type 2 (formerly classified as non-insulin-dependent).<sup>3</sup> Type 2 diabetes is most prevalent; approximately 90% to 95% of people diagnosed with diabetes in the United States have Type 2 and almost all people with diabetes who are 45 years old and older have Type 2. During the past 35 years, diabetes prevalence has increased threefold.<sup>4</sup>

Several minority ethnic populations are more likely to have diabetes than non-Hispanic white individuals of similar age in the United States. As reported by the Centers for Disease Control and Prevention, prevalence of diabetes for members of selected ethnic groups aged 20 years or older is as follows: non-Hispanic whites, 7.8%; African Americans, 8%; Mexican Americans, 6%; other Hispanic/Latino Americans, 2 times higher than non-Hispanic whites; Native Americans and Alaskan Natives, <5% to 50%; and Asian

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American and Pacific Islanders, up to 2 times higher than non-Hispanic whites.<sup>1</sup>

Particularly susceptible individuals or those with chronic poor metabolic control can experience one or more complications leading to a significant burden for the individual and society. This burden includes direct costs of medical care and indirect costs (eg, lost productivity) that result from diabetes-related morbidity and premature mortality.<sup>5</sup> One review reported the

## Learning Objectives:

After reading this article, the reader should be able to:

- describe the current state of evidence regarding diabetes as a risk factor for periodontal diseases.
- discuss the current state of evidence regarding the adverse effect of periodontal infection on glycemic control in people with diabetes mellitus.
- explain the similarities and differences of interrelationships between diabetes and periodontal diseases in the US non-Hispanic white and African American population.

estimated cost of diabetes in the United States in 1997 to be \$98 billion.<sup>6</sup>

Clinicians have long presumed that diabetes and periodontal diseases are biologically linked and that diabetes can have an adverse effect on periodontal health. Indeed, periodontal diseases have been cited as the “sixth complication of diabetes.”<sup>7</sup> Evidence supporting the adverse effects of diabetes on periodontal health comes principally from observational studies conducted around the world. The recently released *Oral Health in America: A Report of the Surgeon General* reviews this evidence, citing reports of cross-sectional and longitudinal studies of children and adults with Type 1 and Type 2 diabetes.<sup>8</sup> Although the preponderance of studies in the existing body of evidence are cross-sectional and describe findings of convenience samples principally from outpatients in hospitals and clinics, there is a set of longitudinal and population-based studies that also support the association between diabetes and increased occurrence and severity of periodontal diseases. The Surgeon General’s report concluded that diabetes is a risk factor for periodontal disease occurrence and progression.



**C***linicians have long presumed that diabetes and periodontal diseases are biologically linked and that diabetes can have an adverse effect on periodontal health.*

As with other complications of diabetes, biologic mechanisms important in diabetes-associated periodontitis are probably multifactorial, consisting of complex, iterative interrelated cellular and molecular interactions resulting from the metabolic abnormalities that characterize diabetes mellitus. Altered host immunoinflammatory response, alterations in collagen metabolism, impaired wound healing, microangiopathy, alterations in the composition of gingival crevicular fluid, altered subgingival microflora, and hereditary predisposition have all been suggested to contribute to increased periodontal inflammation and alveolar bone loss in diabetes.<sup>9-13</sup>

There is also direct and indirect evidence for periodontal infection adversely affecting

glycemic control in diabetes, and although this has been less extensively studied, this literature has recently been extensively reviewed.<sup>8,12,14</sup> Briefly, these reviews cite indirect evidence coming from investigations of relationships between insulin resistance and active inflammatory connective tissue diseases, other clinical diseases, and acute infection. As a result of the high vascularity of the inflamed periodontium, this inflamed tissue may serve as an endocrine-like source for tumor necrosis factor-alpha (TNF- $\alpha$ )<sup>15</sup> and other inflammatory mediators. Because of the predominance of gram-negative anaerobic bacteria in periodontal infection, the ulcerated pocket epithelium could constitute a chronic source of systemic challenge for bacterial products and locally produced inflammatory mediators. TNF- $\alpha$ , interleukin-6 (IL-6), and interleukin-1 (IL-1), all mediators important in periodontal inflammation, have been shown to have important effects on glucose and lipid metabolism, particularly following an acute infectious challenge or trauma.<sup>2,16,17</sup> TNF- $\alpha$  has been shown to interfere with lipid metabolism and to be an insulin antagonist.<sup>18,19</sup> IL-6 and IL-1 have also been shown to antagonize insulin action.<sup>17,20,21</sup> To date, all reports on an infection-related alteration of the endocrinologic–metabolic status of the host have been with acute infections. There is a compelling need to evaluate these relationships in the chronic infection context applicable to periodontal infection.

More direct evidence supporting our current knowledge of the effects of periodontal infection on glycemic control in diabetes comes from treatment and observational studies. Recent reviews of this body of evidence conclude that there is evidence to support periodontal infection/severe periodontitis having an adverse, yet modifiable, effect on glycemic control.<sup>8,12,14</sup> However, as observed in these reviews, not all investigations consistently report an improvement in glycemic control after periodontal treatment. There are major variations in the design, conduct, and results of these clinical studies, thus limiting our current ability for firm conclusions.

Grossi and Genco<sup>12</sup> have observed that despite the variation in the literature, there may be a distinction in the effect of periodontal treatment on glycemic control related to the mode of therapy. They reported that studies involving mechanical periodontal treatment



**Table 1—Percent of US Adults Aged 18+ Years With Severe Active Periodontitis by Diabetes Status and Race/Ethnicity**

Diabetes Status	Non-Hispanic Whites With Severe Active Periodontitis			African Americans With Severe Active Periodontitis			
	N*	Percent†	SE‡	N*	Percent†	SE‡	P-Value
No diabetes	4,406	2.49	0.26	3,287	4.99	0.44	<.001
Diabetes better controlled	204	8.32	2.33	152	16.30	3.41	.052
Diabetes poorly controlled	72	16.67	5.43	95	23.24	4.39	.327

\*Unweighted number of participants with periodontal examinations

†Weighted percent of participants with severe active periodontitis

‡Weighted population estimate of the standard error

SE = Standard Error

alone reported improvement in periodontal status only (ie, no change in glycemic control), while studies including systemic antibiotics with mechanical therapy reported both an improvement in periodontal status as well as an improvement in glycemic control. Additional evidence for supporting a causal association between severe periodontitis and increased risk for poorer glycemic control comes from two longitudinal observational studies.<sup>22,23</sup>

Disparities in periodontal health status between non-Hispanic whites and other racial/ethnic minority populations have been described in the Surgeon General's report on oral health. This report noted greater dental caries experience, higher levels of gingivitis and periodontitis, missing teeth, and oral and pharyngeal cancers in African Americans than in non-Hispanic whites as well as similar patterns of oral health disparities in other racial/ethnic minority groups.<sup>8</sup>

However, knowledge about bidirectional relationships between diabetes and periodontal disease in any US minority group comes principally from the articles published on the Pima Indians of the Gila River Community in Arizona.<sup>15,22,24-29</sup> Beyond those reports, there is limited information based on analysis of data for other minority populations.

## Methods

### Study Source Population

Subjects for this cross-sectional analysis were 8,216 dentate adults who were at least 18 years old and who completed each portion of the dental examination in the NHANES

III. This survey, conducted between 1988–1991 and 1992–1994 by the National Center for Health Statistics (NCHS), examined a cross-sectional sample of noninstitutionalized civilians residing in the United States. This nationally representative sample was selected using a complex, stratified, multistage cluster sampling design. Both the 1988–1991 and 1992–1994 phases of this survey were used on this analysis. The data were obtained from the NCHS.<sup>30-32</sup> Details of the protocol for the dental examination and other aspects of NHANES III have been described previously.<sup>2,33-35</sup>

### Study Variables

Diabetes status was assessed by participant self-report of either being told by a physician that he/she had diabetes or by laboratory assays for fasting plasma glucose or the 2-hour oral glucose tolerance test. Degree of glycemic control was assessed by laboratory assay for hemoglobin A<sub>1c</sub>. Subjects with fasting plasma glucose  $\geq 126$  mg/dL or  $\geq 200$  mg/dL 2 hours after a 75-g oral glucose challenge given after an 8-hour fast were classified as having diabetes. Among subjects with diabetes, those with hemoglobin A<sub>1c</sub>  $> 9\%$  were classified as poorly controlled and those with hemoglobin A<sub>1c</sub>  $\leq 9\%$  were considered better controlled.

Data from the dental examinations were used to define the variables associated with periodontal health status. Severe active periodontitis was defined as having at least 1 tooth with both 6-mm loss of attachment

**Table 2—Percent of US Adults Aged 18+ Years With Poorly Controlled Diabetes (Hemoglobin A<sub>1c</sub> > 9) by Periodontal Status and Race/Ethnicity**

Periodontitis Status	Non-Hispanic Whites With Poorly Controlled Diabetes			African Americans With Poorly Controlled Diabetes			P-Value
	N*	Percent†	SE‡	N*	Percent†	SE‡	
Severe active periodontitis absent	241	25.16	4.11	194	36.47	4.35	.0811
Severe active periodontitis present	35	42.57	11.67	53	47.17	7.99	.7434

\*Unweighted number of participants with diabetes

†Weighted percent of participants with poorly controlled diabetes

‡Weighted population estimate of the standard error

SE = Standard Error

and gingival bleeding. The periodontal measures were performed on randomly assigned half-mouths—one upper quadrant and one lower quadrant selected at the beginning of the examination. The buccal and mesialbuccal aspects of each tooth were scored separately for each periodontal measure: gingival bleeding, calculus, gingival recession, and pocket depth. Additional sociodemographic and dental-care-use variables obtained from the face-to-face interview included race/ethnicity (non-Hispanic white and African Americans [ie, non-Hispanic blacks]) and length of time since last visit to the dentist or hygienist (dichotomized as within past year or more than 1 year).

### Statistical Methods

The descriptive statistical analysis consisted of contingency table analysis using the statistical analysis program SUDAAN.<sup>36</sup> All analyses incorporated population-estimate weighting to adjust variances and standard errors for the complex sampling design used in NHANES III. Tests for statistical significance of differences observed in the two-way and stratified tables used chi-square statistics.

### Results

Table 1 presents a description of the prevalence of severe active periodontitis comparing three groups: those without diabetes, those with

better controlled diabetes, and those with poorly controlled diabetes in the US population aged 18 years and older. For each category of diabetes status, a higher percentage of African Americans have severe, active periodontitis. The greatest statistically significant difference occurs in the group without diabetes ( $P < .001$ ); the group of individuals with better controlled diabetes also demonstrates a noteworthy difference ( $P = .052$ ). The difference between non-Hispanic whites and African Americans is not statistically significant for those with poorly controlled diabetes ( $P = .33$ ).

Table 2 describes an association between severe active periodontitis and prevalence of poorer glycemic control in the US population by race and periodontal status, in adults aged 18 years and older. In both racial groups, a significantly higher proportion of individuals with severe active periodontitis have poorer glycemic control than those without severe active periodontitis. The difference in prevalence of poorer glycemic control between non-Hispanic whites and African Americans approached statistical significance only in the group without severe active periodontitis (25.2% of non-Hispanic whites and 36.5% of African Americans, respectively;  $P = .08$ ). The difference in the proportions of non-Hispanic whites and African Americans with poorer glycemic control among individuals with severe active periodontitis was smaller and not statistically significant (42.6% and 47.2%,

**Table 3—Percent of Dentate US Adults Aged 18+ Years With Diabetes Who Reported a Visit to the Dentist or Dental Hygienist in the Preceding 12 Months, by Diabetes Status, Severe Active Periodontal Disease Status, and Race/Ethnicity**

Diabetes and Severe Active Periodontitis	Non-Hispanic Whites with a Visit in Preceding 12 Months			African Americans with a Visit in Preceding 12 Months			P-Value
	N*	Percent†	SE‡	N*	Percent†	SE‡	
Diabetes absent, severe active periodontitis absent	4,199	73.01	1.10	3,074	59.87	1.30	<.001
Diabetes present, severe active periodontitis absent	240	72.90	4.57	193	53.89	4.29	.0056
Diabetes absent, severe active periodontitis present	181	56.82	6.05	199	48.38	4.05	.2827
Diabetes present, severe active periodontitis present	35	71.22	8.88	53	43.70	8.01	.0204

\*Unweighted number of participants in each category of diabetes and periodontitis status

†Weighted percent of participants with indicated diabetes and periodontitis status

‡Weighted population estimate of the standard error

SE = Standard Error

respectively;  $P = .74$ ).

Consistent with disparities in periodontal health and glycemic control status between non-Hispanic whites and African Americans, there are also significant disparities in dental care use, as assessed by the proportion of individuals reporting having had a visit with the dentist or dental hygienist in the preceding year vs not having had a visit in the preceding year. Table 3 shows remarkably lower percentages of African Americans reporting visiting the dentist/dental hygienist at least once per year in each category of diabetes and severe active periodontitis. These differences are statistically significant ( $P < .001$ ) for each category except for those without diabetes who have severe active periodontitis ( $P = .2827$ ).

## Discussion

Though it is not possible to form causal

inferences from these cross-sectional data, the results are consistent with the body of evidence supporting an adverse affect of diabetes on periodontal health as well as the emerging evidence supporting an impact of periodontal infection on poorer glycemic control in people with diabetes.<sup>8,12,14,37</sup> The focus of this analysis on African Americans provides additional information on oral health-related disparities between African Americans and non-Hispanic whites with diabetes in the US population.

The gradient of increasing prevalence of established active periodontitis—from those without diabetes having the lowest prevalence to those with poorly controlled diabetes having the highest prevalence—is consistent with other reports where investigators have reported a gradient of increasing risk for poorer periodontal health as glycemic control worsened.<sup>28,38</sup> While the prevalence of active, established periodonti-

tis is higher for African Americans in each of the categories of diabetes status, the absence of statistical significance in comparing non-Hispanic whites with African Americans for those with poorly controlled diabetes may be a result of the impact of poorer control, overshadowing any effects due to racial or ethnic differences. An alternative interpretation for this absence of statistical significance in the group with poorer control may be a result of the relatively smaller sample sizes and larger variation in that group.

Finding the significant association between active, established periodontitis and greater prevalence of poorer glycemic control (Table 2) is consistent with evidence from other clinical and epidemiological studies that support the concept of periodontal infection having an adverse impact on glycemic control in individuals with diabetes.<sup>8,22,23,25</sup> As was the case for prevalence of periodontitis, the lack of statistical significance may be the result, in some part, of the relatively small sample size.

As observed by Tomar and Lester,<sup>39</sup> the interrelationship between diabetes and periodontal infection supports evaluating and encouraging access to and use of routine preventive dental care as potentially important in preventing complications of both diseases. However, oral health assessment and dental care provision are not yet universally considered as much a standard of care in the diabetes care community as are eye and foot examinations.<sup>39</sup> This current analysis suggests that dental care use is lower among dentate African Americans with diabetes. Tomar and Lester also reported a lower likelihood of seeing a dentist in the preceding 12 months for dentate adults with diabetes compared with those without diabetes in their analysis of the 1995–1998 Behavioral Risk Factor Surveillance System data. Additionally, they found significantly lower percentages of African American and Hispanic adults with diabetes seeing a dentist in the preceding 12 months. They also found in a multivariable model adjusting for age, educational attainment, household income, and dental insurance coverage that the association between race or ethnicity and dental visits, while largely attenuated, was not eliminated completely. This present study's finding of significantly lower propor-

tions of African Americans with diabetes reporting dental/dental hygiene visits in the preceding year than non-Hispanic whites in any category suggests a need to evaluate and possibly emphasize the importance of targeting oral health promotion and advocacy efforts to increase access to and use of oral health care services among African Americans with diabetes as well as all dentate individuals with diabetes.



**T**he Surgeon General's report concluded that diabetes is a risk factor for periodontal disease occurrence and progression.

Results from the literature review and analyses presented in this report support several directions for future research. Additional rigorous efficacy and effectiveness intervention studies are needed to firmly establish the impact of preventing and treating periodontal infections in glycemic control management. It will be essential for future observational and intervention studies to include a specific focus on African American and other minority populations as well as older adults. Accompanying these studies should be adequate funding support for rigorous application of recent advances in social epidemiological methodology. Additionally, in other diabetes-related epidemiologic and intervention research, there is a compelling need to include measures of oral health in the study methodology. There are also several directions to pursue in health services, outcomes, and educational research. Examples include developing our knowledge base in understanding diabetes-related outcomes associated with dental care use; oral health promotion and oral self-care behaviors; implementing quality-of-care assessment of oral health management protocols in oral disease detection, treatment, and management in the variety of health care delivery systems in which people with diabetes are treated; and developing rigorous interventions for patient education, oral health promotion, and health professional education regarding transfer of knowledge about diabetes–oral health relationships.



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# Chronic Alcoholism: A Common Risk Factor in Oral Cancer and Alcoholic Cirrhosis



**Abstract:** Oral cancer and alcoholic cirrhosis are relatively common diseases encountered in medical and dental practices. This article reviews the clinical, pathophysiological, and epidemiological characteristics of these two conditions. A major risk factor common to both oral cancer and alcoholic cirrhosis is the excessive use of alcohol. A challenge for practitioners and researchers is to become mindful of the connection between oral cancer and alcoholic cirrhosis. Earlier studies exploring these relationships and potential mechanisms are discussed.

Much has been studied and written about the effect of excessive alcohol consumption on the development of oral cancer.<sup>1-3</sup> Much has also been studied and written about the correlation between excessive alcohol intake and the development of alcoholic cirrhosis.<sup>4,5</sup> Although oral cancer and alcoholic cirrhosis are not usually discussed together, there is a connection between these two serious diseases. This article challenges us to make a paradigm shift in our thinking about oral carcinoma and alcoholic cirrhosis. It will also demonstrate that these two diseases disproportionately impact African Americans.

