Hypothesis 12. National Children's Study – Initial Proposal for Core Hypotheses/Questions

Longitudinal Assessment of Dental, Oral and Craniofacial Diseases and Conditions during Childhood and Adolescence

Background

The recent Surgeon General's Report on Oral Health (SGR) highlights that oral health is an integral component of general health and poor oral health can adversely affect children's health and development. However, longitudinal studies on a national level, which would allow estimation of incidence of major oral diseases and conditions and determination of their progression, have not been conducted. The National Children's Study presents the first opportunity to assess the incidence and progression of these diseases and conditions from birth (or near conception) to early adulthood, in the full social and environmental context.

In this proposal, we describe hypotheses in three areas:

1. **Dental Caries and Enamel Fluorosis**
2. **Periodontitis** (particularly Early-onset Periodontitis)
3. **Pregnancy Outcomes** (pre-term and low birth weight; and craniofacial clefts).

The oral diseases **dental caries (tooth decay)** and **periodontitis (gum diseases)** are common, transmissible bacterial infections that are treatable and preventable. These oral infections are transmitted within families (Asikainen and Chen 1999, Tinoco et al. 1998) and from mother to child (Caulfield et al. 1993). Children with more severe oral infections experience poorer overall health and slower development.

Use of fluorides can prevent the lesions and cavities in tooth enamel that are the clinical manifestation of dental caries. OR Use of fluorides can prevent dissolution of the hard surfaces of the teeth and the resulting clinical manifestations that can include cavitation of the tooth, pain, tooth loss, and acute systemic infection. Effective fluoride treatment modalities exist at both the community level (water fluoridation) and personal level (toothpaste, rinses, supplements, other). Excessive use of fluorides while teeth are developing prior to eruption can cause a range of visually detectable changes in enamel opacity, broadly termed **enamel fluorosis**. Cosmetic effects of enamel fluorosis range from lacy, white specks on the tooth surface in the most common milder forms, to brown spots and a pitted appearance in the more severe forms, which are rare. Prevalence of enamel fluorosis has increased steadily in the population since the introduction of water fluoridation and numerous other fluoride products. It is expected that prevalence, incidence and severity of enamel fluorosis will be reduced by adherence to recent guidelines for fluoride use (CDC 2001). Because of the complex nature of fluoride exposure a large population-based study will be required to assess the effects of such exposures.

Periodontitis occurring in children, adolescents and young adults is known as **Early-onset Periodontitis (EOP)** and is characterized by rapid destruction of supporting bone around individual teeth, high rates of caries and loss of permanent teeth. Almost 1 percent of children ages 14 to 17 have EOP (Oliver et al. 1998) with rates much higher in black children (10%) and Hispanic children (5%) (Albandar et al. 1997). Among adults, smoking may account for more than half of adult periodontal cases (Tomar and Asma 2000). Diabetes and periodontal disease have a two-way relationship: diabetics (types 1 and 2) are more susceptible to periodontal disease (Genco 1996), and the inflammatory response to this oral infection may in turn impact glycemic control (Grossi and Genco 1998). Less is known about the relationship of smoking or diabetes with periodontal disease in children and adolescents.

Women may be more susceptible to periodontitis during pregnancy (Yalcin et al. 2002). Pregnant women with even sub-clinical oral infections may be at higher risk of delivering **pre-term or low birth weight** babies (Gibbs et al. 1992).

Craniofacial clefts, although not common, require comprehensive and expensive medical treatment through the first several years of life and severely impact the quality of life of affected children and their families. Like neural tube defects, craniofacial clefts may be preventable with adequate folic acid intake (Tolarova and Harris 1995).

Access to dental services plays an important role in preventing and managing the oral diseases and conditions described above. Families move between insurance plans and many are not insured for dental care – for every child without medical insurance, 2.6 children are without dental insurance (US Department of Health and Human Services 2000). Dental care is the most prevalent unmet health need in US children (Mouradian et al. 2000). Through longitudinal follow-up we can document the use of dental services, both preventive and treatment services, over time, by type, frequency and provider category and assess the effectiveness and cost-effectiveness of these services.

