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for GRANTS and CONTRACTS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

ANNOUNCEMENT

NATIONAL INSTITUTE OF DENTAL RESEARCH
NATIONAL CARIES PROGRAM
GRANT APPLICATIONS SOUGHT ON
MECHANISMS OF ACTION OF FLUORIDE

The high incidence of dental caries in children throughout the world is well recognized. Although dental caries seldom endangers life, it may be painful, debilitating, and expensive and may contribute to long-term suboptimal health. Although early treatment of carious lesions is valuable and promotes better health, the ultimate goal of the National Caries Program is preventing the occurrence of caries. If prevention is to be effective, a substantial proportion of the population must be reached at an early age.

The most dramatic success in the reduction of incidence, severity, and rate of progression of caries has been due to water fluoridation and to topical applications of fluoride by various methods. The preventive value of topical fluorides is universally accepted. There appears to be merit in most topical fluoride formulations and techniques of application. However, the mechanisms whereby fluoride reduces the occurrence of dental caries are only partially understood.

Fluoride may exert its effect in one or more of several ways: (1) by making the enamel more resistant to acid demineralization; (2) by inhibiting the microbial enzyme systems which convert sugars into acids in the dental plaque, or by affecting the type of extracellular polysaccharides formed; (3) by affecting the colonization of tooth surfaces by cariogenic organisms; (4) by a direct bactericidal or bacteriostatic effect; and (5) by stimulating the remineralization process at the enamel surface. Recent studies suggest that these mechanisms are not mutually exclusive, and that it is possible, and indeed probable, that fluoride works in several ways simultaneously or in ways that have not been discovered yet. Experimental and clinical evidence indicates that the potential of fluoride therapy to prevent and control dental caries is much greater than results currently attained by the majority of preparations and delivery methods in use.

The National Caries Program is encouraging submission of high quality research grant applications proposing investigations which would provide a better understanding of the various mechanisms by which topically applied fluoride exerts its cariostatic effects.

Specific examples of areas of program interest include the following:

Effect of Fluoride on Tooth Physiology. Further studies are required to clarify the decreased response to fluoride with tooth age; whether the maturation process and deposition of organic material on the enamel surface interferes with uptake of fluoride by enamel; the selective effect of fluoride on different tooth surfaces; and the effect of fluoride on tooth morphology.

Effect of Fluoride on Fluorapatite Formation - Stability of Fluoride Products. Studies are needed to determine whether there is a correlation between increased fluorapatite formation in enamel and a reduction in the occurrence of caries. It is important to correlate the content, distribution, and depth of fluoride penetration in enamel surfaces with caries incidence. Further studies should attempt to identify the fluoride salts that are formed in the enamel surface as a result of topical fluoride treatments; and whether the cariostatic effect of solutions that deliver large amounts of fluoride into the enamel (such as ammonium fluoride) is only temporary due to conversion of more tooth mineral into larger amounts of calcium fluoride. In addition, studies should endeavor to measure the fluoride concentrations at frequent intervals to determine how much and how quickly fluoride is lost from the tooth surface.

Effect of Fluoride in Promoting Enamel Remineralization. New research in this area should determine the mechanism whereby fluoride promotes remineralization of enamel; whether certain ions retard the progression of carious lesions by encouraging the dissolved enamel mineral to reprecipitate and by preventing hydrolysis of fluoride from the enamel surface. It would be important to find out if the redeposited mineral is more resistant to acid dissolution than sound enamel, and whether it is advantageous to introduce insoluble, non-mineral materials, such as protein together with fluoride, into an incipient carious lesion.

Effect of Fluoride on Response to Other Trace Elements. Definitive studies are required to determine the role and mode of action of trace elements such as boron, strontium, molybdenum, vanadium, and others in enhancing or diminishing the cariostatic effect of fluoride in humans.

Effect of Fluoride on Saliva Composition. Investigations in this area should clarify whether saliva and plaque fluid contain substances which inhibit or enhance fluorapatite formation in enamel after the teeth receive topical fluoride applications.

Effect of Fluoride on Metal Ion Complexes. Additional in vitro and in vivo studies are required to determine the influence of metal ions on the surface properties of hydroxyapatite or tooth materials and their ability to bind topically applied fluoride.

Electrochemical Effects of Fluoride. Desorption of pellicle protein and bacteria may be one of the several mechanisms by which fluoride exerts its cariostatic effect in vivo. Fluoride, in low concentrations, appears to desorb albumin and salivary glycoprotein adsorbed to hydroxyapatite in vitro.

The fluoride ions, competing for cationic sites replace acidic protein groups adsorbed to cationic sites on the mineral surfaces. Microorganisms adsorbed to hydroxyapatite may be desorbed in the same way by a similar mechanism. Further studies are required to confirm this hypothesis.

Effect of Ambient Fluoride. Further studies are required to elucidate the mechanism of action of ambient fluoride at low concentrations: bacteriostatic, favoring enamel remineralization, neutralizing acids produced by plaque microorganisms or other mechanism or combination of mechanisms; to determine the optimal concentration of fluoride, frequency of application, and optimum vehicle for allowing fluoride to be present constantly in the oral environment.

Effect on Oral Microorganisms. Some studies have demonstrated that fluoride inhibits acid production by oral microorganisms. This effect of fluoride has been interpreted by some as interfering with the transport of glucose into the cells or as altering the composition of the extracellular polysaccharides produced by different strains of Strep. mutans by interfering with the synthesis or release of the glycosyltransferases. There is preliminary information indicating that different oral streptococci have different sensitivities to the same concentration of fluoride. Additional studies should explore: the effect of fluoride concentration on selecting the microbial composition of plaque and on the extent of plaque accumulation; the forms of fluoride in plaque; direct bactericidal/bacteriostatic effect versus metabolic inhibitor effect of fluoride; factors that control the uptake of fluoride by plaque microorganisms; the extent and sites of fluoride accumulations by bacterial cells; the effect of fluoride on intermediary metabolism.

Applicants responding to this announcement should utilize the standard NIH grant application kit and procedures described therein. Applicants are encouraged to indicate in a cover letter that the application is in response to the announcement on "Mechanisms of Action of Fluoride." The next three deadlines for submission of new research grant applications to the Division of Research Grants are October 1, 1975; February 1, 1976; and June 1, 1976.

If additional information is needed prior to submission of a grant application, applicants are invited to contact either Dr. Thomas C. O'Brien or Dr. Raquel Halegua:

Caries Grant Programs Branch
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