Early INCAP longitudinal nutrition studies at the community level

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Abstract

This paper reviews the findings of early field studies of INCAP comparing the effects of vitamin B_{12} and animal and vegetable protein on the growth of poorly nourished schoolchildren. It also describes a 5-year community-based intervention study showing that a protein-rich supplement given to preschool children improves growth and cognition and decreases morbidity and mortality. Medical care in one village had no detectable benefits. A classical seven-year community-based detailed observational study of the infection status and growth in children from birth is also summarized.

Key words: antibiotics, Central America, longitudinal study, nutrition, vitamin supplements

Introduction: Dietary surveys

Dietary surveys conducted in the early days of the Institute of Nutrition of Central America and Panama (INCAP) identified low intakes of animal protein, vitamin A, and riboflavin as the primary dietary deficiencies in Central America [1–7]. (Recognition of the importance of iron deficiency came later, and iodine deficiency is not revealed by dietary survey.) The results of parallel clinical surveys and associated laboratory findings revealed a high incidence of infections, frequent signs and symptoms of protein–calorie malnutrition [8–10], and a high prevalence of endemic goiter [11–14]. Surveys also showed low weights and heights for age [15] and slower bone maturation [16] in children of families with limited resources.

A longitudinal study undertaken by INCAP added a battery of psychological tests. The results were used to examine the impact of poor nutrition and high rates of infection on the cognitive performance of children during their preschool years. The study is described in detail in other publications [17–20].

This chapter will focus on the development and execution of INCAP's observational and interventional longitudinal studies. We will examine early attempts to evaluate the effect of improved diets on the physical growth of schoolchildren, consider logical extensions to these early efforts, and describe the implementation and outcomes of two INCAP community-based longitudinal epidemiologic studies.

Schoolchildren's diet and physical growth

Cross-sectional comparisons of longitudinal observations

Diagnostic surveys in some urban and rural areas of El Salvador and Guatemala were completed in 1950, INCAP's first year [4–7, 21, 22]. The results motivated INCAP to undertake diet intervention studies to investigate their effect on the physical growth of schoolchildren from families with limited resources.

Although the data were collected sequentially in time, these early studies cannot be considered truly longitudinal, since the analyses of results were performed using comparisons of pertinent groups at fixed points in time in a "before-after" fashion.

School lunches in El Salvador

Three schools in a rural area of El Salvador and two schools in a poor urban district of San Salvador

Miguel Gúzman (1925–1998) was born in El Salvador and joined the INCAP research staff before its formal inauguration in 1949, initially with responsibility for the nutrient microanalysis laboratory. He soon also assumed responsibility for data management and in 1954 went to the University of North Carolina to obtain a Ph.D. in biostatistics. He returned to INCAP in 1962 as head of the Division of Biostatistics until 1982 when he reached the UN retirement age. He then became head of the Department of Biostatistics of the Louisiana School of Medicine until his return to Guatemala in 2001.

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participated in these trials. All children in the study were between 7 and 11 years of age. The children in one school in the rural area were provided a complete animal protein-rich lunch. In another rural school, half of the children received a complete vegetal protein-rich lunch and the other half received the vegetal protein lunch and 20 mg of vitamin B_{12}. Children in the third rural school served as controls. In the urban area, the children in one school were provided an animal protein-rich lunch, and the children in the other school remained on their regular diet and served as controls [23, 24].

All children were examined at the start of the study and found to be in satisfactory general health but heavily infested with intestinal parasites, with *Ascaris* predominating. The results of all laboratory examinations, with pertinent comments by the project's medical staff, were explained to the parents of the children in the study. Appropriate treatment was provided for all children prior to and during the trial to control generalized parasitic infestation. Success, however, was limited because of a high reinfestation rate [25]. The diet intervention started in mid-1950.

After 3 years of study, comparisons of the supplement and control groups did not show improvement in either the weight or height status of the children who received high-protein lunches on a daily basis, with or without vitamin B_{12} [23]. No significant change in hematological values occurred; the children in the lunch program did not differ hematologically from the control group [24]. It was concluded that the nutritional damage responsible for stunting had occurred in the preschool period and that the nutrition status of the schoolchildren was reasonably satisfactory.

School snacks in Guatemala

Studies similar to those in El Salvador were conducted in Guatemala over a 2.5-year period. In this case, school snacks instead of school lunches were the intervention. Schoolchildren in four rural communities of the Guatemalan highlands participated in these trials. In one village, Santa María Cauqué, schoolchildren were provided an animal protein-rich snack. In a second village, Magdalena Milpas Altas, the children were subdivided randomly into three groups of equal size. One group received only a vegetable protein-rich snack, a second group received the snack and 20 mg of vitamin B_{12}, and the third group was provided with 50 mg of Aureomycin and the vegetable protein snack. In a third village, Santa Domingo Xenacoj, the children were divided into two equal groups; one received 20 mg of vitamin B_{12} and the other was provided with 50 mg of Aureomycin. Schoolchildren in a fourth village, San Antonio Aguas Calientes, served as controls. All snacks and supplements were provided on a daily basis [23].*

Under these experimental conditions, and after 2.5 years of daily snacks, provided either alone or with added vitamin B_{12} or Aureomycin, there was no significant improvement in height and weight adequacy status of the children in the program. On the other hand, the schoolchildren who received either vitamin B_{12} or Aureomycin without the snacks (Santa Domingo Xenacoj) showed significant improvement in their height and weight status 18 months after the program started. However, after 12 months without Aureomycin, the observed gains in height and weight adequacy status were no longer significant. Similarly, 1 year after discontinuation of vitamin B_{12} administration, the observed improvement in height status disappeared, while the weight status continued to improve [26].

No plausible explanation for these observations was given at the time, but it is now tempting to hypothesize that the observed changes could well have been the result of ordinary rhythmic changes in growth patterns. Furthermore, the snacks and additives in Guatemala, as was the case with the school lunch programs in El Salvador, did not result in significant changes in hematologic values that could be associated with the experimental treatments [24]. Evaluation of wrist roentgenograms of the children who received 20 mg of vitamin B_{12} daily did not show improvement in bone maturation after 12 months of treatment [27]. Further investigation revealed that children receiving a full school lunch ate less during the evening meal at home, so there was little net increase in their dietary energy intake [3].

Comparisons of adjusted growth rates

In retrospect, an overview of the results from the schoolchildren studies suggests that the nonsignificant and inconsistent indications of beneficial effects from diet supplements could result from experimental designs that failed to consider the slower growth rate of older children. Lack of information on the amount of supplement consumed may also have contributed to the confounding of experimental outcomes.

To test the hypothesis that subclinical intestinal infections were limiting child growth, INCAP evaluated the effect of 50 mg of either Aureomycin or penicillin on schoolchildren's growth, with proper adjustment for the confounding effects of associated variables such as sex, age, and treatment intensity. In these trials, the

* It is worth noting that neither the INCAP personnel administering the program at the village level nor the recipients could have had any idea whether the children were receiving the vitamin B_{12} or the placebo. In many field studies, such as one in which different diets are fed, a double-blind design is impossible, and frequently only two populations or villages are compared. In the case of our vitamin B_{12} four-village study, when each village was analyzed alone one showed a slightly positive effect, one a negative effect, and two no effect. If we had compared only two villages, the results would have depended entirely on the villages chosen.

effect of daily doses of 20 mg of vitamin B_{12} on the growth rates of schoolchildren and preschool children was also examined. A record of the number of times supplemental agents were taken was kept for each child as a proxy of treatment intensity [28, 29].

Heights and weights were measured regularly at monthly intervals. Data analyses focused on individual rates of gain in height and weight, calculated from regression models. The statistical significance of treatment effects was examined after proper adjustment for confounders by covariance analysis. Under these conditions, the new set of trials was closer to meeting the standards of a longitudinal study [28, 29].

Effects of penicillin and Aureomycin®

At the time, there was abundant evidence of the growth-promoting effect of antibiotics added to animal rations [30]. In the case of children, however, the limited evidence available was highly controversial [23]. To gain first-hand information, INCAP conducted a 25-month trial with 260 children 6 to 12 years of age, mainly of Mayan ancestry. These children attended school in two villages, San Antonio Aguas Calientes and Santa Catarina Barahona, in the Guatemalan highlands. They consumed diets that were low in animal protein and vitamin A but reasonably adequate in calories and other nutrients. The observed deficits in height, weight, and bone maturation represent 2 to 4 years of retardation in terms of the developmental chronology of these children, who were mainly of preschool age [23].

Children in the two schools were subdivided into three groups, each randomly assigned to 50 mg of penicillin, 50 mg of Aureomycin, or a placebo. The basic data obtained were sex, age at the start of the trial, monthly height and weight measures, and treatment frequency for each child. For the analysis, the total experimental period was divided into two of approximately equal duration. The results documented significant effects of Aureomycin in stimulating growth rates in both height and weight in the first 6 months, but these effects were not evident in the second 6 months and there were no differences in height or weight at 12 months among the groups.

Significant sex by treatment interactions were detected in these analyses for both the Aureomycin and the penicillin supplements only in the first six months; the treatment effects were greater for girls than for boys [28], since at 12 months no effect of the antibiotics was observed. It was concluded that the effects of the antibiotics in suppressing pathogenic intestinal organisms wore off as the flora adapted. Thus, there would be no lasting value to giving children antibiotics on a continuing basis, and it could result in the development of antibiotic-resistant strains of pathogenic organisms. *This was one of the first published reports indicating the risk that overuse of antibiotics could promote the development of resistant pathogen strains.*

Effect of vitamin B_{12}

Following the discovery of vitamin B_{12}, reports of its growth-promoting effect in animals prompted investigations of such effects in humans. The results of vitamin B_{12} studies were more controversial than those of studies of antibiotics, because the principal study claiming a strong positive effect in US children was badly flawed and subsequent studies (as cited in reference 29) were negative or inconclusive. Nevertheless, there was considerable pressure on the health authorities in developing countries to add this vitamin, then believed to be a miracle drug, to their school lunch programs. Under these circumstances, INCAP perceived a need to conduct double-blind, randomized trials with these new vitamins in growth-retarded Central American children. The experimental design, data collection, and data analysis procedures were essentially the same as those employed in the antibiotic interventions. In this case, however, a group of 50 preschool children in a highland village, San Lorenzo El Cubo, was added to a basic experimental design that included 228 schoolchildren from four other highland villages: Magdalena Milpas Altos, Santa María Cauqué, San Antonio las Flores, and Chinautla. After provision of 20 mg of vitamin B_{12} or a similar-appearing placebo 6 days a week for 12 months to preschool children or for 18 months to schoolchildren there was no evidence of a stimulus to growth in either height or weight [29]. By extension, this result suggested that growth retardation observed in developing regions will not respond to oral administration of vitamin B_{12}, a conclusion of considerable economic importance at the time for the authorities responsible for school lunch programs in developing countries.

The Three-Village Nutrition and Infection Field Study

General background

It is generally accepted that, during INCAP's first 25 years, malnutrition and communicable diseases were the ranking health problems of developing countries. Failure to collect information on common infections and general morbidity was a regrettable but understandable omission in INCAP's initial studies on the effect of diet-related interventions on the physical growth of children. In the early 1950s, however, there was no recognition of the interrelations between malnutrition and infection, except for the influence of intestinal parasites. The inclusion of overall morbidity information might have provided a preliminary insight into what was to become a major contribution of INCAP, the synergistic interaction of nutrition and infection [31]. However, at the time, neither the financial nor the human resources required were available for the purpose.

As INCAP scientists acquired more experience with and knowledge of events related to malnutrition, the more evident was the synergistic relation between nutritional status and diarrhea, respiratory diseases, and common communicable diseases of childhood. Almost every case of kwashiorkor was precipitated by a series of antecedent infections [32], and the prevalence of these infections was much higher among the malnourished [33].

The reporting of deaths in developing regions is known to be incomplete and inaccurate [18]. Accordingly, the cause of 222 deaths among children 0 to 15 years of age was investigated by INCAP in four villages of the Guatemalan highlands through home interviews of the affected families soon after the death [34]. The results of this investigation made it clear that without infections, there would have been few or no kwashiorkor cases. The results also strongly suggested that most of the children would not have died had they been sufficiently nourished to have normal resistance to infectious diseases [35]. It was becoming increasingly clear that infections precipitated malnutrition, and in turn, malnutrition increased the severity and frequency of infections far beyond those in well-nourished subjects [36, 37].

Study plan

Based on the background information just described, INCAP obtained support from the US National Institutes of Health (NIH) for an investigation comparing the effect of improved nutrition of the preschool children in a village with the effect of making available daily clinical treatment by both a well-trained public health nurse and a physician. A comparable control village received help with civic projects but no change in the availability of either food or medical care.

Specific questions

In this investigation, answers were sought to two basic questions: does malnutrition affect the clinical incidence, duration, and severity of infections, and is this interaction the same for all types of infection? Does infectious disease enhance malnutrition, and is this effect uniform, or does it vary by type of infection? It was expected that answers to these questions would provide a better insight into the interrelations between nutrition and infection [18].

The experimental frame

Malnutrition develops slowly over time, and therefore, cross-sectional surveys for assessing prevalence are limited in their usefulness when causative factors are sought. The significance of infection and its interaction with nutrition relates to a series of events over time, not only to a single episode, making a longitudinal approach necessary to study the interaction between nutrition and disease.

An experimental frame of appropriate interventions, with illness follow-up and periodic nutritional status assessments, was adopted. Curative medical treatment and a supplementary feeding program were chosen as experimental interventions for the study. A third village served as a control. A complete design would have provided three treatments: medical treatment, feeding program, and their combination (medical treatment plus feeding program), as well as the control. Unfortunately, the NIH special committee reviewing the project thought that the combined intervention was unnecessary because "the results were obvious." Financial support was obtained from the US National Institutes of Health to implement a three-village design for 5 years [18].

The communities

Ideally, individuals selected randomly from a common environment should be assigned to each treatment, but given the nature of the chosen interventions, this was not practical. The only possible alternative was allocation of treatments to comparable communities.

After proper rapport had been established with local authorities and the respective populations, three comparable villages were selected. In addition to the overall demographic features generally examined in the process of documenting homogeneity among populations, the selected villages satisfied restrictions of distance from each other and from INCAP. The distance restrictions were considered essential to avoid contamination by social contact and to facilitate transport of biologic samples to the central laboratories. Santa María Cauqué, with 923 inhabitants and an adequate clinic building, was selected for the medical treatment intervention; Santa Catarina Barahona, population 753, was selected for the feeding program intervention; and Santa Cruz Balanya, population 1,363, served as the control. The three villages had broadly comparable population profiles, as well as similar health and nutritional conditions [18, 34, 38]. In each there had been no change in mortality rates over the preceding 10 years.

Field operation

The feeding program implemented in Santa Catarina Barahona was designed to improve the nutritional status of preschool children without changing the sanitary conditions in the village. The program included daily preparation and distribution of a supplement that provided 15g of good-quality protein and 225 kilocalories and met micronutrient requirements. Individual records were kept of both attendance and the amount of supplement consumed. Comprehensive nutrition education activities with mothers, initially (18 months) conducted by a resident home economist, were later part of the routine field personnel's community activities. An experienced nutritionist was in charge of the program [19].