Many patients often consider symptoms of pain and discomfort in the oral cavity to be less important than these same symptoms in other parts of the body. Unfortunately, if the oral discomfort is tolerable, a visit to the dentist is often postponed. In fact, studies have shown that African Americans tend to seek regular dental visits significantly less frequently than other populations.<sup>1,6</sup> Thus, it is important for dentists to stress to every patient that abnormalities seen within the oral cavity might be related to other systemic abnormalities.

Health care providers should consider the total health of the patient. Many physicians tend to overlook the oral cavity when performing a complete "medical examination." Likewise, dentists may not spend sufficient time on the medical questionnaire. Questions about the patient's lifestyle should always be addressed. Discussions on tobacco use, dietary choices, and alcohol consumption should be part of taking a thorough health history and

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performing an examination by both physicians and dentists.

## **Oral Cancer**

Oral cancer is the sixth most common cancer in men living in the United States. It is the

### **Learning Objectives:**

After reading this article, the reader should be able to:

- discuss the correlation between excessive alcohol consumption, the development of oral cancer, and the development of alcoholic cirrhosis.
- discuss the disparity in the prevalence and incidence of oral cancer and alcoholic cirrhosis between majority and minority populations.
- discuss why both oral cancer and alcoholic cirrhosis are largely preventable, and why educating the general public is warranted to decrease the incidence and prevalence of these disorders.

fourth most common among African American men.<sup>1</sup> The leading thought today is that tobacco, especially in combination with alcohol, is a major cause for oral cancer development. The role of alcohol in oral carcinogenesis has been demonstrated experimentally, and appears to be related to the damaging effect of alcohol on the liver.<sup>7,8</sup> This is why it is also interesting to study the incidence and prevalence of alcoholic cirrhosis in the African American population. In fact, epidemiologic studies by Keller in 1977 suggested that cirrhosis of the liver may enhance and/or accelerate a person's risk for developing oral carcinoma.<sup>7</sup>



**A**lcohol, before it is metabolized, acts as a solvent within the oral cavity.

When an excessive amount of alcohol is consumed and metabolized, acetaldehyde concentrations become elevated. Acetaldehyde is one of the major metabolites from alcohol that is released into the bloodstream, salivary glands, and saliva. It is also a known carcinogen in animals and has been linked to oral carcinoma.<sup>1</sup> In addition, alcohol, before it is metabolized, acts as a solvent within the oral cavity. With this in mind, it is logical to assume that other potent carcinogens, such as tobacco, can use alcohol as a solvent when entered into the oral cavity. Alcohol facilitates the penetration of the tobacco carcinogens into the oral tissues. Studies have shown that the tongue is the most common site of oral cancer, followed by the floor of the mouth.<sup>1</sup> It has also been well studied and documented that tobacco and alcohol together produce a greater risk for oral cancer than either substance alone. It is reported that 75% to 90% of all oral and pharyngeal carcinomas are attributed to these 2 substances acting together.<sup>1,4</sup>

Why is this important? Every year 1.2 million people develop cancer in the United States.<sup>9</sup> Oral cancer affects 2.4% of the total number, representing 30,000 new cases per year. Each year 8,000 people die from oral cancer and its complications. Oral cancer rates for African Americans are about 65% higher than for whites in the United States.<sup>10</sup> It has been calculated that the life span of people with oral carcinoma is shortened by as

much as 16.5 years. In addition, the quality of life of these patients is severely affected by disfigurements of surgery, loss of taste, difficulty eating, pain, and difficulty with speech.<sup>1</sup>

The overall 5-year survival rate for oral cancer in the general population is 52%. This survival rate is worse than the 5-year survival rate of prostate, uterine, breast, bladder, cervical, and colon cancers.<sup>1,9</sup> The 5-year survival rate for African American men with oral cancer is even worse; it is approximately 34%.<sup>1,9</sup> Ninety-five percent of all patients diagnosed with oral cancer are at least 35 years old; however, 90% of all patients diagnosed with oral cancer are at least 45 years old, and the cancerous lesions tend to be in the later stages of diagnosis. It is well accepted that the major key to improving the 5-year survival rate is early detection and diagnosis. If found early, the 5-year overall survival rate increases up to 85%. The problem is that generally only 35% of these cancers are detected and diagnosed early.<sup>1,9</sup> In African Americans, an even higher percentage of oral cancers are diagnosed in the later stages, helping to explain the poorer survival rates.

### Alcoholic Cirrhosis

Alcoholic cirrhosis is the most common type of cirrhosis encountered in the United States.<sup>4,5</sup> It is characterized by diffuse fine scarring, fairly uniform loss of liver cells, and small regenerative nodules. Thus, it is sometimes referred to as micronodular cirrhosis. Alcoholic cirrhosis is only one of the many consequences resulting from chronic alcohol ingestion, and it often accompanies other forms of alcohol-induced liver injury. The three major alcohol-induced liver lesions are alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis.<sup>4</sup>

The typical alcoholic patient with cirrhosis has had a daily consumption of at least 16 oz of hard liquor or the equivalent amount of wine or beer for 10 or more years. Therefore, knowing the duration and the actual amount of alcohol ingestion is important when trying to predict severe liver damage and injury.<sup>4,5</sup> When considering men who have been drinking excessively for over 15 years, 30% of this group will eventually develop cirrhosis. The percentage of women who develop cirrhosis after a similar exposure is lower than men, suggesting that there might be a protective hormonal factor involved.<sup>4</sup>

When alcohol is consumed excessively, liver cells, which are called *hepatocytes*, are destroyed. Subsequently, fibroblasts and contractile myofibroblasts appear at the liver injury site.<sup>4,5</sup> The liver is capable of regeneration; however, the rate of destruction due to alcohol is faster than the rate of repair in cirrhosis. As the disease progresses, collagen formation occurs, along with continued hepatocyte loss and shrinkage of the liver. The organ actually takes on a nodular appearance, and has a hard, firm texture. This is the typical end-stage cirrhotic liver.<sup>4,5</sup>

Clinical features of cirrhosis can be silent for several years. However, after 10 or more years of excessive alcohol consumption, the patient tends to become anorexic and malnourished. The patient may experience weight loss, a reduction in skeletal mass, easy bruising, increased weakness, chronic tiredness, and fatigue. Liver cell destruction also includes jaundice, bleeding from gastroesophageal varices, acites, and encephalopathy.<sup>4</sup> When these symptoms present themselves (especially abrupt bleeding from the esophagus), the patient will most likely seek medical attention, often for the first time.<sup>4</sup>

