

The Microbiology of Primary Dental Caries

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(Dedication. To Paul H. Keyes and Robert J. Fitzgerald whose pioneering work on dental caries in experimental animals framed the issues and set the stage for focused consideration of the role of microorganisms in human dental caries, and to the many investigators who have subsequently devoted much of their professional lives to the clarification of the microbial causes of caries in humans.)

This review was conducted to evaluate the implication of certain microorganisms in the causation of human tooth decay. It examines the evidence concerning bacterial species identified in both early and current literature to be involved in tooth decay, whether originally from wild animal, experimental animal and/or human data. It also examines the source of this putative infection of humans. Attention is focused on the mutans streptococci, the sanguinis streptococci, other streptococci, the enterococci, the lactobacilli, and certain actinomycetes, all of which are resident in the human mouth.

There is an immense literature on this topic. Systematic search using MEDLINE and EMBASE, from 1966 to 2000, retrieved 2730 unique English language citations. This retrieval was achieved by requiring that the full-length papers deal with isolation and identification (at some level) of bacteria from human subjects in the context of caries. Studies of so-called secondary or recurrent caries have been excluded from this review (due to time and space limitations), as have studies done either wholly *in vitro*, in experimental animals, or with so-called *in situ* caries models. The literature search thus conducted, nonetheless, failed to retrieve a few papers either known to the reviewers or identified from the bibliographies of articles retrieved by the searches. Of the papers chosen for review, all but 39 could be read from our library's collection or obtained from another library for detailed study. Only in the case of the brief **Background** section of this paper are scholarly review papers and conceptual advances from human or a few experimental animal studies cited, for the sake of economy of presentation.

The **Current Review**, thus, deals with studies of the microbial causes and associations with dental caries in humans only, relying upon cross-sectional, case-control, longitudinal, and experimental/interventional studies. It addresses tooth decay in young children having only deciduous (primary) dentition, older children and adolescents having mixed and permanent (secondary) dentitions, adults and seniors, whose secondary dentition often presents varying degrees of root exposure. As such, patients and experimental subjects with incipient enamel lesions (white spots) and established cavitations (cavities) of the tooth crowns and root surface lesions are considered. (The authors acknowledge that their review may have missed potentially important information contained in papers that were not available or, under the charge for this review, not appropriate for review. They also express sincere apologies to the authors of many excellent studies whose description space does not allow, although those papers were considered and are cited in the evidence tables.)

Extensive evidence tables accompany this review and should be considered as the full list of cited literature and its summarization/evaluation. The tables are constructed according to the questions posed (below) and categorized according to the microorganisms which were the focus of the literature search. Individual papers, while retrieved in the search for one or another microorganism, also reference the simultaneous study of other implicated microorganisms in that same publication.

Background

Earlier studies had characterized the biological behaviors of the most strongly caries-implicated microorganisms. The essentials of those behaviors are summarized below as background:

Mutans streptococci colonize the host only after the first teeth erupt, and their preferential colonization site is the teeth (1) (2); they are highly localized on the surfaces of the teeth and their abundance in the plaque is highest over initial lesions (3) (4); their level of colonization within the plaque is increased by sucrose consumption (5) (6); they synthesize certain macromolecules from sucrose that foster their attachment to the teeth (7) (8); they are rapid producers of acid from simple carbohydrates, including sucrose, and are tolerant to low pH (9) (10) and they are essentially always recovered on cultivation of initial and established carious lesion sites (11) (12) (13). Interest in them grew after the demonstration of their potency in induction and progression of carious lesions in a variety of experimental animals, including mono-infected gnotobiotics (14) (15). Their virulence expression is strongly associated with consumption of carbohydrates, especially sucrose (16) (17). However, caries does not occur in germ-free animals, no matter what their genetic background or their diet; it is an infection.

Lactobacilli do not avidly colonize the teeth and may be transiently found in the mouth before the teeth erupt; they preferentially colonize the dorsum of the tongue and are carried into saliva by the sloughing of the tongue's epithelium (18); their numbers in saliva appear to be a reflection of the consumption of simple carbohydrates by the host (6) (19); they, too, are highly acidogenic from carbohydrates and are acid tolerant (20). They are often cultured from established carious lesions (21). Some lactobacilli are cariogenic in experimental animals and their cariogenicity is dependent upon consumption of carbohydrate rich diets of animals (22).

Non-mutans streptococci of several types, including the sanguinis (formerly sanguis) group of organisms, and *S. salivarius*, are extremely abundant in the mouth; some are tooth surface colonizers, some mucosal colonizers. Some are quite acidogenic from carbohydrates and are acid tolerant (23) (9) (24). Less evidence exists of their virulence in experimental animals than either the mutans streptococci or the lactobacilli.

