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Dental Caries: Prospects for Prevention

Combined utilization of available and imminent measures should largely prevent this ubiquitous disease.

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Dental caries is localized, progressive decay of the teeth, initiated by demineralization of the outer surface of the tooth due to organic acids produced locally by bacteria that ferment deposits of dietary carbohydrates. With progressive loss of tooth mineral and secondary destruction of tooth protein by continued bacterial action, cavities form which, if untreated, extend and destroy most of the tooth, often leading to serious infection of the surrounding tissues. Almost everyone in the United States experiences dental caries to some degree, mostly before adulthood. This disease is the leading cause of lost teeth before age 35, when chronic progressive destructive periodontitis (pyorrhea) begins to supervene. Though not ordinarily considered to be endangering to life, these two diseases are among the most prevalent and troublesome afflictions of man. Both are consequences of selective colonization of tooth surfaces by bacteria indigenous to the oral cavity.

During the past decade, dental caries research has experienced an impressive resurgence on a broad front, catalyzed primarily by experimental substantiation of the concept that caries results from one or more transmissible infections (*1*). Specifically, caries results from colonization of vulnerable surfaces of the teeth by a characteristic group of bacteria, harbored by many members of a susceptible host species and transmitted from them to previously uninfected members of the same species. These bacteria ferment dietary carbohydrates in situ, principally to lactic acid which, at susceptible sites, initiates the carious lesion by demineralizing the enamel surface. In particular, the predominant group of cariogenic bacteria identified until now can metabolize sucrose in a peculiar way, producing extracellularly an adhesive polysaccharide (dextran) from the glucose moiety, and mainly lactic acid from the fructose moiety. Typically, these bacteria also store intracellular polysaccharide (amylopectin) during periods of environmental carbohydrate abundance and utilize it with the formation of lactic acid during periods of environmental carbohydrate deficiency. The development of caries requires critical relationships between tooth surface, oral microbiota, and dietary carbohydrate (Fig. 1). The logical approach to control, therefore, is to modify one or more of the three factors in this host-parasite-environment complex.

Yet despite the advances in our understanding of its pathogenesis, caries continues to be a major public health problem. In the United States, nearly everyone sooner or later develops some caries; it has been estimated that we now spend about $2 billion annually to repair the resultant damage. Even so, we obviously meet only a minor fraction of the need. Since caries is principally a disease of young people, recent experience of the U.S. Army gives a representative picture of the problem. Army surveys indicate that every 100 inductees require 600 fillings, 112 extractions, 40 bridges, 21 crowns, 18 partial dentures, and one full denture (*2*). To repair completely the damage caused by caries nationwide would cost an estimated $8 billion more annually than we now spend.

On the other hand, review of the caries research accomplished warrants expectation that we could greatly speed amelioration of such deplorable statistics by a concerted effort to apply existing knowledge, to develop established leads, and to foster the fundamental research judged most likely to produce utilizable new information. To this end the National Institute of Dental Research has embarked on a National Caries Program.

For control of caries, priority must be given to prevention, rather than repair or cure, because there are no clearly evident therapeutic leads that promise to do more at best than arrest a carious lesion once it is clinically detectable. On the other hand, experience cautions us that prevention will be achieved only gradually. Meanwhile, heavy demand for restorative dentistry will continue and so will the research for improved restorative materials and procedures. This discussion, however, is limited to prevention.

In seeking areas where action seems most likely to benefit the most people promptly, three questions were asked. What measures of proved efficacy are being used inadequately? What measures have been sufficiently proved by preliminary clinical trials to warrant large-scale field demonstration or national application? What fundamental research is ready for intensive development and clinical trial? The currently most likely answers follow, as they pertain respectively to tooth, diet, and cariogenic bacteria.

