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THEME ARTICLE

Cystic fibrosis: a current review

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Abstract

Cystic fibrosis (CF) is the most common severe genetic disorder seen in Caucasians. Defective exocrine gland secretions result in chronic diseases of the respiratory and gastrointestinal systems. However, the CF gene recently has been located and cloned. Currently, genetic technology allows identification of sibling carriers and antenatal diagnosis within families.

Oral implications associated with CF include enamel hypoplasia and tooth discoloration, salivary gland involvement, reduced incidence of dental caries, reservoir for potentially pathogenic respiratory bacteria, mouth breathing, and anterior open bite associated with nasal and sinus obstruction. Continued efforts to improve early diagnosis and treatment of CF should increase life expectancy. Affected patients are expected to seek regular dental care more frequently as they learn to view the disease as manageable.

Introduction

Cystic fibrosis (CF) is the most common of the severe genetic disorders seen in Caucasians. The relationship of congenital cystic pancreatic fibrosis and bronchiectasis was reported in 1936 (Fanconi). However, the first detailed description of the associated pathology was made by Andersen (1938). Defective exocrine gland secretions due to abnormal water and electrolyte transport across epithelial cells, result in chronic disease of the respiratory and gastrointestinal systems, elevated sweat electrolytes, and impaired reproductive function. Retarded growth and development, even that of the dentition, have been observed and are believed to be associated with an endocrine-mediated pleiotropic effect of the CF locus (Primosch 1980; Mahaney and McCoy 1986). Affected patients, once unlikely to survive their first decade of life, now are living into the second or third decades and beyond. Improved diagnosis and treatment, largely in clinical care centers sponsored by the Cystic Fibrosis Foundation (CFF), have increased survival and resulted in identification of 30,000 persons with CF in the United States and Canada. Approximately one-third of these individuals now are adults. Thus, a disease once thought to be the sole responsibility of the pediatrician is becoming a challenge for internists, family physicians, and other adult-care providers.

Patients with CF require routine dental care similar to that of the general population. Since optimal dietary intake is of utmost importance for nutrition and growth, dental care is a prime requisite. Unless acutely ill, the CF patient can and should receive regular dental care. Although these patients suffer from chronic lung infections, they are not contagious to others. Neither are they more susceptible to contagious infections than healthy persons. They may present some minor problems peculiar to CF, but none of these requires more than a basic understanding of the disease, which is one of the goals of our review.

This is an exciting time for CF patients, their families, and those who provide their health care. As a result of a concerted effort by the CFF and the National Institutes of Health (NIH) to promote research programs, the main genetic mutation responsible for CF has been discovered, and the metabolic abnormalities which alter secretory function are being defined. Although more research will be required to determine the exact pathophysiological mechanisms, these recent advances should lead to a more complete understanding of the disease, including ways to correct and prevent the defective functions caused by the CF gene. This review provides a background and describes recent developments in the pathophysiology, diagnosis, and treatment of CF and focuses on aspects of particular interest to dentists providing care for these patients.

Genetics

Cystic fibrosis is an autosomal recessive disorder most commonly associated with Caucasians of Northern and Western European ancestry. Epidemiologic surveys show an incidence ranging from 1:1700 to

1:6500 live births (Boat et al. 1989). The overall incidence for North American Caucasians is 1:2500 and for American Blacks 1:17,000. The disease also is seen in American Indians and Mexican Americans, but incidence figures for these groups are not available. Orientals studied in Hawaii have the lowest reported incidence, 1:90,000.

The carrier rate for the gene (i.e., heterozygote frequency) is approximately 4% for American Caucasians. Thus, the risk of random pairing of heterozygotes is 1:625 (1:25 x 1:25). Factoring in the 1:4 chance of homozygous-affected offspring, the mathematical expectation is 1:2500. Since heterozygotes express no clinical features of the disease, they can be detected only by genetic analysis. This technology is quite new and expensive but should become generally available in the near future as specific probes for the CF gene are developed.