The medical treatment program in Santa María Cauqué included medical care for the sick and preventive medicine for the healthy, without introducing nutritional measures. This program's services were intended for the community, with special attention to children under 5 years of age. It included the following: full-time services of a physician, a public health nurse, and a sanitarian; routine immunization by the government health service against common childhood diseases; support, promotion of construction, and use of sanitary privies in each household; assurance of a safe and continuous, centralized water supply; and promotion of better sanitary practices in the community. The clinic's physician was in charge of the program, coordinated all of its activities, and visited the community 5 or 6 days a week. This is obviously medical care far beyond the possibility of the governments of the region to provide to any rural community [19].

The control community remained without change in their medical, sanitary, and nutritional practices. A variety of social activities were provided for this village; the schoolrooms were improved and the access road to the village was rebuilt and upgraded. These activities were welcome and were sufficient incentives for the control community to continually cooperate in the same routine collection of data as was established in the other two villages.

In addition to the specific village activities described, the study plan called for the collection of basic data in the three communities using the same standardized tested procedures. These included recording of all deaths and related circumstances; population censuses and evaluation of diet adequacy through home visits at yearly intervals; programmed biweekly home visits to record disease counts for incidence, number of injuries in children aged under 5 years, number of stools with registry of consistency, and presence of mucus and blood when diarrhea was present; monthly height and weight measurements and yearly wrist roentgenograms to monitor growth as proxy for nutritional status; and a yearly population census. The prevalence and frequency of enteric infectious agents were monitored at quarterly intervals, and a special in-depth investigation of diarrheal disease etiology was undertaken in the medical treatment community [19].

Data management

All data collected were reviewed on a daily basis by field supervisors for correction of discrepancies and identification of omissions. A physician reviewed and interpreted the clinical data collected by nonmedical fieldworkers, and an epidemiologist reviewed all data on a weekly basis. Data coding, production of interim reports, and statistical analyses were the responsibility of the INCAP Statistics Division [19].

Pilot study

A 2-month pilot study, beginning in March 1959, preceded the start of the project. Its primary purpose was to train the newly assembled staff and to provide a practical field test for all aspects of the selected methodology. Late in April, a week-long staff review of the pilot study experience introduced some refinements in procedures but demonstrated that the study's chosen line of attack in principle was feasible [19].

Comment

The preceding summary of events in the definition of the experimental frame and field operations is intentionally presented in greater detail than might be expected, particularly because they relate to underlying basic principles. The chain of events in the planning and establishment of the Three-Village Study comprise a classic model for the development of field studies. They reflect the insights and experience of the field epidemiologist, Professor John E. Gordon (1890–1983), former Head of the Department of Epidemiology at the Harvard School of Public Health, who contributed greatly to this study and to INCAP's overall studies of the interaction of nutrition and infection.

Results

Details and interpretation of results of the 5-year field study were published in a series of nine articles [18, 19, 39–45]. In the course of long-term studies, unanticipated events occur that must be considered when interpreting results. In this study, the first 3 years of operations were closely controlled by the original investigators, but over the last 2 years the project was the responsibility of an investigator primarily interested in the cognitive performance of children who had been receiving the supplement in the feeding-program village (Santa Catarina Barahona). The added activities and change in priority of this subproject affected the overall field operations, particularly in the feeding-program village. Several of the most experienced personnel were reassigned to support the new study. This must be taken into account in interpreting the results in the first 3 and the last 2 years of the study.

Breastfeeding and weaning

Breastfeeding and weaning merit special comment, since they are significant factors in most nutrition and infection studies. In the INCAP Three-Village Study, nearly all children were breastfed for at least 12 months, and most were breastfed for a longer period. Systematic addition of supplements to the infant's diet was usually started only at 8 to 9 months after birth. Most infants continued receiving some breastmilk, often beyond 2 years of age. Frequency of complete weaning according to age among 267 children in the three villages is shown in **Table 1** [41, 46].

TABLE 1. Frequency of complete weaning according to age among 267 children in three rural Guatemalan villages

Age (mo)	No. weaned	Relative frequency (%)	Cumulative frequency (%)
0–5	1	0.4	0.4
6–11	4	1.5	1.9
12–17	25	9.3	11.2
18–23	99	37.1	48.3
24–35	123	46.1	94.4
36–47	15	5.6	100.0
Total	267	100.0	—

Source: adapted from Scrimshaw and Guzmán [46].

Infectious disease morbidity

In the feeding-program village (Santa Catarina Barahona), children receiving 75% or more of the prescribed protein-rich supplement had the least number of illness days and an overall shorter duration of illness days. Both rates were significantly lower than the rates for children who received less than 25% of the prescribed supplement. During the first 3 years of the study (**table 2**), the feeding-program village had markedly fewer overall infections than the medical-treatment village (Santa María Cauqué) and slightly less disease than the control village (Santa Cruz Balanya) [37, 41, 46].

Diarrheal disease morbidity

The data included in **table 3** show that during the first 3 years of the study, the incidence of diarrheal disease in the feeding-program village was lower than that in the control village and substantially lower than that in the medical-treatment village. After the third year of the study, however, there was a sharp increase in the incidence of diarrheal disease in the feeding-program

TABLE 2. Illnesses of children aged 0 to 60 months in three rural Guatemalan villages

Village	Year ending (April)	No. of children	Mean no. of days of illness/child/yr	Mean duration of illness episodes (days)	Mean no. of illness episodes/child/yr
Santa María Cauqué (medical treatment)	1960	189	71.1	20.9	3.4
	1961	207	59.8	12.7	4.7
	1962	212	57.7	11.6	5.0
	1963	211	41.8	10.8	3.9
	1964	224	48.2	10.2	4.7
Santa Catarina Barahona (feeding program)	1960	118	10.0	7.6	1.3
	1961	138	11.4	8.7	1.3
	1962	151	9.6	6.8	1.4
	1963	146	16.7	6.5	2.6
	1964	150	46.6	9.5	4.9
Santa Cruz Balanya (control)	1960	199	13.3	7.2	1.9
	1961	230	12.0	8.0	1.5
	1962	231	12.9	7.6	1.7
	1963	241	17.5	8.5	2.1
	1964	240	22.3	7.7	2.9

Source: adapted from Scrimshaw and Guzmán [46].

TABLE 3. Acute diarrheal disease among children aged 0 to 4 years in three rural Guatemalan villages

Year ending (April)	Santa María Cauqué (medical treatment)		Santa Catarina Barahona (feeding program)		Santa Cruz Balanya (control)	
	No. of cases	Incidence (cases/1,000)	No. of cases	Incidence (cases/1,000)	No. of cases	Incidence (cases/1,000)
1960	380	200.0	59	48.0	245	122.5
1961	547	264.2	112	80.0	230	99.6
1962	636	299.1	144	94.7	254	109.5
1963	480	227.5	239	164.8	349	143.6
1964	481	214.7	326	218.8	398	165.1

Source: adapted from Scrimshaw and Guzmán [46].

village, coincident with the change in project management. By the fifth year, the incidence of diarrheal disease in the feeding-program village equaled that in the medical-treatment village and surpassed that in the control village.

In the three villages, the incidence of diarrhea was lower in the dry season than during the rainy season. On average, during any given quarter of the year, 11% of the children had at least one episode of moderate diarrhea, 8% had at least one episode of mild diarrhea, and 1% had at least one episode of severe diarrhea; the frequencies of each type of diarrhea decreased with age. In the feeding-program village, 34% of diarrheal episodes lasted for less than 4 days, whereas only 25% of episodes in the medical-treatment village and 21% of episodes in the control village lasted for less than 4 days [42, 46].

Respiratory disease morbidity amd mortality

Respiratory disease occurred with significantly lower frequency in the feeding-program village than in the medical-treatment village, but the control village had the lowest frequency among the three study villages, presumably because it was more isolated. In the feeding-program village, however, respiratory disease decreased with greater participation in the program. On average, children receiving less than 25% of the prescribed amount of the supplement had 107 days of respiratory disease per year as compared with 65 for those receiving 25% to 74% of the prescribed amount and 54 for those who received 75% or more of the prescribed amount [42, 46].