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Protecting the Teeth

Adequate incorporation of fluoride in teeth, particularly in the outer layers of the enamel, remains the one thoroughly proved means to increase resistance of teeth to caries (*3*). The experience of 25 years leaves no doubt that daily intake throughout life of about 1 milligram of fluoride per person, as commonly provided by from 0.7 to 1.2 parts of fluoride per million parts of water in public water supplies, harmlessly lowers the caries rate by from 50 to 60 percent in permanent teeth and slightly less in deciduous teeth, under present conditions in the United States. Logically, a national program to prevent caries should be based on universal fluoridation at this level. Yet in 1967 only 52.8 percent of our population using public water supplies received this benefit, 46.3 percent by controlled artificial fluoridation and 6.5 percent by natural fluoridation (*4*). Twenty-two percent of the total U.S. population, or 44 million persons, do not have access to public water systems, though presumably many ingest naturally fluoridated water and some receive controlled amounts of fluoride by other means. Clearly a major effort is still needed, to fluoridate more communal water supplies and by alternate means to get fluoride to the large fraction of our population not thus accessible. The latter group could be reached by controlled fluoridation of water supplies at central schools in rural areas; via the diet, as by addition of fluoride to salt, sugar, flour, milk, or other widely consumed foodstuffs; by direct ingestion of fluoride tablets or solutions; or by do-it-yourself topical application of fluoride, whether in dentifrices or in aqueous solutions (*3, 5*). Essentially, this seems to be a problem of public health administration.

What about the enormous number of carious lesions that develop despite fluoridation? Are we recommending a sufficient dosage of fluoride? The thorough epidemiological studies of the past indicated that more than 1 ppm of fluoride in the water supply did not confer much additional protection against caries in permanent teeth (*6*). Some investigators, however, have recommended 2 ppm as more beneficial for deciduous teeth, though at some risk of slight fluorosis (mottled enamel) in permanent teeth. Alternatively, the fluoride content of enamel can be increased by direct (topical) application, with practically no risk of fluorosis. Recent studies indicate that intensive topical application of fluoride, to increase the fluoride content of the outer few microns of enamel to two or three times the average level acquired from fluoridated water, can reduce caries by as much as 75 to 80 percent—that is, half again as much reduction as is brought about by controlled fluoridation of water supplies (*7*). Furthermore, the anticaries effect and the elevated fluoride content of the enamel persisted for at least 23 months without additional topical application and without fluoridated water (*8*). By using a slightly acid-phosphate-fluoride solution and prior treatment of the teeth with cations such as aluminum or titanium, which complex strongly with fluoride ion, it should be possible to reduce greatly the number of applications needed to achieve the desired levels of enamel fluoride (*9*).

Caries that develops despite optimum fluoridation of teeth occurs principally in the pits and fissures that are a normal feature of the occlusal (grinding) surfaces of the molars and bicuspids (*10*). This vulnerability is usually attributed to impaction of food residues and bacteria plus thinness of the enamel in these areas, at least in newly erupted teeth; with age, the enamel thickens and the susceptibility to caries lessens. On the other hand, it was shown in the 1920's that areas with pits and fissures could be protected against caries either by drilling them out to form wide nonretentive grooves or by preparing them like cavities and then filling them with dental amalgam (*11*). No matter how effective, these procedures obviously were not destined to gain wide popularity. Now the same result can be accomplished by sealing the occlusal surfaces with a newly developed adhesive polymer (*12*). The surface is cleansed, conditioned for bonding by a brief etch with a solution of phosphoric acid and zinc oxide, washed, and dried. The monomeric adhesive solution is painted on with a fine brush and allowed to flow out briefly to form a smooth coat. Polymerization is initiated by a short exposure to ultraviolet light of wavelength 3660 angstroms, which is shorter than the visible but longer than the "sunburn" range. One year after a single application, this sealant was retained in 99.5 percent of treated sites, which remained free of caries, whereas 42 percent of untreated contralateral sites in the same mouths had become carious. After a second year, sealant could not be discerned in 13 percent of treated sites on permanent teeth or in 50 percent on deciduous teeth; nevertheless, respective caries reductions of 99 percent and 87 percent were found. This simple, rapid, painless procedure can be carried out entirely by properly instructed and supervised dental assistants. Optimally, occlusal surfaces should be sealed soon after eruption of the tooth to protect them during their most caries-susceptible period—the first several years at least. It will be important to ascertain whether such early sealing impedes the previously mentioned normal maturation and development of resistance to caries, thereby possibly leaving the pits and fissures indefinitely susceptible to caries, if uncovered. Even if so, routine inspection and reapplication of sealant, if necessary, could compensate for this limitation. Application of this measure on a public health scale would, of course, have to overcome an enormous manpower problem, quite likely necessitating a great increase in auxiliary dental personnel.

