# CAUSE AND CONTROL OF FATAL, INFANTILE DIARRHEAL DISEASES*

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The United Nations Conference on the Application of Science and Technology for the Benefit of the Less Developed Areas is concerned with the practical means by which "science and technology can best serve the needs of the less developed countries." The problem of fatal, infantile diarrheal diseases is being considered in this connection, because they are a major or principal cause of death in infancy and early childhood among the economically underprivileged populations of the world.

According to Hardy and Schliessmann,[1] consultants of the World Health Organization, the acute diarrheal diseases are estimated to account for about 5 million deaths of infants and children each year throughout the world. Among the economically more privileged populations, these diseases disappeared as an important cause of death only after the achievement of high living standards, which include improved nutrition, better housing supplied with safe, abundant water, sanitary disposal of excreta and facilities for proper refrigeration and storage of food, sanitary control of processing, storage and distribution of milk and other food products, control of feces-transmitting insects, increased availability of good medical care, and last but not least a markedly increased level of education. The question that I shall particularly consider is whether the tremendous mortality from acute diarrheal diseases can be eliminated only after all of these desirable objectives have been achieved by the great complex of other activities designed to improve the economic status and conditions of dignified existence of the hundreds of millions of underprivileged people in the world, or whether there may be some shortcut based on a correct, scientific evaluation of the underlying causes of this tragic annual loss of millions of children.

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### *Statistics on Magnitude of Problem*

Statistics generally are grossly inadequate in the very parts of the world where diarrheal deaths are of major public health importance. The enormous magnitude of the problem, however, is clearly evident from the limited reports that are available. The diarrheal diseases generally considered for statistical evaluation include those reported as gastritis, duodenitis, enteritis, colitis or, especially in Latin America, dyspepsia, enterocolitis and toxicosis. Omission of diarrhea of the newborn, affecting infants under 1 month of age, and deaths specifically reported as due to *Salmonellae* or *Shigellae* does not significantly affect the data, because they constitute a very minor part of the total reported mortality. Diarrheal disease was thus found to be the leading cause of death in 8 of 17 Latin American countries forwarding data in 1954, and in 4 of the remaining 9 countries it was among the five principal causes. In children under 5 years of age, diarrheal disease was the principal or major cause of death in most of the reporting Latin American countries in 1954, with rates up to 150 times greater than that obtaining in the U. S. A.[2] The data in Table 1 show that in 1901 in New York City diarrheal mortality in infants under 1 year of age was higher than any reported by the Latin American countries for 1955–56, and that even as late as 1920 New York City had rates comparable to current rates in many of the Latin American countries. The extraordinary low level of diarrheal deaths in infants achieved in the U. S. A. and Canada by 1955 apparently was associated more with other improvements in the standard of living than the mere provision of water and sanitary disposal of excreta in the homes already in existence in New York City between 1901 and 1920.

Penido[3] reported that in Brazil in 1958, the infant mortality rate was 160 per 1,000 live births. He, therefore, estimated that there were 421,000 infant deaths per year, and on a very

TABLE 1

*Death rates from diarrheal disease in infancy and early childhood**

| City or country | Year | Deaths per 100,000 per annum | |
|---|---|---|---|
| | | Children under 1 year† | Children 1–4 years‡ |
| New York City | 1901 | 4496 | 470 |
| | 1920 | 1796 | 120 |
| U. S. A. | 1955 | 120 | 4 |
| Canada | 1956 | 150 | 5 |
| Mexico | 1955 | 1820 | 784 |
| El Salvador | 1955 | 1880 | 867 |
| Guatemala | 1955 | 1250 | 956 |
| Brazil | 1956 | 3800 | 442 |
| Ecuador | 1955 | 3250 | 717 |
| Colombia | 1956 | 1840 | 368 |
| Chile | 1956 | 1720 | 167 |
| Puerto Rico | 1955 | 1510 | 125 |

* Except for New York City, the data are from: *Summary of four-year reports on health conditions in the Americas*. Scientific Publication No. 40, Pan American Sanitary Bureau, Washington, D. C., 1958. Data for New York City are from: Hardy, A. V., 1956. Diarrheal diseases of man: a historical review and global appraisal, *Ann. N. Y. Acad. Sci.*, **66**: 5–13.

† Deaths from diseases of the digestive tract per 100,000 live births.

‡ Deaths from gastritis, duodenitis, enteritis and colitis.

