Influence of recurrent infections on nutrition and growth of children in Guatemala[1,2]

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An exhaustive review on the interactions of infection and nutrition has been made by Scrimshaw, Taylor, and Gordon (1). There is abundant evidence that infection is one of the most important negative factors for the nutrition and growth processes of man (1–4).

Observations derived from a long-term prospective field study of a Guatemalan Indian village will be presented. The design, methods, and certain preliminary findings have been described elsewhere (4–6). This communication refers to growth retardation in the human at certain stages of development and illustrates the influences of infection on the nutritional status and growth of children. The study was conducted in a typical representative highland rural community of low socioeconomic development where environmental intervention was minimized during the study period.

Growth of children

Weight, height, and circumference of the head and thorax were determined at birth, weekly for 1 month, fortnightly for 1 year, monthly for another year, and every 3 months thereafter. The study showed marked growth retardation at birth, throughout infancy, and in the preschool years. Birth weight, recorded within 60 min of delivery in 91% of all live births occurring in the community in a 6-year period, was 2,540 ± 409 g (mean ± SD). Birth weights were arbitrarily classified into four groups (Table 1); groups 2 and 3 included all babies with weights within one standard deviation of the mean (7). Forty percent of all newborns were underweight (less than 2,500 g). Eleven percent were premature by the standard of an estimated gestation of less than 37 weeks and 29% were born at term but were considered to show fetal growth retardation. Forty infants (12%) (group 4, Table 1) had birth weights similar to those babies from the higher socioeconomic group of Guatemala (8) and from industrial societies throughout the world (9). The great variability in the size of infants cannot be completely explained by the mother's weight (53.08 ± 5.90 kg; mean ± SD) or height (143.08 ± 4.43 cm; mean ± SD), which are quite similar for all mothers of cohort babies, although birth weight and mother's weight and height were significantly correlated (r = 0.25 and 0.28).

Postnatal growth appeared adequate, on the average, during the first 3 months of life (Fig. 1). This period is characterized by exclusive breast feeding and relative protection from infection mediated by passive immunity (4, 5). At 3 to 4 months a departure from the expected growth pattern was observed. By 1 year of age, virtually all children showed growth retardation that extended throughout the preschool and school age with no apparent tendency to improve.

Causes of growth retardation

Fetal growth. INCAP studies in four mestizo population groups of Guatemala have

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TABLE 1
Birth weight and fetal growth, 323 live newborns (Santa María Cauqué, Guatemala, 1964–1970)

	Group			
	1	2	3	4
No. of infants and % of total	42 (13.0)	89 (27.6)	152 (47.0)	40 (12.4)
Birth weight, g	<2,131	2,131–2,499	2,500–2,949	>2949
Average weight, g	1,794 ± 102	2,341 ± 102	2,704 ± 128	3,134 ± 175
No. of infants and % of total with <37 weeks of gestation	26 (61.9)	10 (11.2)	1 (0.7)	0

One hundred thirty-one with low birth weight = 40.5%; 37 prematures = 11.4%; and 95 with fetal growth retardation = 29.4%.