Modifying the Diet

An abundance of epidemiological and experimental evidence indicates that sucrose is a particularly cariogenic culprit in our modern diet (*13*). So far as we know this unfortunate property relates to the peculiar way in which sucrose can be metabolized by cariogenic streptococci, as mentioned previously (*1*); admittedly, much more investigation of this point is needed. Whatever the mechanism, if we got practically all of our carbohydrate from starchy foods, and if we were adequately fluoridated, caries on the crowns of the teeth would almost certainly be negligible. Such is the case in regions of Southeast Asia, for example (*14*). Though the number of subjects is necessarily small, data on persons suffering from hereditary fructose intolerance point to the same conclusion (*15*). These persons are deficient in the liver aldolase that splits fructose-1-phosphate, an essential step in human fructose metabolism. They become violently ill if they ingest more than very small amounts of sucrose or fruit containing fructose. Consequently they tend to avoid sweetstuffs of all kinds, and consume starchy foods instead. They experience little or no caries.

Nevertheless, a low sucrose diet does not necessarily guarantee freedom from caries. Teeth in skulls from presucrose cultures exhibit a significant prevalence of caries (*16*). Though the attack rate in the original population can only be conjectured, it seems to have been much lower than in modern times. On the other hand, some geographically isolated populations currently subsisting predominantly on locally grown starchy diets, and presumably consuming little or no sucrose, experience a caries prevalence as great as half that recorded in unfluoridated regions of the United States (*17*). Since nearby groups on similar diets experience little or no caries, environmental factors presumably are involved—possibly a peculiarly high level of fluoride and other trace elements in the diet (*18*).

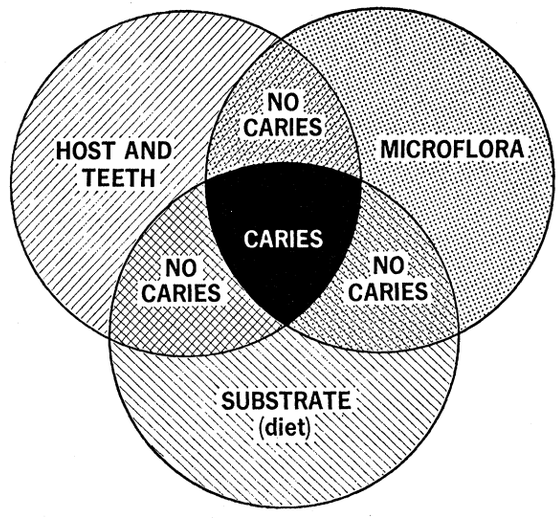

Fig. 1. Host-parasite-environment complex as it affects the teeth. Caries is initiated only when particular acidogenic bacteria colonize vulnerable sites on teeth (most often on the crown) and when in addition the diet provides sufficient fermentable carbohydrate to produce enough acid to effect progressive demineralization of the outer layer of the enamel.

Whether replacement of dietary sucrose by other sugars would reduce human caries as effectively as replacement by starch has not been ascertained; there are no data. In experimental caries of hamsters and rats, however, glucose or fructose, or an equimolar mixture of the two, have on the whole induced much less caries than sucrose (*19*). Comparisons between these studies are very difficult because of differences in strains of animal, consistency and composition of diets, methods of scoring caries, and measures to ensure presence of cariogenic bacteria. The reductions in caries activity have been most pronounced on smooth surfaces of teeth, where development of caries seems to depend on *Streptococcus mutans* and its adhesion by extracellular dextran produced from sucrose. In the hamster, all caries is of this type because of the morphology of the teeth. In the deep fissures of the rat molars, on the other hand, food impaction makes adhesion unnecessary and indigenous acidogens, as well as *S. mutans*, can initiate caries if provided with various fermentable sugars, such as glucose, fructose, maltose, or sucrose (*19, 20*). Substitution of starch for sugars, however, consistently reduces the caries scores to very low levels.