Enterococci were the first bacteria shown experimentally to induce caries in gnotobiotic animals (25). While carbohydrate users, acidogenic, and acid tolerant, they are not frequently abundant in the human oral cavity (23) (9) (24).

Actinomycetes are abundant in the human mouth and induce root surface caries in hamsters and gnotobiotic rats (26). They are also carbohydrate users, but are not powerfully acidogenic or acid tolerant.

Current Review

I. The association of specific bacteria with tooth decay (Table 1)

Question 1:

Are persons who have high levels of specific oral microorganisms at an increased or decreased risk for developing carious lesions compared to persons who do not have high levels of those same microorganisms? (The question, developed in PICO [population interventions comparisons and outcomes] format, addresses the association of specific bacteria with tooth decay.)

The search strategy developed to answer this question contained two primary concepts: 1) oral microorganisms and 2) carious lesions. For the concept of oral microorganisms, five separate hedges of terms were created, one for each of the following groups of bacteria -- mutans streptococci, lactobacilli, sanguinis (formerly sanguis) and other non-mutans streptococci, enterococci, and actinomycetes. A sixth, very broad hedge, was created to capture the concept of bacteria in general; the purpose of it was to retrieve pertinent articles indexed under the broad terms--bacteria, streptococcus, or enterococcus--but not under a specific microorganism.

The concept of carious lesions was represented in the searches by the caries hedge developed for common use by all reviewers in this systematic review. A dental plaque enhancement was added to the caries hedge to account for instances when pertinent articles were indexed under the concept of dental plaque rather than dental caries or carious lesions.

The oral microorganism and carious lesion hedges, as well as all other hedges used in this review, were created with respect to possible term and conceptual variants, past taxonomical references, misspellings, and indexing omissions and oversights.

The search was limited to human subjects and English language articles only.

Table 1. Summary of Search Retrieval on The Association of Specific Microorganisms and Dental Caries

Bacterial Group	Total Retrieved	Total Selected	Interventional	Longitudinal/ Retrospective	Case- Control	Cross Sectional
Mutans streptococci	854	189	25	59	20	85
Sanguinis/other streptococci	1245	16	1	2	2	11
Enterococci	253	3	0	0	0	3
Lactobacilli	657	144	9	40	20	75
Actinomycetes	700	27	1	3	3	20

The mutans streptococci

Randomized clinical trials

Twenty-five interventional studies which monitor the putative cariogenic flora and record effects on caries scores are found in the literature of human caries. Several of these applied extremely complex strategies [e.g. (27)] -- some focused on mitigation of the solubility of the teeth with fluorides; some on repair or sealing of the teeth; some on diet management and/or use of sugar substitutes and, thus, indirectly on changing the implicated tooth surface flora; and some directly on the flora by mechanical plaque control and/or use of antiseptic agents.

Because the questions for the present review are more straight-forward (*viz.* what are the bacterial determinants of caries and what is known of the transmission of those bacteria), such multi-strategic studies confound interpretations of antibacterial effects with anti-tooth demineralization effects. It is understandable that investigators wish to accept this problem, because of the ethical need to offer patients at high risk the perceived best available anticaries strategies. Nonetheless, multi-strategy approaches to experimental interventions set a very high threshold for detection of effects of interventions on the flora and attribution of anti-caries responses to them. Some notable studies are less confounded, however.

Partial suppression of mutans streptococci by topical chlorhexidine use and dietary counseling in randomized to treatment (or control) Swedish children (28) inhibits mutans streptococcal recoveries and carious lesion development during 3 years, while lactobacillus titers in saliva are not detectably affected.

Study of primiparous mothers with 3-8 month-old infants in a Swedish community, alternately assigned to treatment or control groups, was aimed at reduction of mutans streptococcal salivary levels by sucrose avoidance counseling, professional tooth cleaning (and topical fluoride application), oral hygiene instruction, and excavation of large carious lesions if present, and, if test mothers had salivary mutans streptococcal levels that exceeded a pre-set threshold, by treatment with topical chlorhexidine. This strategy increased the time to colonization by mutans streptococci of their young children, time to caries experience of those children, and the severity of caries experience of those children (29). There was no significant difference in titers of salivary lactobacilli. Preventive strategies were discontinued when children had become colonized. The study ran until children were 36 months old. Four years later (30), with the same children now 7 yr old, treated mothers had lower mutans streptococci and lactobacilli than control mothers, and far lower percentages of children of treated mothers carried mutans streptococci compared with children of control mothers. The children of test mothers who were carriers also had lower levels of mutans streptococci than those of the mutans carrier control mothers. 23% of children of test mothers were caries free, compared to 9% of the children of control mothers, and total group caries experience for test and control children were 5.2 vs 8.6 def, respectively.