On physical examination, the following are noted in patients with cirrhosis: a firm liver on palpation, palmar erythema, spider angiomas, clubbing of fingers, splenomegaly, lacrimal gland enlargement, and parotid gland enlargement.<sup>4</sup> Laboratory findings include anemia from acute and chronic gastrointestinal blood loss, leukocytes, thrombocytopenia, increased alkaline phosphatase, increased bilirubin, vitamin deficiency (especially folic acid and B<sub>12</sub>), and prolonged prothrombin time (reflecting reduced synthesis of clotting proteins). There is a reduction in the synthesis of fibrinogen (I), prothrombin (II), and factors V, VI, IX, and X.<sup>4</sup> As a consequence, medical and dental professionals should be fully aware of these parameters before scheduling any surgical procedure.

Dental practitioners should suspect alcoholic cirrhosis when confronted with a patient who has a history of prolonged or excessive alcohol intake and physical signs of chronic liver disease. The dentist should perform a thorough head, face, and neck examination. A thorough intraoral examination, including oral cancer screening, is critical. Suspicious white lesions or ulcerative lesions should be evaluat-

ed, using biopsy when necessary. Dentists should educate and counsel the patient regarding the effects of alcohol, tobacco, diet, and lifestyle on oral cancer and other systemic diseases, including alcoholic cirrhosis. Patients with risk factors who have not yet developed any clinical disease should be advised to change



**E**ach year 8,000 people die from oral cancer and its complications. Oral cancer rates for African Americans are about 65% higher than for whites in the United States.

their lifestyle and behavior. They should be advised to cease excessive drinking and smoking immediately. In addition, more community programs are needed to assist patients in tobacco and alcohol cessation. A healthy diet, rich in fruits and vegetables, should be instituted into a daily routine.<sup>1</sup> These measures, in combination with regular visits to the dentist and physician for routine examinations, can prevent oral cancer, alcoholic cirrhosis, and many other systemic diseases, especially within the African American community.

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# HIV/AIDS: Impact on the African American Community

**Abstract:** *The human immunodeficiency virus (HIV) infection has had a devastating impact on the lives of African Americans. In the United States, it is estimated that almost half of all cases of HIV infection in men occur among black men and almost 70% of the cases in women occur among black women. Acquired immunodeficiency syndrome (AIDS), which results from HIV infection, has become a leading cause of death of African Americans between the ages of 25 and 44. Denial regarding how the disease is spread, particularly among heterosexuals, and stigmatization about the disease continue to be barriers to effective prevention campaigns within African American communities. Aggressive cultural and ethnic-specific educational campaigns, focusing on prevention, are needed to curb the current spread of HIV within this population.*

The human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic has had a dramatic impact on racial and ethnic minority Americans since the beginning of the epidemic.<sup>1</sup> In the United States, the impact of HIV and AIDS in the African American community has been devastating.<sup>2</sup> Through December 2000, the Centers for Disease Control and Prevention (CDC) had received reports of 774,467 AIDS cases, and since 1996 more cases have occurred among African Americans than among any other racial/ethnic population.<sup>3</sup>

Initially, HIV—which causes AIDS—was thought to be a disease affecting white homosexual men. National prevention campaigns targeted this group, resulting in a decline in the number of new cases reported. However, since 1996 AIDS has become the leading cause of death among African Americans between the ages of 25 and 44.<sup>4</sup> Representing only an estimated 12% of the total US population, African Americans make up 38% of all AIDS cases reported in this country.<sup>3</sup> Furthermore, the percentage of African Americans with AIDS continues to grow. Between 1981 and 1987, 25.5% of all cases of AIDS were found among African Americans. This percentage increased to 31.2% between 1988 and 1992, 38% between 1993 and 1995, and reached 44.9% since 1996.<sup>3</sup>

Of those infected with HIV, it is estimated that more than 130,000 African Americans were living with AIDS at the end of 1999.<sup>5</sup> By 1999, African Americans accounted for 46% of

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all HIV cases among US men and 68% of all HIV cases among US women.<sup>6</sup>

## Transmission of HIV

HIV, a retrovirus, can be transmitted from one person to another when the blood, semen, vaginal fluid, or breast milk of an HIV-infected person enters another person's body. This can occur through a vein (during injection drug use); the vagina, anus, or rectum;

## Learning Objectives:

After reading this article, the reader should be able to:

- describe the most common modes of HIV transmission among African Americans.
- discuss the most recent statistics regarding the morbidity and mortality of HIV and AIDS among black Americans.
- categorize the AIDS-related oral manifestations of HIV infection.
- describe the role of oral health care providers in responding to the HIV and AIDS epidemic within the African American community.
- describe the global impact of HIV and AIDS.

the mouth; or through cuts and sores.<sup>1</sup> The most common ways of transmitting HIV are sexual intercourse, sharing needles or injection equipment, or during childbirth or breastfeeding.<sup>1</sup> The virus also can be transmitted through a blood transfusion, but that risk is now quite low because all donated blood in the United States is tested for HIV. The virus does not survive well in the environment, making the possibility of casual or passive transmission highly unlikely. Unbroken human skin is an effective barrier to HIV and latex products (gloves, condoms, etc) provide strong protection.<sup>1</sup>



*Since 1996 AIDS has become the leading cause of death among African Americans between the ages of 25 and 44.*

Racial and ethnic minority populations in the United States are most affected by injecting drug use (IDU)-associated AIDS. According to the CDC, IDUs accounted for 26% of all AIDS cases among African American and Hispanic adults and adolescents in 1999, compared with 14% of all cases among non-Hispanic white adults and adolescents.<sup>6</sup> Among African American women, IDU has accounted for 42% of all AIDS cases since the epidemic began, with 40% a result of heterosexual contact.<sup>6</sup> Unlike the non-Hispanic white population, 64% of AIDS cases within the black and Hispanic populations occurred among heterosexuals.<sup>6</sup>