Replacement of sucrose in our diet would require quite a cultural and technological revolution, but might not be as impractical as it seems. Trials with candies made with a hydrogenated starch hydrolyzate have been made in Sweden (*21*). Even if sucrose could be replaced by other sweets in candy or other between-meal snacks alone, the result might be quite beneficial, judging by animal studies and epidemiological data. Merely reducing the frequency of eating a high-sucrose diet significantly reduces caries in rats (*22*). In humans, increased frequency of between-meal eating of sugary snacks correlates with increased caries attack (*23*). Furthermore, in vitro at concentrations of sucrose below 0.5 percent, *Streptococcus mutans* makes little or no dextran (*24*). This fact emphasizes the importance of keeping as low as possible the intraoral accumulation of sucrose, whether by reducing the frequency of intake, avoiding adherent sweetstuffs, or diluting the sucrose in sweetstuffs with other sweeteners. The considerations in this paragraph are, of course, predicated on the as yet untested assumption that in human diets other sugars would be less cariogenic than sucrose.

If it is not practicable to replace sucrose in our diet, can anything be added to the diet to mitigate its cariogenicity? Phosphates are a possible answer (*25*). More than 150 laboratory studies agree that addition of any of a wide variety of inorganic and organic phosphates to high-sucrose and other cariogenic diets significantly reduces caries in rats and hamsters, in some experiments almost completely. On average, the phosphorus content of the diet must be doubled to get a marked caries reduction. So far, the cyclic condensed salt, sodium trimetaphosphate, has been the most effective one. How phosphates mitigate caries has not been ascertained, except that they act locally in the oral cavity and seem to benefit newly erupted teeth the most. Unfortunately, the relatively few clinical trials reported so far do not tell us unequivocally whether or not a phosphate dietary supplement reduces caries in humans. Translating the conditions of the animal model into a regimen suitable for delivering adequate extra phosphate to humans presents many complexities. Conceivably it might be helpful if a phosphate were incorporated in sweetened between-meal snacks alone. Also, since phosphates evidently prevent caries by local action in the oral cavity, frequent direct application of concentrated solutions to the teeth might be beneficial.

Thirty years ago, epidemiologists of the U.S. Public Health Service were struck by the wide variations in caries experience between different localities (*26*). These differences were greatest between low-fluoride areas, though they were discernible between high-fluoride areas also. It was suggested that caries resistance might be attributable not only to the fluoride content of drinking water but also to other trace elements or to unusually high concentrations of ordinary constituents of the water. Only recently, however, has this experiment of nature begun to receive the epidemiological and laboratory study that it merits (*17, 27*). One study indicates a correlation between low caries experience and increased concentrations of boron, lithium, molybdenum, strontium, titanium, and vanadium in the drinking water. Except for fluoride, however, available data indicate that from 80 to 99 percent of our trace element intake comes from foodstuffs. Consequently, attention to the mineral content of water alone might mislead us. Thus, another study emphasizes the "alkaline earth"

factor in the soil—the content of strontium, calcium, barium, magnesium, lithium, and potassium and, to a lesser degree, zirconium and boron. Though it is clearly premature to consider controlled administration of such elements to humans, if these correlations can be validated and shown to signify a causal relation, an anticaries measure as potent as controlled fluoridation should eventuate.

Combating Cariogenic Bacteria

A comprehensive program for preventing caries should logically include measures to reduce colonization of the teeth by cariogenic bacteria or to suppress their activities, as by topical application of antibacterial agents, metabolic regulators to inhibit production of cariogenic products, or enzymes to digest products conducing to adhesion of bacteria to teeth, and immunological measures (*28*). Paradoxically, while strong emphasis has been given to increasing the resistance of teeth to caries and to reducing the cariogenicity of the diet, proportionately little attention has been given to antimicrobial measures, possibly because until recently evidence was lacking for specific agents in caries.

The cariogenic importance of a group of anaerobic streptococci now designated as *Streptococcus mutans* has been well substantiated (*29*). *Streptococcus mutans* occurs indigenously in the human mouth in widely separated parts of the world and often constitutes the majority of streptococci in dental plaque (*30*). Its preferred habitat is the surfaces of teeth, whether natural or artificial; it is scarce in the mouth before teeth erupt and becomes practically undetectable by direct culture in the mouths of edentulous adults when they stop wearing their dentures (*31*).