A similar strategy was used to treat 50-60 yr old Swedish patients of private dentists (31). Two randomized groups of high and low risk patients (defined by salivary mutans, salivary flow rate, and salivary buffer capacity) were assigned test protocol or served as controls who were given standard care as deemed appropriate by their dentists. At year's end, the treated high risk group had lower caries increments and lower mutans and lactobacillus titers than high risk controls, but there was no difference between the two low risk groups. The intervention was discontinued. Four years later there was no difference in microbiological parameters or caries increment between the former treated and untreated high risk and low risk groups, and the one year differential benefits of the test intercession had been lost.

A 3 year study (32) of initially 12 yr old Swedish children, using an intervention of chlorhexidine-impregnated dental floss treatment of approximal surfaces compared with placebo-impregnated floss, and with no floss treatment resulted in about 50% reduction of new DFS of the chlorhexidine-floss compared with the placebo-floss group, and about a 60% reduction compared with the no floss group. Chlorhexidine impregnated floss effects were about 42% better than placebo-floss. Salivary monitoring of bacteriology (rather than approximal plaque monitoring) evidenced no differences among the groups, as could have been expected.

A 3 year intensive program (33) focused on personalized education to avoid sucrose, excavation of cavities, fluoride varnish application, professional tooth cleaning and oral hygiene instruction. All study participants were randomized by school class and had group instruction on sugar avoidance, tooth brushing, fluoride toothpaste use, and were provided tooth brushes. The personalized program resulted in about a 6-fold decline of new DFS in 10-12 yr old Polish children and, after 3 years, significant reductions of mutans and lactobacillus salivary counts.

A 2 year randomized 4 group study of 13 year old Swedish children (34) compared supervised chlorhexidine gel treatment to fluoride varnish, topical FeAlF professional application, and to untreated controls status with no intercession. The antibacterial treatment resulted in about a 50% reduction of new DFS when compared with the untreated controls and lesser, but still substantial and significant, DFS reductions compared with the fluoride treated groups. There was a correlated reduction of salivary mutans streptococci in the chlorhexidine group.

Finnish 10-12 year old children were randomized to either high content xylitol gum use or not, during a first experimental phase (35). When two years later the controls were randomly recruited for evaluation, some had begun the voluntary use of xylitol gum, i.e. a self imposed cross-over. The approximal plaque mutans levels were lower in the xylitol users and the continuous users of xylitol gum had lower decay scores 6 years after the beginning of their xylitol use than did non-users. Mutans streptococci were lower at approximal sites that were clinically and radiographically sound than at decayed sites.

The use of a xylitol chewing gum by Finnish mothers (36) (37) until their children were 3 years old was recently reported to inhibit the mutans streptococcal colonization of their

children and reduce the caries experience of those children during a 5 year period of observation. Mothers were randomized to either xylitol gum use, chlorhexidine varnish, or fluoride varnish applications. The children did not use the gum or receive varnish treatments. The probability of being caries free was 70% for non-mutans-colonized children compared to about 25% for mutans colonized ones at 5 years of age and the group mean dmf score for the xylitol intercession cohort was 0.83, while those for the chlorhexidine and fluoride varnish groups were 3.22 and 2.87, respectively.

Longitudinal and case-control studies

Seventy nine longitudinal (prospective and retrospective) and case control studies indicate an important role of mutans streptococci in caries. They examined the relationship between salivary titers or plaque relative abundance of mutans streptococci (and often simultaneously quantified other implicated bacteria, especially lactobacilli, actinomycetes, and sanguinis streptococci) as well as the inception, prevalence or incidence of carious lesions of various surfaces of crowns or roots of teeth. Many studies have used randomized subjects, some being dental or medical patients; some subjects were almost totally naïve dentally. Some studies have used population samples and some compared cohorts of high or low caries experience, fluoridated or non-fluoridated communities, diverse racial/ethnic groups, diverse socioeconomic statuses, diverse methods to pay for dental health care, ambulatory and non-ambulatory health status, and, of course, diverse ages. The longitudinal, case-control, and cross sectional (not discussed here) studies come from all continents except Antarctica. A few illustrative of the diverse study populations are cited here [(38) (39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (19) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65)] and provide, overall, a remarkably consistent picture.