The classic CF phenotype includes chronic, progressive pulmonary disease, pancreatic insufficiency with steatorrhea and failure to thrive, excess sweat electrolyte content, male sterility, and decreased female fertility. Variations of phenotypic expression range from patients with all of the above features to those with no digestive component or only very mild respiratory symptoms. Occasionally, patients present only with nasal polyposis or biliary cirrhosis and a few even have normal sweat chloride levels. While phenotypes tend to be similar within families, combinations of severely and mildly affected siblings also are seen. A genetic explanation for some of the variability of expression is suggested by the recent discovery that one major genetic defect accounts for 70% of CF gene alterations, with several other genetic variants likely accounting for the remainder (Karem et al. 1989). Correlations of presenting manifestations and disease progression with specific genotypes soon should be possible.

Placement of the CF gene on the long arm of chromosome 7 was achieved in the mid-1980s with DNA linkage technology. As DNA probes closer and closer to the CF gene were developed, its location became more and more precise. Finally, in 1989, collaboration between geneticists in Toronto and Michigan resulted in cloning of the gene, which spans approximately 250,000 base pairs of DNA (Rommens et al. 1989). A deletion of three base pairs results in the omission of a single phenylalanine moiety from the protein transcript (Riordan et al. 1989). This membrane protein has ATP binding and phosphorylation sites and has been designated the CF transmembrane regulator (CFTR) protein. Its exact function in producing disordered transport of ions currently is the subject of intense research.

Current applications of genetic technology include identification of sibling carriers and antenatal diagnosis by studying restriction fragment-linked polymorphisms (RFLP) within families. As probes for the CF gene become available, genotypic identification of random carriers will be possible. This technique also will provide a "gold standard" for diagnosis of cases with questionable diagnostic findings including subjects with normal-range sweat tests. If cost is sufficiently modest, genetic analysis likely will replace sweat testing for routine diagnosis of CF once all the mutations are identified.

Pathophysiology

Most patients with CF have "sticky" or thickened mucous secretions which lead to obstruction and malfunction of respiratory and gastrointestinal systems. Until recently, this concept was based upon clinical observations only. In the early 1980s, Knowles et al. (1981) discovered that CF subjects generated abnormally high electrical potentials across the nasal respiratory epithelium. This anomaly was correctable with amiloride HCl, a sodium channel blocker. Further studies revealed that the defect extended to epithelial surfaces in the trachea and bronchi, and that excessive sodium reabsorption from surface secretions could be documented consistently in CF airway epithelia. These observations led to the hypothesis that disordered salt and water transport accounts for the thickened respiratory secretions in CF (Knowles et al. 1986) (Figs 1 and 2, next page).

Quinton (1983) described a block in the chloride channel in sweat glands which results in failure to reabsorb electrolytes from the sweat fluid. This results in elevated levels of electrolytes, including Na^+ and Cl^-, in secreted sweat. Further studies have shown that a chloride channel in respiratory epithelia also is impermeable to chloride ions, preventing Cl^- secretion across the apical cell membrane into the surface fluid (Knowles et al. 1986). Both excessive sodium reabsorption and impaired chloride secretion seem to be caused by abnor-

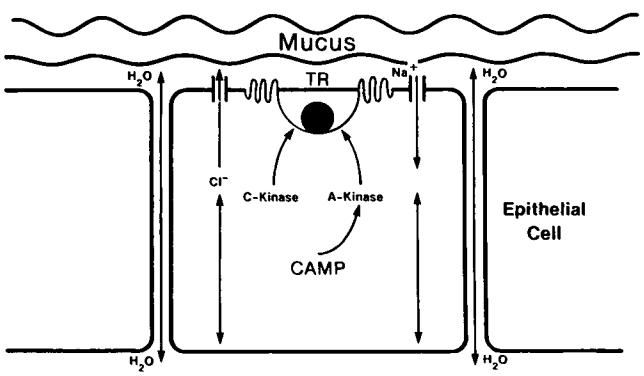

Fig 1. Normal epthelial electrolyte transport. Normal chloride secretion and sodium reabsorption permits the movement of water to the cell surface. This provides hydration to the respiratory epithelial surface and mucous secretions. TR = transmembrane regulator protein); CAMP = cyclic adenosine 3',5'-monophosphate.

mal regulatory mechanisms in CF cells. Consequently, the amount of water in cell surface fluid is limited, and there is dehydration of the respiratory mucous secretions. Inadequate hydration is at least, in part, responsible for problems with clearance of mucous from airways.