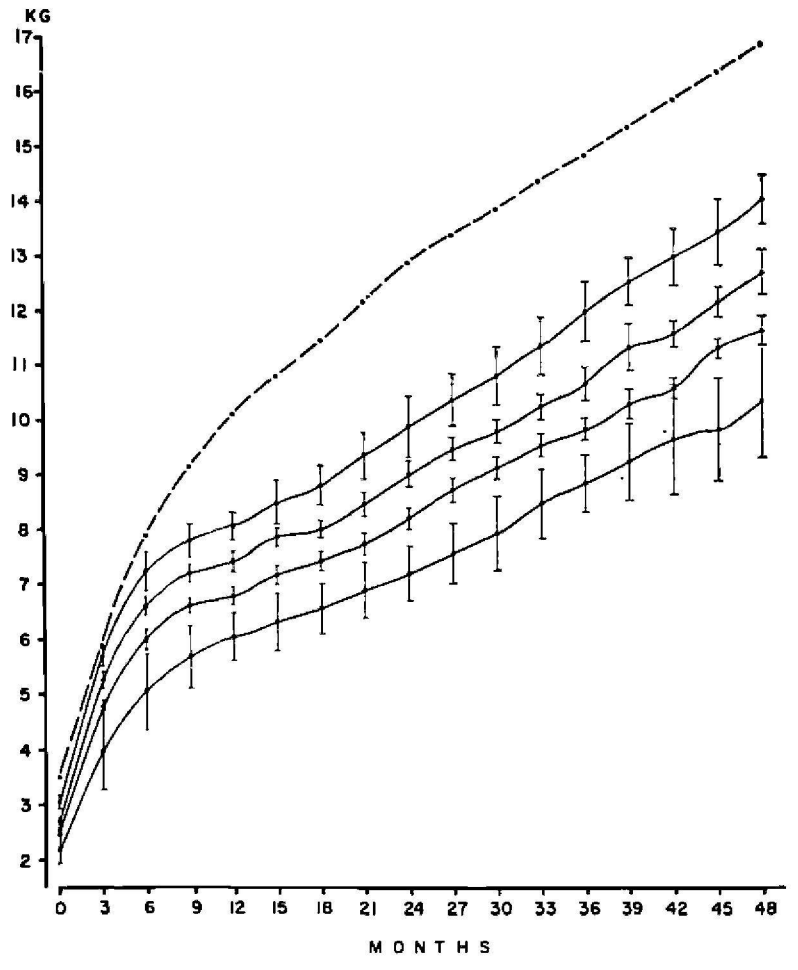

FIG. 1. Average weight curve of village children, by quartiles, in comparison with the standard (Santa María Cauqué, Guatemala, 1964–1970) (15).

shown an association between fetal growth and caloric intake of the mothers. Furthermore, adequate dietary supplementation of mothers during pregnancy resulted in greater infant birth weight (10). Malnutrition in the mother is presumed to be an important cause of fetal growth retardation in the village study reported here, particularly in view of the poor dietary intake of the general population, and especially of mothers (4, 5, 11). However, other factors such as intrauterine infection should be considered in light of the recent demonstration of frequent asymptomatic infection of the fetus in underprivileged population groups (12). In this regard, cord immunoglobulins in 123 consecutive newborns from the study village were measured by radial immunodiffusion using Meloy plates. All specimens suspected to have been contaminated with maternal blood were discarded. The results in Table 2 show that approximately one-half the babies were born with "high" IgM values, thus confirming preliminary observations (13). If only cord sera without detectable IgA are tabulated, 37% of 88 specimens still show high IgM concentrations. The finding indicates frequent fetal antigenic stimulation because this immunoglobulin does not readily cross the placental barrier (14). The strong correlation between high levels of cord IgM and intrauterine infection (12), the poor nutrition of the mothers, and low birth weight of infants support the hypothesis that the interaction of infection–nutrition–growth demonstrated so far for infants and children may begin in utero in areas where maternal nutrition and hygiene are poor.

Growth in the first 3 months of life. As indicated before, this period is characterized by adequate growth of many infants, probably for the reasons mentioned above. Comparison was made with the growth charts of Iowa children (15), which are also used as standards for Guatemalan children living under better conditions of nutrition and sanitation (16).

Infection with enteric viruses in the first 3

months of life nevertheless appears to have an effect on the growth curve. Children experience frequent virus infections, mostly asymptomatic, as early as the 1st week of life (5). Figure 2 illustrates the magnitude of viral infection during the 1st year of life for the first 18 children of a cohort of 45, studied by weekly fecal cultures, described elsewhere (4, 6). Infections occurred in all children with varying intensity but tended to increase with age. The cohort of 45 was divided into groups A, B, and C of 15 infants each, according to the frequency of viral infection detected in the first 3 and 6 months of life. Some overlapping was observed in the viral infection of the children of groups A and B; less between groups B and C, but distribution of infection in infants in overlapping groups was at random. Table 3 shows viral infection rates per child, per period, for the three groups. The growth curve for weight and length for each child was fitted using the model: $y = a + b_1 t + b_2 \, lnt$ (unpublished observations). All fittings resulted in values of R^2 greater than 95%. The weight and length at 3-month intervals during the 1st year of life were then predicted for each child from individually fitted curves using the model mentioned above.

The means for predicted weights and lengths at 3, 6, 9, and 12 months of age for the three groups of infants with infection rates established during the first 3 months of life are in Tables 4 and 5. It became evident that group C, with a greater viral infection rate during the first 3 months of life, showed a significantly lower weight at all ages than the other two groups (Table 4). Furthermore, the difference observed at each age was of similar magnitude. This phenomenon, however, was not observed for length (Table 5). When virus infection occurring during the first 6 months of life was taken into account, the predicted weight for group C, with the greater infection rate, was also significantly lower at all ages than that of the other two groups (Fig. 3). Again, the differences observed were of similar magnitude (Table 6). The predicted heights at this time were significantly lower at all ages for the group with a greater infection rate than for the other two groups (Table 7). This suggests that whatever

TABLE 2

Cord immunoglobulin levels (milligrams/milliliter) of 123 newborns (Santa María Cauqué, 1964–1970)

	IgM	IgA
Mean ± SE	0.344 ± 0.038	0.114 ± 0.022
Range	0–3.40	0–1.95
Percent of "high" levels[a]	54.4	37.3

[a] High levels = IgM $\geq$ 0.20 mg/ml; IgA $\geq$ 0.10 mg/ml.