These (and cross-sectional) studies, with few exceptions, support a strong positive statistical association of mutans streptococci with inception or incidence of carious lesions. They often report concomitant positive associations with lactobacilli, especially if saliva, rather than discrete plaque samples, had been monitored. When studied, they sometimes report negative associations of sanguinis streptococci with mutans streptococci and with lesions. Some suggest that *S. sobrinus* (the less common of the mutans streptococci, the more common one being *S. mutans*) are favored in their ability to colonize the teeth by prior colonization of *S. mutans*. There is suggestion of an association of *S. sobrinus* and lactobacilli.

While mutans streptococci can be found in the mouths of infants only after the teeth erupt, they colonize the mouth much earlier when obturators are placed for cleft palate management, again supporting the notion that mutans streptococci require solid non-shedding surfaces as their preferred colonization site (66).

Often these studies (randomized clinical trial, longitudinal, and cross-sectional) gather data on other variables of interest – socioeconomic status, sucrose consumption (usually as food types or patterns of consumption), fluoride exposure, oral hygiene status, breast feeding or close personal contact between mothers and their children and, especially, initial or baseline

caries status. Some studies ask the clinical examiners to predict the decay experience of the study participants depending on the examiners' beliefs.

Several of these studies focused on a related question, *viz.* the prediction of carious lesion increments as a function of the sum total of many of the variables of interest to cariologists and caries epidemiologists, rather than on the microbiological variables targeted for this review. In such studies when predictive values were estimated and when multiple regression models included other caries-associated variables (such as candy or soft drink consumption, oral hygiene, SES and, especially, prior numbers of lesions), the amount of variance explained by the bacteria of interest became predictably smaller. Prediction of the dependent variable, caries score, by inclusion of the baseline caries score as an independent variable appears inherently tautological in the context of explaining the causation of the disease (and arguably a *post hoc, ergo propter hoc* problem).

Discernment of microbial etiology from several longitudinal (and cross-sectional) studies was probably blunted by using salivary (or pooled plaque) monitoring of mutans streptococci as a surrogate for monitoring small samples of plaque in areas of high caries risk, as the knowledge of the biology of the mutans streptococci and expected locations of carious lesions would have seemed to dictate.

Lactobacilli

Interventional trials

The concerns for confounding and ambiguity of interpretations in interventional clinical trials stated above for the mutans streptococci are applicable to the lactobacilli as well. Several of the randomized clinical trials which yielded data concerning the mutans streptococci also evaluated changes in the lactobacilli. Generally they resulted in inconsistent evidence that inception of carious lesions in children or adults were associated with lactobacillus titer increases in saliva [ex. (67) (30) (31) (33) (34)].

Longitudinal and case-control studies

Longitudinal and case-control studies were perhaps more informative. Lactobacilli are late colonizers of the mouth (68) (18) (1) (57) (4). Lactobacilli are recovered from carious lesions, but they are later colonizers of those lesions than the mutans streptococci (43) (51) (19). Some data suggest that they are favored in their ability to colonize by pre-existing colonization by the mutans streptococci, especially *S. sobrinus*. These data thus indicate that lactobacilli are not requisite for the development of lesions. Nonetheless, they may potently contribute to the demineralization of the teeth once lesions are established on either crowns or roots (43) (69) (70) (71) (72) (63) (73) (74). Little information is available concerning the species of lactobacilli that colonize the human tongue and teeth. The many pertinent cross-sectional studies will, similarly, not be described here, but their descriptions can be found in the evidence tables.

Non-mutans streptococci

Essentially no data support a causative role of sanguinis streptococci or *S. salivarius* in human caries. In fact some data suggest an inverse relationship of the abundance of sanguinis streptococci and the mutans streptococci, and that the sanguinis streptococci are inversely related to lesion development [ex. (38) (40) (75) (76)].

Enterococci

No human data support a significant role of enterococci in the development of human carious lesions or in their prevalence in the human mouth.

Actinomycetes

Actinomycetes are prevalent in the human mouth and are frequently found in association with both carious and sound root surfaces, as well as sound crown surfaces. Evidence of their role in root surface carious lesion induction, from interventional, longitudinal, case-control and cross-sectional data, are variable and inconclusive. In fact, they sometimes suggest actinomycetes are more reflective of non-cariogenic than cariogenic status, by contrast with the mutans streptococci and the lactobacilli.

The source of infection by the cariogenic bacteria (Table 2)

Question 2:

Are persons who have undetectable levels of cariogenic flora more likely to acquire them from persons who have high levels of cariogenic flora than from persons who have low levels of cariogenic flora? (The question is developed in PICO format.)