I. Proposed Core Aims:

a. To determine the **incidence** of dental caries, enamel fluorosis and EOP.

b. To determine **potential risk factors**, such as nutritional factors, host immune characteristics, oral microbial colonization/infections and underlying genetic factors, and their inter-relationships, related to the incidence of these oral diseases and conditions.

c. To evaluate all the sources of **fluoride exposure** and total fluoride exposure during the first 8 years of life, and the cumulative effects on the incidence and severity of dental caries and enamel fluorosis through adolescence.

d. To more fully describe the relationship between **maternal oral infections** and **folic acid consumption** and **pregnancy outcomes**, such as pre-term delivery, low

birth weight and craniofacial clefts, and **long-term oral health consequences** in the affected children.

e. To determine the timing, number and type of **dental services** received, and the effectiveness and efficiency of those services.

II. Workgroups:

Immunity, Infections, and Vaccines
Health Services

III. Contact Person:

Dolores M. Malvitz, DrPH
Chief, Surveillance, Investigations, and Research Branch
Division of Oral Health
CDC NCCDPHP
dmalvitz@cdc.gov
770.488.6065 work

IV. Public Health Significance

1. The social impact of oral diseases and conditions in children is substantial. Over 50 percent of 5-9 year old children have at least one cavity or filling, and that proportion increases to 78 percent among 17-year olds (US Department of Health and Human Services 2000). More than 51 million school hours are lost each year to dental-related illness. Poor children suffer nearly 12 times more restricted-activity days than children from higher-income families. Untreated dental caries in the primary (baby) teeth has been associated with pain, difficulty eating, and underweight. (US Department of Health and Human Services 2000). Early Childhood Caries (ECC) is characterized by aggressive caries in the primary teeth, occurring in children age 6 and under. In current dental practice, most general dentists recommend a first visit by age However, in children with ECC the disease may be extensive by age 3. The American Academy of Pediatricians recently recommended that all children see a dentist by the first birthday. However, there is a lack of evidence to support this policy.

2. Dental caries is the **single most common chronic childhood disease**; it is 5 times more common than asthma and 7 times more common than hay fever. Dental caries (tooth decay) is a multifactorial but preventable disease, caused by a transmissible bacterial infection that results in the dissolution of the hard tissue structure (crystals of hydroxyapatite) of the teeth. Dental caries can occur at any age but is particularly damaging when vulnerable primary teeth are affected. Current public health prevention efforts for dental caries include use of fluorides, protective sealants (plastic coatings on the chewing surfaces of posterior teeth), and access to dental care.

   Understanding the time-sequence pathogenesis of these infections would provide the basis for developing age-appropriate interventions to reduce the incidence and long-term consequences of dental caries.

3. Water fluoridation is the primary community-based intervention for prevention of caries and was named one of the ten important public health achievements of the century (CDC 1999). In the 1930's H. T. Dean studied the relationships among fluoride in drinking water, enamel fluorosis and dental caries. These studies concluded that fluoride in drinking water had an inverse relationship with caries and a direct relationship with fluorosis (Dean 1942). Sources of fluoride now also include foods and beverages prepared with fluoridated water, fluoride toothpaste, dietary supplements, and other professionally applied and over-the counter topical agents (such as gels, varnishes, and mouthrinses). Excessive ingestion of fluoride during the first 8 years of life can produce enamel fluorosis. Since the introduction of fluoride vehicles other than water fluoridation, the prevalence of fluorosis has increased from 7-10% to 25% in optimally fluoridated areas. In addition, reports of persons with moderate and severe fluorosis have become more

frequent (Beltran et al. 2002). Adherence to recent guidelines on fluoride use (CDC 2001) should promote more optimal use of fluorides that will maximize their protective effects and reduce the prevalence, incidence and severity of enamel fluorosis. Recently, an association between fluorosis-like hypoplastic lesions and early antibiotic use has been hypothesized based on anecdotal reports.

Currently, however, we do not know how much fluoride children are ingesting from all sources, the incidence of enamel fluorosis, or the incidence of dental caries. Additionally, a long-term study of fluorosis has not been conducted to determine if severity of this condition decreases with age as a consequence of attrition, or wearing down, of enamel. A prospective, longitudinal study including measurements of both cumulative fluoride exposure and antibiotic use would permit a deeper understanding of the origin, progression, and consequences of these variations in tooth enamel.