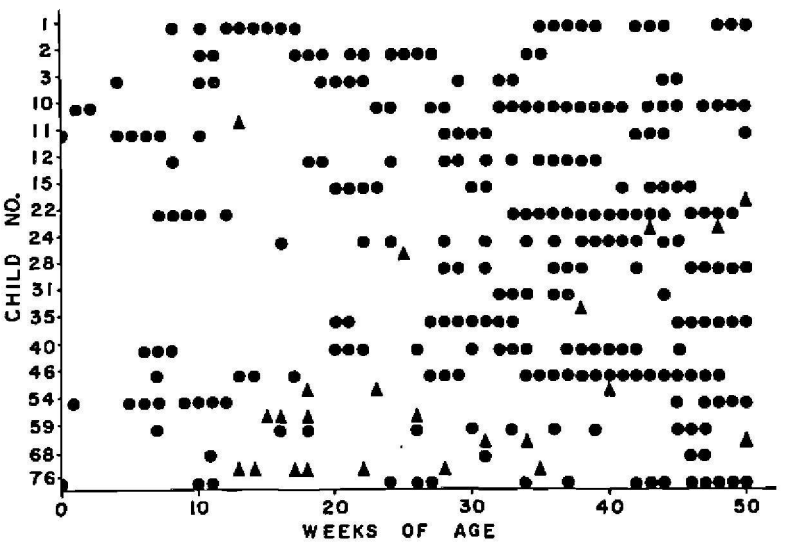

FIG. 2. Enteric viruses in 18 of the infants of a cohort of 45 studied from birth to 1 year of age, determined by weekly fecal cultures (Santa María Cauqué,. 1964–1966). Circles are enteroviruses; triangles, adenoviruses.

TABLE 3

Enteric viruses in a cohort of 45 infants (Santa María Cauqué, 1964–1966)

	First 3 months of life			First 6 months of life		
Group	A	B	C	A	B	C
No. of infants	15	15	15	15	15	15
Total viral isolates	6	31	71	50	93	146
Infection rate/child/period	0.40	2.27	4.73	3.33	6.20	9.73

negative effect virus infection has on growth, it becomes apparent more readily and earlier in weight than in height.

Weight and length at 3 months were adjusted, by analysis of covariance, for birth weight and length. The values at 6, 9, and 12 months were also adjusted for the values attained in the preceding trimester. This analysis showed that weight at 6 months adjusted

TABLE 4
Weight in grams for a cohort of 45 infants, estimated at 3-month intervals, by virus infection rate, 0 to 3 months

Group	Infection rate/child	No. of subjects	Age, months				Total
			3	6	9	12	
A	0.40	15	3,734	4,285	4,661	4,965	4,411
B	2.07	15	3,731	4,269	4,632	4,922	4,388
C	4.73	15	3,623[a]	4,145[a]	4,504[a]	4,796[a]	4,267[a]

$LSD^{b}_{0.05}$ n = 15: 72 $LSD_{0.05}$ n = 60: 36
$LSD_{0.01}$ n = 15: 93 $LSD_{0.01}$ n = 60: 46

[a] Significant, $P < 0.01$. [b] LSD = least significant difference.

TABLE 5
Length in centimeters for a cohort of 45 infants, estimated at 3-month intervals by virus infection rate, 0 to 3 months

Group	Infection rate per child	No. of subjects	Age, months				Total
			3	6	9	12	
A	0.40	15	49.39	51.96	53.72	55.13	52.55
B	2.07	15	49.85	52.57	54.39	55.81	53.16
C	4.73	15	49.63	52.09	53.75	55.07	52.64

$LSD_{0.05}$ n = 15: 0.24 $LSD_{0.05}$ n = 60: 0.12
$LSD_{0.01}$ n = 15: 0.31 $LSD_{0.01}$ n = 60: 0.15