The search strategy developed to answer this question contained two primary concepts: 1) oral microorganisms and 2) disease transmission.

For the concept of oral microorganisms, five separate hedges of terms were created, one for each of the following groups of bacteria -- mutans streptococci, lactobacilli, sanguinis and other non-mutans streptococci, enterococci, and actinomycetes. A sixth, very broad hedge, was created to capture the concept of bacteria in general; the purpose of this was to retrieve pertinent articles indexed under the broad terms--bacteria, streptococcus, or enterococcus--but not under a specific microorganism.

The hedge for disease transmission took into account such variant concepts as infection; transmission; communicable diseases; mother(s), and persons likely to transmit infection. The search was limited to human subjects and English language articles only.

Table 2. Summary of Search Retrieval on The Transmission of Bacterial Species Implicated in Dental Caries

Bacterial Group	Total Retrieved	Total Selected	Molecular and genetic tracing: bacteriocin/mutacin/ phage typing/endonuclease mapping/ribotyping	Interventional	Longitudinal/ Case-Control	Cross Sectional
Mutans streptococci	122	40	17	8	13	1
Sanguinis/other streptococci	772	1	0	0	1	0
Enterococci	129	0	-	-	-	-
Lactobacilli	104	7	0	4	3	0
Actinomycetes	114	0	-	-	-	-

Just as modern molecular and genetic methods are now widely used in forensic science, they are now used to trace the spread of infection. They provide perhaps the strongest evidence of the source of transmission of infection in the case of dental caries. That evidence will be briefly abstracted here. Nonetheless, other evidence of the source of transmission of the bacteria etiologically involved in caries, from experimental and longitudinal studies, is consistent with the even more compelling genetic evidence. The convincing data on the source of infection by cariogenic bacteria almost entirely pertain to the mutans streptococci.

Study of the mutans streptococci isolated from children and their parents/siblings/caretakers by bacteriocin typing, phage typing, mutacin typing, endonuclease DNA mapping and ribotyping establish that these bacteria are transmitted to humans early in their lives, after the first teeth erupt, and that they originate mainly from their mothers, i.e. vertical, matrilineal transmission [(77) (78) (79) (80) (81) (82) (83) (84) (85)]. Only two reports suggest significant patrilineal transmission. While it is common for children to share more than one genotype or bacteriocin type of mutans streptococci with their mothers, failure to detect all of the types longitudinally among mother/child pairs suggests that some genotypes may be lost with time. New genotypes not detected in mothers have also been reported to colonize children during longitudinal studies, suggesting that additional and extra-familial transmission sometimes occurs, perhaps from other caretakers.

Longitudinal study of children led to the proposal of a “window of infectivity” by mutans streptococci (86), but that concept does not appear presently well-supported. Children become colonized both before and after that “window” period (87) (66) (88) (89)]. Also, as reported in essentially all of the studies of adults (cited above), virtually all dentate adults appear to some degree colonized by mutans streptococci. Hence, there are likely to be other events of transmission or, alternatively, the methods historically used to cultivate the mutans streptococci may be of insufficient sensitivity to detect transmission which had in fact occurred.

Interventional studies of transmission are clearly inhibited by the ethical impossibility of exchanging children shortly after birth among mothers for foster-rearing. Nonetheless, controlled experiments aimed at reducing the salivary levels of mutans streptococci and, thus, altering the probability of transmission of mutans streptococci from mothers to their children strongly support the concept that mother is the usual source of transmission of these bacteria to her child (30) (90) (36).

There are few data on the source of transmission of lactobacilli to children. Despite the use of very specific selective media for the cultivation of oral lactobacilli, speciation of lactobacilli has been laborious and usually not done in a cariological context. As for the mutans streptococci, speciation studies would not seem useful for tracing the transmission of the oral lactobacilli; molecular/genetic marker tracing would seem more promising. Also, literature search does not reveal studies of the genetics of the lactobacilli in the mouth, vaginal, or GI tract of mothers and their children in the context of dental caries. While lactobacilli can be found in the mouths of infants, they appear to be transient and not a common feature of the oral cavity until after teeth erupt or after obturators are placed for cleft palate management.

There is little information on the source of colonization of the mouth by sanguinis group streptococci, enterococci, and actinomycetes. *S. salivarius* is long known to colonize the mouth usually within a day of birth, suggesting mother's oral or vaginal flora as the source.

Problems of methods and literature interpretation

Many questions inevitably arise concerning the methods and data handling in this area. Of them, three perhaps warrant special note.

Benefits and shortcomings of salivary and plaque monitoring of the cariogenic flora.