4. Early-onset Periodontitis (EOP) or gum diseases are a group of infection-induced inflammatory disorders characterized by rapid destruction of bone and periodontal attachment in children, adolescents and young adults. The clinical features include overt gingival inflammation, dental calculus and a high rate of caries and permanent tooth loss.

   In the United States, the prevalence of EOP ranges from about 1% in 14 to 17 years old to 3.6% in young adults aged 18 to 34 (Oliver et al. 1998). In 1986 and 1987, about 10% of African-Americans, 5% of Hispanics and about 1% of white adolescents had EOP (Albandar et al. 1997). In a study of Hispanic children, alveolar (tooth-supporting) bone loss was reported in 7.8% of children; some as young as 4 years old (Carranza et al. 1998). Certain forms of EOP are a major health problem in Native Americans (Skrepcinski and Niendorff 2000).

   Oral colonization by certain organisms coincides with clinical cases of EOP. Studies have reported that the endemic presence of highly leukotoxic strains of *A. actinomycetemcomitans* (*A.a*) results in an unusually high prevalence of localized forms of EOP, while combinations with other organisms such as *P. gingivalis* and *B. forsythus* may be involved in generalized EOP (Haraszthy 2000). Intra-familial transmission of *A.a* is well documented (Asikainen 1999, Tinoco 1998). Currently, it is uncertain if mother to child transmission of leukotoxic strains of *A.a* increases the risk for EOP in the child. Also, EOP generally involves defects in neutrophil function (Genco 1992) and is considered to have a genetic basis, which is not clearly defined. Several genetic factors are suspected as influencing EOP. Most important are genetic polymorphism of immune response genes, whose products play a role in the inflammatory process, e.g. IL-1A, IL-1B, and TNF-alpha.

Understanding the time-sequence pathogenesis of EOP would provide the basis for developing age-appropriate interventions to reduce the incidence and long-term consequences of EOP.

5. Emerging evidence suggests associations between oral infections and pre-term delivery and low birth weight (Offenbacher et al. 1998). Craniofacial clefts share common embryogenesis with the central neural tube. Prenatal use of folic acid supplements has been associated with prevention of neural tube defects. It has been proposed that periconceptual use of folic acid can prevent craniofacial clefts (Tolarova and Harris 1995). In the U.S., pre-term low birth weight occurs in 1 in 10 live births (Gibbs et al. 1992) and craniofacial clefts occur in 1 in 600 live births. These two conditions are associated with higher levels of morbidity and mortality and incur large medical costs. It has been estimated that 18 percent of pre-term low birth weight could be prevented if periodontal disease is eliminated in expectant mothers (Offenbacher and Beck 1998) and 65% of craniofacial clefts may be prevented by periconceptual use of folic acid and multivitamins (Tolarova and Harris 1995). These birth outcomes can have oral health consequences throughout life that have not yet been fully evaluated.

6. Access to dental services, especially recommended preventive services should be associated with the maintenance of oral health and prevention and control of certain oral diseases and conditions. This applies to services delivered to both mother and child, as oral health status of and use of services by the mother may be related to the child's oral health status and use of services.

   Oral health care is the **most prevalent unmet need** among US children (Mouradian et al. 2000). The American Academy of Pediatricians recently recommended that all children see a dentist by their first birthday. However, there is a lack of evidence to support this policy and some evidence that general dentists are not comfortable seeing children younger than 3 years old (Cotton et al. 2001). Although periodontal disease is preventable and treatable with self-care and routine dental care, and there is no evidence to support discontinuing care during pregnancy, many dental professionals are reluctant to provide care to pregnant women.

   Describing receipt of dental services over time by number and type can assist in assessing effectiveness and cost-effectiveness of recommended preventive interventions. If the study design permits, collection of data from dental record would help validate self-reports of services received.

V. Justification for a large, prospective, longitudinal study

1. Dental Caries

This is the first opportunity to estimate the incidence of dental caries, and enamel fluorosis and to evaluate important risk factors in a large cohort of children from birth (or near conception) to their late teen years and beyond.

Sample Size issues:

Dental caries is common, occurring in an estimated 45% of children 5-17 years of age (NHANES III 1988-1991). Based on a "lift the lip" protocol (examining upper anterior teeth) approximately one percent of children aged 12-23 months experienced Early Childhood Caries or ECC (Kaste et al, 1999). Using the same protocol 1,000 cases would be expected in a sample size of 100,000 although it is likely that this cursory examination underestimates the prevalence of ECC. We would need to examine all 100,000 children between the 1st and 6th birthdays for ECC to provide sufficient sample size for this outcome. We anticipate that a cohort of 100,000 would sufficiently represent major social and demographic groups and permit assessment of disparities among these groups, and suggest better prevention and treatment strategies.

Fluorides and Fluorosis

Currently, there is one longitudinal assessment of dietary fluoride exposure among children in Iowa (Levy et al, 1995). This study obtained exposure information from dietary histories, the best technique available when the study was designed. The limitations of this study include recall bias of fluoride exposure, using subjects of only white race, significant attrition (lost-to-follow-up) over the 7 years, and a small sample size. Fluorosis needs to be studied in a larger sample size that allows for collection and analysis of multiple risk factors among diverse populations. In addition, we propose to perform a quantitative analysis of fluoride content in consecutive fingernail samples to adequately measure cumulative fluoride exposure over time (See IV for details).

Sample Size issues:

Enamel fluorosis occurs in an estimated 26% of schoolchildren in optimally fluoridated areas and 18% in sub-optimally fluoridated areas; 1.5% and 0.6% of schoolchildren have moderate and severe fluorosis, respectively (Beltran, Griffin and Lockwood, 2002). Almost all children are exposed to fluoride toothpaste; in addition, children in fluoridated areas are exposed to water fluoridation and children in sub-optimally fluoridated areas are exposed to fluoride supplements, and foods and beverages prepared in fluoridated areas.

Sorting out the effects of fluorides from multiple sources on the occurrence of dental caries and enamel fluorosis, especially moderate to severe fluorosis and among subgroups, will require study of multiple overlapping exposures (e.g., diet, drinking water sources, frequency of brushing with fluoride toothpaste, professionally applied topical fluorides, use of mouthrinses), and possible interactions as the exposures have different routes (topical vs. ingested). Since age at exposure may influence fluorosis, analyses by age groups would require relatively larger sample sizes.

2. Early Onset Periodontal Disease

Similarly, this is the first opportunity to estimate the incidence of EOP, and to evaluate the relative importance of specific risk factors in the first 18 years of life.

Sample Size issues:

In the United States, the prevalence of EOP ranges from about 1% in 14 to 17 years old to 3.6% in young adults aged 18 to 34 (Oliver, Brown and Loe, 1998). In 1986 and 1987, about 10% of African-Americans, 5% of Hispanics and about 1% of white adolescents had EOP (Albandar, Brown and Loe, 1997). In a study of Hispanic children, alveolar bone loss was reported in 7.8% of children; some as young as 4-years of age (Carranza, Garcia-Godoy and Bimstein, 1998). Overall, EOP is twice as common in females than males (Oliver, Brown and Loe, 1998). Certain forms of early onset periodontitis are a major health problem in Native Americans (Skrepcinski and Niendorff, 2000).

In adults, diabetes and periodontitis have been linked - periodontitis is more common among diabetics, especially among diabetics in poor glycemic control, and the inflammatory response triggered by a local periodontal infection may negatively impact glycemic control. In children, less is known about the interrelationship of periodontal diseases and glycemic control in diabetics. Diabetes (Type I and Type II) occurs in just under 0.2% of the population under age 20; these numbers are expected to increase in the near future unless trends in overweight and obesity among children reverse (CDC, 2002). Among adults, smoking plays a key role in development of periodontitis. Among high school students, smoking is more common than having diabetes or periodontal disease 28.5% report being current smokers, 13.8% current frequent smokers (CDC, 2002).

We expect a cohort of 100,000 will provide sufficient sample size to assess EOP within gender groups and racial and ethnic groups, and to assess the importance of diabetes and smoking in EOP during adolescence.

