

I. Proposed Core Hypothesis/Question

Exposure to Respiratory Viral Agents and/or Gastrointestinal Agents such as: Paramixo viruses, Pneumo viruses, Rotaviruses, Caliciviruses, EAD, etc. as well as environmental factors including chemicals such as heavy metals during the first year of life predisposes to reactive airway diseases such as asthma and other respiratory diseases subsequently which may be accompanied by a decrease in pulmonary function. In contrast, exposure to some infectious agents of bacterial enteritis, depending on the period in life may yield some protection or sensitize subsequently to Reactive Airway Diseases.

II. Workgroup: Infection, Immunity and Vaccines

III. Contact Person(s) for Proposed Core Hypothesis/Question

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IV. Public Health Significance

A reactive airway disease process such as asthma has a prevalence rate under the age 18 years of 690 per ten thousand. It is known that approximately 1/3 of children suffer from Reactive Airway Disease following infection with respiratory viruses. The significance of the early exposure to infections and environmental agents is not known.

Except that historically, those diagnosed with asthma later in life have a past history of reactive airway disease and/or obstructions. This is not a “sine qua none” since some individuals who suffer from asthma later in their childhood have a negative past medical history for RAD. Amongst the reactive airway diseases, asthma is perhaps the most common chronic condition in our children. The consequences of such a condition is enormous, leading to parent loss of workdays, numerous office visits, absences from school, ER visits or hospitalization. We have chosen to use the term reactive airway disease, essentially, which would include asthma, to make the outcome more inclusive. This condition will have major public health significance in terms of time loss from schools, hospitalization and utilization of medical care, outpatient care, loss of time from work for parent or caregiver.

V. Justification for a large, prospective, longitudinal study

Specifically, we know that patients, who have had severe respiratory virus infection such as bronchiolitis and pneumonias leading to hospital admissions in infancy, may have an increase in wheezing, at least during the initial or the immediate follow-up period. There is also concern that these infections may sensitize the individual to allergens with subsequent development of reactive airway disease conditions such as asthma, particularly if there is an individual predisposition to asthma or allergy or atopic disease. We are aware that the bronchial reactivity, which follows an acute viral infection, may, in a number of patients, diminish over time. Also, there are reports that exposures to heavy metals *in utero* could be associated with immunotoxicological changes promoting subsequent reactive airway disease during post-natal life. Similarly, there have been studies suggesting that the exposure to enteric bacterial agents may also be associated

with modification of risk of Reactive Airway Disease on follow-up. The possibility of accessing a cohort of 100,000 children will offer the opportunity to look in a heterogenous population, the effect of exposure to various infectious agents as well as environmental agents in the context of the various phenotypes and also allow us to explore the net outcome of the interaction between these and the environmental exposures.

The significant contribution of identification of specific subsets in the cohort at risk for severe outcomes would be of significant Public Health benefit. Hence prospective follow-up from pregnancy to adulthood would allow examination of the various subgroups and examine the effect of the various exposure at different times of development

VI. Scientific Merit

It has been postulated that a shift in the balance between the Th₁ cells and Th₂ cells may occur early in life on exposure to viruses and environmental chemicals in certain individuals. This shift to Th₂ may increase secretion of interleukins that produce allergic inflammation and stimulate B cells to produce antibodies such as Ig E, which may enhance the inflammatory response. Some investigators, such as Volovitz, have noted leukotriene C₄ in the naso/pharyngeal secretions from 67% of children with a bronchiolitis, compared to those from 1/3 of parents with upper respiratory infections. These concerns have lead us to review communications which attempt to ascertain the relation between exposure to a upper respiratory or other stimulating agents which affect the Th₁/Th₂ relationship and response to antigen, as well as environmental factors, which may do likewise. However, there are controversial views about the effect of some

specific viral infections in the Th1/Th2 relationships. Confirming or denying the hypothesis should yield information which might lead to strategies for prevention and modification of these conditions, which lead to RAD. The role and nature of the cytokines elicited on exposure to agents or factors also need to be examined prospectively. Realizing that the etiology may be varied or multifactorial, our approach will involve examples of the various hypothesis that have been presented in the literature such as the inhalational exposure for heavy metals, exposure to early viral infections, exposure to enteric bacterial agents at various stages of development, and the family history of asthmas, allergies, etc. Throughout this, the timing of exposure will be collected. We will hope to interact with the Asthma Working group.

How will answering our hypothesis, questions advance our understanding?

This study will offer opportunity to look at a representative population where we will be able to develop a better understanding of the interaction between the organism and the environment and the differing prevalence of the condition in certain groups. The approach should lead to a better understanding of susceptibility, pathogens and potential interactions both preventative as well as therapeutic. It is only by identification of these involved factors that we will be able to develop these effective approaches.

VII. Potential for innovative research

As the study attempts to identify interactions, it should stimulate outcomes such as efficiency of collections of samples and data, query methods of diagnosis, method of detection of agents or toxicants. In examining the genetic and phenotypic expression of

the participants, it should help us examine the susceptibility to the microbial and other environmental factors.