TABLE 2

*Total deaths and deaths from diarrheal diseases among infants under one year of age in three large Brazilian cities**

| City | Period | Total deaths | Deaths from diarrheal diseases | |
|---|---|---|---|---|
| | | | No. | Percent |
| Rio de Janeiro.... | 1956–57 | 14,870 | 5,197 | 34.9 |
| São Paulo..... | 1956 | 8,288 | 3,208 | 38.7 |
| Recife..... | 1957 | 5,895 | 1,766 | 30.0 |

* Data from Penido, H. M., Prevention of mortality from diarrhoeal diseases in Brazil, *Bull. World Health Organ.*, **21**: 368–371.

TABLE 3

*Total deaths and deaths from diarrheal diseases among populations of African and European descent in Johannesburg, South Africa, 1951**

| Population | Total no. | Total deaths all ages all causes | Diarrhea deaths | | | |
|---|---|---|---|---|---|---|
| | | | All ages | <1 month | <1 year | <2 years |
| African.... | 355,000 | 5,658 | 1,152 | 84 | 829 | 1,064 |
| European.. | 311,000 | 2,715 | 29 | 0 | 0 | 24 |

* Data from Kahn, E.: 1957. The aetiology of summer diarrhoea, *South African M. J.*, **31**: 47–54.

conservative assumption that at least 35% of these deaths were caused by diarrheal disease, it appeared that at least 147,000 infants were annually dying from diarrheal disease in Brazil. Penido's data for 3 large Brazilian cities with "ample medical facilities", shown in Table 2, support his conservative estimates.

In Egypt, districts with health bureaus reported that the infant mortality in 1949 was 134 per 1,000 live births. Of 64,914 infant deaths in which a cause was recorded, 54% (35,083) were attributed to "diarrhea and enteritis."[3] In Sindbis, a village under special study by the Egyptian Ministry of Public Health and The Rockefeller Foundation, the infant mortality rate during the period of 1948–1951 was found to be 245 per 1,000 live births.[4]

Perhaps the most striking illustration of the relationship between the standard of living and mortality from diarrheal disease is contained in 1951 data for the populations of African and European descent in Johannesburg, South Africa, shown in Table 3. It may be seen that for total populations of similar size, the total number of diarrheal deaths was 1,152 for the African population and only 29 for those of European descent —and with only few exceptions the deaths were in infants under 2 years of age in both groups.[5] I am informed that in 1951, the African population in Johannesburg received its water from the central municipal supply, although largely from spigots outside their homes. In the U. S. A., in a city with a population of approximately 300,000 during the period of 1946 to 1949, Schliessmann[6] found that the death rate from diarrheal disease in children under 2 years of age was 6 times higher in the slum areas than in the better parts of the city. The influence of changes in the standard of living on mortality from diarrheal disease was also emphasized by Maslov and Grechishnikova,[7] who reported that in 1913 in Russia infant mortality was 273 per 1,000

live births with approximately one-third attributable to gastro-intestinal deaths, while in 1956 in Leningrad infant mortality was 45 per 1,000 with only 4% of the total attributable to gastro-intestinal diseases (toxicosis, gastritis enterocolitis and dysentery). In a recent review Hardy[8] concluded that diarrheal disease—one of the world's oldest problems—remains today the chief killer of infants in many lands, the mortality affecting predominantly children under 2 years of age.

### *Present Knowledge of Etiology of Morbidity and Mortality*

The human enteric tract is subject to infection or infestation by many pathogenic bacteria, viruses, protozoa and helminths, but the impression gained from recent reviews[8, 9] is that the *Shigella* bacteria are *presumably* the chief pathogenic agents of morbidity and mortality from diarrheal disease in populations living under conditions of poor sanitation and hygiene. In an analysis of the environmental controls that would be needed in dealing with the acute diarrheal disease problem in economically less developed areas, Schliessmann[6] worked on the assumption that "in areas of high endemicity there is substantial evidence that the primary cause of acute, infectious diarrheal disease is infection with a species of the genus *Shigella*." It should be noted, however, that Hardy[8] stressed the importance of recognizing "the narrow limits of knowledge of the etiology of diarrhoeal diseases in the economically less favoured countries, where malnutrition in infants and children is of such common occurrence," and Ordway[9] concluded that in young infants, particularly in the first 6 months of life, "the infecting agents most likely to be causative, on the basis of present information, are *E. coli* types and viruses." My own analysis of the available data led me to conclude that particularly in children under 2 years of age, the age group that is most important from the point of view of mortality, the *Shigellae* and other specific bacterial pathogens, while still important, may frequently constitute only a small proportion of the etiologic agents.