Case-fatality rates for respiratory illnesses in the medical-treatment and feeding-program villages were less than half of the rate observed in the control village (1.2% and 1.7% vs. 4%, respectively). Thus, although there was less respiratory disease in the more isolated control village, in the village in which antibiotic treatment was available it was less lethal. However, the lowest case fatality rate was observed for the children receiving the food supplement.

Parasitic infections

By 6 months of age, 21% of the children had at least one intestinal parasite. This rate increased with age, so that 89% of children 4 or 5 years of age were parasitized. *Ascaris* and *Trichuris* were the most common parasites, but they only rarely produced identifiable symptoms. Making sure that the single water source for the village was safe and introducing a few latrines in the medical-treatment village was not sufficient to modify the situation, and the rate of parasitic infection remained unchanged after 3 years of intervention in all three villages [42, 46].

Mortality

The control village also showed a decline in mortality that exceeded that observed in the medical-treatment village. Mortality among children aged 1 through 4 years in the medical-treatment village showed a 50% greater decline than expected from the rates of the 9 preceding years. The best result, however, occurred in the feeding-program village, with a threefold improvement over that expected.

The profiles of causes of mortality were similar in the three villages. The leading causes of deaths among infants were the characteristic diseases of the newborn, respiratory infections with only a minor representation of acute diarrheal disease. Diarrheal disease, however, dominated all other causes among children 1 through 4 years of age. Respiratory disease had less prominence, whereas the common diseases of childhood and kwashiorkor became more prominent. Among toddlers and older infants, malnutrition was an underlying associated factor in nearly all of the deaths attributed to specific infectious diseases. The patterns of death rates in this study show that older toddlers and children in the second year of life merit as much consideration as younger infants [40, 46]. This was also true for other developing countries, although it was not recognized at the time of the study in the 1950s [40].

There were three epidemics of measles in the feeding-program village during the 5 years of the study, probably because it was so close to a market town. Although surrounding villages had relatively high case-fatality rates from measles during the 5 years (6.8% in one outbreak), the only death from measles in the feeding-program village occurred in a child who did not participate in the study [40].

Physical growth

In both sexes, head circumference at birth was about 70% of the measurement at 5 years of age. The head circumference of boys increased faster than that of girls in the three villages. Children in the feeding-program village had greater head circumferences than children in the other two villages. For all three villages, these measurements were smaller than those reported for US children of comparable ages [43].

The mean height and weight of boys and girls did not differ statistically among the three villages. As shown in **table 4**, boys and girls in the feeding-program village showed a tendency to faster rates of gain in both height and weight than their counterparts in either the medical-treatment or the control village. The faster growth rate of children in the feeding-program village resulted in a net difference of approximately 1,000 g in weight and 3 cm in height by the fifth year of life compared with those in the control village.

Wrist ossification T-scores were low in all three villages compared with reference standards for well-nourished children. The feeding-program village had a slight advantage over the other two villages at the start of the study, and this advantage increased with

TABLE 4. Height and weight gain among children aged 1 to 4 years in three rural Guatemalan villages

Village	Sex	Height		Weight	
		No. of data points	Gain (cm/mo)	No. of data points	Gain (kg/mo)
Santa María Cauqué (medical treatment)	Male	1,427	0.0553	1,427	0.143
	Female	1,602	0.0543	1,602	0.141
	Total	3,029	0.0547	3,029	0.141
Santa Catarina Barahona (feeding program)	Male	733	0.0604	733	0.161
	Female	817	0.0613	818	0.157
	Total	1,550	0.0610	1,551	0.159
Santa Cruz Balanya (control)	Male	1,366	0.0525	1,369	0.137
	Female	1,611	0.0576	1,612	0.148
	Total	2,977	0.0552	2,981	0.143
Sex LSD (0.05)		0.02		0.009	
Village LSD (0.05)		0.01		0.005	

LSD, Least Significance Difference
Source: adapted from Guzmán et al. [43].

time, since improvement of ossification scores did not occur in either the medical-treatment or the control village [43, 46].

Collateral studies

The results from the Three-Village Study were sequentially presented in a series of nine papers [18, 19, 39–45] covering specifically defined objectives. As the study progressed, numerous reports originated from collateral findings or were stimulated by initial observations and corresponding evaluation of preliminary results. These include additional observations on diarrheal disease [40, 47–55], bone maturation [35, 56, 57], common communicable diseases of childhood [58–61], and child growth and development [62–64]. The village populations were also used by other investigators for "piggyback" studies of oral conditions [65, 66] and breastfeeding and weaning practices [67, 68]. The medical-treatment village (Santa María Cauqué) subsequently became the site of an 8-year longitudinal cohort study of children from birth to 5 years of age, which examined the associations of nutrition and infection in greater detail [20].

An overview of practical outcomes

The results from this study have been available for more than 30 years and have been discussed and interpreted in a variety of ways. The epidemiologic self-appraisal of the project by the investigators [44] was, perhaps, too conscientious in emphasizing perceived weaknesses in terms of confounding factors and the inevitable variation among apparently well-matched communities. Consequently, reviewers tended to dwell on the confounding factors instead of the clear result that nutrition interventions, when properly designed and adhered to, have favorable effects on the morbidity, growth, and development of preschool children, whereas exceptionally good medical care without improvement in nutrition, sanitation, and personal hygiene does not.

The findings of the Three-Village Study document significant beneficial effects of the nutritional supplement for preschool children and, surprisingly, an almost total lack of demonstrable benefits from the costly, high-quality medical care offered in the treatment village. To avoid accepting this unexpected finding, some study reviewers have either emphasized the possible effects of confounding factors or suggested that the medical treatment must have been inadequate. The latter certainly was not the case. No industrialized nation, much less any member of the emerging nations group, could afford the quality of health care provided in this study for a community with a population of only 923 persons, except on a heavily subsidized, experimental basis.

The Guatemalan physician, Werner Ascoli, was a graduate of Temple University in the United States with advanced training in public health who visited the village, less than an hour from INCAP, almost every day for 5 years. He was supported by a nurse with public health training who lived in the village for the duration of the project. A small medical clinic and a laboratory were set up in the village with prompt access to the main INCAP clinical biochemistry laboratory. There was no limitation on the medicines available. The conclusion is inescapable that medical care alone cannot prevent the synergistic interaction of malnutrition and infection that seriously affects the underprivileged populations of the world unless nutrition, environmental sanitation, and personal hygiene are improved concurrently.

In addition to comparisons of medical care and food supplement programs, the Three-Village Study contributed significant information to a better definition and understanding of prevailing health conditions among the children of rural Guatemala. Among the poorly nourished children of the rural Guatemalan highlands, communicable diseases of childhood were more severe, lasted longer, and, consequently, were more likely to be fatal than among well-nourished children. The study confirmed a high incidence of acute diarrheal disease and upper respiratory infections. It also documented the prominent role of communicable diseases of childhood in malnourished children as serious risk factors for the health and survival of underprivileged children and, hence, the need for comprehensive vaccination programs, not only in Guatemala but in all developing countries [44].

In summary, in spite of the possible effects of confounding factors, an incomplete experimental design, and administrative changes in the terminal stages of the experimental period, this study produced important results that are readily applicable to specific actions for improving health delivery systems, with particular attention to nutrition and pregnant and lactating women [44–46].

The children of Santa María Cauqué: A prospective 9-year field study of health and survival under deprivation

General background

Poor nutrition in combination with infectious disease constitutes the main health problem in Central America and other developing regions in the world [36, 37]. In Guatemala, this was clearly documented by the results of the study described in the preceding section. However, in-depth studies were required for a better characterization of the synergistic association of nutrition and infection, which was strongly suggested by the Three-Village Study. A systematic, prospective, long-term study of infant cohorts observed during gestation and through infancy and the preschool years was considered appropriate and possible in a medium-sized rural community, in spite of the high costs and acknowledged inherent difficulties. Accordingly, upon completion of the Three-Village Study, INCAP's Leonardo Mata, a Harvard-trained microbiologist from Costa Rica, selected Santa María Cauqué as the site of this longitudinal investigation.

With proper adjustments, the general principles used as guidelines for the Three-Village Study [18, 19], and the experience gained from a multidisciplinary approach in its execution provided a frame of reference for the design and execution of the proposed prospective cohort study using the facilities and rapport with the communities established by the Three-Village Study. As was the case with the Three-Village Study, the insight of John Gordon, played a major role in developing the study.

Study plan

A prospective study of cohorts of newborn children was designed to describe the natural history of growth and health conditions as they are affected in their natural environment by related factors. Particular attention was given to nutrition and morbidity from infection during the 9 years of the study (1963–72).

The village

Santa María Cauqué was the medical-treatment village in the Three-Village Study described above. At the time, it was a small rural village in the Guatemalan highlands with very low rates of emigration and immigration and high prevalence rates of infections and nutritional deficiencies among children that were well documented from previous INCAP studies [4, 19, 40, 43]. The village was also conveniently located 35 km from Guatemala City.

At 1,900 m above sea level, Santa María Cauqué has a pleasant climate, with a daily temperature range of 5° to 29°C. The dwellings were closely clustered along well-defined streets. Few houses had running water, and household and environmental hygiene were poor. Electricity was introduced in 1966, but only about one-third of the houses had electricity in the early years of the study. Nearly all of the population was of Mayan origin. The village economy relied on rudimentary agriculture, in which maize and beans were grown on small, family-owned parcels of land. Village authority was centralized in local municipal officials. At the household level, women had most of the authority for decisions on child rearing, health, food, and shelter and a voice in land transactions [20].

The data

All information was collected with the use of standardized procedures that remained unchanged throughout the period of observation. To minimize transcription errors, all field personnel recorded their observations and data directly on precoded forms. A member of the professional staff edited the forms at regular intervals, depending on the nature of the data. The prompt editing allowed corrections and recovery of missing information and helped maintain staff interest in the project.

Basic data were collected for the entire community, but the main focus was on two target populations: pregnant women and newborn cohorts, defined by the year of birth. Observations of several kinds were made occasionally on practically all of the inhabitants of the village. Community information was obtained through population censuses conducted at the beginning, at the middle, and near the end of the study. In addition to population estimates for evaluation of vital events, the censuses provided important information for characterization of the community environment and a socioeconomic index (SEI) for each family. The SEI for this study was adapted from those used by INCAP for studies in the rural areas of Guatemala [69, 70]. It is calculated from observations on three variables in each of four categories: land and animal resources, housing materials, sanitary facilities, and educational and cultural features.

Enrollment of women as they became pregnant during the study was the best way to recruit newborns for the cohort study. Identification of pregnancies was a continuous process based on repeated contacts with women of reproductive age by midwives, nurses, field-workers, and occasionally by a physician. The physical examination included abdominal palpation and assessment of uterine height. Gynecologic examinations were not performed, and all observations were made with the pregnant woman fully clothed. Anthropometric measurements were restricted to height, weight, arm and leg circumferences, and triceps skinfold thickness. Systematic laboratory tests were not performed, but severe infections were studied bacteriologically and patients with severe disease received the medical attention that the field station could provide. Ordinarily, project field nurses were present at the time of delivery to weigh the newborn, note its general health status, and collect a sample of umbilical cord blood. A complete anthropometric and pediatric examination was performed by a staff physician, normally within 24 hours after birth.

Every child born during the study period was observed prospectively for physical growth by measuring height and weight from birth to whatever age the child achieved at the end of the study (**Table 5**). Head and chest circumferences were also measured in most of the children.

Procedures carried out in the field laboratory included the initial processing of fecal samples and preparation and preliminary evaluation of bacterial and yeast cultures prior to processing in INCAP's central laboratories for definitive counts and characterization of bacterial groups. Preparation, freezing, and temporary storage of Hanks' solution viral suspensions and parasite suspensions were the responsibility of the field laboratory. Throat swabs, pus, blood, urine, and other clinical specimens were also cultured in the field. Isolation and identification of common pathogens was carried out in the field laboratory, with confirmation at the central laboratory for certain organisms.

Central laboratory procedures included identification of enteric viruses, enteric bacteriology, bacteriology of the indigenous intestinal microflora, identification of yeasts, and detailed investigation of intestinal parasites. Serologic procedures and hematology were also done to the extent possible. Resistance to giving more than a capillary blood sample limited routine determinations to hemoglobin, hematocrit, and differential white blood cell counts [20].

Results

Preliminary observations

In compliance with the requirements for INCAP studies, the investigators in this long-term study reviewed and interpreted information as it was collected. This effort was important for maintaining the efficiency of field and laboratory staff and prompt publication of results.

Several findings were soon apparent from inspection of growth charts and their epidemiologic associations

TABLE 5. Clinical and anthropomorphic measurements from Santa María Cauqué cohort children, 1963–72

Type of information	Frequency of collection
Growth	
Weight	At birth; daily during first week of life
Weight, height, head, and thorax circumferences	Within 24 hr of birth; weekly during neonatal period; every 2 wk from 1 to 12 mo; every 4 wk from 2 to 3 yr; every 3 mo from 4 to 7 yr
Hand x-ray	Every 6 mo, beginning at 6 mo
Diet	
Feeding practices and nutrient intake	Weekly from birth to 3 yr; if weaned, up to 3 mo after complete weaning
Infection	
Fecal specimen	Weekly from birth to 3–5 yr
Fecal or other specimen	When certain diseases are present, from birth to 5 yr
Health	
Physical examination	Weekly during neonatal period; every 2 wk from 1 mo to 5 yr
Morbidity surveillance	Weekly from birth to 3–5 yr
Clinical examination	When symptoms are present, from birth to 5 yr; at death

Source: adapted from Mata [20].

[71]. Thus, preliminary reviews of the data yielded valuable basic information on fetal and postnatal growth [72], infant mortality [73], microbial colonization of the intestine [74], intestinal infection [75], and the interaction of malnutrition and infection [76]. All analyses in early reports were carried out by conventional hand tabulations, mechanical calculators, or portable computers and, consequently, were limited in depth and scope and were unable to consider correlations among different types of data.

Investigation of associations among variables requires a comprehensive approach and analytical tools of greater capacity. Accordingly, the massive volume of longitudinal observations made in this study was distributed in nine basic data files with proper provisions for merging, prior to performing computer-based integrated analyses. Each file included data originating in common from specific areas of observational activity in the longitudinal investigation of mothers and their children [20].

Maternal environment

Information about the mothers (physical, physiological, pathologic, and obstetrical) and their immediate surroundings (environment) contributed substantially to the understanding of the growth and survival of their children. In Santa María Cauqué at that time, women entered motherhood at an early age and continued to give birth over a span of 20 to 25 years. Despite differences, all the village women would be classified as "poor" by the common standards of industrialized societies.

During the 9 years of the study, 203 native village women had 465 pregnancies and 446 live singleton births. The duration of pregnancy ranged from 37 to 42 weeks in 415 (92.5%) of the pregnancies that resulted in live singleton births. Fertility was high, as illustrated by the finding that 124 women 20 to 24 years of age had a third pregnancy after two deliveries and a mean of 1.6 surviving children. The fact that women aged 35 to 39 years had an average of 9.4 pregnancies and women aged 44 and 45 years were still having live births provides additional evidence of high fertility for the village. In most cases, spacing between pregnancies was more than 2 years, perhaps as a result of the common practice of prolonged breastfeeding and prevalent chronic undernutrition [20].