Abnormalities of mucins produced by CF subjects also have been described, but it is not clear to what extent these abnormalities play a pathophysiologic role. Perhaps the best documented of these changes is oversulfation of secretory glycoproteins. Oversulfation also is a feature of glycoproteins on epithelial cell surfaces in CF airways. Increased sulfation could change the physical properties of mucous secretions as well as the binding of bacteria to cell surfaces. However, it has not been shown that sulfation abnormalities are directly linked to either pathologic process (Cheng et al. 1989).

Since epithelial cell surfaces are common to other affected organ systems, such as the pancreas, salivary glands, mucous surfaces in the upper and lower gastrointestinal tract and reproductive organs, it is presumed that defective ion transport accounts for most, if not all, failure to clear secretions in CF. This supposition is supported by abnormal electrical potential differences in upper and lower respiratory epithelium, gastrointestinal and rectal mucosa, and sweat glands. Although earlier studies suggested that humoral factors were responsible for many abnormalities in CF, cultured respiratory epithelial cells from patients retain the defect — proving it is a genetic characteristic intrinsic to the affected cells (Yankaskas et al. 1985).

Most of the clinical manifestations of CF are produced by abnormal secretions. Chronic sinusitis and nasal polyps are common in the respiratory tract. Interference with mucous clearance not only obstructs airflow but also allows bacterial colonization of the normally sterile lower airways, first with oropharyngeal flora and later with pathogenic bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. This infection, in turn, stimulates more mucous secretion and leads to focal areas of atelectasis and bronchiectasis. This continued cycle of obstruction, infection, and destruction of airway tissues ultimately ends in respiratory failure, the most common cause of death.

Obstruction and obliteration of pancreatic ducts occurs during fetal development, and most patients exhibit digestive enzyme insufficiency, although only 85% require replacement therapy. The biliary system also is affected by inspisated secretions, and up to 10% of patients may develop frank biliary cirrhosis. Problems with gall bladder disease, including cholelithiasis also are relatively common. Male infants are born with atretic vas deferens, presumably due to obstruction and fibrosis or resorption of Wolffian ducts in utero. Thus, approximately 98% of adult males are sterile. Adult females secrete a thickened viscous mucous plug in the cervix uteri which hinders sperm mobility and tends to decrease fertility.

Identification of the CF transmembrane regulatory protein provides evidence that absence of a single amino acid, phenylalanine, can be responsible for defective epithelial ion transport. Correction of the defect may be feasible once it has been determined how this abnormal regulatory protein operates. Alternatively, transfer of normal genetic material into CF airway epithelial cells may be possible someday. These approaches represent the ultimate therapy for CF, and possibly the only truly effective approach, since treatment of clinical manifestations has failed to halt the inexorable progression of the disease process.

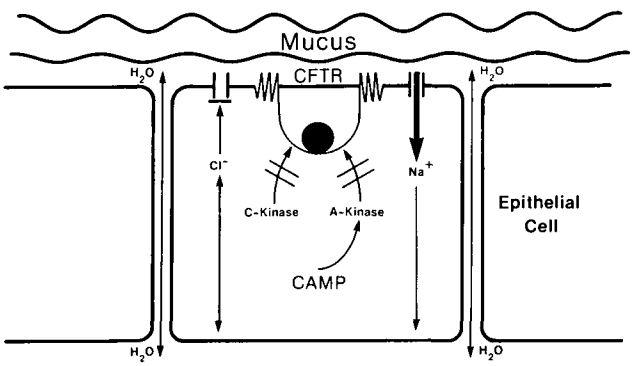

Fig 2. Cystic fibrosis epithelial electrolyte transport. A defect in the ion transport system of CF patients' respiratory epithelia produces a block in the chloride channel preventing normal cellular chloride excretion and sodium reabsorption. This disruption in electrolyte transport restricts the movement of water to the cell surface. It is hypothesized that this inadequate hydration contributes to the production of thick respiratory mucous. CFTR (cystic fibrosis transmembrane regulator protein); CAMP = cyclic adenosine 3',5'-monophosphate.