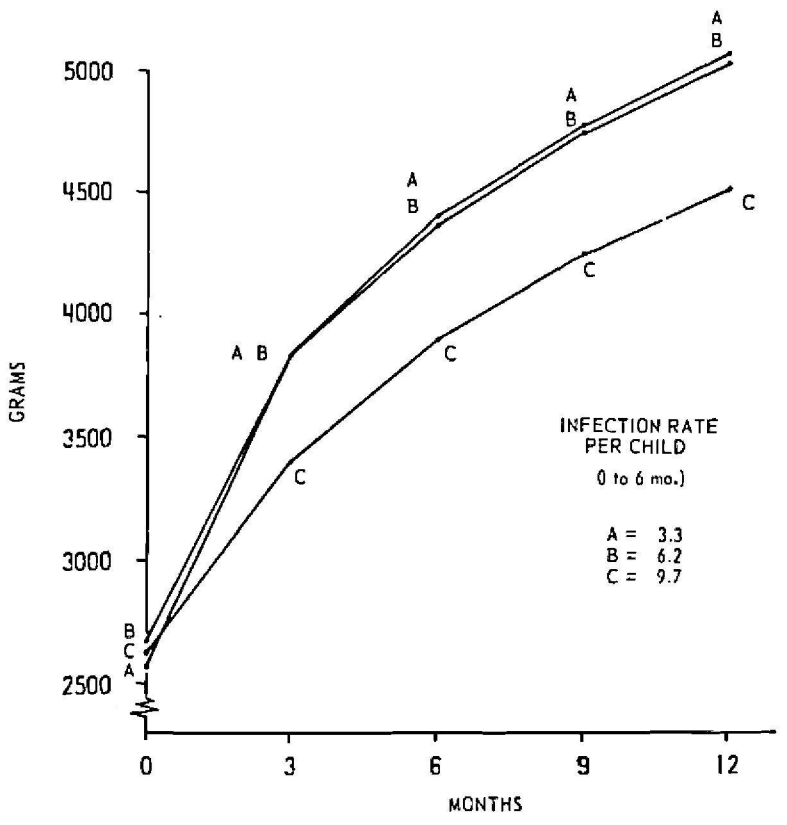

FIG. 3. Estimated weight curves of three subgroups of children, from the same cohort, with different virus infection rates during the period 0 to 6 months of life (Santa María Cauqué, 1964–1968).

for the weight achieved at 3 months was not different for the 3 groups (Table 8). A similar finding was obtained for length, which suggests that the observed association of virus infection and retarded physical growth applies to infections in the first 3 months of life, and that the growth effect observed at 6 months is related mainly to virus infections in the first 3 months of life. When weights and lengths at 9 and 12 months were also adjusted for the values observed during the preceding trimester, the differences disappeared. On the other hand, the differences in growth noted at 3 months of age persisted after an adjustment for birth weight was made (Table 9), which indicates that the phenomenon described is not related to birth weight, but to virus infection in the first 3 months of life. Although it is likely that viruses have a negative effect after the first 3 months of life, the high frequency of infection after 3 months in all children does not permit differentiation of children by rate of growth in terms of infection.

Growth after the first 3 months of life. As indicated before, most children depart from the standard growth curve at 3 to 4 months of life. This period marks the beginning of weaning with the introduction of small amounts of fluids, later (at 6 to 9 months) gruels, and finally solids (4, 5). Human milk becomes insufficient to meet the nutrient demands of the growing child by approximately 4 months of age. The dietary supplement is poor in terms of quality and quantity partially because the protein is derived mainly from corn, which has low biological value. The deficient dietary intake is

TABLE 6

Weight in grams for a cohort of 45 infants, estimated at 3-month intervals, by virus infection rate, 0 to 6 months

Group	Infection rate/child	No. of subjects	Age, months				Total
			3	6	9	12	
A	3.33	15	3,840	4,405	4,787	5,094	4,532
B	6.20	15	3,838	4,385	4,756	5,056	4,509
C	9.73	15	3,409[a]	3,909[a]	4,253[a]	4,533[a]	4,026[a]

$LSD_{0.05}$ n = 15: 70 $LSD_{0.05}$ n = 60: 35
$LSD_{0.01}$ n = 15: 90 $LSD_{0.01}$ n = 60: 45

[a] Significant, $P < 0.01$.

TABLE 7

Length in centimeters for a cohort of 45 infants, estimated at 3-month intervals, by virus infection rate, 0 to 6 months

Group	Infection rate/child	No. of subjects	Age, months				Total
			3	6	9	12	
A	3.33	15	50.13	52.71	54.49	55.89	53.31
B	6.20	15	50.05	52.75	54.52	55.92	53.31
C	9.73	15	48.68[a]	51.16[a]	52.84[a]	54.20[a]	51.72

$LSD_{0.05}$ n = 15: 0.24 $LSD_{0.05}$ n = 60: 0.12
$LSD_{0.01}$ n = 15: 0.31 $LSD_{0.01}$ n = 60: 0.16

[a] Significant, $P < 0.01$.