Several studies have demonstrated, on a population basis, that the level (titer) of mutans streptococci per ml saliva is a reflection of their levels on the teeth. Thus, saliva, rather than dental plaque (the location of colonization by mutans streptococci), has been used as a surrogate for plaque monitoring. Use of this strategy was attractive for the study of potentially uncooperative young children. It also required virtually no equipment or thought about where mutans streptococci colonize the teeth, compared with the careful taking of small, localized plaque samples. Such sampling was also attractive because of the assumption that saliva was the likely vehicle for transmission of mutans streptococci among humans, an assumption shown subsequently to have strong support. To a probably significant extent, the use of salivary monitoring systems was also driven by the availability of commercial kits designed for salivary mutans monitoring. The method assumes that all tooth sites are equally colonized and available for sampling.

Mutans streptococcal levels in mastication-stimulated saliva reflect something akin to a pooled, averaged plaque, sampled from those tooth surfaces from which plaque is most likely to be dislodged. Collection of stimulated saliva is commonly effected by chewing a piece of paraffin, thereby partially disrupting the plaque, on the exposed-to-the-paraffin tooth

surfaces. Such saliva samples can be expected to bias data against the sampling of plaque located in the fissures of the teeth, below the approximating contact areas, below the maximal curvature of buccal and lingual surfaces of teeth, and on the root surfaces, *viz.* all of the surfaces of the teeth most likely to decay and those most heavily colonized by mutans streptococci. They would bias for the disproportionate sampling of plaque located on cusp inclines and about one half to two thirds of the buccal and lingual surfaces of the teeth (*viz.* the least likely surfaces of the teeth to decay), as can readily be observed by viewing the impressions of the teeth made in chewed softened paraffin or chewing gum. Hence, the sampling method fosters underestimation of the mutans streptococcal colonization levels on the teeth and assumes that the teeth are uniformly blanketed with them. [As expected, if prostheses that have not been disinfected are left in the mouth during chewing of paraffin, saliva levels of prosthesis-dislodged plaque organisms are increased (see evidence table)]. The method also either assumes that patients would not brush their teeth before saliva sampling or that brushing and, thus, plaque amount reduction before sampling, would have no effect on the numbers of plaque bacteria available for dislodgment into saliva. It furthermore assumes that there would be no effect of eating and brushing before sampling, despite data (91) to the contrary. Most clinical studies have not standardized saliva collection conditions, likely increasing variance of data.

It is, nonetheless, clear that for naïve subjects, especially young ones with all of their teeth, there is a strong correlation between mutans streptococcal numbers/ml saliva and the percentage of mutans streptococci in pooled (accessible) dental plaque. Saliva sampling has served well in this context. Such correlations have notably been demonstrated with large numbers of study participants, *i.e.* with populations. Salivary sampling is especially convenient for field studies. It is less established, however, as evidence of individual patient status, risk, results of treatment, or prognosis for individual management.

Salivary sampling has been done by several methods: the collection of pooled saliva from the floor of the mouth with a cotton swab, with care not to mechanically disrupt the plaque; the pressing of a stick or tongue blade, often called a “spatula”, against the dorsum of the tongue, to obtain a saliva sample (there is no evidence that mutans streptococci have a differential affinity for the tongue epithelium); the drooling of collected saliva, without stimulation, into a collection vessel. All of these are usually referred to as “unstimulated” saliva samples. For stimulated salivary samples, subjects are commonly supplied a masticatory stimulus, usually a standardized piece of paraffin wax that at mouth temperature is easily chewed and serves to dislodge some of the plaque from the accessible areas of the teeth. Saliva is then usually spat into a collection vessel.

Salivary samples are, by various techniques, cultivated on so-called selective (actually, differential) media for growth of mutans streptococci (or lactobacilli). Some kits have been marketed to facilitate this. Alternatively, samples may be added to viability preserving media (most commonly VMGII or RTF) or simply chilled or frozen for transport to a laboratory where they are disaggregated and diluted to avoid confluent colony growth on differential media. After incubation, some workers view these agar surfaces with the naked eye, using manufacturer-supplied reference standards, with the assumption that all of the

mutans streptococci (or lactobacilli) in the sample, and only they, grow into visible colonies. Other studies more carefully confirm that only mutans streptococci (or lactobacilli) are being enumerated, but most of these do not exclude false negatives. That false negatives occur commonly using the most popular of these culture media, and perhaps to various degrees with all analogous culture media, is abundantly documented (not reviewed in this paper). Results are reported in colony forming unit count/ml of saliva. For example, 1×10^6 cfu/ml, is generally accepted as a high count for mutans streptococci. It should be recognized that if non-selective media were used, total recoveries would be between 10^8 and 10^9 cfu/ml. Thus, at most, mutans streptococci constitute less than 1% of the bacteria in saliva.