The great stress on the etiologic role of *Shigellae* can be traced to early American studies, which have been assumed to apply to both diarrheal morbidity and mortality in the less developed areas of the world today. Hardy[8] refers to the studies of Flexner and Holt on hospitalized patients in northeastern metropolitan centers of the U. S. A. in 1903, and points out that, even with the less satisfactory media in use at that time, 66% of 421 patients were positive for *Shigellae*. In an excellent study of "summer diarrhea" in Cincinnati in 1938, utilising multiple stool specimens and multiple media, Cooper *et al.*[10] found *Shigellae* in 49% of 209 patients, but made the important observation, subsequently confirmed by many others, that 75% of patients under 1 year did not yield *Shigellae* while 75% of those over 1 year did. Cooper *et al.*, furthermore, noted that clinically the disease associated with *Shigellae* could not be differentiated from that without *Shigellae*—the case fatality rate was about 13% in the *Shigella* patients and 16% in the others. It is noteworthy, therefore, that in 1955–56[11] and in recent years generally (Personal communication from M. L. Cooper, Children's Hospital Research Foundation, Cincinnati, Ohio) *Shigella* organisms have been recovered from not more than 5% of patients with "summer diarrhea" in Cincinnati, and that fatalities are very rare—none having been recorded among the 153 patients observed in the 1955–56 study.[11] In a series of studies by Hardy and Watt in New Mexico and Georgia during the period of 1939–48, *Shigella* organisms were found in 58% of the milder cases, and in 76% of the severe cases, the isolation rate in the severe cases rising to 90% when more than 3 examinations were made during the course of the illness.[8] Moreover, during the period before 1948, Hardy and Watt[12] isolated *Shigellae* from 75% of 52 fatal cases.

As regards *Salmonellae*, Hardy[8] concluded that while these organisms may cause serious diarrheal disease in children, the relative frequency of such infections was unknown. The etiologic role of certain serotypes of pathogenic *E. coli*, particularly in nursery groups of newborn children in well-sanitated countries, was acknowledged by Hardy,[8] who believed, however, that their "pathogenic significance in the less developed regions has yet to be determined."

The results of tests for *Shigellae*, *Salmonellae* and pathogenic strains of *E. coli* among young children with endemic diarrheal disease in different parts of the world during the past decade are shown in Table 4. It may be seen that the reported isolations of *Shigellae* ranged from lows

TABLE 4

*Isolation of "bacterial pathogens" from children with diarrhea in different parts of the world*

| Country and year | Group | No. tested | Percentage of indicated "bacterial pathogens" | | | |
|---|---|---|---|---|---|---|
| | | | *Shigella* | *Salmonella* | *E. coli** | None |
| Morocco, 1956[13] | Mostly hospitalized | 109 | 2 | 5.5 | 50 | 42 |
| Tunisia, 1956[14] | Summer diarrhea | 400 | 12 | 3.5 | 0.25 | 84 |
| Tunisia, 1956[14] | Winter diarrhea | 420 | 5.5 | 5.7 | 0 | 89 |
| Uganda, 1957[15] | 10 days–4 years | 100 | 25 | 6 | 3 | 66 |
| Chile, 1955–56[16] | 96% <1 year | 134 | 9 | 0 | 36 | 55 |
| Venezuela, pre 1955[17] | Sporadic cases; <1 year | 95 | 4 | 4 | 7 | 85 |
| Mexico, 1955–56[18] | Severe diarrhea | 497 | 13 | 2 | 30 | 55 |
| USA, Arizona, 1957–59[19] | 78%, 1–24 months | 630 | 26 | 7 | 31 (15) | 43 |
| USA, Ohio, 1955–56[11] | Summer diarrhea; <4 years | 127 | 5 | 4 | 29 (24) | 62 |
| | Controls—no diarrhea | 101 | 0 | 0 | 20 (6) | — |
| Finland, 1950–1953[20] | Diarrhea—under 2 years | 790 | 0.5 | 2 | 23 (12) | 74 |
| | No diarrhea—under 2 years | 2410 | 0 | 0 | 5 (2.6) | — |
| Northern Italy, 1956[21] | 1 month–2 years | 190 | 0.5 | 3 | 7 (0) | 90 |
| Sicily, 1959[22] | Summer diarrhea; <2 years | 139 | 0 | 0 | 32 | 68 |
| | No diarrhea; <2 years | 57 | 0 | 0 | 12 | — |
| North. France, 1952–56[23] | 1 day–4 years | 380 | 3 | 4 | 53 | 40 |
| Indonesia, 1954–57[24] | Most <3 years | 355 | 12 | 0 | (8) | 80 |
| Philippines, pre 1958[25] | Infants | 500 | 8 | | (12) | 80 |