The newborn infant

In the period from February 1964 to January 1972, 465 pregnancies resulted in 446 singleton live births, 10 live-born twins, and 14 stillbirths. The birth of these children occurred with practically no intervention by the midwife present at each event and virtually no attention to asepsis.

Pediatric examination of the newborn, performed in most cases within 24 hours after birth, revealed varying degrees of jaundice in 23 children (2.7%), and 12 (2.8%) were found to be cyanotic. Jaundice faded in a few days, but the cyanotic babies, as well as those considered of "poor" appearance by the examining physician, had a poor survival rate. Two infants had an abnormal amount of mucus in the respiratory tract, two exhibited bradycardia (< 100 beats per minute), and nine (2.3/100 births) had overt congenital malformations such as polydactylia, clubfoot, harelip, and preauricular papillomas. This prevalence of congenital malformations is probably an underestimate, since diagnosis was limited to physical examination [20].

Live-born infants had an average birthweight of 2,533 ± 398 g, a length of 45.6 ± 1.8 cm, a head circumference of 32.0 ± 1.5 cm, and a thorax circumference of 29.9 ± 1.8 cm. Compared with female newborns, male newborns averaged 100 g heavier and had body lengths and head and thorax circumferences that were about 1 cm greater [20].

Cases with elevated umbilical cord and serum immunoglobulin levels suggesting fetal antigenic stimulation were common [72, 77]. Isolation of cytopathogenic, enteric, and respiratory viruses from feces collected in the first 2 days after birth provided additional evidence of frequent congenital infections in the study village, and the tertile with the highest frequencies of these viruses showed further impairment of growth in their first years [20].

Low birthweight is a common problem of lower-socioeconomic population groups. It is associated with higher rates of neonatal death and impaired physical growth, immune competence, and intellectual performance. In Santa María Cauqué, birthweights are among the lowest reported anywhere [78]. In this study, it was possible to examine birthweights in conjunction with gestational age in 415 live-born singleton infants. Preliminary examination showed that a high proportion (34.4%) of term babies (37 to 42 weeks of gestation) were born with low birthweight (< 2,501 g), suggesting fetal growth retardation. Only 242 term babies (58.3%) weighed more than 2,500 g, and all 30 preterm infants (< 37 weeks of gestation) weighed less than 2,501 g [20].

Maternal factors and fetal growth

Of the various indexes used to evaluate adequacy of fetal growth, duration of pregnancy (gestational age) and birthweight were considered the best indicators. These indexes were examined with maternal factors to identify associations.

Maternal and infant weight were positively correlated ($r = 0.26, p < .01$), and mothers with greater mid-pregnancy weights, on the average, delivered heavier newborns. Since weight is a highly variable individual characteristic, the mother's height was also examined in conjunction with birthweight. The calculated correlations again were positive and statistically significant

($r = 0.23, p < .01$). These findings warrant an expectation of a lower rate of low birthweight among infants of "large"-sized women [20]. Indeed, in Santa María Cauqué, 14% of infants born to women who weighed less than 47 kg, but only 1.8% of infants born to women who weighed 59 kg or more, had low birthweights. A similar trend was apparent in the relationship to mother's height. The rate of low birthweight was 5.6% for babies of taller women (> 147 cm), in contrast with a rate of 16.7% for babies of shorter women (< 138 cm). These results, described below, can be interpreted as an indication that the mother's health and nutritional status, as reflected by her height and weight, have an effect on the infant's gestational age and weight at birth [20].

Parity apparently decreases the risk of low birthweight. The rate of low birthweight was 53% when the mother had a parity 2 or less and 32% for mothers with parity from 6 to 11. No low birthweights were recorded when parity was greater than 11. There was also evidence of a direct association between the length of the birth interval and the infant's weight and gestational age at birth, but not with the infant's length at birth, which appears to be related to the mother's height. Shorter birth intervals were consistently associated with poor fetal growth, probably as a result of deteriorating health and nutritional status of the mother. Higher demands are imposed on these village women by the continuous burden of pregnancy and lactation with closely spaced pregnancies.

The role of diet during pregnancy has been the topic of several investigations [78–80], but their findings are not conclusive. Some studies have shown beneficial effects of improved diets during pregnancy on fetal growth in populations with satisfactory birthweights (averaging 3,000 g) [81]. In Santa María Cauqué, a community with a 40% rate of low birthweight, investigation of the diet of 47 women during pregnancy showed a trend toward a lower frequency of low birthweight among mothers who consumed diets of higher caloric and protein content. Birthweight, head and thorax circumferences, and gestational age at birth increased with higher socioeconomic scores and better diets [20].

Infectious disease of the mother was associated with a higher frequency of fetal synthesis of IgM, indicating that the probability of fetal infection and antigenic stimulation increases with a higher incidence of maternal infection [82, 83]. Mothers with greater morbidity did not tend to deliver smaller babies, except in cases of clinical infection of the urinary tract. This observation, however, must be interpreted with caution, since the methods of the study did not permit detection of all diseases and abnormalities of pregnancy.

Data from regression analyses indicate that among all the maternal attributes considered, duration of pregnancy (gestational age at birth) is the best predictor of the newborn's size. This variable is highly interrelated and confounded with parity, maternal age, and socioeconomic status. If duration of pregnancy is excluded from the set of maternal characteristics included as independent variables in the stepwise regression models, then maternal age, parity, and maternal size (height and weight) are the significant variables for predicting the newborn's size. This result can be interpreted as direct evidence that the mother's health is an important determinant of fetal growth, as expressed in the newborn's size. Improvement of living conditions, therefore, can be expected to bring about better health for mothers and beneficial effects on birthweight. This will promote the health, growth, and development of children in currently developing societies [20].

Infancy and early childhood

Breastfeeding is considered a natural event in Santa María Cauqué. It is maintained over a long period of time, often beyond 2 years. Some women continue breastfeeding during their next pregnancy. Most women produced enough milk to nurse their children adequately for 3 to 6 months. Complementary foods were introduced at 3 to 5 months and were mainly tortillas, broths, and beans. These foods are bulky, have low calorie content, and are often contaminated [84, 85]. Dietary deficiencies were due primarily to economic reasons and the low availability of foods in rural communities. No substantial changes in the weaning pattern were noted in the five yearly cohorts studied [86].

The children had marked caloric deficits during infectious disease episodes but adequate caloric intake when they were free of infectious diseases. Thus, poor environmental sanitation and personal hygiene, both associated with poverty, contributed to dietary deficiencies [87].

Birthweight was a good predictor of survival. Children weighing at least 2,000 g at birth generally survived the first week of life. Those with a birthweight of at least 2,750 g almost always survived for the first 3 months. Over the entire study, only one postneonatal death occurred in a child who weighed more than 3,000 g at birth. Both birthweight and gestational age were associated with mortality throughout the first 4 years of life, as shown in **table 6** [20].

Acute respiratory disease was identified as the cause of death in 9 of 18 neonatal deaths. Cord serum IgM or IgA was elevated in half of the children who died in the neonatal period. Twenty-five deaths were recorded during the postneonatal period of infancy; a reliable diagnosis was possible for 23 of the 25 deaths. The leading cause of death was pneumonia–bronchopneumonia (9 of 25 deaths), followed by whooping cough (5 deaths), diarrheal disease (4 deaths), measles (2 deaths), sudden infant death (2 deaths the causes of 3 deaths were not diagnosed [20].

Pneumonia–bronchopneumonia, either as the primary cause or as a complication of whooping cough or measles, continued as the main contributor to mortality during the second, third, and fourth years of life. It was diagnosed in 19 of the 33 deaths that occurred in the 14-year age range. Diarrheal disease was diagnosed as accounting for 16% of the deaths; however, if considered not only as a primary cause but also as an associated cause, it ranks with measles and is second only to lower respiratory disease and whooping cough [20].