Of the 733,374 AIDS cases reported to the CDC through 1999, blacks and Hispanics accounted for 55% of the total. Black and Hispanic women and children accounted for 77% and 82% of the cases, respectively.<sup>6</sup> However, 57% of the women were African Americans, and African American children represented 59% of all reported pediatric AIDS cases.<sup>6</sup>

This increase in prevalence and mortality represents a failure in the nation's health system to launch effective prevention campaigns and respond to the health care needs of these populations. The African American community also has been slow to mobilize effective pre-

ventive strategies. In an effort to address this epidemic, more than 100 African American leaders gathered at Harvard University in 1996 to respond to the AIDS crisis in the African American community. Convened as the "Leading for Life" summit, participants referred to AIDS as one of the worst health emergencies to face African Americans.<sup>7</sup> It was predicted at that summit that by the year 2000, more than half of all people with AIDS in the United States would be African American and that in only 3 years, an African American would be 9 times more likely to have an AIDS diagnosis than a non-African American.<sup>7</sup> Now 5 years later, the AIDS case rate (cases/100,000) among African Americans is 9 times the rate among whites, according to a recent report by the CDC.<sup>3</sup>

African Americans represent 39% (292,522) of all AIDS cases reported to the CDC, and Latinos represent 19% of all cases.

African Americans now represent the majority of AIDS cases, accounting for 45% of new AIDS cases, and representing 40% of Americans living with AIDS,<sup>1</sup> almost 300,000 in the United States. Again, African Americans represent only 12% of the population.

In 1999, the AIDS case rate (cases/100,000) among African Americans was almost 9 times the rate among whites. The rate among African American men was more than 7 times higher than white men (125.2/100,000 compared to 17.8/100,000).

Among black women, the gap was even greater: 49.8 compared to 2.4 among white women, which is more than 20 times higher.



*By 1999, African Americans accounted for 46% of all HIV cases among US men and 68% of all HIV cases among US women.*

### **AIDS-Related Diseases**

HIV disease (HIVD) is a viral disease characterized by progressive destruction of the immune system. AIDS, the end-stage of HIVD, is defined by numerous opportunistic infections and neoplasms, as well as severe immune suppression.<sup>8</sup> The main immune abnormality in HIVD results from the virus

infecting and consequently causing destruction of CD4 T lymphocytes. B lymphocytes, macrophages, and other cells of the immune system are also affected. Although AIDS is a fatal disease, AIDS patients do not actually die from AIDS. Instead, they die from secondary infections associated with an impaired immune system. Not every person exposed to HIV becomes infected and not all who test antibody-positive for HIV actually develop AIDS and AIDS-related diseases. In 5% to 15% of cases, HIV infection shows no clinical progress for periods up to 10 years, possibly because of variations in pathogenicity of HIV strains, or stronger host-immune responses.<sup>9</sup> Actual development of AIDS depends on a number of factors. These include, but are not limited to, preexisting conditions of the immune system, nutritional status, and repeated exposure to HIV. Numerous stressors weaken the immune system, including abuse of alcohol or tobacco, poor diet, lack of sleep, or generally poor health.



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Oral manifestations associated with HIVD are usually opportunistic infections, secondary to a compromised immune system. Depending on CD4 cell levels, certain oral lesions can be predictive of the onset of AIDS; some lesions may have some predictive value of longevity.<sup>10</sup> Oral manifestation of AIDS can be categorized into five categories: fungal, viral, bacterial, malignant, and non-specific or idiopathic.<sup>11,12</sup> Oral candidiasis is frequently observed as an early manifestation of immune dysfunction, and may be the first indicator of HIV infection. Hairy leukoplakia, a corrugated, white keratotic lesion, is frequently found on the lateral border of the tongue. Herpes simplex virus (HSV) may also be seen in poorly controlled patients during

HIVD progression. Bacterial lesions include linear gingival erythema (LGE) and necrotizing ulcerative periodontitis (NUP). Kaposi's sarcoma appears in the oral cavity late in the infection. Other malignancies observed with varying degrees of frequency are non-Hodgkin's lymphoma and squamous cell carcinoma. Idiopathic conditions, such as recurrent aphthous ulcers (RAUs) may also suggest progressive immune destruction, while xerostomia is most commonly associated with side effects from medications. Petechiae, ecchymoses, and hematomas are rare but may indicate underlying hematologic impairment. Since the introduction of more potent anti-HIV medications in the mid-1990s, a marked reduction of oral lesions has been noticed except the appearance of oral warts.<sup>13</sup> These lesions may be associated with immune dysfunction rather than immune deficiency.

### **Morbidity and Mortality**

Although the number of AIDS-related deaths have declined among all racial and ethnic groups, the decline has been slower among African Americans and Latinos.<sup>1</sup> Recent treatment advances, particularly the increasing availability of effective drug therapies for AIDS-related opportunistic infections (OIs) and the introduction of new drugs, which combat HIV (eg, protease inhibitors), have positively impacted individuals infected with HIV.<sup>14,15</sup> Treatment advances have led to some optimism about the future of the epidemic.<sup>14</sup> For example, AIDS-related mortality appears to be dropping as many people are living longer with HIV. However, this drop has not been occurring at the same rate for all populations.<sup>14</sup> Since 1995–1996 the number of AIDS deaths has declined compared to previous years.<sup>6</sup> However, there is a striking difference between whites and African Americans. While the decline among whites in 1996, 1997, and 1998 was 34%, 50%, and 21%, respectively, it was only 16%, 35%, and 15% among African Americans during the same time periods.<sup>6</sup>

In a survey conducted by the Kaiser Family Foundation, inquiry was made regarding the perceptions and attitudes of African Americans on this subject. Responses from 811 interviews of African American adults,

aged 18 years or older, revealed that African Americans see HIV/AIDS as an urgent health problem facing the nation and local communities, and that they are very concerned about HIV/AIDS personally, both for themselves and for their children.<sup>14</sup>