* Percentage in parentheses refers only to 0111:B4 and 055:B5.

of 0 to 0.5% in Sicily,[13] Northern Italy[21] and Finland[20] to a maximum of 25 to 26% in Uganda[5] and Arizona, U. S. A.[19] While the *Shigella* isolation rates are generally higher in the areas with high endemic prevalence of diarrheal disease, the *Salmonella* isolation rates were low everywhere. The isolation rates of "pathogenic" strains of *E. coli* varied from 0.25% in Tunisia[14] to about 50% in Morocco[13] and Northern France.[22] The fact that some so-called pathogenic strains of *E. coli* were encountered more frequently in children without diarrhea was brought out in the Cincinnati study,[11] which, however, also indicated that the strains of definitely established pathogenicity, *e.g.*, serotypes 0111:B4 and 055:B5 were found 4 times more often in children with diarrhea than in carefully matched controls without diarrhea. Controlled studies carried out in Finland[20] yielded entirely comparable results, when the analysis is limited to these two serotypes (Table 4). Even more striking results were obtained in Poland where Brokman[26] found that among 2,975 "nursling" infants with diarrhea, 26% yielded 0111:B4 and 10% 055:B5, while among 1,246 healthy, non-hospitalized "nurslings" only 3% yielded 011:B4 and 1% 055:B5. Although these two serotypes of *E. coli* have also been reported in endemic infantile diarrhea in the Philippines[25] and Indonesia,[24] the results shown in Tables 5 and 6 indicate no significant role for pathogenic *E. coli* during certain periods in Guatemala[27] and Mexico,[28] where carefully controlled studies yielded the same low numbers of pathogenic *E. coli* in young children with and without diarrhea.

The importance of including controls, carefully matched for age, socio-economic status and season of the year, in critical studies on the etiology of endemic diarrheal disease is well illustrated by the data shown in Tables 5, 6 and 7. The studies in Guatemala[17] thus showed that *Entamoeba histolytica*, other intestinal parasites, as well as pathogenic *E. coli* were recovered just as often from properly matched controls as from children with diarrhea, while *Shigella* organisms, although found in only 13.5% of their 201 patients, were recovered less frequently (6%) from the 215 matched controls. The results shown in Table 7 establish even more strikingly the role of ECHO

TABLE 5

*"Bacterial pathogens" and intestinal parasites in children 1 to 5 years of age with acute endemic diarrheal diseases and in "matched controls" without diarrhea in Guatemala, 1957–1958**

| Group | No. tested | Percentage of indicated "bacterial pathogens" or parasites | | | | |
|---|---|---|---|---|---|---|
| | | *Shigella* | *Salmonella* | *E. coli* | *E. histolytica* | Other parasites |
| Rural—diarrhea | 101 | 12 | 0 | 2 | 14 | 58 |
| Rural—controls | 100 | 4 | 0 | 2 | 18 | 65 |
| Urban, low social status—diarrhea | 100 | 15 | 2 | 3 | 6 | 53 |
| Urban, low social status—controls | 115 | 9 | 0 | 2 | 6 | 69 |
| Urban, high social status—controls | 98 | 2 | 0 | 2 | 1 | 36 |

* Data from Pierce, V. *et al.*, Studies of diarrheal disease in Central America. III. Specific etiology of endemic diarrhea and dysentery in Guatemalan children, *Am. J. Trop. Med. & Hyg.*, **11**: 395–400.

TABLE 6

*Recovery of enteropathogenic bacteria and viruses from rectal swabs of 246 children less than 3 months to 5 years of age with diarrhea and from 107 "Matched controls" without diarrhea in Mexico City, June 1–November 15, 1960**

| Agents recovered | Percent positive | |
|---|---|---|
| | Diarrhea (246) | Controls (107) |
| Viruses only | 35 | 10 |
| *Shigella* only | 7 | 0 |
| *Salmonella* only | 6 | 2 |
| *E. coli* only | 6 | 8 |
| Mixture of bacteria only | 2 | 1 |
| *Shigella* + viruses | 7 | 0 |
| *Salmonella* + viruses | 5 | 0 |
| *E. coli* + viruses | 8 | 6 |
| Mixture of bacteria + viruses | 3 | 0 |
| Total | 78 | 28 |
| Total viruses | 58 | 16 |
| Total *Shigella* | 14 | 0 |
| Total *Salmonella* | 11 | 2 |
| Total *E. coli* | 14 | 14 |

* From unpublished data of Ramos-Alvarez, M., Olarte, J. and Martin, S., Hospital Infantil de Mexico, Mexico 7, D. F.

TABLE 7

*Enteric viruses in children under 4 years of age with summer diarrhea and in matched controls without diarrhea in Cincinnati, 1956**

| Group | No. tested | No. indicated virus recovered | | | | |
|---|---|---|---|---|---|---|
| | | ECHO | Coxsackie B | Coxsackie A† | Polio | Adeno‡ |
| Diarrhea | 97 | 30 | 5 | 6 | 3 | 3 |
| Controls | 100 | 5 | 6 | 6 | 3 | 0 |

* Data from Ramos-Alvarez, M. and Sabin, A. B., 1958. Enteropathogenic viruses and bacteria—role in summer diarrheal diseases of infancy and early childhood, *J. Am. M. Assoc.*, **167**: 147–156.

† Viruses pathogenic for newborn mice but not for monkey kidney cultures.

‡ Only monkey kidney cultures used, which are not suitable for optimum detection of adenoviruses.

viruses in summer diarrhea in Cincinnati, where the isolation rate was 6 times higher among infants and young children with "summer diarrhea" than in a similar number of carefully matched controls.[11] Although the prevalence of enteric viruses is much higher in Mexico than in Cincinnati, a recent carefully controlled study by Ramos-Alvarez *et al.*[28] showed that enteric viruses, as the sole pathogens recoverable by human kidney cultures, were found 3.5 times more often in infants and young children with diarrhea than in those without; moreover, while enteric viruses were found in 57.5% of the patients, *Shigellae* and *Salmonellae* were isolated from a total of only 24.5% (Table 6). In a recent virologic, bacteriologic and parasitologic study on 29 infants with gastro-enteritis in Puerto Rico, Young *et al.*[29] isolated viruses from 14, *E. coli* sero-

types 0111:B4 and 055:B5 from 8, and *Shigella*, *Salmonella* and *E. histolytica*—each from one patient but in each instance associated either with a virus or with *E. coli*, 0111:B4. It should be pointed out, however, that in at least two other studies—one in Sicily[22] and one in Johannesburg, South Africa, (personal communication from Dr. H. Malherbe, South African Institute for Medical Research)—there was no difference between the virus isolation rates in infants with and without diarrhea. Since only monkey kidney cultures were used in these studies one must consider the possibility that adenoviruses and enteroviruses that can be isolated in various human cell lines but not in monkey kidney, might have been more prevalent in the community at the time of these studies, and their possible role in gastro-enteritis could thus be missed. It may be pertinent to recall here that in the Cincinnati study on the role of pathogenic *E. coli*, a significant difference between infants with and without diarrhea was found when the analysis was limited to certain serotypes but not when all serotypes were included. Moreover, in such control studies it is necessary to follow up the infants under investigation and eliminate those who may develop diarrhea during the subsequent 2 weeks.

The role of various enteric viruses, including adenoviruses, in diarrheal disease of infants and young children has recently been studied by many investigators.[11, 21, 22, 28-36] Although a great variety of enteric viruses are recovered from endemic cases, institutional outbreaks caused by single ECHO viruses have also been reported—ECHO 11,[34] ECHO 14,[31] and ECHO 18.[30] The true quantitative role of viruses in acute diarrheal disease of infancy and early childhood has not yet been determined because most investigators have not used the multiple tissue culture lines and newborn mice that are necessary for their demonstration. In addition to the viruses that can be demonstrated by the above methods, one must also keep in mind others, *e.g.*, the agents that thus far have been demonstrated to cause gastro-enteritis only by tests on human volunteers[37] and the viruses of infectious hepatitis[38] as causes of infantile diarrhea. However, even with the incomplete methods used thus far it has been possible to associate pathogenic bacteria and viruses with at least 70 to 80% of endemic diarrheal disease in Mexico,[18] where the rates are high, as well as in the U. S. A.,[11] where the rates are low.

In the preceding discussion, as in most analyses of this problem, attention was focused on infection with known pathogenic agents. It must not be forgotten, however, that the consumption of milk, milk substitutes or other foods that are contaminated with billions of ordinary non-pathogenic bacteria may also be a significant factor in infantile, diarrheal disease among economically underprivileged populations. Buttiaux[39] especially stressed the importance of the microbial mass or the associated bacterial products, and pointed out that acute, profuse diarrhea is not a rare phenomenon among nursing infants receiving supplements prepared without the fundamental, hygienic precautions.

The importance of the diarrheal disease problem in the economically less developed areas stems not so much from the high morbidity as from the high mortality. In countries with higher standards of living the case fatality rate in infantile diarrheal disease, which as late as 1938 was as high as 14% (and 16% in infants without *Shigellae*[10]), has in recent years dropped to less than 1 percent. The chief factor in this achievement is not the introduction of antibiotics as some may assume, but rather proper fluid and electrolyte therapy. The results shown in Table 8 indicate the importance of malnutrition in relation to the case fatality rate among hospitalized infants in Mexico City,[40] where modern fluid therapy was being utilized. Among infants with little or no evidence of malnutrition the case fatality rate was 14 to 15% or about the same as among children hospitalized in Cincinnati in 1938,[10] while with increasing malnutrition the

TABLE 8

*Nutritional status and mortality from infantile diarrhea**

| Extent of malnutrition | Number patients | Case fatality rate (percent) |
|---|---|---|
| None | 67 | 14.9 |
| 11%–25% below "normal" | 149 | 14.1 |
| 26%–40% below "normal" | 488 | 29.1 |
| Over 40% below "normal" | 370 | 51.6 |

* Data from De La Torre, J. A., 1956. Mortality from infectious diarrhea in hospitalized children under 2 years of age, *Bol. med. Hosp. infant. (Mex.)*, **13**: 785–792.

case fatality rate rose progressively to as high as 52 percent. Studies carried out jointly by the Hospital Infantil of Mexico City and the Children's Medical Center of Harvard University[41] indicated that the biochemical disturbance in infants with diarrhea and severe malnutrition is different from that observed in dehydrated infants without malnutrition, and that this may account for some of the poor results with the modern methods of intravenous fluid therapy in Mexico. This important observation does not explain, however, the 14% case fatality rate in the infants without obvious malnutrition (Table 8). Thus, if there were no malnutrition the mortality from diarrheal disease might conceivably be reduced three- to fourfold, but because of the high morbidity rate the total mortality would still be high. If the case fatality rate could be so high among infants with diarrhea admitted to one of the best children's hospitals in Latin America, it is evident that it must be still higher where medical care is absent or inadequate.

One must consider the possibility that the etiologic agents involved in the fatal cases of diarrheal disease may be qualitatively or quantitatively different from those involved in the nonfatal cases. To obtain a better understanding of the etiologic factors in mortality from infantile diarrheal disease it is necessary to carry out comprehensive microbiologic and pathologic studies on the fatal cases in the economically less developed areas and only two such studies, both as yet unpublished, have come to my attention. Ramos-Alvarez and his associates[28] in Mexico City looked for enteropathogenic viruses and bacteria in the intestinal walls and organs of 52 fatal cases of diarrhea and 12 cases without diarrhea. In the 12 control cases, only 1 yielded a virus and one a *Shigella flexneri 4*, an organism of doubtful pathogenicity for man. Thus, 91% (or at least 83%) of those in the control group had no demonstrable enteropathogenic viruses or bacteria. The results shown in Table 9 indicate that enteropathogenic bacteria and viruses, alone or in various combinations, were found in 67% of the fatal cases with diarrhea, and that the viruses alone were recovered about 3 times less frequently and pathogenic *E. coli* alone 3 times more frequently from the fatal cases than from those coming to the hospital with diarrhea. Quantitative tests on the jejunum, ileum and colon have yielded $10^6$ to $10^8$ *E. coli* and $10^3$ to $10^5$ tissue culture infective doses of various viruses per gram of tissue. In post-mortem studies on 100 infants with diarrhea in Poland, Brokman[16] recovered *E. coli* 0111:B4 in 18 cases and 055:B5 in 5 cases in tests on the mesenteric lymph nodes or intestinal walls. In Italy, ECHO 11[34, 36] and Coxsackie B 3[35] have been associated with fatal cases of infantile gastro-enteritis.

Drs. Gustave J. Dammin and Donald Feldman[42] of the Department of Pathology of the Harvard Medical School carried out detailed post-mortem studies on consecutive infant deaths from all causes at the Roosevelt Hospital in Guatemala City during September–November, 1958 (total of 35) and May–June, 1960 (total of 28). Fifty of the 63 fatal cases had diarrheal disease. Malnutrition was evident in 70% of the 50 with diarrheal disease, and in 40% of the 13 without diarrhea. Bacterial pathogens were recovered from the tissues and fecal specimens of 44% of the 50 with diarrhea and of 23% of the 13 without diarrhea. *Shigellae* accounted for only a part of the bacterial pathogens, and *E. coli*, which often occurred together with *Shigellae*, accounted for most of the remainder. Only 8 viral agents (5 of them associated with pathogenic bacteria) were recovered from all 63 fatal cases by the methods employed, which is surprising in the light of the results on infants with diarrhea in Mexico City (Tables 6 and 9) and the finding of 50 to 70% of viral carriers in a random survey (without reference to diarrhea) among infants aged 2 months to 6 years in Toluca, Mexico.[43] There was no evidence that protozoal or helminthic infections might be of significance, and these investigators concluded that either unidentified pathogens or factors other than specific bacterial and viral infections were important in the pathogenesis of the fatal cases of diarrheal disease that they had studied. They were impressed by the presence of large numbers of ordinary bacteria in the upper small intestine, a site ordinarily free of bacteria soon after death, and wondered whether endotoxins or other products derived from these bacteria might be responsible for an alteration in the intestinal mucosa leading to loss of water and electrolytes. Ulcerative intestinal lesions were absent in 36 of the 50 cases with diarrhea. A study of 11 cases with diarrhea and gross evidence of malnutrition, but without bacterial pathogens or ulcera-

TABLE 9

*Relative role of enteropathogenic bacteria and viruses in morbidity and mortality of diarrheal disease in infancy and early childhood in Mexico City**

| Agents recovered | Percent yielding indicated agents among | |
|---|---|---|
| | 246 hospital patients† | 52 fatal cases‡ |
| *Shigellae, Salmonellae, E. coli* alone or in association with one another, or with viruses... | 43 | 54 |
| Viruses alone or in association with bacteria..... | 58 | 33 |
| Viruses—alone..... | *35* | *13* |
| *Shigellae*—alone..... | 7 | 8 |
| *Salmonella*—alone..... | 6 | 6 |
| *E. coli*—alone..... | *6* | *17* |
| *Shigellae* + viruses..... | 7 | 6 |
| *Salmonellae* + viruses..... | 5 | 4 |
| *E. coli* + viruses..... | 8 | 4 |
| None..... | 22 | 33 |

* From unpublished data of study begun in 1960 at Hospital Infantil de Mexico (Mexico 7, D. F.) by Doctors M. Ramos-Alvarez, J. Olarte and S. Martin.

† Rectal swabs tested (Table 6).

‡ Intestinal wall and viscera tested.

tive lesions, revealed an intact intestinal mucosa with some nuclear debris and polymorphonuclear leukocytes in the lamina propria, suggesting an active inflammatory process similar to that seen in acute cholera. These investigators concluded that malnutrition per se is not the basis for the diarrheal disease.

It is obvious that more post-mortem studies of the type just mentioned, with even greater efforts for recovery of agents in a greater variety of tissue cultures, will have to be carried out in different parts of the world where the diarrheal diseases are the most important killers of infants and young children before a clearer composite picture of the etiology can be drawn. From the studies, just mentioned, however, it would appear that many enteropathogenic agents, including pathogenic *E. coli*, *Shigellae*, *Salmonellae* and viruses—alone or in combination—contribute in varying degree to the etiology of fatal infantile diarrheal disease, but that in about 30 to 50% of the cases there may be no demonstrable or identifiable specific pathogens. Since the consumption of unhygienically prepared and stored milk, milk substitutes or other supplementary feedings, contaminated by billions of ordinary bacteria, must be considered as an important factor in infantile diarrheal disease, one cannot help but wonder about the role of this factor in those fatal cases in which no specific pathogens are found but, as in the Guatemala studies, enormous numbers of non-pathogenic bacteria in the ordinarily bacteria-free upper intestine. Moreover, while malnutrition increases the chances of a fatal outcome (Table 8), 30% of the fatal cases of diarrhea in Guatemala had no obvious signs of malnutrition.