TABLE 6. Infant and early childhood mortality in the first 4 years of life according to birthweight and gestational age at birth among children in three rural Guatemalan villages

Birth-weight (g)	Gesta-tional age (wk)	No. of deaths per 1,000 children alive at beginning of period			
		Yr 1	Yr 2	Yr 3	Yr 4
< 2,501	< 37	516	0	0	0
< 2,501	≥ 37	84	76	39	50
≥ 2,501	≥ 37	50	44	33	8
Total		96	52	33	21

Source: adapted from Mata [20].

In all of these cases, malnutrition was a contributing factor to the death. Moderate protein–calorie malnutrition, marasmus, and kwashiorkor were associated with at least a quarter of the deaths in the second year of life; retarded physical growth was evident in nearly all infant deaths [20].

An important conclusion from these findings was that the high mortality observed in early childhood could be reduced significantly by timely vaccination against measles and whooping cough. Diarrhea, respiratory infections, and malnutrition would still

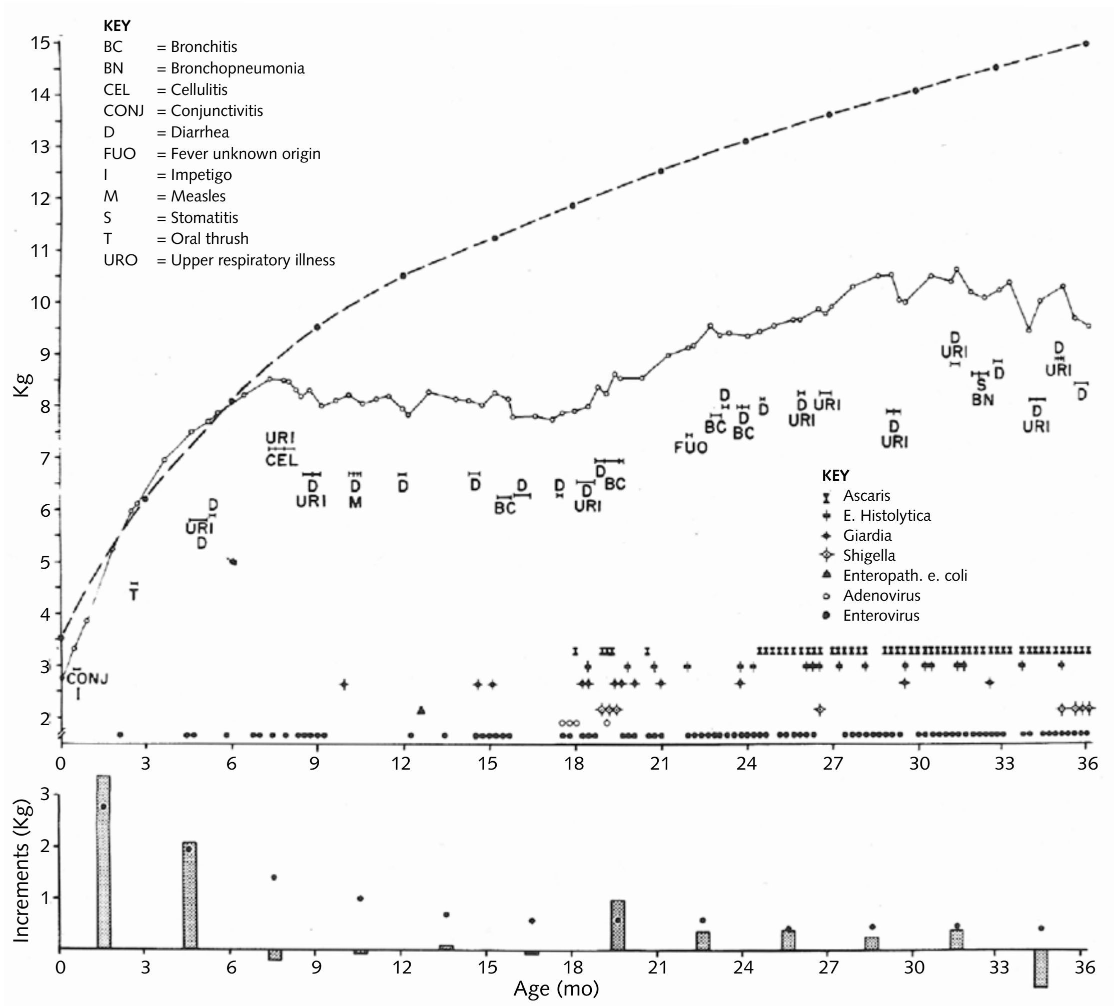

FIG. 1A. Weight, infections, and infectious diseases of two male children from Santa María Cauqué. Solid line is the child's weight; dashed line is the median of the INCAP standard. Duration of disease is indicated by the length of horizontal bars. Each week of infection is indicated by a filled circle. Bar charts indicate weight increments versus the standard (dots). Adapted from Mata [20] contribute to the observed high child mortality and would continue requiring attention to sanitation and improved nutrition.

Severe protein–calorie malnutrition has signs and symptoms that complicate the diagnosis of coexisting infectious diseases of infants and toddlers. Epidemiologic investigations suggest that malnutrition also contributes to the morbidity and mortality of weanlings [52, 88]. The Santa María Cauqué Study showed significant differences in physical growth (a proxy for nutritional status) between children dying of endemic diseases and control children who survived such diseases [20].

Physical growth is an important indicator of the general health and nutritional status of preschool children. In less-developed societies, however, children's physical growth and body dimensions are not a concern for parents. Santa María Cauqué was no exception to this; no growth consultations were requested at the village clinic throughout the study period.

Interactions between nutrition and infection

These comments illustrate the impact of infection on food intake and the nutritional status of children living in the typical environment of the rural communities of Guatemala and other developing countries. The impact of enteric infections and infectious diseases on nutritional status is illustrated by a graph showing changes in body weight and episodes of infection over time in a growing male child in Santa María Cauqué (**fig. 1A**).

Body weight during the first 3 years of life is an indicator of nutritional status. This child grew normally for the first 7 months because he was protected from clinical infections by exclusive breastfeeding. However,