While the impact of HIV is dramatic across racial lines, it is most dramatic across economic lines. Socioeconomic status has long been an indicator of health-seeking behaviors and health outcomes. Because of the stigma associated with HIV infection in the general population and specifically within the African American community, many African Americans present for medical care at a later stage in their disease than whites. Cultural and religious beliefs, as well as financial barriers, play a role in health care-seeking behavior and the quality of medical care received. The influence of current models of health policy, public health, and health care administration has often served to exclude and disempower communities of color.<sup>16</sup> Additionally, the climate of anxiety and certain myths surrounding the origin of the virus combined with the legacy of distrust many African Americans have for the institutions of medicine and public health present barriers to care.<sup>17</sup> African Americans are much less likely, because of distrust, to participate in research testing new antiretroviral drugs than whites. Hence, most drugs are prescribed based on data from the response of white males.<sup>15</sup>



**I**n 1999, the AIDS case rate among African Americans was almost 9 times the rate among whites.

### Global Impact

Since AIDS was first reported in the United States it has become a major worldwide epidemic.<sup>18</sup> According to the American Association for World Health and the Joint United Nations Programme on HIV/AIDS, 1999 saw a higher total of deaths from HIV/AIDS than any year since the beginning of the epidemic, despite new treatments that are reducing deaths in developed countries.<sup>19,20</sup> Globally, an estimated 15,000 new HIV infections occur

every day.<sup>20</sup>

In 1999, an estimated 570,000 children aged 14 years or younger were infected with HIV. More than 90% were babies born to HIV-positive women. They acquired the virus at birth or through their mother's milk.<sup>19,20</sup> Worldwide, 13.2 million children have been orphaned by AIDS since the beginning of the epidemic.<sup>19,20</sup> Seventy percent of the people infected with HIV worldwide live in sub-Saharan Africa, which is home to just 10% of the global population. At the start of the 21st century, more than 24 million people in sub-Saharan Africa are estimated to be living with HIV or AIDS.<sup>19,20</sup>



**G**lobally, an estimated 15,000 new HIV infections occur every day. In 1999, an estimated 570,000 children aged 14 years or younger were infected with HIV.

### Observations and Recommendations

My first encounter with an AIDS patient, a white woman working as a prostitute, was in 1982. Now in my private dental office, located in a predominately African American community, where most of the patients are HIV-negative, most of the HIV-positive and AIDS patients are white males. Many of these white patients participate in clinical antiretroviral drug trials. Few black HIV-positive/AIDS patients participate in clinical antiretroviral drug trials.<sup>15</sup> One advantage of participating in clinical drug trials is that it makes new drugs available early; secondly, these drugs are provided at no cost to the participant, eliminating a financial barrier to access.

Based on the number of black HIV-positive/AIDS patients presenting for care in my practice, it appears that white patients tend to present for care earlier and are more likely to seek dental care. White patients appear more likely to take advantage of local and national governmental and nongovernmental support programs than blacks.

Denial, particularly among heterosexuals, and stigmatization about the disease is still prevalent in African American communities. Aggressive cultural and ethnic-specific educa-



## Table 1—Recommendations

- Dentists should encourage high-risk patients to get tested for HIV/AIDS. They should provide this encouragement in the dental office and in community forums.
- Dentists must know the oral signs and symptoms of HIV infection so that appropriate and early diagnosis can be made.
- Oral health care providers should initiate preventive oral hygiene care along with curative care for their HIV-positive patients.
- Oral health care providers must become culturally competent in providing care to individuals with diverse sexual orientation.
- All members of the oral health care team must provide compassionate care.

tional campaigns focusing on prevention are needed in the African American community to curb the current spread of HIV (Table 1).

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Dr. Warren

1. According to the 1985 Secretary's Task Force Report on Black and Minority Health, the six causes of "excess deaths" for African Americans are:
  - a. heart disease and stroke; homicide and accidents; cancer; pneumonia; infant mortality; and diabetes.
  - b. heart disease and stroke; homicide and accidents; cancer; infant mortality; cirrhosis; and diabetes.
  - c. heart disease and stroke; HIV/AIDS; homicide and accidents; cancer; infant mortality; and diabetes.
  - d. cancer; heart disease and stroke; HIV/AIDS; diabetes; homicide and accidents; and cirrhosis.
2. For which of the following groups is cardiovascular disease not a leading cause of death?
  - a. African American men
  - b. Hispanic American women
  - c. Native American men
  - d. Asian American women
3. Which racial/ethnic group is less likely to be correctly diagnosed, treated, and/or referred for cardiovascular diseases?
  - a. African American women
  - b. Hispanic American men
  - c. Native American women
  - d. Asian American men
4. Which of the following characteristics is exhibited in benign tumors?
  - a. slow growth
  - b. can be life threatening based on location
  - c. nonmetastasizing
  - d. all of the above

5. Which of the following racial groups is part of the Hispanic ethnic group?
  - a. Native Americans
  - b. white
  - c. black
  - d. all of the above



Drs. Enwonwu and Sanders

6. Common features of chronic malnutrition include:
  - a. immune suppression.
  - b. growth retardation.
  - c. changes in oral microbial ecology.
  - d. all of the above
7. Prolonged folic acid deficiency causes:
  - a. microcytic anemia.
  - b. hypermethylation of DNA.
  - c. disruption of DNA integrity.
  - d. all of the above
8. Which nutrients yield energy on being oxidized during metabolism?
  - a. carbohydrates, proteins, and water
  - b. proteins, water, and minerals
  - c. carbohydrates, lipids, and proteins
  - d. vitamins, fats, and carbohydrates
9. Dietary constituents can hinder or promote the development of which chronic diseases?
  - a. diabetes
  - b. cardiovascular pathologies
  - c. cancer
  - d. all of the above
10. Acute-phase protein response, which influences healing of injured tissue, is:
  - a. promoted by malnutrition.
  - b. impaired in the malnourished.
  - c. episodic in the malnourished.
  - d. none of the above