Clinical Aspects of Cystic Fibrosis

Early and late manifestations

As suggested previously, CF presents in a variety of ways and occasionally may escape diagnosis for many years. The earliest manifestation is intestinal obstruction in the newborn — meconium ileus. This occurs in 10% of cases and tends to run in families. It often can be managed by therapeutic radiopaque enemas but may require surgical intervention. Usually, it presents no further problems once corrected. Most infants are diagnosed because of persistant loose, bulky, oily stools, failure to thrive, and/or recurrent pneumonia in the absence of meconium ileus, or a family history of CF. Some patients manifest few or no diagnostic symptoms for several years, although 70% of cases are now identified by age two years. Mild respiratory symptoms may

be mistaken for allergic illness, especially in the 10–15% of patients who have normal digestive function. Other unusual presentations include nasal polyposis, rectal prolapse, recurrent abdominal pain, biliary chirrosis and fat-soluble vitamin deficiencies. Adults with very mild disease initially may present because of infertility.

Diagnosis

The diagnostic criteria for CF include a sweat chloride level greater than 60 meq/L, chronic obstructive pulmonary disease, exocrine pancreatic insufficiency, and a familial history of CF. At least two of these criteria are necessary for diagnosis, in addition to a positive sweat chloride test (Wood et al. 1976).

The diagnostic test for CF is based upon quantitative analysis of sweat chloride concentration. This method first was described in 1953 and has remained a standard (National Academy of Science 1976). It utilizes pilocarpine iontophoresis to induce maximal sweating in a small area of the forearm with quantitative collection and analysis for Cl^- content. Results are very reliable when performed by experienced personnel, but a high frequency of false positive and negative values are obtained when tests are conducted by inexperienced technicians. It is important that all suspected cases be confirmed in a facility with appropriate expertise, such as one of the 126 CF Centers approved by the CFF. When one child is diagnosed, all siblings, and perhaps other family members, should be tested. As mentioned above, DNA analysis soon may replace the sweat test as the diagnostic procedure of choice.

Treatment, progression of disease, and survival

Once diagnosed, most patients respond quite impressively to nutritional therapy with pancreatic enzymes and vitamin supplementation. Special infant formulas, comprised of protein hydrolysates and medium chain triglycerides, are used during the first year of life. Thereafter, a regular diet is adequate for most patients. Any evidence of pulmonary disease is explored with microbial cultures, chest radiographs, and pulmonary function tests in older children. Appropriate antibiotics are administered aggressively (by IV, if necessary). Bronchodilators are given orally or by aerosol inhalation to patients with evidence of airway reactivity (i.e., asthmatic symptoms). Chest physical therapy is taught to parents and performed several times daily to promote drainage of bronchial secretions. The goal of initial treatment is to achieve as normal a status as possible. Most patients rapidly regain normal growth percentiles and clear most, if not all, symptoms of respiratory disease.

When combined with psychosocial support and education, this therapeutic approach has changed the natural course of CF impressively. However, the basic defect remains, and slow but inexorably progressive involvement continues, particularly in the lungs. Compliance plays a major role in the effectiveness of recommended therapy for each patient. Family education, continued review, and support are important components of long-term care. Study of patient outcome as a function of frequency and intensity of medical care suggests that patient survival is related directly to these factors (Wood 1985).

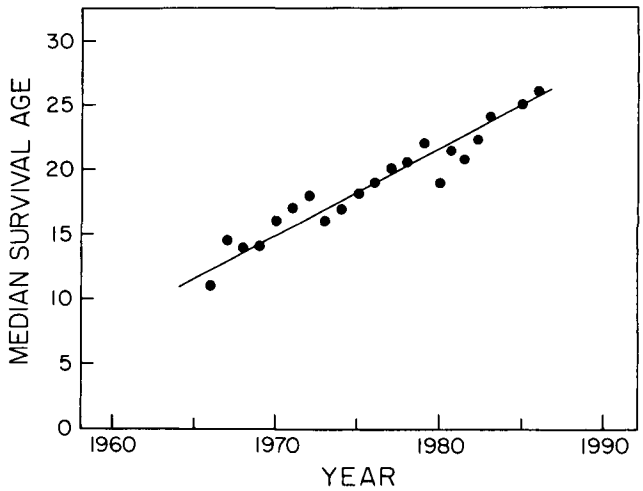

Fig 3. Projected survival age for cystic fibrosis. Based on data from the Cystic Fibrosis Foundation Patient Registry, expected survival has increased from 10 to 26 years since 1964 (as of 1986).