TABLE 8

Weight and length at 6 months adjusted for the weight and length attained at 3 months, by virus infection rate, 0 to 3 months

Group	Weight		Length	
	6 months	6 months (3 months)	6 months	6 months (3 months)
A	4,405	4,239	52.71	52.17
B	4,385	4,239	52.75	52.28
C	3,909[a]	4,239	51.16[a]	52.16

$LSD_{0.05}$ n = 15: 70 $LSD_{0.05}$ n = 15: 0.24
$LSD_{0.01}$ n = 15: 90 $LSD_{0.01}$ n = 15: 0.31

[a] Significant, $P < 0.01$.

TABLE 9

Weight at 3 months adjusted for the birth weight, by virus infection rate, 0 to 3 months

Group	Birth weight	Weight	
		3 months	3 months (birth)
A	2,552	3,734	3,794[a]
B	2,666	3,731	3,673
C	2,612	3,623[a]	3,621

$LSD_{0.05}$ n = 15: 72
$LSD_{0.01}$ n = 15: 93

[a] Significant, $P < 0.01$.

further aggravated by frequent infection. Weight loss was observed in most village children in association with infectious diseases. To illustrate this point, case histories of village children have been presented elsewhere (4–6). The continuous appearance of disease at all stages of development of a typical boy is shown in Fig. 4. Weight loss was not appreciable in association with most illnesses, but significant loss was demonstrated in relation to a bout of diarrheal disease appearing at 49 weeks of age. It is likely that losses were not apparent in relation to most clinical infections because they appeared in a con-