Oral infection with *S. mutans* and a diet high in sucrose are important and probably essential components for caries in hamsters, and for smooth-surface caries in rats (*32*). Streptococcal strains closely resembling the cariogenic *S. mutans* indigenous to rats and hamsters have been isolated by direct culture regularly from human carious lesions, where they frequently constitute the majority of the streptococci (*33*). Such strains induce caries when implanted in the oral cavity in conjunction with a suitable diet in germfree and "relatively gnotobiotic" rats, and in hamsters, gerbils, mystromys, and monkeys (*34*). The evidence for etiologic significance of *S. mutans* in human caries is therefore comparable to Koch's (1882) classic evidence for the causative role of the tubercle bacillus in human tuberculosis. Strains of *S. mutans* labeled by acquired resistance to streptomycin have been implanted in the human oral cavity (*35*). The high endemicity of wild-type *S. mutans* in the test population, however, prevents conclusions about the cariogenicity of the implanted strain (*30*).

Some strains of several other bacterial species have induced coronal caries in hamsters, gnotobiotic rats, or "relatively gnotobiotic" rats, when implanted in the oral cavity in conjunction with a high-sucrose diet. Included are strains of *Streptococcus faecalis, Streptococcus sanguis, Streptococcus salivarius*, streptococci not identifiable as recognized species, *Lactobacillus acidophilus*, and *Lactobacillus casei* (*36*). On the whole, however, these organisms have induced caries less regularly and less extensively than strains of *Streptococcus mutans*, particularly on coronal smooth surfaces.

Lactobacilli, long the leading contender as the microbial factor in human caries, have understandably been eclipsed of late by the evidence favoring streptococci. I believe there is good reason to keep them in the running. In addition to the experiments just cited, showing that monoinfection with some pure cultures of lactobacilli can induce caries in rats, other investigations have demonstrated a preferential accumulation of lactobacilli, commonly in conjunction with streptococci, in dental plaque prodomal to caries and in carious lesions in humans and monkeys (*37*).

The greater cariogenicity of *S. mutans* seems to relate to its characteristic of producing from sucrose extracellular water-insoluble "dextrans" of high molecular weight (*38*). Such dextrans conduce to greater adhesiveness of *S. mutans* to the tooth surface. They adsorb strongly to plain and saliva-coated powdered hydroxyapatite and consequently to the tooth surface. Suspensions of glucose-grown (that is, dextran-free) cells of *S. mutans* are agglutinated specifically on addition of high-molecular-weight dextran; accordingly, such cells attach to dextran-coated teeth (*39*). *Streptococcus sanguis*, another ubiquitous dextran-forming indigene of the tooth surface, does not exhibit similar behavior; though its dextran is water-insoluble, one must assume that it lacks cellular receptor sites for dextran (*40*). Nevertheless, its dextran might contribute to plaque accumulation by trapping *S. mutans*. In contrast to *S. mutans*, however, the relative abundance of *S. sanguis* in dental plaque has not been correlated with smooth surface caries in children (*33*).

Dextran accounts for as much as 10 percent of the dry weight of plaque, or a third of plaque matrix (*41*). Long-continued apposition of suitably acidulated gels, such as agar, gelatin, or cellulose derivatives, to teeth in vitro produces lesions closely resembling natural early enamel caries (*41*). Thus, dextran gel in plaque, acidulated by bacterial fermentation, might help initiate natural caries.

A measure which decomposes dextran or impedes its synthesis should mitigate caries. Accordingly, incorporation of a dextranase preparation in the diet and drinking water, or in the water alone, dramatically reduces both plaque accumulation and caries in hamsters on a high-sucrose diet and harboring *S. mutans* (*42*). Similar experiments in rats give less impressive results, particularly in caries of the molar fissures, where presumably the production of dextran and adherence of plaque are not essential and mechanical retention of cariogenic diet and bacteria suffices to induce caries (*1*, *43*).

A dextranase mouthwash can eliminate the dextranous portion of human dental plaque, though the gross diminution of the accumulation is not noteworthy, probably because human dental plaque is only partially composed of *S. mutans* and its dextran (*44*). Whether dextranase can be used to reduce the caries increment in humans will be learned from controlled clinical trials in progress.

Continuing oral administration of antibacterial agents via food and water can suppress specific cariogenic bacteria in rats and hamsters and reduce their caries scores by 90 percent or more (*45*). Following withdrawal of the agent, a stock of animals may remain free of the specific organism and nearly free of caries through a number of successive generations (*1*, *46*). An irreducible low level of car-

ies activity has always remained, presumably due to drug-resistant cariogenic bacteria that are normally present in the oral microbiota.

