A LONGITUDINAL PROSPECTIVE STUDY OF DIARRHEAL MORBIDITY, NUTRITION AND IMMUNOLOGICAL STATUS IN A RURAL BANGLADESH VILLAGE

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Background:

In three-fourths of the world's population the single major cause of childhood morbidity and mortality is diarrhea, concentrated in the period of infant weaning. Studies in Guatemala and India (1) revealed that the high prevalence of weanling diarrhea was not due entirely to the usually incriminated factors of common source epidemics, lack of acquired immunity and agent virulence. Epidemiologic data suggested that host nutrition was compromised during the weanling's transition from breast milk to solid food. One-third of deaths in children aged 1 to 4 were due to kwashiorkor, regularly preceded by a precipitating infectious disease. Another third died of acute diarrheal disease, rarely fatal in the wellnourished child. This two-way synergism between infection and malnutrition, both as protein deficiency and caloric deprivation, has also been welldocumented in laboratory models.

The mechanism by which malnutrition renders the child more susceptible to diarrheal pathogens is still unexplained. Host resistance to intestinal pathogens is the summation of acquired immunity, gastric acid, mucosal integrity, general inflammatory capacities, and others, all of which seem dependent on host nutrition in some degree. Studies on the effect of poor nutrition on the immune response have concentrated on the severely malnourished, moribund hospitalized child (2,3), ignoring the vast majority of ambulatory children in the early stages of the vicious cycle of malnutrition and infection, when nutrition intervention would be economically efficient.

The INCAP and Punjab studies gathered morbidity data at monthly or bi-monthly intervals. This method relied heavily on recall and lost information relevant to diarrheal severity, which was assessed by duration and presence of blood. Nutrition assessments did not routinely include serum proteins, nor was the exact age of each child known. Immunological parameters were not measured, in those or any studies on an epidemiological scale.

Previous censuses in Matlab provide the basis for surveys which can expand and clarify the pioneering work done in Guatemala and India. An ongoing "tube-well" study is prospectively recording morbidity and mortality due to diarrhea, respiratory complaints, exanthems and febrile illnesses. We propose to examine the triangle of morbidity, nutrition and certain immunological parameters within the same prospective two-year Matlab study, to fulfill the following goals.

Goals:

1. To further explore the synergistic effects between malnutrition and morbidity.

2. To identify the marginal child who has no physical stigmata of malnutrition but who is beginning to enter the downward nogrowth-infection spiral.

3. To develop epidemiological parameters of morbidity and nutrition which are specifically relevant to rural Bangladesh. These should form background information for later studies employing sanitation and nutrition intervention.

4. To develop field-study immunological parameters which are relevant to the epidemiology of nutrition and infection. Specifically, are measurements of cellular immunity, the inflammatory response, serum proteins and serum iron-transferrin levels useful predictors of susceptibility to diarrheal and respiratory episodes, and are they in turn related to nutritional status?

Overall Plan:

One entire village in Matlab, Village C with 550 families, in which daily morbidity is recorded, will be visited at least 3 times each year for anthropomorphic measurements among all children up through age 12. Following the first survey, to be conducted as soon as

possible, 50 children, aged 1-4, from each of first and fourth growth quartiles, as calculated from 1972 urban nutrition survey curves (4), will be selected for a pilot study to identify which immunological parameters yield the most information. This data, weighted in favor of demonstrating a difference between the extremes of the nutrition spectrum, will serve as a guide for future surveys.

Subjects:

All children aged 0-8 for whom the exact date of birth is known are potential subjects. Data will be analyzed in terms of four age cohorts: age 0-18 months, when breast feeding provides most of the nutrition; age 18-36 months, the period of weaning off the breast; 3-5 years; and 6-8 years. Also included, is a group of female adults aged 25-35 inclusive, a period at their last child-bearing years in which nutrition is likely to be compromised. The numbers in each age cohort and the process of selection (random or weighted samples) will be determined after the pilot study. Since well and poorly nourished groups will be studied, no external control population is needed. However, reference will be made to the weight-height age measurements made previously in Bangladesh for comparison.

Morbidity Data:

The Division of Epidemiology has begun a longitudinal study of morbidity and water use in several Matlab villages. Recording of diarrhea, respiratory symptoms, fever and exanthems will be obtained in visits by trained health workers to the village every third day. An oral thermometer on the day of the visit will provide a check on the accuracy of the historical information.

Nutrition Data:

Anthropometry includes height, weight by spring scales, and mid-arm circumference. The latter is solely for later calculation of the QUAK stick index, in order to evaluate

morbidity and immunological predictiveness for the [illegible] epidemiological tool. Hematocrit and serum for total protein and albumin will be obtained on all subjects by fingerstick. Lastly, a physical exam on all subjects will document the presence or absence of hair change, seleral xerosis or keratomalacis, stomatitis, skin disease, peripheral edema, hepatomegaly and an overall nutrition impression (5).

Immunological Data:

The observations that depressed cellular immunity renders the host more susceptible to infection and that poor nutrition depresses cellular immunity directs us to investigate parameters of cellular immunity and inflammation. In the pilot study subjects will have a series of six simultaneous skin tests applied on the forearm and upper back. Four ubiquitous antigens (PPD), streptokinase-dornase, Trichophyton and Candida) elicit delayed skin reactions in the majority of normal subjects. Croton oil applied in a bandaid elicits a non-specific vesiculated inflammatory response. Dinitrochlorobenzene (DNCB) first elicits an inflammatory response, followed by a delayed hypersensitivity skin reaction appearing 1-2 weeks later at a challenge site.

Malnutrition may suppress the immediate and delayed reactions to any of these agents, but the skin response expected among rural Bangalis is unknown. Furthermore, as these agents may produce brief itching and local discomfort, and skin discoloration for several months, the acceptability of these skin tests among our subjects must be ascertained prior to any large survey. However, a severe reaction can be detected at the time of reading and aborted by the topical application of corticosteroid ointments.

Iron-Transferrin Data:

Studies in Africa (6) have suggested that low serum transferrin levels and high serum iron levels are associated with bacteremic diseases. In vitro elevated free iron permits greater bacterial multiplication, while transferrin itself has documented bacteriostatic properties. The relevance of these laboratory observations to morbidity in Bangladesh can be tested in a prospective study which records febrile illnesses. A weighted sample of 100 well-nourished and 100 poorly-nourished children from a cross-section of all pediatric age-cohorts will be selected for one phlebotomy of 3 cc of venous blood, in lieu of a fingerstick. Serum iron is measured by a chemical assay, and serum transferrin by radial diffusion immunoplate.

Consent Precedure:

Participation in this study will be voluntary. Informed consent will be obtained from adults and parents of children, working with Dr. Khan and Mr. Aziz and the village headman to establish initial contact and explain the risks involved. The risks are minimal, being confined essentially to itching or minimally painful skin reaction which can be moderated by the use of topical medication if necessary. To induce cooperation and follow-up, all skin diseases (scabies and impetigo predominantly) will be treated. This will in turn constitute the primary direct benefit to the subjects; indirect benefit might accrue through the greater understanding of malnutrition-immunodeficiency-infection synergism. The initial and long range benefits should thus far outweigh the monor discomforts entailed.

Investigators and Facilities:

Dr. George Curlin will direct the field studies and subject selection.
Dr. Khan and Mr.K.M.A. Aziz will provide epidemiology assistance.
Drs.Palmer, Jackson and Koster are responsible for data collection.
Dr.S.D'Souza will assist with statistical analysis.

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