The size of the study, as well as the geographical distribution, should allow examination of the difference in environmental exposure, as well as allow for examination of findings with sufficient statistical power to make valid conclusions.

VIII. Feasibility

Our specific goals are to enroll pregnant individuals and obtain the basic base-line information, to follow them (and their immediate families) during pregnancy and after delivery so to ascertain the significance of exposure to infections and environmental chemicals in either development of reactive disease and/or decreased pulmonary function.

The critical period for studying exposure and outcomes begins during pregnancy and will extend throughout infancy and childhood and to adolescence. We will examine exposure to the various factors whether infectious (by rapid methods, DNA probes etc.) and the environmental factors such as toxicants by measuring toxins in biological samples such as sera obtained from the participants as well as also including measurements of the environmental chemicals (such as lead in dust samples) from home, daycare and hopefully school environments. Additionally, by collecting data from the whole family, factors such as order of birth, pet and farm animal exposure and socioeconomic influence will be available.

More specifically, we propose to study whether exposure to infectious agents, as well as environmental toxicants has effect on the development of reactive airway disease. We plan to collect mother's history and paternal medical history, social-economic

information, medicines that are being taken, including alternative ones including herbal. This history would also include the presence of asthma or atopic illness. We will also collect this information from the immediate family. We expect that a sample of 100 thousand children and their families would allow us to detect a 20% change or difference in rate of conditions that may occur (such as infant mortality 5/1000) or a 50% difference in rate of condition (such as autism 2/1000). We hope to enroll the mother, father and child, from early in the prenatal period and follow the child to adulthood with subsequent formalized evaluations which will be “piggy backed” into the regular childhood medical visits that are scheduled in early life and additional formalized visits for: Infant newborn, 6 mos, 1yr; childhood 2, 4, between 4-6 years, 10-11 years, adolescent 11-12, 16-17 and adulthood 18 years to 20-21. These will include all visits for evaluation, which will be done when the child is healthy, i.e. well child visits. Age appropriate outcome observations measure will be part of the evaluations. For illness, which we will expect will occur on a regular basis, respiratory as well as gastrointestinal we will collect information and samples. First of all, we will monitor the illnesses severity and whether it results in hospitalization, doctor visit or management in the house. We also will measure the use of health care facilities such as the ER or the hospital. The severity of the illness will be assessed, as well as the use of medicines, which are either prescribed, OTC or herbal or inhalants. At appropriate intervals, and when feasible, we will evaluate the pulmonary functions with the appropriate instrument. We expect to use the methods that are available and use these with age and weight adjustment for pulmonary function. At predetermined times we will plan also to challenge with methacholine for reactivity. All these evaluations will be done after obtaining informed consent and where indicated

assent from the child. We will minimize the risk to participants and respect the ethics of research: respect, beneficence and justice. Appropriate evaluations and protection mechanisms of subjects will be observed. We will evaluate factors such as the size of the sample that is collected from the patient, as well as which types will be collected from respiratory, stools if indicated, and blood. Samples would also include urinary specimens and saliva as necessary. We will also concurrently consider exposure to other factors such as socio-economic, childcare issues and whether the child lives in the inner city or in the suburban/rural area. Environmental samples such as dust will be collected to measure the presence of environmental chemicals such as lead. We will also follow such parameters as the growth and development of the child and as samples become available, not only will we look for the appropriate known offending micro organisms associated with upper respiratory and gastrointestinal illnesses, but also evaluation of the environment. The clinical data will be collected prospectively during the visits, also from medical records and school records. Among the specimens for specific pathogens to be sampled, serum and saliva as well as throat or NP swabbed will be needed. We will also sample for environmental toxins and/or toxic metabolites. Antibodies in the serum or saliva will be measured as well as other factors, such as microbial DNA detection, the T cell function where indicated and where the sample allows the presence of appropriate cytokines. The immunization history will also be followed. In terms of the development of the child we will evaluate not only the upper respiratory factors, but also the intellectual development and school performance. Among the data collection, we will also collect information of confounders such as race, ethnicity, access to healthcare, socio-economic status and the way these surveillances are being ascertained, whether it's

active, passive or self-reporting or from the review of an existing record. Other data on upper respiratory disease must be collected such as if patient has recurring acute otitis media which exceed the expected norm for age.

We will collect information on the respiratory and enteric illness etiology as well as severity and exposure to medicines and the need for health resource use will be reported. All this information needs to be collected prospectively. We will respect the need for preservation of privacy while collecting such information as personal resources. The risk and discomfort from blood sampling and cord blood sampling and oropharyngeal swabbing (buccal) samples are minimal. Pulmonary function test at predetermined ages and exposure to methacholine should be of minimal risk. Questionnaires for information at entry and subsequently will be developed hopefully in collaboration with the Asthma Group.

We feel the family participation will be mutually beneficial, particularly if information such as the diagnosis-viral, bacterial data is made available to them in a prompt manner. Identification of children who manifest elements of RAD (such as asthma) should be followed by communication with parents and recommendations for appropriate medical support.

Statistics: