

Viral infections during pregnancy and in early life^{1, 2}

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ABSTRACT There is evidence that fetal antigenic stimulation and intrauterine infection is much more frequent in developing rural populations than in industrialized societies. A similar contrast is observed for postnatal intestinal infection that is significantly greater in the less developed areas. The differences are explained by the divergence in environmental sanitation and personal hygiene. Intestinal infection is important in that diarrheal disease is one of the main factors leading to malnutrition. It is apparent that for developing nations to attain better nutrition, much of the present burden of intestinal infection needs to be controlled. *Am. J. Clin. Nutr.* 30: 1834-1842, 1977.

Under optimal conditions the fetus is well protected from the infectious environment of the mother and her surroundings. However, a variety of factors, some only suspected, permit occasional infection of the membranes or the fetus itself. The development of technology to identify viral infections in the mother and in the unborn has demonstrated an increasing number of viral agents causing prenatal infection, and has shown that the fetus is not so invulnerable as we once thought.

Often, infection in the mother does not cause clinical manifestations in the fetus, although interruption of pregnancy, preterm delivery, fetal growth retardation, embryopathy, overt disease, and sequelae on growth and performance may occur (1-5).

After birth there is an increased opportunity for infection and the beginning of a series of manifestations of host-parasite interactions. Microbial invasion, including viral infection, influences the development of immune competence of the host, and at the same time, exerts profound effects on his nutrition, growth, development, and survival (6-8).

This paper will touch on some aspects of antenatal and early postnatal infection with special reference to viruses, and will give particular attention to the phenomenon as observed or expected in developing, preindustrial societies. Part of the data to be presented have been obtained from the long-term prospective observation of chil-

dren of an Indian village in Guatemala (9-11) and from prevalence observations of hospitalized children in Costa Rica (12). The problem of viral infection in the fetus, infant, and preschool child will be discussed first in more advanced, industrial societies, and then in the less developed ones, placing emphasis on the latter.

Antenatal viral infection

The concept of fetal sterility has been challenged with the apparent finding that "C type" particles are a common occurrence in human fetal tissues (13) and that they may be transmitted in utero to increase risk of degenerative disease in later life. Aside from this biological possibility, viruses have a relatively well-defined course of action in the human host, to which the response is inflammation, cell proliferation, and necrosis, with the corresponding sequelae (1-5, 14, 15).

Industrialized countries. Studies in socie-

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² Supported in part by USPHS-NICHD Contract NO1-DH-2-2737, and by the University of Costa Rica, the National Children's Hospital and CONICIT, Costa Rica.

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ties living under conditions of good sanitation have shown that synthesis of immunoglobulin M (IgM) by the fetus, frequently a response to intrauterine infection, is a rare event (16, 17). Detailed prospective observations in the lower socioeconomic strata, however, indicate that intrauterine infection is not so rare (18). Evidently there is quite an impressive incidence of maternal infection which becomes evident through systematic serological or clinical prospective study (19, 20). Many antenatal viral infections are silent in the mother and without apparent consequences on the fetus, although a considerable number of infants in industrial nations are born handicapped or will become so as a result of antenatal infection (21-23). A large number of viral agents (Table 1) have been found to cause intrauterine infection and damage to the fetus (1-5, 21, 23); the list has a good possibility of enlarging.

Preindustrial countries. Of the very few studies done on this aspect in developing nations, most were circumscribed to the hospital environment and did not adequately represent the rural population. In one rural Indian village of Guatemala, prospective observations were carried out that are probably representative of the situation

in similar rural areas of the region. The description of the village and its population and of the methodologies used have been given elsewhere (8-11, 24), and some of the findings will be discussed here.

Viral infection in the small village setting is determined in great part by the deficient environmental conditions influencing women from the moment of conception. Even though rural communities are relatively isolated, particularly in nonindustrial, agricultural societies, present transportation facilities provide effective means of communication with the larger population centers. Thus, a continuous supply of viral and microbial agents is insured (24). Agents are brought into the community and spread by person to person contact and other mechanisms until susceptibles become immunized and transmission is arrested. Some agents, however, tend to persist, either as latent or silent infections (healthy and convalescent carriers) or in association with mild recurrent disease. Still others, like cytomegalovirus infection, probably have always been transmitted from mother to child in the villages. Nevertheless, it is possible to conceive that some isolated communities were free from these and similar viral agents in ancient times.

The village mother does not escape the force of infection. Table 2 summarizes the infectious disease experience of a cohort of 82 village women studied prospectively (25). It is striking that in 30% of the pregnant women, lower respiratory tract infection was noted, and in 36%, diarrhea or dysentery. Undoubtedly, morbidity rates are much greater than those found in industrial societies (20).

It is not surprising that just as the village women have greater opportunities for infec-

TABLE 1
Viral agents infecting the fetus^a

Polio, coxsackie A, coxsackie B, echovirus
Western-, Eastern-, Venezuelan-equine encephalitis
Lymphocytic choriomeningitis
Influenza, mumps, measles
Rubella
Cytomegalovirus, herpes simplex, varicella-zoster
Smallpox, vaccinia
Hepatitis A, hepatitis B

^a Virological, serological, or epidemiological evidence.

TABLE 2
Incidence of infectious disease during pregnancy, 82 women, Santa María Cauqué, 1972-1973^a

Trimester of pregnancy	Urinary tract bacterial infection ^b	Diarrhea and dysentery	Respiratory tract infection		Other illnesses ^c
			Upper	Lower	
1st	8 (10) ^d	7 (9)	37 (45)	5 (6)	7 (9)
2nd	8 (10)	9 (11)	26 (32)	6 (7)	5 (6)
3rd	6 (7)	13 (16)	41 (50)	14 (17)	8 (10)
Incidence, per 100 pregnancies	27	36	127	30	25

^a From Urrutia et al. *Am. J. Diseases Children* 129: 558, 1975. ^b $\geq 10^5$ colony-forming units per milliliter of urine. ^c Conjunctivitis, otitis media, skin infection, stomatitis. ^d Episodes (percentage).

tion during pregnancy than women in industrial societies, so too, their fetuses are stimulated by antigens more frequently. Table 3 shows the distribution of IgM and IgG in umbilical cord serums of 250 consecutive village newborns. Specimens with IgA values above 0.09 mg/ml were removed from the tabulation on the suspicion that they might have been admixed with maternal blood at the time of collection, which was done by two traditional Indian midwives. It is striking that 40% of the specimens had elevated values of IgM (24, 25). In fact, 10% of the cases had values of 0.40 mg/ml or greater, clearly indicating fetal antigenic stimulation. Still, some of the specimens could have had admixture with maternal blood. Then a more detailed study of consecutive newborns in four rural lowland mestizo communities, which had health problems similar to those in the highland village, was conducted. This time blood was obtained from the femoral vein within 3 or 4 days of delivery, and IgM concentrations were determined as in the preceding study (26, 27). Again, a large number of infants, specifically 15%, had unquestionable evidence of having been stimulated by antigens in utero.

A prospective serological study of 61 of the 82 pregnant women mentioned above revealed a 12% conversion rate to cytomegaloviruses, herpesviruses and *Toxoplasma gondii* (Table 4). No antibody responses were noted against rubella or syphilis; no testing was made for any of the several other dozen agents that may cause prenatal infection (3, 18, 23). What the data indicate is the frequent occurrence of infection in the pregnant woman, and a likely infection

and/or antigenic stimulation of the fetus. The events are apparently more frequent than described for societies living under better conditions.

Postnatal infection

From birth onwards the child can be infected with viruses mainly through the respiratory and alimentary routes. The risk and probability of infection are determined by the nature of the ecosystem in which the child lives.

Industrial countries. Due to a variety of conditions that determine cleanliness, early infection with intestinal viruses is a relatively rare event in societies of industrial nations and in well-to-do sectors of the urban areas of developing countries. This fact undoubtedly contributes to the slower rate of "maturation" of the serum immunoglobulins in children from industrial societies (28). This circumstance favored the assessment of pathogenicity of certain viruses in the diarrheal syndrome, because viral infections occurred in relative isolation from other infections that could make it difficult to interpret the results. Thus, several "filterable agents," which, unfortunately, are not now available for identification, were described in the pretissue culture era (20). The advent of cell cultures permitted recognition of many serotypes of enteroviruses and adenoviruses in the causation of diarrhea (30-33). It became apparent later that infection with enteroviruses and fecal shedding was a relatively common event, particularly during the summer (34) and among institutionalized individuals

TABLE 3

Determination of IgM and IgG levels in 250 umbilical cord serums from Santa María Cauqué, 1964-1971^{a, b}

IgM		IgG	
mg/ml	cases (%)	mg/ml	cases (%)
< 0.20	149 (59.6)	< 0	36 (14.4)
0.20-0.39	76 (30.4)	10-14	148 (59.2)
0.40-0.59	16 (6.4)	15-19	46 (18.4)
0.60-0.79	7 (2.8)	20-24	16 (6.4)
0.80-0.99	2 (0.8)	25-29	4 (1.6)

^a All serums with IgA ≥ 0.10 mg/ml were not tabulated. ^b From Mata and Villatoro, Kroc Foundation Series 7, New York: Raven Press, 1977, p. 201.

TABLE 4

Incidence of antibody responses to specific agents,^a 61 women studied through pregnancy Santa María Cauqué, 1973^b

Agent (test)	No. of Women	No. of seroconversions (%)
Cytomegaloviruses (CF)	51 ^c	3 (5.9)
Herpes virus (CF)	60 ^c	3 (5.0)
Rubella virus (HI)	61	0
<i>T. pallidum</i> (VDRL)	61	0
<i>Toxoplasma</i> (FA)	61	1 (1.6)
Total	61	7 (11.5)

^a 4-fold (or higher) rise in antibody titer. ^b From Urrutia et al. Am. J. Diseases Children 129: 558, 1975. ^c Anticomplementary sera excluded.

(35). However, an intestinal "viral flora" did not seem to exist in individuals living in highly developed environments.

The identification of the calf diarrhea virus (36) and its study by the electron microscope (EM) was the beginning of a new era in intestinal virology. The application of immune sera to viral preparations permitted agglutination of the virions and easier observation in the EM (37). Examination of fecal preparations of young children by the EM revealed reovirus-like agents or rotaviruses (38, 39) and several other viruses, such as the Norwalk agent (40), astroviruses (41), and caliciviruses (42). The agent of hepatitis A was also demonstrated in fecal extracts (43), as well as coronaviruses (44), adenoviruses, picornaviruses, and bacterial viruses (45).

The relationship of these agents to diarrheal disease is summarized in Table 5. Rotaviruses and 27nm particles are agents which appear to be important in the etiology of outbreaks of diarrhea in industrial countries, particularly in winter months.

Preindustrial countries: No village child escapes early intestinal infection. Delivery occurs without any elaborate preparation of the mother. One study revealed that 25% of the women may carry enteroviruses (8). Maternal defecation, detected in almost all of the deliveries (24), provides ample opportunity for the infant to acquire the viruses she harbors.

Early infection of the child's intestinal tract is expected under these conditions (Table 6). Children's fecal extracts were inoculated into primary human amnion, primary human kidney (post mortem) and HEp-2 cells (24). Among a cohort of 79 infants, one showed an infection with echovirus seven in the first day of life; the viral concentration was 10^2 TCID₅₀ per gram. Of

54 infants 7% were shedding viruses in the second day of life; one child had poliovirus 1 at a titer of 10^5 TCID₅₀ per gram. Of 61 children 8% showed infections on the third day of life, and these had large virus concentration in their feces.