The most convincing comparable data for humans have come from patients receiving penicillin by mouth daily for rheumatic fever or for chronic respiratory diseases (*47*). During periods from 2 to 5 years, these patients developed 54 to 69 percent fewer carious tooth surfaces than a comparable, untreated group. The anticaries effect tended to persist after cessation of therapy.

Strangely, there has been a general reluctance to exploit the promising lead implicit in data of this kind, possibly because the microbial target was not well enough defined, possibly because of undue concern about deleterious changes in the oral microbiota, possibly because of unfavorable effects of certain antibiotics, such as tetracyclines, on the teeth. Now the target is more nearly defined, and bacteriological studies indicate that long-term administration of penicillin, for example, does not alter the oral flora harmfully (*48*). Surely a vigorous program to develop rational use of antimicrobial agents topically in oral hygiene is long overdue. Not only should such regimens help prevent caries but also they should help avert the onset and progress of chronic destructive periodontitis, the major cause of lost teeth during middle and later life (*28*).

Prospect of chemical control of plaque, however, should not be allowed to eclipse the continuing usefulness of mechanical oral hygienic measures (*28, 49*), that is, the toothbrush and adjuvant means for interdental cleansing. Such cleansing can keep the bacterial population at the gingival margin low enough to avert chronic periodontitis. The old adage that a "clean tooth never decays," however, has not been proved conclusively. What appears to the unaided eye to be a clean tooth still harbors bacteria in fissures, minute surface faults, and organic tracts of the enamel.

Though antibiotics have received the more attention recently, some investigators maintain that antiseptics (synthetic antibacterial chemicals) have a theoretical advantage. Since their antimicrobial spectrum is generally not very specific, their use could be expected to hold the oral biota in check overall and thereby entail less risk of altering its normal balance deleteriously (*50*). On the other hand, at the higher concentrations that could be used topically, the specificity of many antibiotics broadens, so that they inhibit both gram-positive and gram-negative bacteria, for example.

Much evidence indicates that a partial or selective reduction of plaque-forming oral bacteria would go far to reduce caries. Analysis of a physical model for plaque action in the tooth-plaque-saliva system, based on experimental data, indicates that caries would be negligible if the cariogenic flora were only repressed and kept at a sufficiently low level (*51*). In these circumstances, vulnerability of sites on teeth and cariogenicity of diet would become minor concerns. Animal experiments suggest that it might be feasible to control the human oral flora adequately to prevent caries by infrequent but regular intraoral application of suitable antimicrobial agents (*52*). Favoring the success of this approach is the slow average multiplication of the plaque biota in situ, estimated to be of the order of two or three cell divisions a day, compared to about one every half hour under optimal conditions in vitro (*53*). In the mouth, these organisms theoretically would require about half a day at least to recover from exposure to an inhibitory agent, and longer if the agent is one of those whose effects carry over through several generations.

Naturally one does not propose indiscriminate dosing. Antimicrobial agents for topical application to prevent caries should be carefully selected and used according to recognized criteria of safety and efficacy. A few tests in humans have demonstrated that plaque accumulation can be prevented, in some cases to the point of macroscopic indetectability, by agents meeting many of these criteria, but the field remains largely undeveloped (*50, 54*).

Caries-conducive activities of plaque bacteria might be controlled selectively without resorting to a direct attack on their viability with antibiotics and antiseptics. Theoretically one could find metabolic regulators that would inhibit or divert, for example, bacterial utilization of cariogenic substrates such as sugars, production of acids, formation of adherent extracellular polysaccharides, and accumulation of intracellular polysaccharides as reserve nutrient. Alternatively, bacterial colonization of the teeth might be averted by chemically altering the enamel surface so that bacteria cannot adhere to it.

Finally, the cariogenic flora might be kept under control by active immunization, either with antigens of the bacterial cells proper or with antigenic bacterial products such as dextransucrase. Lively interest in a "caries vaccine" continues, despite the great paucity of data warranting anticipation of success (*55*). First of all, unlike the majority of infectious diseases, dental caries confers no resistance to a subsequent attack. Caries does not engender a characteristic serum antibody response, for example, to cariogenic streptococci (*56*). The antibody content of serum, however, does not indicate the level or type of antibody operative in the oral cavity.

