HYPOTH-Health Disparities Environmental Justice Hygiene Hypothesis August 5 2002.doc

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National Children's Study

I. Proposed Core Hypothesis

Large U.S. studies such as NHANES suggest that socio-economic disadvantage is a risk factor for asthma and allergy among some U.S. populations (e.g. Puerto Rican communities in Eastern U.S. Cities)[1] and yet appears to be a protective factor for other populations (e.g. Mexican-American in the South Western U.S. [Carter-Pokras, 1993; [2-4]]. On a world-wide basis, the evidence is even more well established: poverty is associated with low rates of asthma and allergy in some communities (e.g. rural Kenya; rural China) and yet is a strong risk factor for asthma and allergy in other communities (e.g. New York City, U.S.)(ISAAC). The environmental factors responsible for the geographic and ethnic differences in the effects of socioeconomic disadvantage on allergy/asthma risk are poorly understood. The main aim of this proposal is to test whether the "hygiene hypothesis"[5-8] partially explains geographic and ethnic/racial differences in the relationship between socio-economic disadvantage and the development of allergy and asthma.

The hygiene hypothesis states that infant exposure to certain bacterial/viral/protozoal infections or to bacterial components (e.g., endotoxin) may be protective against the subsequent development of asthma and allergy in childhood. The proposed mechanism for the protective effect of early bacterial/viral/protozoal exposure(Matricardi. BMJ 2000. 320:412-16) is through protection of the infant immune system from development of a bias toward allergic inflammation localized to the lung. Alternatively, early bacterial/viral exposure may increase airway hyperreactivity. We therefore propose the following stage-of-development specific hypotheses:

1. Within the United States, there will be geographic differences (eg. urban:rural; regional) and ethnic/racial differences in the relation between socio-economic disadvantage and exposure to:
    a. Large family size and day care
    b. Endotoxin
    c. Full vaccination according to practice recommended by the American College of Pediatrics
    d. Prenatal or early childhood exposure to Hepatitis A and *Toxoplasma gondii*
    e. Infant proximity to large farm animals including cows and pigs

2. Within the United States, geographic differences (eg. urban:rural; regional) and ethnic/racial differences in the impact of socio-economic disadvantage on wheeze and lower respiratory infection in <u>the first year of life</u> will be predicted by by family size, day care and endotoxin[9]. These exposures, controlling for the effects of other likely risk factors (environmental tobacco smoke, family history, perinatal factors, gender, lower respiratory illness, and home allergen exposure) <u>will increase</u> the risk of wheeze and lower respiratory infection <u>in the first year of life</u>.
3. Within the United States, geographic differences (eg. urban:rural; regional) in the relation between socio-economic disadvantage and cytokine production by allergen-stimulated mononuclear cells by age 3 will be predicted by:
    a. Large family size and day care
    b. Endotoxin
    c. Full vaccination according to practice recommended by the American College of Pediatrics
    d. Prenatal or early childhood exposure to Hepatitis A and *Toxoplasma gondii*

e. Infant proximity to large farm animals including cows and pigs

By age 3, these factors will predict reduced lymphocyte proliferative response to allergen and nonspecific mitogens. The cytokine profile (IL-5, IL-10, IL-13, TNF-alpha and interferon-γ) for children with early wheeze and high endotoxin exposure will follow a Th-1 profile while that of children with low exposure and wheeze will follow a Th-2 or global proinflammatory profile.

4. Within the United States, geographic differences (eg. urban:rural; regional) in the relation between socio-economic disadvantage and the development of allergy by age 3 will be predicted by:
    a. Large family size and day care
    b. Endotoxin
    c. Full vaccination according to practice recommended by the American College of Pediatrics
    d. Prenatal or early childhood exposure to Hepatitis A and *Toxoplasma gondii*
    e. Infant proximity to large farm animals including cows and pigs

These factors will be independent protective factors associated with reduced total IgE and total eosinophil count by age 1 and reduced allergen specific antibody responses by age 3.

5. Within the United States, geographic differences (eg. urban:rural; regional) in the relation between socio-economic disadvantage and the development airways responsiveness and the asthma/wheeze syndrome by age 7 will be predicted by:
    a. Large family size and day care
    b. Endotoxin
    c. Full vaccination according to practice recommended by the American College of Pediatrics
    d. Prenatal or early childhood exposure to Hepatitis A and *Toxoplasma gondii*
    e. Infant proximity to large farm animals including cows and pigs

These factors will be independent protective factor for airways responsiveness and the asthma/wheeze syndrome by age 7.

6. Finally, the allergy/asthma protective effects of endotoxin will vary by ethnic/racial population, and this variable effect will be partially be explained by gene-by-environment interactions. The genes of interest will be those for the pattern recognition molecules CD-14/ TLRs(Toll like receptors)[10]. These molecules are essential components of the in the pathway of endotoxin binding and cell activation.(Wright. Science 1990: 249:55-61) (Pugin. Proc Natl Acad Sci USA. 1993; 90:2744-8). Variation in genes for these molecules have been shown to predict variation in allergy[11].

II. Workgroup

Health Disparities/Environmental Justice

III. Contact Person for Proposed Hypothesis

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IV. Public Health Significance

Asthma, the most common cause of chronic childhood disease in the U.S., is the most frequent admitting diagnosis to pediatric hospitals, and accounts for over $6 billion in health care costs per year.[12] Moreover, there is evidence that asthma prevalence, emergency room visits, and hospitalizations are increasing.[13] Earlier U.S. studies suggested that the median age of onset of childhood asthma was 5 years in boys and 9 years in girls.[14] More recent U.S. studies suggest that half of all cases of childhood asthma are diagnosed by age 3, and two-thirds of all childhood asthma cases are diagnosed by age 5.[15] Regardless of precisely when they are diagnosed, for the majority of asthmatic children, the roots of their disease are in early childhood. It is in the first five years of life when their immune system, its cellular and serologic components, differentiate into an atopic or TH-2 phenotype. Over 80% of childhood asthmatics are atopic.[16] Family history of allergic disease is the single most important predictor of the development of allergic diseases such as asthma and atopic eczema. An individual with one asthmatic/allergic parent has a 30-50% chance of becoming allergic or asthmatic. The question is: what environmental influences determine whether a child who is susceptible by virtue of family history becomes asthmatic or not?

Several large U.S. studies have shown that indices of poverty, race (Black versus White), and ethnicity (Puerto Rican versus non-Puerto Rican) are associated with higher rates of asthma and wheeze in children. However, socio-economic disadvantage is not globally a risk factor for allergy or asthma. Large U.S. studies such as NHANES suggest that socio-economic disadvantage is a risk factor for asthma and allergy among some U.S. populations (e.g. Puerto Rican communities in Eastern U.S. Cities) and yet appears to be a protective factor for other populations (e.g. Mexican-American in the South Western U.S.(NHANES III/Hispanic NHANES). On a world-wide basis, the evidence is even more well established: poverty is associated with low rates of asthma and allergy in some communities (e.g. rural Kenya; rural China) and yet is a strong risk factor for asthma and allergy in other communities (e.g. New York City, U.S.)(ISAAC).

V. Justification for a Large, Prospective, Longitudinal Study

Only a National U.S. study can provide the geographic, socio-economic, rural:urban, and ethnic/racial diversity to test this series of hypotheses. The influence of the exposures on immune expression and the expression of disease will change over time. Gene-by-environment interactions that we propose can only be tested with sufficient numbers in each ethnic/racial stratum.

For example, if we want to understand whether African-American children who live in the rural South have lower asthma rates than African-American children who live in the urban Northeast or West because of differential endotoxin or early viral/protozoal infection, we would have to sample sufficient numbers of African-American children in rural and urban settings in various parts of the U.S. Now imagine asking whether there was a gene-by environment interaction in the influence of endotoxin. (e.g. a difference in Toll-like receptor genotype), stratifying by race/ethnicity (African-American, Mexican American, Puerto Rican, etc). The power calculations are difficult to perform, but there is no question that you will need not only an N of 100,000, but also a very carefully thought out sampling scheme.

The hypotheses vary by stage-of-life and require a longitudinal study design.

VI. Scientific Merit.

See above.

VII. Potential for Innovative Research

See above.

VIII. Feasibility

Critical period for exposure and outcomes:
Pregnancy through 7-8 years of age

Sampling needs:
a. sampling for home and neighborhood/farm endotoxin and potential confounders (allergens/fungi) in the first 3 months of life and at age 7
b. sampling of maternal serum for viral/protozoal serology during pregnancy (optimally twice, in early and late pregnancy)
c. sampling of child serum for eosinophil count, IgE, specific allergy, viral/protozoal serology at ages 1, 3, and 7
d. sampling of child cells for lymphocyte proliferation, cytokine production measurement, age 3
d. skin testing and methacholine challenge testing at age 7
e. Questionnaire tracking of day care, family size, parental history of allergy and asthma

Contact---see above
Nature of measurement:

Standard methodology is available for measurement of each exposure and outcome.
Two measurements can only be done in a subset of the population:

1. measurement of the lymphocyte/mononuclear response to allergen stimulation. It is expensive and labor intensive. This work may need to be done within 24 hours of gathering the specimen, depending on whether or not it is considered acceptable to freeze the cells. Freezing cells results in some loss of cells and cellular activity. Whether it results in significant differential loss of cellular function needs piloting before acceptance of this approach.