In older children and adults, living under poor conditions of sanitation and hygiene in the less developed areas of the world, enteric infections with *Shigellae, Salmonellae*—especially *S. typhosa*, *Vibrio cholerae*—in the remaining endemic areas, and the protozoal and helminthic infestations contribute significantly to the sum total of human misery, but, by comparison with the diarrheal diseases of the first 2 years of life, they are relatively unimportant as a cause of death.

### *Potentialities of Vaccines, Chemoprophylaxis and of Various Sanitary Improvements for the Control of Infantile Diarrheal Mortality*

Controlled studies in Egyptian villages indicated that a *Shigella* vaccine was ineffective, and that prophylaxis with sulfadiazine, streptomycin, and oxytetracycline was neither practical nor effective in the dosage used.[44] Neither vaccines nor chemoprophylaxis directed against the viruses and pathogenic *E. coli* involved in the etiology of infantile diarrheal mortality represent either a possible or practical approach to the problem. Most people who have been concerned with this problem have focused their attention on the various environmental factors which contribute to the extraordinarily easy transport of fecal matter among persons living under primitive or even poor conditions of sanitation and hygiene. And yet it must be realized that it is not only the fecally-transmitted infections of the enteric tract but also the infections of the respiratory tract that kill so many more infants and young children in the economically less developed areas than in the economically advanced countries with high standards of living. Thus, in 1955–56 the mortality from respiratory disease was 280 per 100,000 under 1 year of age in the U. S. A., while the rates in Chile, Mexico and Guatemala were

3,180, 2,140 and 2,120 respectively; for 1 to 4 year old children the mortality rate per 100,000 was 20 in the U. S. A., 660 in Guatemala, 500 in Mexico, and 420 in Chile.[45] Dirty hands are probably as important in the spread of respiratory infections as in enteric infections. It is for this reason that high infantile, diarrheal mortality did not quickly disappear from the economically advancing countries even after more food, better housing with both abundant, pure water and toilet facilities in the homes had been provided (see statistics for New York City in Table 1). It also required a higher level of health education, pasteurization of milk, facilities for home refrigeration, and greatly improved medical care before the present extraordinarily low levels were finally achieved. We cannot expect that the provision of pure community water supplies and the building of sanitary privies, however important and desirable they may be for other reasons in the initial public health improvements, will significantly affect infantile diarrheal mortality. Education of mothers in the simple principles of infant care and the establishment of fluid and electrolyte therapy centers wherever possible are important and desirable, but by themselves also cannot be expected to have any marked effect on infantile diarrheal mortality.

## CONCLUSION

On the basis of present knowledge that infantile diarrheal mortality has multiple causes among which direct transmission of human enteropathogenic bacteria and viruses by dirty hands, consumption of food that has served as a culture medium for billions of bacteria, and malnutrition are perhaps most important, it is not surprising that it remains an important problem until very high standards of living are achieved in a population. It is necessary to ask, therefore, what public activity is most likely to contribute to a significant reduction in infantile, diarrheal mortality before the great improvements in the general standard of living are achieved in the parts of the world now plagued by poverty, hunger, ignorance and disease. It seems to me that until the "have-not" nations can help themselves, the "have" nations should increase the present scope of their activities in providing appropriate food for the undernourished and malnourished infants of the world, and here science and technology could help immeasurably[46] in developing inexpensive, protein- and vitamin-rich, palatable and acceptable milk substitutes *with safe antibiotic or other bacteriostatic additives*, that will prevent the profuse growth of bacteria even under the most unhygienic conditions. Fortification of animal diets with small doses of antibiotics has proved very beneficial, and at least one controlled study on undernourished African infants has yielded similar results.[47] If malnutrition during the first 2 years of life could be largely eliminated, and breast-feeding could be supplemented and followed by feedings free from heavy bacterial growth, there is reason to expect a very significant reduction in the current, tragic infantile mortality, even though "dirty" hands might continue to transmit infectious agents for a long time to come.

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