Survival statistics have been collected by the CFF Patient Registry since 1966 and have shown a steady increase in median survival rate from 10 to 26.5 years of age as of 1986 (Fig 3). Thus, the majority of newly diagnosed patients can expect to live into and beyond their third decade. This increase in life expectancy is very encouraging to patients, their families, and also to health care workers, many of whom were influenced by the gloomy predictions they had encountered in their training.

Prolonged survival of this aging population presents another great challenge. Support of adolescents and young adults is important as they strive to achieve an education, experience courtship and marriage, and find suitable employment in modern society. All members of the CF care team must be involved in promoting these goals.

Cystic Fibrosis and the Dental Patient

Considering the foregoing, it is obvious that CF children and adults must consume a nutritious diet to achieve and maintain normal growth and development. In most cases, a normal age-appropriate diet is recommended along with pancreatic enzymes and vitamin

supplements. The dentition must be maintained in an optimal state to assure proper dietary intake. Dental development should be within normal limits in patients with stable health and good nutrition.

Many CF patients have a chronic cough and may appear to be ill. However, they are **not** contagious to dental personnel or other patients, unless they have symptoms of an acute upper respiratory infection with fever and coryza. A simple history will determine whether they are attending school and have had any recent changes in health status.

CF patients often will be taking antibiotics for treatment of their lung infection, including penicillins, cephalosporins, or trimethoprim-sulfa formulations. In advanced cases, antibiotics such as chloramphenicol or ciprofloxacin may be prescribed. Tetracyclines, which became notorious for staining teeth in the past, are not recommended for children younger than eight years old and now are used less frequently in older patients. Prescribed antibiotic therapy should be continued while dental care is being provided. Oropharyngeal candidiasis is seen only occasionally in CF patients, although protracted or excessive use of antibiotics may cause changes in the oral flora.

CF patients often are mistakenly assumed to have defective immunity because they have chronic lung infections. If fact, their immune system is stimulated constantly, and frequently they have higher than normal immunoglobulin levels. Most microorganisms seem to be phagocytosed normally, although interactions between phagocytic cells and *Pseudomonas aeruginosa* may be inhibited in chronically infected patients. In summary, CF patients usually are capable of resisting infections outside the respiratory tract without difficulty and should not be considered immune deficient.

Oral Manifestations

The delay in dental and skeletal maturation observed with CF generally resolves if survival to the second or third decade is obtained. However, there have been several oral complications/manifestations associated with the disease which deserve description.

Coronal Discoloration

A high incidence of tooth discoloration and hypoplastic defects of the permanent teeth have been reported among patients with CF (Swallow et al. 1967; Jagels and Sweeney 1976). However, this appears to have been incidental to ingestion of tetracycline during tooth formation. Recognition of this undesireable side effect of the drug prompted the use of alternative antibiotics with subsequent significant reduction in dental hard tissue involvement.

Salivary Glands

The effects of CF on the major salivary glands range from minor to significant. The mucous-secreting glands are pathologically affected, but the serous glands reveal no significant impact (di Sant'Agnese and Davis 1976). The parotids are virtually pure serous glands. Consequently, their saliva is only minimally affected. Submandibular glands usually are enlarged and easily palpable. There are significant changes in the submandibular, sublingual and minor salivary gland architecture, and saliva composition (Mandel et al. 1967; Wiesmann et al. 1972). The submandibular gland is mixed, containing both serous and mucous acinar cells. However, the sublingual gland is almost exclusively mucous. Therefore, it is logical that the sublingual gland is more severely affected. Disruption of normal parenchymal architecture is evident with distended acini and loss of distinguishing cellular morphology. The acinar lumina and ducts of both the sublingual and submandibular glands often are clogged with cellular debris and fine filaments. The pathological changes noted in these glands would appear to be associated principally with ductal obstruction, although some may be secondary to the disease process itself. The calcium content is found to be elevated along with the mean pH and buffering capacity of the whole saliva (Wotman et al. 1973; Kinirons 1983, 1985).

Caries

The frequency of sugar-containing food consumption generally is greater in children with CF as a result of their need to maintain elevated caloric and salt intake. In spite of these nutritional guidelines, the caries incidence among these patients has been reported to be lower than in an age-matched healthy population (Primosch 1980).

It also has been observed that there is less dental plaque and gingivitis in CF patients. The reduced caries rate may be related to the effects of long-term antibiotic and pancreatic enzyme replacement therapy on the oral microbiota (Littleton and White 1964; Sweeney and Shaw 1965).