3. Pregnancy outcomes

While rates of pre-term or low birth weight deliveries and of craniofacial clefts can be estimated from vital records or registries, assessing risks and protective factors for

these pregnancy outcomes and the long-term consequences on the children born with these conditions requires a longitudinal study. In the US, pre-term low birth weight occurs in 1 in 10 live births (Gibbs, Romero and Hillier, 1992). Craniofacial clefts occur in 1 in 600 live births. Periodontal diseases are expected to occur in 10 to 15% of women of childbearing age. Two thirds of women do not consume enough folic acid to prevent neural tube defects (CDC 2002).

Sample Size issues:

We expect that 10,000 cases of pre-term low birth weight would occur in this cohort and about 167 craniofacial clefts cases in this cohort.

VI. Scientific Merit

Dental research has accumulated sufficient evidence on the etiological aspects of **dental caries** from animal models and observational and intervention studies (Bowen and Tabak 1993). However, to date we do not have a prospective evaluation of these factors as they interact to determine the incidence of disease. We do not know whether the risk of dental caries changes as etiological factors change over time. For example, recent cross-sectional data suggest that some teeth are at higher risk of dental caries than others. However, we do not know if this is an effect of surface susceptibility (as in the case of pit and fissures), length of exposure to the intra-oral environment, or atypical dietary patterns, such as bottle-feeding with liquids sweetened with fermentable carbohydrates or ad libitum breast-feeding. These questions could be answered only with a longitudinal assessment of outcomes, risk factors and protective variables.

On the preventive aspects of dental caries, we know, from the pioneer cross-sectional studies of McKay and Dean in the 1930s, that **fluoride exposure** is associated with **a decrease in dental caries** and an **increase in enamel fluorosis**. In the last 20 years, some researchers have reported an increase in the prevalence of enamel fluorosis that could be attributed to exposure to fluoride from multiple sources including water fluoridation, dietary supplementation and unintended ingestion of fluoride from toothpaste. In our current model to assess fluoride exposure, the outcome, enamel fluorosis, is measured years after the exposure has occurred. This retrospective assessment, therefore, is strongly subject to recall bias and misclassification, as exposure to fluoridated water may change as residency and dietary and drinking behaviors change with age. Currently, renal fluoride excretion rates (Marthaler, 1999) and fluoride concentration in fingernails (Whitford et al, 1999) have been developed to measure total fluoride exposure. The longitudinal and periodical assessment of fluoride exposure using a measure of total fluoride exposure, such as fingernail analysis, and outcomes such as dental fluorosis and dental caries, will allow determination of exposures that maximize the preventive effect of fluorides while minimizing the prevalence and severity of fluorosis.

It is well established that periodontal diseases are infectious diseases. It has been well documented that important periodontal and caries-related pathogens are transferred from mother to child (Caulfield 1993, Asikainen 1999, Tinoco 1998). However, it is uncertain if mother to child transmission of periodontal pathogens (eg., leukotoxic strains of *A.a*) increases the risk for EOP in the child. Further longitudinal studies to monitor these organisms prior to disease onset, during progression, and following clinical intervention are necessary to fully evaluate their role in the initiation of EOP. Monitoring of antibodies to these organisms will enhance our understanding of the role of humoral immune responses in protection versus disease destruction. Our proposed studies may identify important genetic markers for increased risk to EOP possibly within genes that regulate important immune responses to EOP. Longitudinal studies may lead to understanding of differences in prevalence of EOP observed among race and ethnic groups.

Recently, a series of reports in the literature claim an association between periodontal disease in mothers and a negative pregnancy outcome such as premature birth or **low birth weight**. The underlying connection is through the presence of high levels of inflammatory mediators, which may trigger pre-term delivery. In order to answer this question, pregnant mothers will be required to have one clinical examination for their periodontal status. In addition, levels of C-reactive protein and other inflammatory markers will be included in the assessment. Also, a detailed medical history, including tobacco use will be obtained from the mother. These data will be obtained for other components of the NCS. The dental eruption patterns and incidence of other dental diseases and conditions among children born with low birth weight (LBW) will be examined, and reported associations of LBW with ECC and enamel defects will be assessed.