Dr. Holmes-McNary

11. Hepatocellular carcinoma:
  - a. is one of the most common human tumors.
  - b. has increased in incidence over the years.
  - c. generally develops based on the development of liver cirrhosis.
  - d. all of the above
12. Risk factors in the etiology of liver cancer include:
  - a. hepatitis B and C viruses.
  - b. diet, smoking, alcohol, and oral contraceptives.
  - c. a and b
  - d. none of the above
13. Which of the following population groups have the highest prevalence of hepatocellular carcinoma?
  - a. African and Chinese
  - b. African American and Japanese
  - c. Native American and African American
  - d. Chinese and Native American
14. Which of the following are not risk factors for hepatocellular carcinoma?
  - a. carcinogens including aflatoxin
  - b. oltipraz and dithiolethiones
  - c. viral and bacterial infections
  - d. obesity, diabetes, altered gene expressions
15. Therapeutic modalities successful in cirrhotic patients include:
  - a. chemoprevention and nutritional intervention.
  - b. interferons and transforming growth factors
  - c. gene therapy and chemotherapy
  - d. all of the above

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**Dr. Desvarieux**

16. Differing results from studies of periodontal infections and vascular disease are evidence that:
  - a. there is no association.
  - b. all these studies are badly conducted.
  - c. there is definitely a causal relationship.
  - d. it is difficult to ascertain a relationship when a risk factor is as ubiquitous as chronic periodontal infections and when the putative risk is of such small magnitude.
17. Establishing the validity of periodontal infections as independent risk factors for vascular disease is:
  - a. important because the association, if sustained, would lead to a significant contribution to the attributable risk of vascular events because of the common prevalence of periodontal infections.
  - b. not important because periodontal infections are not prevalent enough.
  - c. not important because the risk is likely to be too low to matter.
  - d. not important because all the risk factors for myocardial infarction and stroke have already been described.
18. Which of the following statements describing stroke (cerebral infarction) is true?
  - a. the etiology of all strokes is well known in the US.
  - b. stroke is not a major cause of excess mortality in black Americans.
  - c. cerebral infarction of unknown etiology represents about 40% of cases in stroke databanks and the importance of potential precipitants is not well defined.
  - d. all of the above
19. In the most comprehensive study of periodontal disease conducted by NIDCR from 1988 to 1991, the overall prevalence of periodontal disease, as defined by attachment loss of > 5 mm, was:
  - a. 20% in people aged 55 to 64 years.
  - b. 35.1% in people aged 55 to 64 years.
  - c. 80% in people aged 65 years and older.
  - d. less than 10% in people aged 55 to 64 years.
20. A 1991 national survey of employed adults suggests that the prevalence of periodontal pockets in black Americans:
  - a. was equal to that of white Americans.
  - b. was less than that of white Americans.
  - c. was twice that of white Americans.
  - d. was 10 times that of white Americans.
21. The preponderance of evidence supporting the adverse effects of diabetes on periodontal health comes principally from:
  - a. longitudinal observational studies.
  - b. randomized controlled trials.
  - c. experimental studies.
  - d. observational studies in convenience samples.
22. The recently released Surgeon General's report on oral health has concluded that:
  - a. diabetes is a risk factor for periodontal disease occurrence and progression.
  - b. periodontal infection adversely affects glycemic control in diabetes.
  - c. only the prevalence of periodontal disease is affected by diabetes.
  - d. the effect of diabetes on periodontal health is seen only in children with Type 1 diabetes.
23. Direct evidence supporting an adverse effect of periodontal infection on glycemic control comes from:
  - a. consistent results in randomized controlled trials.
  - b. treatment and observational studies.
  - c. cross-sectional studies in convenience samples.
  - d. large population-based cross-sectional studies.
24. Analysis of the NHANES III data for US adults shows that:
  - a. among those with poorer glycemic control, the percentage of African Americans with severe active periodontitis is not significantly different than the percentage of non-Hispanic whites with severe active periodontitis.
  - b. diabetes and severe periodontitis are not causally related.
  - c. the presence of severe active periodontitis is not associated with a larger percentage of people with poorer glycemic control.
  - d. diabetes and severe periodontitis are causally related.
25. The percentage of US adults with poorer glycemic control in the NHANES III survey is:
  - a. significantly higher in African Americans with severe active periodontitis than in non-Hispanic whites with severe active periodontitis.
  - b. higher in both African Americans and non-Hispanic whites with severe active periodontitis than in those without severe active periodontitis.
  - c. higher in African Americans without severe active periodontitis than in non-Hispanic whites with severe active periodontitis.
  - d. not related to race/ethnicity or presence/absence of severe periodontitis.



**Dr. Taylor**



**Drs T. Perkins  
and I. Perkins**

26. The major cause of oral cancer is:
- tobacco usage in combination with excessive alcohol consumption.
  - genetic predisposition.
  - mouth breathing.
  - previous history of skin cancer.

27. The most common site for an oral cancerous lesion is the:
- tongue.
  - tonsil.
  - attached gingiva.
  - hard palate.

28. What percent of oral and pharyngeal carcinomas are attributed to excessive alcohol consumption and tobacco acting together?
- 5% to 15%
  - 99%
  - 75% to 90%
  - 0%

29. Approximately how many persons in the United States die each year from oral cancer?
- 1,000
  - 8,000
  - 10,000
  - 80,000

30. The "overall" 5-year survival rate in the general population for oral cancer is:
- 87%.
  - 11%.
  - 52%.
  - 100%.



**Dr. Hodge**

31. Since 1996, which racial/ethnic population has reported the most AIDS cases?
- white homosexual men.
  - white heterosexual women.
  - Hispanic injecting drug users.
  - African American men and women.

32. African Americans represent 12% of the US population and:
- 38% of all AIDS cases.
  - only 5% of new AIDS cases.
  - half of all injecting drug users.
  - 25% of all new AIDS cases.

33. Among African American women, 40% were infected with HIV through:
- blood transfusions.
  - heterosexual contact.
  - injecting drug use.
  - unknown sources.

34. Because African Americans are less likely to participate in antiretroviral drug clinical trials:
- the new drugs are not offered to African Americans.
  - the new drugs are ineffective for African Americans.
  - the drugs given to blacks are based on results from white men.
  - the drugs given to blacks have little therapeutic value.

35. Globally, an estimated 15,000 new HIV infections occur:
- every week.
  - every month.
  - every year.
  - every day.

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1. Velpe AR, et al. J Clin Dent. 1996;7(suppl):S1-S14. 2. Data on file, Colgate-Palmolive Company.

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