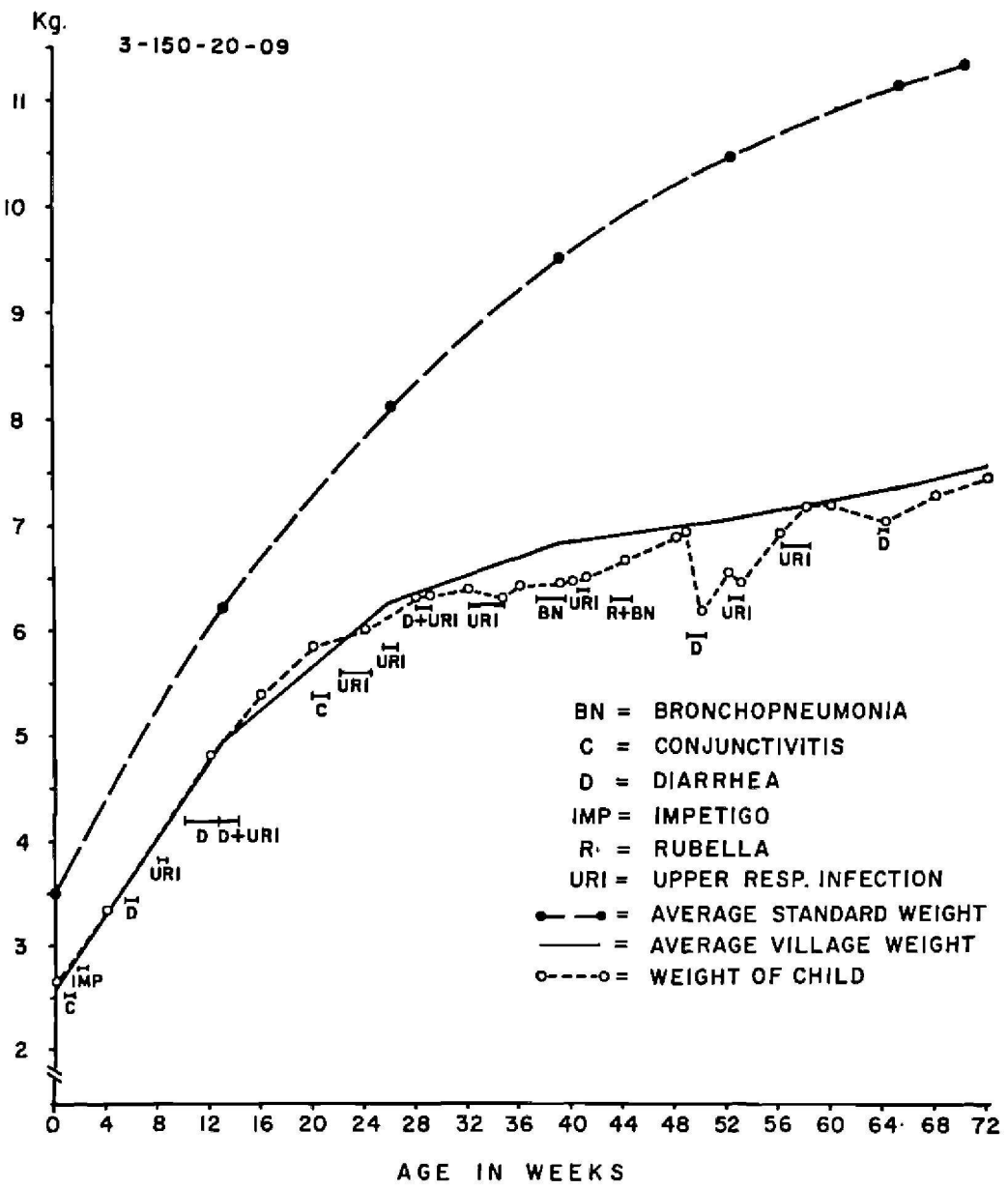

FIG. 4. Weight curve and infectious diseases in a boy from Santa María Cauqué. Solid curve is average village weight curve; upper curve is the standard for boys (15).

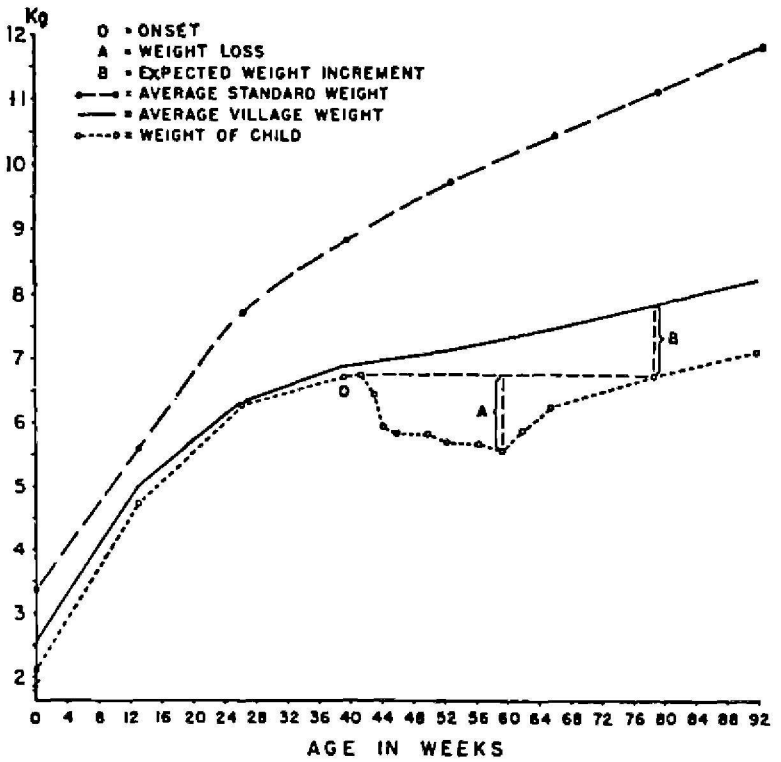

FIG. 5. Deterioration of nutritional status in a boy from Santa María Cauqué after onset of whooping cough. Solid curve as in Fig. 3; upper curve is the standard for girls (15); O = onset of disease; A = acute weight loss; B = additional weight deficit in relation to village curve.

tinuum, not allowing time for them to be noticeable in the weight curve. The same phenomenon was observed in virtually all children. The interrelationship between frequency of infectious diseases and retarded growth in a cohort of 42 children, separated into 4 quartiles according to growth rates estimated from growth curves fitted by regression lines (17), was apparent for dysentery and bronchopneumonia. The trend indicated more infectious disease episodes in children with the lowest growth rate (4, 5).

Certain infectious diseases have a greater impact on nutrition and growth than others (1, 2). Figure 5 shows the impact of whooping cough in a girl with a prolonged convalescence characterized by reduced dietary intake. The damage to nutritional status was equivalent to the intial weight loss (Fig. 5[A]), plus the weight the child did not gain during the prolonged recuperation phase (Fig. 5[B]). Dietary studies indicated long periods

of reduced dietary intake during convalescence from whooping cough. Both anorexia and family attitudes regarding care of the ill child are important determinants of reduced intake. Table 10 presents the evolution of 44 cases of whooping cough observed during an epidemic in relation to the duration of recuperation of initial weight loss. Sixteen percent of the cases required 17 to 24 weeks to recover from the initial weight loss, and 25% took more than 25 weeks.