Plaque samples, by contrast, are collected either by scraping the surfaces of the dentition to harvest all accessible plaque, thus pooling it and doubtless underestimating the levels of colonization of the highly localized mutans streptococci (92) (93) (3) (94), or by taking tiny amounts of plaque at selected areas of the teeth. Samples are plated usually on the same differential media as used for salivary sampling, but are also plated on a non-selective medium such as trypticase soy blood agar. Data by these methods are reported usually as the % of total recoverable colony forming units which are mutans streptococci (or lactobacilli). Such data are expected to be relatively unaffected by time-of-day, tooth brushing, and eating artifacts; there is no evidence that any of these conditions differentially dislodge or fail to dislodge bacterial components of the dental plaque. Plaque sampling by comparison with salivary sampling requires good lighting and trained personnel to take samples, cultivate them, and microscopically view plates for identification of characteristic colonial morphologies, and at least semi-quantitate them. By such methods, it is not unusual to recover more than 50% of the total flora over white spot lesions as mutans streptococci.

Lactobacillus monitoring using saliva has less uncertainty of interpretation than saliva monitoring for mutans streptococci, probably because lactobacilli are mucosal colonizers, not tooth colonizers (evidence table). Mucosal cells slough into the saliva, carrying their adherent bacterial burden of lactobacilli (especially from the tongue). When lactobacilli are recovered from the surfaces of teeth by plaque sampling, lactobacillus colonies may substantially reflect salivary contamination of that tooth surface. Lactobacilli do not colonize the mouth with stability until the caries process is underway (evidence tables) and acidogenic conditions associated with the consumption of abundant carbohydrate are established. Nonetheless, these bacteria may contribute significantly to lesion formation, especially in the context of their advancement.

The medium most used for the selective enumeration of lactobacilli does not provide speciation, and we know of no data on the possible loss of oral lactobacilli on it, thus leaving open the possibility of significant false negative recoveries, both qualitatively with regard to specific lactobacilli and quantitatively. Thus, a considerable information gap may exist re the significance of lactobacilli in caries.

The role of sugar(s) in decay as it relates to the presumptive cariogenic flora.

Time did not allow the systematic review of the role of various sugars and sugar substitutes in the context of the status of infection or colonization by the mutans streptococci and the

lactobacilli. The evidence tables for Question 1, however, abound with data to indicate that for caries-active patients, sugar consumption, especially that of sucrose, may be very potently cariogenic and is associated with the ecological emergence of the mutans streptococci and of the lactobacilli, as was indicated by the old literature (reviewed by others). Surely, detection of sucrose's or other fermentable carbohydrate's effects on lesion formation may be dampened in the setting of abundant exposure to fluorides, and the effect may consequently be of less moment for some citizens of Western societies. Much of the US and most of the world, however, do not have abundant exposure to fluorides. Some of those populations, especially in the economically emerging nations, are increasingly exposed to sucrose (not reviewed here). Cross-sectional analysis of impact on caries of various sugars is likely to be less sharp in detecting their significance than randomized experimental studies that manipulate sugar use. (Indeed, the most powerful interventional strategies described in the present review of the role of bacteria in caries involve sucrose restriction or substitution.) Similarly, analysis of sugar(s) use without regard to the pattern, frequency, duration and quantity of exposure, or estimation of the time of exposure of the high risk areas of the teeth to specific fermentable carbohydrate foods may mitigate detection of powerful effects on the cariogenic flora and on the development of lesions. Two human genetic diseases that mandate that patients consume essentially no sucrose, hereditary fructose intolerance and intestinal sucrase deficiency, make clear its great impact on both colonization of the dentition by cariogenic bacteria and development of lesions (95) (96).

Modeling strategies to predict lesion score increments, as distinct from estimation of the impact of specific bacterial types in caries.

A number of studies understandably have sought to characterize caries risk by evaluation of independent variables such as implicated bacteria, socioeconomic status, sugar intake, specific food intakes, oral hygiene, fluoride exposure, etc. and existence of carious lesions, whether cavitated or initial (white spot). Not surprisingly, the inclusion of the existence of the disease's result (carious lesions) as an independent variable in the multifactorial or predictive analysis of the dependent variable, carious lesion score increment, has resulted in the conclusion that the biggest predictor of lesions was preexisting caries lesions. Generally, the more variables considered in regression equations, the smaller the impact of any one of them. It would not seem that such an analysis is substantially different from using the presence of gangrenous toes in diabetic patients as a predictor of occurrence of more gangrenous toes. Use of carious lesions to predict that the patient will get carious lesions appears tautological, true on its face.