   The rationale behind focusing on this outcome is that asthma involves lymphocyte mediated inflammation, and differential T-cell behavior may be not only a key to whether or not the child will develop allergy or asthma, but may also be a key to approaches that may result in early allergy or asthma prevention.

2. methacholine challenge testing. This requires a clinic visit and in expensive and more labor intensive. While it has been considered a safe technique to evaluate bronchial reactivity, one of the two major secondary phenotypes of asthma (the other being allergy), its use has recently come under scrutiny and the ethics of stimulating bronchial constriction via either methacholine or cold air or exercise challenge

should be carefully reviewed by the lay as well as academic committees of this study before incorporating it into the study.

Community Involvement: From the very beginning, participants must feel like they or their community is getting benefit from involvement in the study. It is worth while considering whether each community (once defined) should individually express what give-back they feel would be most useful, rather than having a national approach to lay groups suggesting what very different communities might need or want as part of their involvement in the study.

Community involvement is also essential in deciding on a local or regional basis which procedures are acceptable to the community and what kind of feed-back might be useful to the individual families as well as the group.

Since this proposal involves follow-up regarding vaccination and early viral/protozoal infection, one potential benefit might be feed-back to primary care physicians and families regarding vaccination history and viral titres.

Since many families will have parents with asthma or symptomatic allergy, if allergens are measured as a potential confounder of endotoxin effects (since animals also carry allergen) then, one form of give-back would be to allergy test the parents and to give allergy appropriate advice and materials regarding allergen avoidance/reduction (e.g. mite impermeable mattress covers, vacuum cleaners). We believe that the effect of this intervention can be tracked and can be integrated into the observational study.

Ethical considerations: as in the entire cohort study, we will need to follow strict guidelines on protection of privacy. Methacholine challenge testing will need to stricting follow ATS (American Thoracic Society) guidelines—see above.

Selected References

1. Call, R.S., et al., *Risk factors for asthma in inner city children [see comments]*. J Pediatr, 1992. **121**(6): p. 862-6.
2. Lester, L.A., et al., *Ethnic differences in asthma and associated phenotypes: collaborative study on the genetics of asthma.* J Allergy Clin Immunol, 2001. **108**(3): p. 357-62.
3. Homa, D.M., D.M. Mannino, and M. Lara, *Asthma mortality in U.S. Hispanics of Mexican, Puerto Rican, and Cuban heritage, 1990-1995.* Am J Respir Crit Care Med, 2000. **161**(2 Pt 1): p. 504-9.
4. Lara, M., et al., *Elevated asthma morbidity in Puerto Rican children: a review of possible risk and prognostic factors.* West J Med, 1999. **170**(2): p. 75-84.
5. Strachan, D.P., *Allergy and family size: a riddle worth solving.* Clinical and Experimental Allergy, 1997. **27**: p. 235-236.
6. von Mutius, E., et al., *Skin test reactivity and number of siblings.* British Medical Journal, 1994. **308**: p. 692-695.
7. von Mutius, E., et al., *Prevalence of asthma and atopy in two areas of West and East Germany.* Amercian Journal of Respiratory and Critical Care Medicine, 1994. **149**: p. 358-364.
8. von Mutius, E., et al., *Exposure to endotoxin or other bacterial components might protect against the development of atopy.* Clin Exp Allergy, 2000. **30**(9): p. 1230-4.

9. Park, J.H., et al., *House dust endotoxin and wheeze in the first year of life.* Amer J Respir Crit Care Med(IN PRESS), 2000.
10. Baldini, M., et al., *A Polymorphism* in the 5' flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum immunoglobulin E.* Am J Respir Cell Mol Biol, 1999. **20**(5): p. 976-83.
11. Gao, P.S., et al., *Serum total IgE levels and CD14 on chromosome 5q31.* Clin Genet, 1999. **56**(2): p. 164-5.
12. Gergen, P.J., D.I. Mullally, and E. R3d, *National survey of prevalence of asthma among children in the United States, 1976 to 1980.* Pediatrics, 1988. **81**: p. 1-7.
13. Institute of Medicine (US). Committee on the Assessment of Asthma and Indoor Air., *Clearing the air: asthma and indoor air exposures.*. 2000, The Institute of Medicine: Washington.
14. Sherman, C.B., et al., *Early childhood predictors of asthma.* Am J Epidemiol, 1990. **132**(1): p. 83-95.
15. Croner, S. and N.-I.M. Kjellman, *Natural history of bronchial asthma in childhood: a prospective study from birth up to 12-14 years of age.* Allergy, 1992. **47**: p. 150-157.
16. Sears, M.R., et al., *Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children.* N Engl J Med, 1991. **325**(15): p. 1067-71.