TABLE 10
Time needed to recover from weight loss after whooping cough (Santa María Cauqué, March to August 1968)

Time, weeks	No. of cases
0–4	6 (14)[a]
5–8	8 (18)
9–12	8 (18)
13–16	4 (9)
17–24	7 (16)
25 +	11 (25)
Total	44 (100)

[a] Figures in parentheses indicate percentage.

Nutritional status and the outcome of infection

In societies with low socioeconomic development, the problem of malnutrition begins early in life and continues throughout the preschool age, as described above. Its origins are in the poor dietary habits of mother and child, and in the common and widespread infection characteristic of such ecosystems. Babies with low birth weight have a significantly lower capacity for survival (7). Table 11 illustrates the neonatal (0 to 28 days) and postneonatal (29 days up to 1 year) mortality of infants and shows that the probability of death increases as birth weight decreases. Seven of thirteen neonatal deaths were due to pneumonia; the cause of death in the other six was not determined. Of 23 postneonatal infant deaths, 21 were attributed to acute infections, and 2 were of unknown origin (7).

TABLE 11
Infant deaths in relation to birth weight, 323 live newborns (Santa María Cauqué, 1964 to 1970)

Birth weight, g	No. of infants	Deaths		
		Neonatal	Post-neonatal	Total
<2,131	42	8 (19.0)	13 (30.9)	21 (50.0)
2,131–2,499	89	3 (3.4)	3 (3.4)	6 (6.7)
2,500–2,949	152	2 (1.3)	7 (4.6)	9 (5.9)
>2,949	40	0	0	0
Total	323	13 (4.0)	23 (7.1)	36 (11.1)

Nutritional status has a relationship to survival from disease in postnatal life. Figure 6 presents an unusual and extreme case in a girl born deficient in weight. Growth appeared adequate in the first few weeks; but, after several infections, an episode of *Diplococcus pneumoniae* meningitis was established, marking considerable stagnation of growth. Weight recuperation was excellent during the period of early breast feeding. With weaning and frequent infections, the nutritional status deteriorated, and at 12 months of age, the child showed severe physical and mental retardation. A series of infectious diseases and weight losses ended with death before 2 years of age.

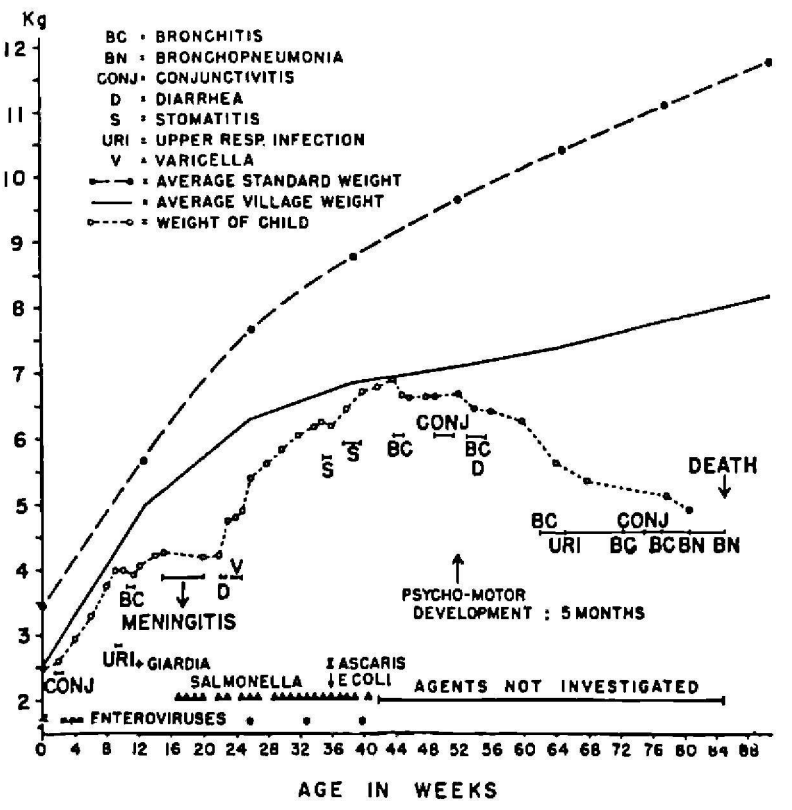

FIG. 6. Enteric infections, infectious diseases, and growth in a village girl from Santa María Cauqué. Curves as in Fig. 4.

Comment

The significance of the present study lies in its prospective nature and the fact that it

is conducted in a typical Guatemalan village of low socioeconomic development, where attempts have been made to avoid intervention in the ecosystem. The study revealed a high frequency of fetal growth retardation and deficient growth in postnatal life. The growth potential of this population seems adequate for various reasons: *a*) 10% of the babies had birth weights comparable to those of infants of the higher socioeconomic strata of Guatemala and industrialized societies throughout the world; *b*) most infants exhibited adequate growth rate in the first few months of life; and *c*) children with the same ethnic background as the village children grow as well as those from industrialized countries provided that they live under better nutritional and hygienic conditions (unpublished observations).

In pre-industrial countries, the readily recognized and accepted cause of fetal growth retardation is inadequate nutrition of the mother. However, the high frequency of elevated values of cord blood IgM detected in the typical Guatemalan study village suggests the possibility of frequent intrauterine infection as another cause for poor fetal growth. This would not be surprising in view of the already known high rates of infection of the general population, and of the mother in particular, that characterize pre-industrial societies. The problem, therefore, needs immediate study.

Infection has an important effect on postnatal growth as revealed by long-term observations of children in their ecosystem. Virus infections in the first 3 months of life were shown to be associated with a deficit in weight detected throughout the 1st year of life, a deficit independent of birth weight and length. The phenomenon acquires additional significance because the first 3 months of life are characterized by a satisfactory supply of breast milk and by passive immunity. In this period, most virus infections are asymptomatic, although, allegedly, they may cause a negative effect on the host economy as a result of replication. It should be pointed out that the weight deficit associated with virus infections in the first 3 months persisted throughout the 1st year of life. No effect of virus infections occurring after 3 months of life was detected, likely because the frequency of virus infection was similar in all children, thus making it difficult to detect any differences in infection rate among them.

Infectious diseases are known to have a negative effect on both the well-nourished and malnourished host (1, 3). The present study village permitted recognition of important and lasting weight losses consequent to infectious disease. Such observation was possible only through frequent weight measurements in each child. Recuperation of weight loss was prolonged in many cases, placing the child at a notorious disadvantage in terms of growth with regard to nonaffected village children. It should be kept in mind that the average village weight curve reflects growth of all children subjected to a continuous sequence of infection and infectious diseases. In all probability, the village growth curve would have been better were there not so many infections present in the community.

Several authors accept that a deficient nutritional status lowers resistance to infection, as reviewed by Scrimshaw et al. (1). In this study, infants with low birth weight showed a lower capacity to survive infectious diseases than infants with adequate birth weight. Furthermore, in children with deteriorated nutritional status there was a trend towards greater mortality from infection during endemic and epidemic episodes. Whether the lower resistance exhibited by malnourished children is due to immunological deficiencies or to decreased tissue mass, or other causes, remains to be determined.

The long-term prospective studies described herein point out the marked growth retardation of children from a typical rural community of Guatemala. Evidence is presented on the negative effect of asymptomatic infection and infectious disease on growth of children. Furthermore, indirect evidence is provided suggesting the possibility of a high rate of intrauterine infection. To bring about an improvement in growth of children, control of infection in addition to orthodox treatment of disease and nutritional measures are indicated.

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Discussion

Dr. Keusch: The analysis of the data on the virus infections in that early period of life was impressive. I wonder if you have done the same sort of analysis with bacterial infections, and whether there is a correlation between the bacterial and the viral infections. Can we separate these two kinds of agents in the effects that you have shown?

Dr. Mata: We intend to do a similar analysis for bacterial infections. Because the children are breast fed, few bacterial enteropathogenic agents are detected in the first 9 months of life. This phenomenon has been attributed directly to breast feeding. Infections with bacteria (*Shigella* or *Salmonella*) may occur in this period, but clinical symptoms usually are not apparent.

Dr. Keusch: You have described, though, asymptomatic *Shigella* infections in that early period of life.

Dr. Mata: The children may have *Shigella* and *Salmonella* in the early months, but it is in the 2nd year of life and beyond that they become frequent. We are particularly interested in the effect of early infection on growth and development of these children, even if they are asymptomatic; it may be more important than we realize.

Dr. Beisel: How frequent is otitis media in your group?

Dr. Mata: We looked very hard for this, but did not find it frequently.