Perhaps more appropriate issues would be either 1) the prediction of who among populations of children (or adults) may develop carious lesions when they are essentially free of them, so that disease preventive strategies may target those individuals and/or 2) the prediction of management outcomes for people with existing lesions from the evaluation of microbiological, dietary, fluoride, and/or salivary conditions. It is arguably dangerous and wasteful to presume that real individual dental patients with carious lesions are at high risk for more, when clinicians know that many carious lesions may have been formed years previously and may not have advanced. For the clinician or dental educator to think

otherwise is to commit all patients with a history of decay (dmfs or DMFS) to endless restorative therapies, to exalt restorative procedures over preventive ones.

Conclusions of Review

Evidence from the current review strongly supports a central role of the mutans group of streptococci in the initiation of caries on the smooth surfaces and fissures of the crowns of the teeth of adults and children, and suggest a potent etiologic role of them in the induction of root surface caries also. Lactobacilli are also implicated as important contributory bacteria in tooth decay, but their role in induction of lesions is not well supported. Evidence that other streptococci, enterococci, or actinomycetes are prominent etiological agents of dental caries in humans is equivocal at best. The mutans streptococci are spread vertically in the population, mostly but not exclusively, from mothers to their children. These findings suggest strategies for improvement of the dental health of both children and adults in the US and in other countries.

Future Directions for Microbiological Clinical Caries Research

It would seem overdue that facile methods for the molecular detection of colonization of tooth sites by mutans streptococci be established and validated. These methods should be used to indicate individual patient and individual tooth site risk for lesions and, ideally, should be executable in the dental office. They must be reimbursed by third-parties. They should save enormous amounts presently expended for repeated restorative care.

Such development would also make more feasible the study of outcomes of individual patient management, the compliance of patients with dietary advice, the assessment of effects of antimicrobial treatments, the establishment of prognosis for further decay, and the estimation of the probability of failure of restorative treatment. Such development and issue focus would move the practice of restorative dentistry out of a fundamentally reparative mode into a diagnosis-based, infection control-oriented, tooth surface-protective, and selectively-restorative mode.

There is need for the development of more potent topical antimicrobial agents that target the suppression of the mutans streptococci by topical treatment of the teeth. Although chlorhexidine was once seen as a promising agent of this sort, and it has shown considerable efficacy, its effects have been less than ideal and its potency at presently allowed concentrations is marginal. There is considerable literature (not reviewed here) to suggest other agents and avenues for such antibacterial therapies.

The reported effects of xylitol confections in the reduction of decay increments are notable. Public health promotion of strategies to reduce the probability or level of colonization of mothers and, perhaps, other caregivers, by mutans streptococci, whether based on use of xylitol, restriction of certain sugars, excavation and filling of carious lesions, antiseptic treatment, and/or other strategies are of great interest. The literature indicates that these strategies can effect delay of cariogenic microbial infection of children and consequent

mitigation of their caries experience. It would seem appropriate for practitioners to use such strategies to protect the dental health of children now, and for health research funding agencies/industry to conduct large scale clinical trials to assess population dental health improvement of children by treatment of their mothers and caretakers. Other caretakers should include grandmothers and daycare personnel who increasingly participate in the rearing of children in this time of growing parental obligations to the workplace.

Special attention should be given to secondary decay occurring at the junction of restorative material and the enamel cavosurface. Abundant data (reviewed by others) indicate that a very large part of practitioner time and patient money is spent re-filling previously filled teeth. Although there is a literature on the bacterial correlates of secondary decay, it is limited. The issue warrants substantial funding for longitudinal and interventional clinical trials.

With the aging of Western societies and the increasing use of medications which compromise salivary function (reviewed by others) tooth decay should be increasingly seen as not a pediatric/adolescent disease but also as a disease of adults and the elderly, as demonstrated by national survey data. Special interventional strategies accordingly need to be developed to care for the aging.

Lastly, it is paramount that the term “dental caries” not be equated with “cavities” by dentists and dental educators. The lesion is not the disease, but the effect of the disease. The disease does not occur without infection by cariogenic bacteria. To prevent, detect, and manage caries throughout life one must not be restrictively focused on the end result of the disease, cavities.

Note:

References (97) to (313) are to papers which were also considered in this review, but for which space did not allow discussion or individual citation in the text. They, as papers (1) to (96), are presented in the Evidence Tables accompanying this paper.

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