Enteric viral infection in newborns increases as a function of age; they become chronic virus shedders by 6 months of age. Figure 1 depicts the natural history of viral infection in 18 infants during their first year of life. Some were practically free of infection for about 3 months, while others had infections in the first weeks of life. The prevalence of fecal excretion of viruses is in Table 7. About 20% were shedding viruses in the first 6 months of life; 42%, in the second half of the first year of life, and 53% in the third 6 months. The prevalence was over 50% during the second and third years of life. Most of the cytopathogenic viruses isolated were echo-like. The remainder were polio-, coxsackie-, and adenoviruses.

TABLE 6
Viruses in meconium and feces within the first 3 days of life, Santa María Cauqué, 1964-1966

Day of life	No. of children	No. and % positive	Viruses isolated	Virus concentration log ₁₀ TCID ₅₀ per gram
1st	79	1 (1.3)	E7	2
2nd	54	4 (7.4)	P1	5
			E6	3
			E6	3
			E6	3
3rd	61	5 (8.2)	P1 + E6	4
			E6	5
			E7	5
			E9	5
			E11	5

TABLE 7
Fecal excretion of enteroviruses and adenoviruses by 6-month intervals, 45 children observed from birth to 3 years of age, Santa María Cauqué, 1964-1969

Age, mo.	No. of fecal specimens	Enteroviruses		Adenoviruses	
		No. positive ^a	%	No. positive ^a	%
0-5	1116	230	20.6	34	3.1
6-11	1162	483	41.6	46	3.9
12-17	917	481	52.5	33	3.6
18-23	953	438	45.9	60	6.3
24-29	908	446	49.1	58	6.4
30-35	867	530	61.1	48	5.5

^a Isolation in primary human amnion, primary human kidney (post mortem) and HEp-2 cell cultures.

TABLE 5
Viral agents in feces of children detected by electron microscopy

Agent	Association with diarrhea
Rotaviruses (reovirus-like, duov-, orbiviruses)	Yes, endemic, outbreaks
27 nm particles (Norwalk)	Yes, outbreaks
Coronaviruses	Yes, endemic
Astroviruses	Suspected
Caliciviruses	Not known

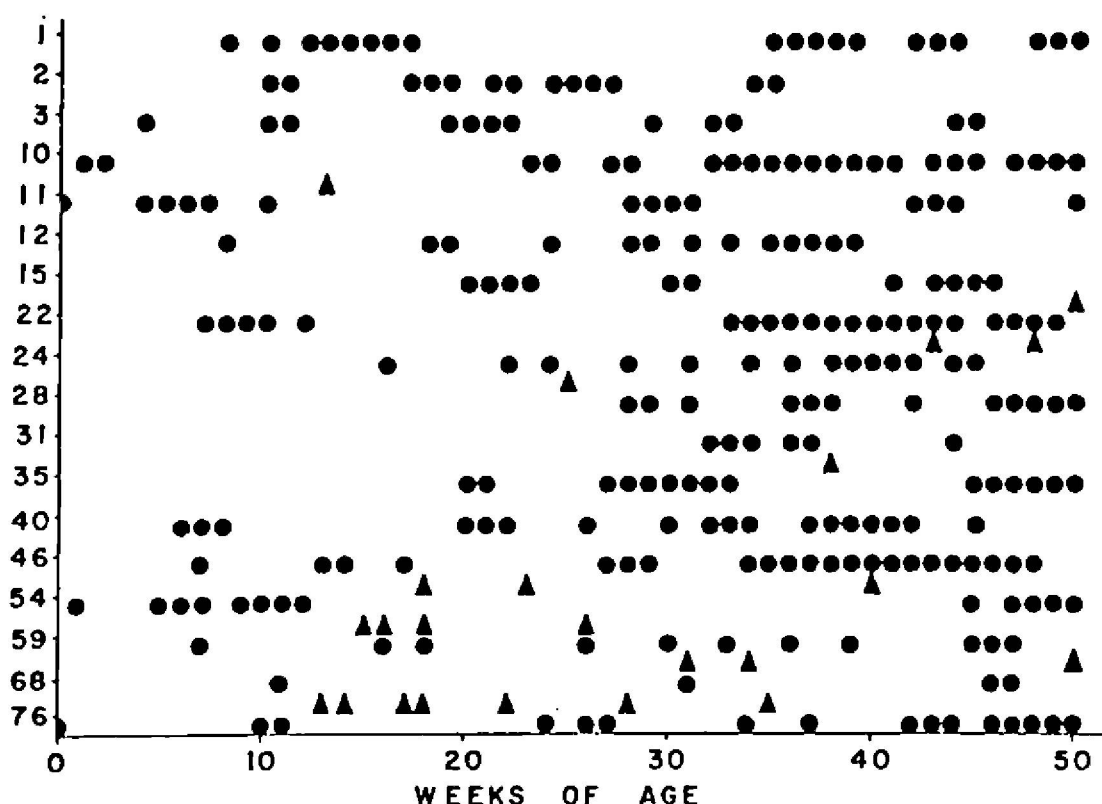


FIG. 1. Viruses shed in feces of 18 village infants (*ordinate*) observed during their first year of life (11, 24) in Santa María Cauqué. Circles are enteroviruses and triangles, adenoviruses. Data are from weekly cultures of fecal extracts inoculated onto primary human amnion, primary human kidney (post mortem) and HEp-2 cells. The prevalence of adenoviruses is likely higher than shown; the greater lytic capacity of enteroviruses lowers the probability of isolation of adenoviruses.

A recent study of hospitalized children in Costa Rica revealed rare infection of the intestine with the rotaviruses (12) (Fig. 2). Fecal extracts prepared by treatment with fluorocarbon were examined in formvar-coated grids after negative straining. No antibody treatment was necessary and viruses were easily detected by EM (Hitachi HU-12A). The preliminary results extended with additional unpublished data indicate that rotaviruses are found primarily in young children; most children in this study were weaned at an early age or were not breast-fed at all.

In view of the frequent difficulty of showing a clear cause-effect relationship, the significance of virus infection in diarrheal disease has been questioned. The clear cytopathogenic and lytic capacity of viruses make it untenable to disregard their participation in diarrhea, malabsorption, and colitis. Part of the problem for instance, resides in the finding of as many enteroviruses in cases of diarrhea as in the controls. Nevertheless, studies of well defined outbreaks clearly show an association of several serotypes of enteroviruses and adenoviruses, and of rotaviruses and other agents with diarrheal syndrome.

In endemic diarrhea the role of enteroviruses is difficult to demonstrate (46). The rotaviruses appear to have a much greater pathogenic potential than other enteric agents; in Costa Rican children they were found only in diarrhea episodes, Table 8. It should be emphasized that in this study the controls were children of comparable age from the same wards where the cases occurred.

Comment

The technological advance in virology and immunology has permitted demonstration that the human fetus is infected with viruses with some frequency (18, 22, 23). Fetal infection and antigenic stimulation seem to be directly related to low socioeconomic development and appear greater in preindustrial tropical regions (25, 47) than in industrial nations (16-18). The practical consideration is that the phenomenon of antenatal infection contributes to fetal wastage, fetal malnutrition, premature delivery, and sequelae. In fact, a very high incidence of fetal growth retardation has been recorded in the Indian village from which much of the data presented here were de-

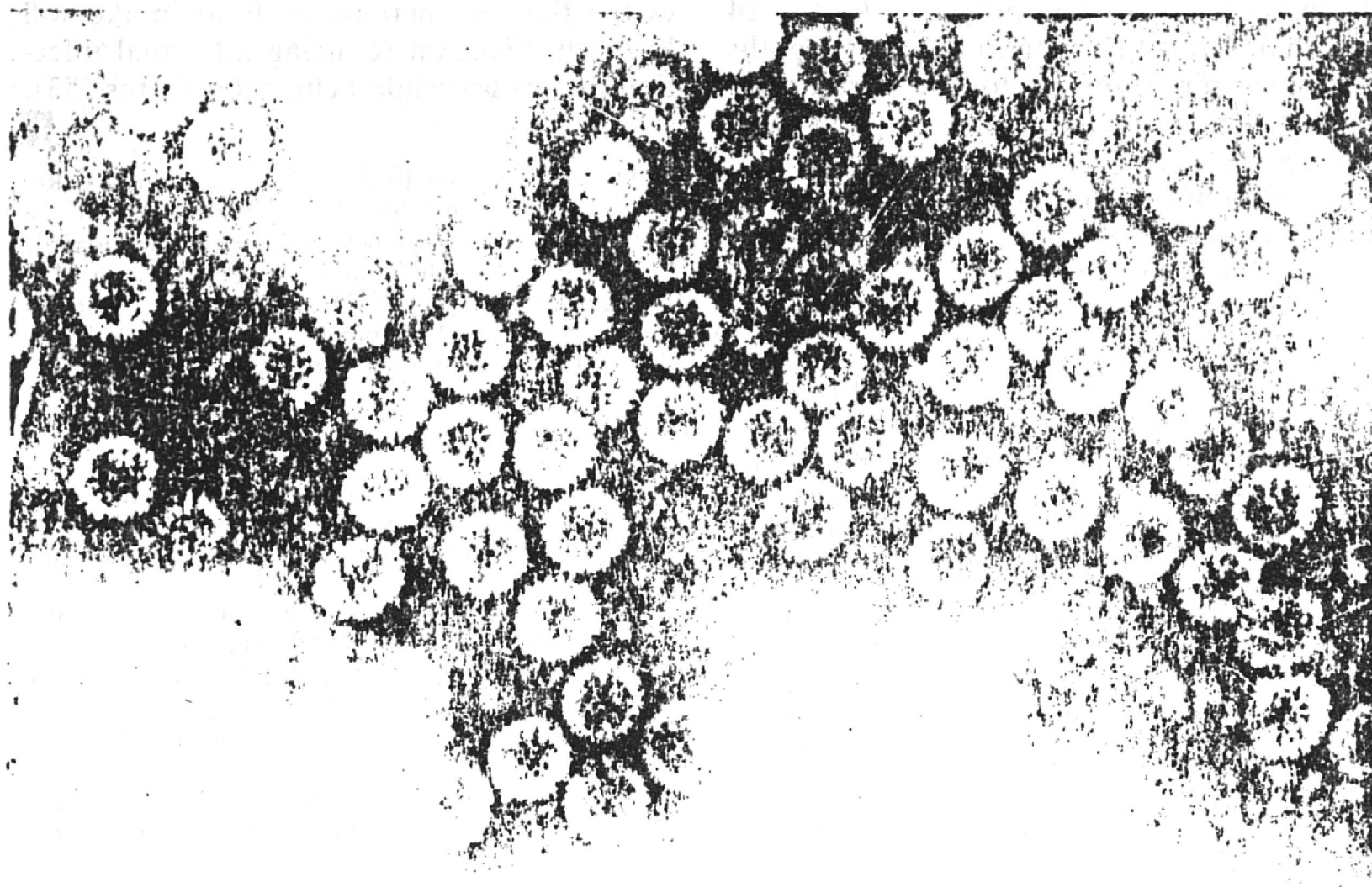


FIG. 2. Rotaviruses in a fecal extract of a Costa Rican child. Formvar preparation negatively stained with phosphotungstic acid. $\times 160,000$.

TABLE 8
Prevalence of viruses in feces of hospitalized children,
by age, San José, Costa Rica, January–March, 1976

Age, Mo.	With diarrhea			Without diarrhea		
	No. of cases	Positive		No. of cases	Positive	
		Rota	Adeno		Rota	Adeno
0–5	4	2 ^a	1	3	0	0
6–11	7	0	1	4	0	0
12+	3	0	0	3	0	1
Total	14	2	2	10	0	1

^a One child also had picornavirus-like particles.

rived (46). However, how much of the overall problem of low birth weight is due to infection and to factors related to maternal nutrition and infection background, remains unknown. Maternal malnutrition, as reflected by the mother's height, appears to be one of the most important factors in causation of fetal malnutrition (46). Infection, in turn, is a determining component of the nutritional status of the mother by a variety of mechanisms, including the restriction of calorie intake in the anorexia that so often accompanies infectious disease.

The cell-dependence and cytopathogenic properties of viruses appear incompatible with the concept of a "normal" viral flora in postnatal life. Children in industrial nations have a significantly lower incidence of intestinal viral infection (34, 49) than their counterparts in developing countries (46, 50, 51). The reasons are a better hygiene and the seasonality of the climate in those countries. Childhood populations in underdeveloped areas are normally infected with intestinal viruses, particularly in the first years of life. The phenomenon is probably related to the precocious "maturation" of the serum immunoglobulins in rural populations (28).

Frequent viral infection, together with bacterial and parasitic infections is a factor in the high morbidity observed in traditional societies living in poverty. In the Guatemalan Indian village, surveillance of families by a physician and nurses permitted accurate collection of morbidity data (24). High rates of diarrhea and other illnesses were observed since early infancy, but especially

during the weaning process (6 to 24 months). Breast-feeding in the first months was an important factor in protection against some of the infection observed (52). During the period of exclusive breast-feeding, children were relatively free of disease, and when disease occurred symptoms were milder. Mortality, however, was very high in preterm and small-for-gestational age infants (24, 26, 48). Infectious disease has an associated negative effect on the nutritional state of the child, which becomes more important after 3 to 6 months of age in breast-fed village infants. The damage of infection, particularly when diarrhea is present, is weight loss, arrest in height, metabolic alterations in cell function, nutrient wastage, and nutrient diversion (6-11). Weight loss in diarrheal disease is acute and detectable within a few hours or days from the onset of disease. It results from dehydration and loss of tissue mass, and may become aggravated or persist for weeks or even months. Anorexia and despondency are symptoms commonly observed among ill weanlings (24, 53). They are the main factors in determining reduction of caloric and (to a significantly lesser extent) protein intake (8, 52, 53).

In a recent analysis we have shown that diminished caloric intake during illness is one of the most important determinants of malnutrition in the village (52, 53). The decrease in intake evident in the analysis was mainly due to infectious diseases such as diarrhea, often accompanied by anorexia. These accounted for the more drastic low caloric intakes among village children. On the other hand, repetitive infections with enteric agents are undoubtedly related to the abnormalities in the intestinal mucosa acquired by individuals in highly infectious, tropical environments (54).

Lowering the rates of intestinal infection and diarrheal disease becomes increasingly important and priority in the process of national development. It seems evident that this cannot be accomplished by any means but by an improvement in living conditions, particularly personal hygiene and environmental sanitation. Actions along this line will have a direct effect on the nutritional status. On the other hand, there is no evi-

dence that an increase in food intake will have an effect on reducing intestinal infection and its associated clinical features (53).



The authors want to thank Takaisa Fukuoka, Rodolfo Bolaños, and Ma. Elena Peñaranda, of the Instituto de Investigaciones en Salud, Universidad de Costa Rica, for collaboration in this research. The authors are indebted to Olegario Pellecer, Roberto Rosales, and Elba Villatoro of the Instituto de Nutrición de Centro América y Panamá in Guatemala.

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