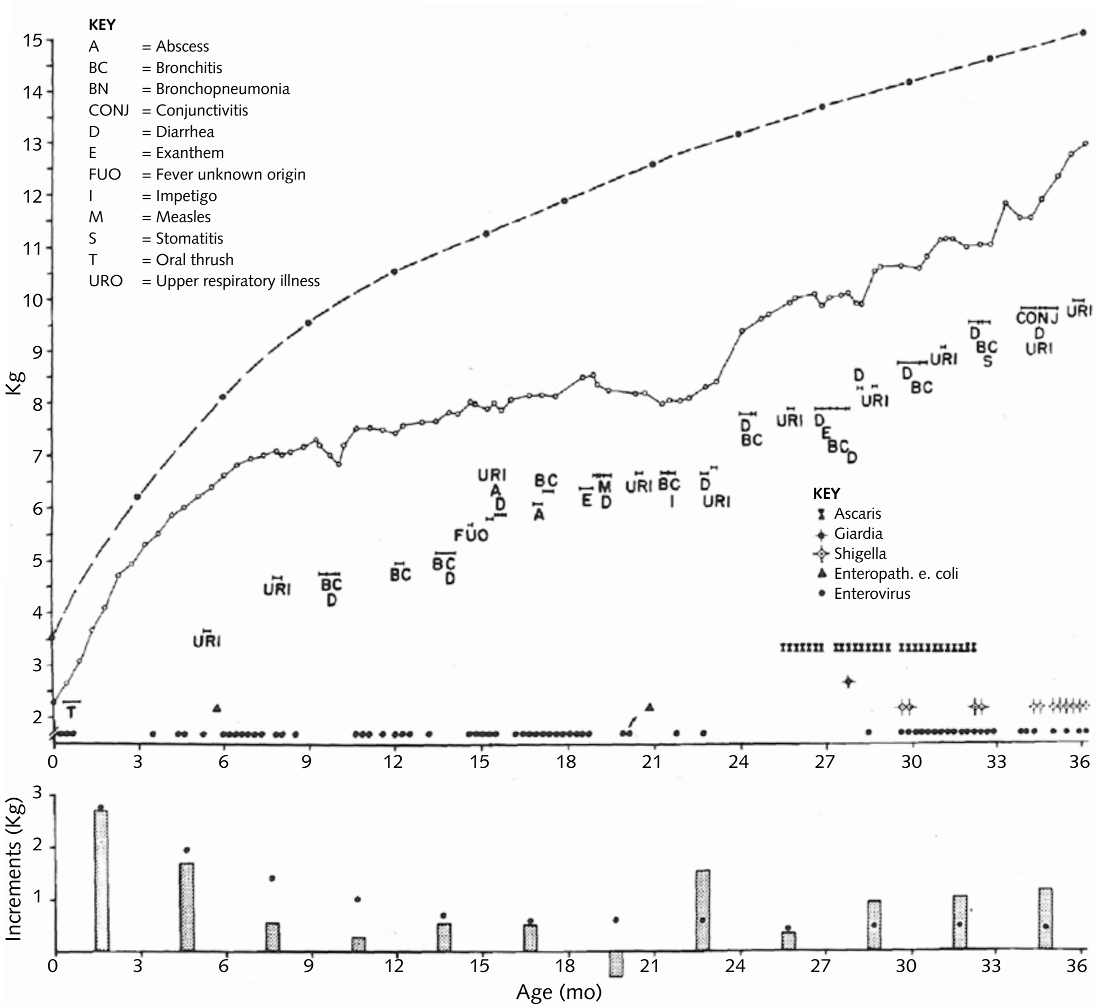

FIG. 1B. Weight, infections, and infectious diseases of two male children from Santa María Cauqué. Solid line is the child's weight; dashed line is the median of the INCAP standard. Duration of disease is indicated by the length of horizontal bars. Each week of infection is indicated by a filled circle. Bar charts indicate weight increments versus the standard (dots). Adapted from Mata [20] once breastfeeding was no longer a sufficient source of food, infections became frequent and contributed to poor growth. During the 36 months of observation, the child had many episodes of diarrhea and other illnesses as well [20, 52, 88].

Infectious diseases can be even more devastating for children born prematurely or with low weight-for-gestational age. **Figure 2** presents a chronologic sequence of events that illustrate the fatal consequences of the interaction of infectious disease and malnutrition. This child was born with low birthweight but with breastfeeding grew at a rate parallel to that of well-nourished children for the first 6 months. However, she showed no catch-up growth with the reference standard. An acute respiratory infection evolved into bronchitis followed by meningitis, diarrhea, and chickenpox, during which she showed no further growth. She recovered from these episodes and caught up with the village average, which was about the third percentile of a growth curve for normally nourished children, but she suffered anorexia and failed to make appreciable weight gains over a 4-week period. At 15 weeks of age, she developed confirmed meningitis and did not gain weight throughout the course of this illness. After recovery, however, continued breastfeeding allowed growth recovery, and by 44 weeks of age she had attained the village average weight for her age. Failure to introduce appropriate complementary foods, in combination with a new series of intestinal and respiratory infections, once more depressed her nutritional and health status, making her an easy prey for a terminal fatal disease, bronchopneumonia, at 18 months of age [89].

Many similar examples from this study providing evidence of nutrition–infection interactions have been published [89–92]. They leave no doubts as to the negative impact of interactions between nutrition and infection on the health of children among the rural poor.

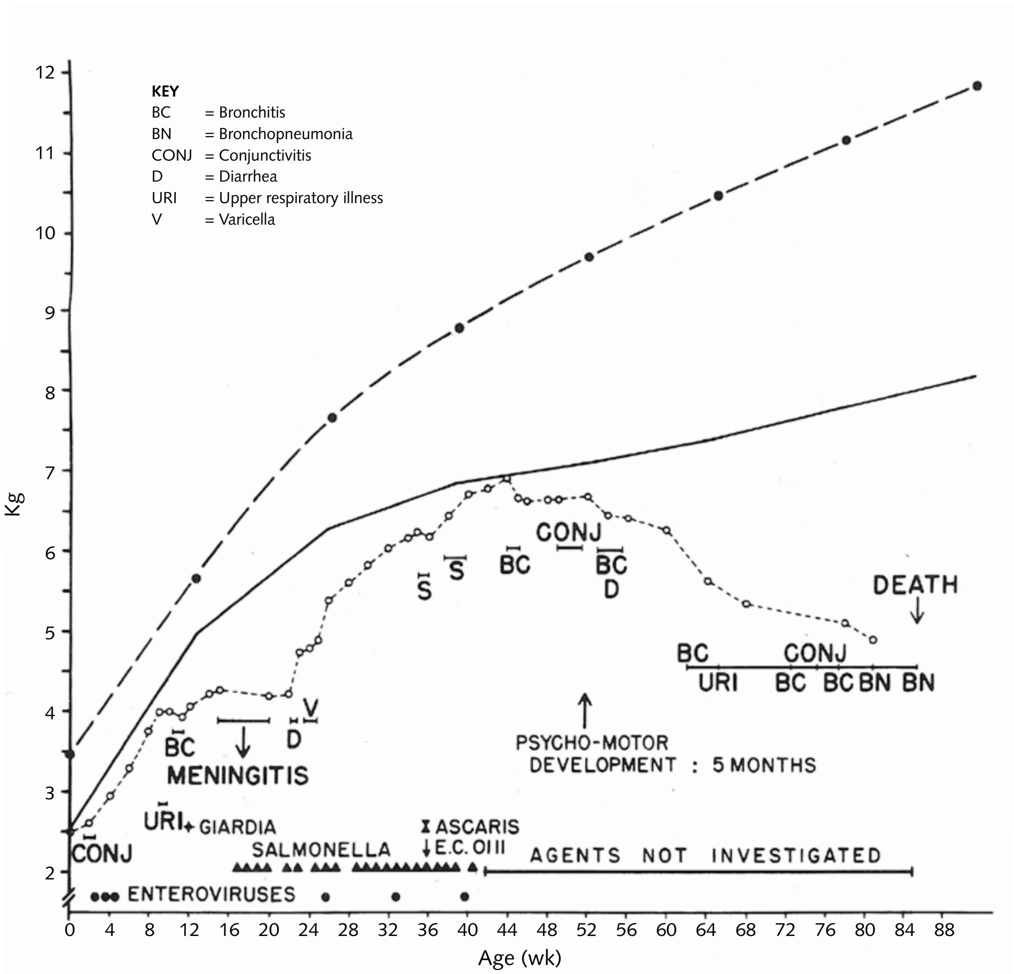

FIG. 2. Weight, infections, and infectious diseases in a female child from Santa María Cauqué. Upper dashed line is the INCAP standard; solid line is the mean weight curve for children in the village; lower dashed line is the child's weight. Adapted from Mata [20]

Concluding general comment

INCAP's early longitudinal studies document the very negative impact of interactions of poor nutrition with high rates of infection on the health, well-being, and survival of children in environments where such conditions are prevalent. Additionally, and most importantly, these INCAP findings provided a basis for practical guidelines for the definition of policies and implementation of efficient programs to promote health and well-being. Such programs have contributed not only to the improvement of children's health, but also to improvement of the general quality of life and productivity of the underprivileged population of developing countries.

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