Except for a minor contribution from plasma via exudate from gingival crevices, the predominant immunoglobulin in the human mouth comes from the salivary glands and belongs to the distinctive class known as secretory immunoglobulin A (IgA) (*57*). Defensive functions of secretory immunoglobulins in general remain conjectural or unexplored, though considerable evidence indicates that they protect against viruses that invade the respiratory and intestinal tracts. Similarly, the occurrence in the gut of secretory immunoglobulins ("copro-antibodies") reactive with enteric bacteria suggests that they help protect this very heavily polluted region of the body.

Various antibacterial antibodies occur in whole saliva and pure parotid secretion, though their origin and immunoglobulin class have been identified in few cases (*57*). Natural exposure to the antigenic stimulus of an α-streptococcus in the oral cavity has been shown to engender specific antibody locally (*58*). A bactericidal effect of antibodies, however, depends on adjuvant reactions with components of complement or on phagocytosis by leukocytes, or on both; neither seems to function more than minimally in the lumen of the oral cavity (*57, 59*). Besides, IgA does not activate or consume complement (*57*). Neutrophilic leukocytes enter the oral cavity continuously in considerable numbers after the teeth erupt, mostly via the gingival crevice. Oral neutrophils exhibit some degree of phagocytic activity in vivo, particularly in the gingival crevice and in the surface film of the oral mucosa (*59*). Immunofluor-

escent staining shows that some of the cocci and bacilli in saliva and dental plaque have adsorbed IgA in vivo (*60*). Some of the coated bacteria have been found in neutrophils, suggesting that they had been sensitized for phagocytosis. In general, however, neutrophils quickly degenerate in contact with saliva (*59*).

On the positive side, some people develop very little caries, and one or two persons per thousand remain free of caries indefinitely, seemingly despite exposure to cariogenic bacteria and diets (*61*). Such persons have often been designated as caries-immune. The basis of this natural freedom from caries has not been ascertained—whether it correlates with other parameters, whether it is innate or acquired, whether it depends on antibodies or nonspecific physiological factors, whether it can be developed by artificial means. Familial influences are indicated, for such caries-free persons are about 40 times as numerous among relatives as in the general population. Sex factors are indicated also, for caries-free male adults outnumber females by about two to one. Caries-free adults are considerably more numerous in regions where environmental fluoride is naturally high, but they are by no means absent in other regions. Saliva from caries-free subjects has been reported to contain a nonspecific heat-labile bacteriolytic factor active against lactobacilli and streptococci. Blood neutrophils from caries-free subjects tend to phagocytize cariogenic streptococci to a greater degree than blood neutrophils from caries-active subjects (*62*).

Though the probability of preventing caries by artificial immunization seems quite small, it must not be ignored on a priori grounds; after all, the essence of research is the accomplishment of the seemingly impossible. Continued fundamental investigation of immunity in the oral cavity should be encouraged (*63*). Immediately pertinent areas include parameters of natural caries immunity; identification of cariogenic bacteria and their serological grouping; immunochemical analysis of their cell-wall antigens and extracellular products; local antibody formation in regional lymph nodes, other lymphoid tissues, and salivary glands; consequences of local administration of antigens; possible protective functions of salivary IgA; and, eventually, more exactly aimed attempts to immunize animals against caries.

Conclusions

Combined utilization of measures now available or imminent could reduce caries of the crowns of the teeth to the point of negligibility as a public health problem, if public desire were great enough to motivate changes in some of our habits (*64*). Universal optimum application of fluoride and substitution of starchy foods for sugary ones (or even simply judicious consumption of sugar) would alone do most of the job. Sealing of susceptible occlusal areas with adhesive polymers promises to protect the sites where fluoride evidently cannot be maximally effective. It seems unlikely that any single measure will be found sufficient to control this multifactorial disease. Consequently, we must continue the search for new means to increase the caries resistance of teeth, to reduce the cariogenicity of foodstuffs, and to check the deleterious activities of cariogenic bacteria. Anticaries food additives and antibacterial agents for intraoral use seem to be approaching practicability. Past performance warrants expectation that ongoing fundamental investigations will produce leads for future development and application.

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65. I am deeply indebted to colleagues too numerous to list here for invaluable advice.