Clefts of the oro-maxillo-facial region are developmental defects due to incomplete fusion of the developmental processes during the embryogenic (facial clefts) and early fetal (palatal closure) development. The normal process requires a proliferation of mesenchymal cells that originate in the neural crest and the disruption of the ectoderm and neuroectoderm that cover the developmental processes. There is evidence that spina bifida, a neural tube defect, is a defect directly associated with low levels of folic acid in the metabolism of amino acids during fetal growth. As oro-facial clefts share many anatomical and embryological similarities with neural tube defects, it has been proposed that perinatal supplementation of folic acid also may prevent the non-syndromic type of oro-facial clefts (Tolarova and Harris, 1995). Clefts are clinically visible at birth and, we expect, will be recorded in the dataset on birth outcomes. We will use this outcome and the dietary/nutritional history of the mother to ascertain periconceptional use and dosage of folic acid. In addition, as the management of children with clefts varies, we will follow these children to assess the oral health effects of these defects later in childhood and teens.

VII. Potential for innovative research

Urinary fluoride excretion rates are currently recommended to measure total fluoride exposure. Some of these techniques have been tested in the US, but the method requires a 24-hour urine collection, which may be methodologically difficult in toddlers and small children. Fluoride levels vary in the system based on daily fluoride exposure and individual metabolic rates. Another available method to sample fluctuations is to test a blood sample taken every 3-4 hours or acquire a sample of bone. Neither is practical for a clinical study. We propose to measure fluoride concentration in multiple fingernail samples as proxy for total fluoride exposure. A few studies have used this technique and correlated their results with systemic fluoride exposure. During the time of developing a full proposal, this technique will be validated in ongoing studies, in terms of exposure and size of the biological sample.

VII. Feasibility

The examination techniques for dental caries, enamel fluorosis and EOP are those used in previous and current epidemiological evaluations at the national level (e.g., NHANES). Questions to be included in a structured questionnaire related to fluoride exposure, dental visits, and diet/nutrition, have been used in many populations with representation at local, state, and national levels. The isolation of microorganisms from sub- and supra-gingival plaque will follow standard microbiological techniques. Finally, the only technique in need of further validation is cumulative fluoride exposure by determining the fluoride concentration in a fingernail sample. In the following months, we will work closely with the Dr. Gary Whitford at the Medical College of Georgia to further validate this technique.

Both pre-term low birth weight and craniofacial clefts will be assessed at birth. Oral infections status and periconceptual folic acid consumption will be assessed during pregnancy. Of these, we expect that other workgroups are already planning to assess pre-term low birth weight, craniofacial clefts and folic acid consumption. The oral infections assessment would support all three of the oral diseases and conditions hypotheses: transmission of oral pathogens causing caries and EOP from mother to child, and the association of maternal oral infections with pre-term low birth weight.

None of the clinical techniques, including plaque samples, are invasive. They do not carry more risk than those associated with a regular dental appointment. We will adhere to standard CDC infection control protocol while collecting clinical data. We expect that the mother will clip the nails of their children and send the samples for analysis. Data will be obtained under an overall informed consent, but we will request assent before clinical activities. Therefore, we do not foresee mothers or children to be at unreasonable risk during their participation in this project.

On privacy issues regarding the reporting of results, we will follow either the CDC/NCHS standards or those agreed upon by NCS, whichever is more stringent.

Results of clinical evaluations will be returned to the family including a referral note and follow-up if required.

A list of the kinds of examinations and tests required to address these hypotheses are listed below.

Dental examinations
"Lift the lip" for children under age 1
Routine dental examination every 6 to 12 months
Visual fluorosis examination, annually, ages 2-6 (primary teeth); 8-15 (permanent teeth)
Periodontal examination: mother, once during pregnancy; child, annually 13-21
Direct observation of toothbrushing, every 6 months

Medical examinations
Craniofacial clefts, at birth
Pre-term or low birth weight, at birth
Growth and development benchmarks

Lab tests
Oral plaque, obtained at dental exams
Blood samples, can be timed with other draws
Fingernail clippings, every 6 months until 9th birthday
Drinking water sample, every six months

Questionnaire
Nutrition: mother's prenatal, child's postnatal and periodically throughout study
Socio-demographic information, annually
Fluoride toothpaste use, toothbrushing behavior
Antibiotic use*
Dietary intake of fluorides*

*If collection of medical or dental records or prescriptions is planned, then these self-reported measures could be validated, or records used to prompt recall.

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