The previously described elevated calcium content and buffering capacity of the whole saliva provide additional explanation for the reduction in dental caries. This favors tooth remineralization and also is consistent with the observed increased prevalence of dental calculus on the teeth.

Bacterial Colonization

Pathogenic bacteria, especially mucoid *Pseudomonas aeruginosa*, are associated with chronic obstructive pulmonary disease. It has been shown that many CF patients are carriers of *P. aeruginosa* in the pharynx and on the buccal mucosa, dorsum of the tongue, and in the saliva (Lindemann et al. 1985). The role of this coloniza-

tion played by indigenous oral organisms and salivary coaggregation properties is unresolved. However, aspiration of these oral bacteria may be the source of pulmonary reinfection in high-risk patients.

P. aeruginosa has shown an ability to develop resistant strains to chlorhexidine-containing products. The use of antimicrobial oral rinses, singularly and in combination, is being investigated to address this concern.

Malocclusions

Mouth breathing and anterior open bite have been associated with chronic nasal and sinus obstruction often seen in patients with CF (Blacharsh 1977). The severity of systemic disease and prognosis for life expectancy must be considered prior to initiating definitive orthodontics. In addition, because of the additional sites for bacterial plaque formation associated with orthodontic appliances, a well-defined caries prevention program of improved oral hygiene and fluoride use is essential prior to beginning any malocclusion-corrective therapy.

Dental Management

There have been many recent advances in the medical management of CF. However, there remain precautions which must not be overlooked by the treating dentist. Patients with pulmonary involvement may be more comfortable if appointments are kept short. They also may prefer to be maintained in an upright sitting position while being treated, since it often is necessary for them to clear secretions from the bronchi and trachea by coughing frequently.

The concern of precipitating an atelectasis makes patients with CF poor candidates for conscious sedation techniques. The use of **any** agent that interferes with pulmonary function, such as narcotic analgesics and sedatives, should be avoided. Nitrous oxide/oxygen also is contraindicated in patients exhibiting evidence of emphysema and should be used only after consultation and concurrence by the patient's physician.

Persisting treatment limitations emphasize the importance of an aggressive dental disease prevention program. Regular professional care and good home oral hygiene habits are extremely important in CF patient management.

Future Projections

Continued efforts to improve early diagnosis and treatment of CF should further extend life expectancy for this population, although CF remains a major cause of death in the first decade of life. Families can be expected to seek regular dental care more frequently and consistently as they learn to view this disease as a long-term management challenge. Dentists who provide oral health care to CF patients and their families will derive considerable satisfaction from following them as they grow and develop throughout childhood, adolescence, and adulthood.

Research on the genetic control of CF soon should reveal new deletions in the genome which account for the variety of observed clinical patterns. This will lead to more exact diagnosis, particularly in unusual cases, and effective genetic counseling, whether for antenatal diagnosis, identification of heterozygosity in siblings, or in random members of the population.

Long-range research goals are focused on defining the exact pathophysiology of the exocrine glandular secretions. Therapeutic correction of the defect may become feasible as these pathogenic mechanisms are clarified. The replacement of a missing substrate, administration of a competitive analog, or insertion of normal DNA in place of the defective gene, i.e., "gene therapy", are all possibilities. Fulfillment of these expectations will undoubtedly require much time and effort. However, it now is apparent that more precise diagnosis, treatment, and even prevention of CF is becoming a reality. The high degree of success achieved in understanding this disease is the result of the combined efforts of a concerned public, the CFF, and medical scientists with special interests in solving the CF puzzle. The results of these efforts already have reduced human suffering and medical costs associated with this disease, and ultimately may prevent its occurrence.

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Bad teeth related to heart attacks?

One in three heart attacks cannot be explained by the usual risk factors, and cardiologists have been looking for the other common "missing" factors.

The *British Medical Journal* reports that researchers in Finland may have discovered one of these missing factors. Persistent infection in the mouth from dental caries or periodontal disease was found to be much more common in heart attack victims than among people of similar age and sex not having heart attacks.

The researchers speculate that bacterial toxins get into the circulation whenever food is chewed and pressure exerted on gums and teeth. Bacterial toxins are known to have injurious effects on the lining of blood vessels and might help set the stage for coronary artery narrowing with deposits of cholesterol, leading to heart attacks.