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Diarrhoeal Disease and its Control *

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The diarrhoeal diseases are an important cause of illness throughout the world and a leading cause of death among infants and young children. Unfortunately, the greatest wealth of clinical material is found where the facilities for its study are least available. This article deals with a number of the many problems which therefore arise. The etiology is multiple, and often obscure. The relationship between the diarrhoeal diseases and malnutrition is as yet far from being elucidated. Many epidemiological questions require an answer. There is no standard treatment. Prevention, it is universally agreed, depends largely upon improvement in environmental sanitation, especially upon the provision of a safe and adequate supply of piped water, but this apparently simple measure is fraught with difficulties. Much remains to be done before anything like satisfactory control of this group of diseases can be achieved.

" Diarrhoeal disease " is a conglomerate term which covers the disease states in which diarrhoea is a major sign. High prevalence of diarrhoeal disease is associated with inadequacy of personal and public hygienic facilities, and with crowding, poverty, and malnutrition. As a public health problem, concern is chiefly with infants and young children because of the high morbidity and mortality in this age-group. Programmes for the control of diarrhoeal disease must be designed to promote (*a*) improvement of personal and public hygiene, so as to lower morbidity, and (*b*) early and effective treatment of affected individuals, so as to lower mortality.

CLINICAL CONSIDERATIONS

Pathological physiology of diarrhoeal disease

Diarrhoea is conceived of as a disturbance of intestinal motility and absorption which, once and by whatever means initiated, may become self-perpetuating as a disease through the production of dehydration and profound cellular disturbances, which in turn favour the continuing passage of liquid stools. This state of disturbed intestinal physiology is seen with greatest frequency and in greatest severity in infants and young children, particularly in association with malnutrition. The initiating factor may be considered in the vast majority of instances to be a primary infection of the intestinal tract.

Expressed in simple terms, dehydration is a state of depletion of body water and electrolytes, chiefly sodium and chloride. In severe diarrhoeal disease, fever and vomiting are frequent, and these in turn accentuate the loss of body fluids. Since diarrhoea occurs chiefly in hot weather, the losses may be still further aggravated by sweating. The almost inevitable accompanying acidosis is countered by over-breathing, which further contributes to the loss of water. The function of the kidneys, which normally maintain homeostasis of the internal environment through selective excretion of water and electrolytes, soon becomes compromised because of reduction of renal blood flow. As dehydration becomes more severe, consciousness becomes clouded and the patient appears " toxic ".

Clinical types of diarrhoeal disease

The sign " diarrhoea " varies from the passage of a slightly increased number of stools of greater than normal water content to the almost continuous passage of large quantities of liquid material. The

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associated clinical disease is to a considerable extent conditioned by the associated factors briefly outlined above, and is further affected by the quantity and composition of the fluids offered to the patient. The clinical picture may thus vary from that of an infant who is passing a few liquid stools but is otherwise not apparently ill to the child who is severely dehydrated and even comatose. The variety of terms that have been applied to different clinical forms of diarrhoea has given rise to a nomenclature based on largely unjustified etiological and pathological preconceptions, confusing enough within any one language but exasperatingly complex when similar words in related languages are used with divergent meanings. In English the word " dysentery " is used as a descriptive term for severe diarrhoea, but implies as well diarrhoeal disease due to *Shigella*. In Latin America, " enterocolitis " commonly refers to the passage of stools containing blood, pus, and mucus; " dispepsia " to diarrhoea without inflammatory elements but associated with vomiting and at times with dehydration; and " toxicosis " to a severe clinical condition characterized by clouding or loss of consciousness and cardiovascular collapse.

The clinical picture may be at best only roughly related to the type of inciting agent and there are frequent exceptions. The presence of blood and pus in the stools is classically associated with *Shigella* infection but occurs also with acute, severe *Salmonella* infection. On the other hand, diarrhoea associated with *Shigella* may be characterized by only a few watery stools. In a recently reported study of cases of diarrhoea attributed to viruses, Ramos-Alvarez & Sabin (1958) noted the presence of blood in the stools of seven of 34 patients with alleged virus diarrhoea as well as in those of one of six patients with *Shigella* or *Salmonella* infections. Enteropathogenic *Escherichia coli* infections, by way of contrast, are almost uniformly stated not to be associated with the presence of blood in the stools. An exception is a contradictory report from Chile (Rodríguez et al., 1956) attributing two-thirds of 54 cases of " enterocolitis " to infection with *E. coli*.

CLASSIFICATION OF DIARRHOEAL DISEASE

An international classification of causes of death, necessarily dependent on diagnostic terms used over the world, is at once beset by difficulties because of the variety of these terms. This is particularly true in the case of a disease complex as variable as diarrhoea, as illustrated in the foregoing section. Difficulties in classification also derive from the fact that the International Classification of Diseases offers at the same time etiological, topographical, symptomatic, and age-specific categories. Thus, diarrhoea may appear as a disease due to a specific micro-organism, a morbid condition of the gastro-intestinal tract, a symptomatic gastro-intestinal disturbance, or a disorder of early infancy.

The confusion in the classification of diarrhoeal diseases resulting from the multiple diagnostic terms used in Latin American countries has been pointed out by Verhoestraete & Puffer (1958). They note that " toxicosis " is used frequently to signify a specific clinical entity, essentially the result of severe and rapid dehydration from diarrhoeal disease. When toxicosis is stated as the cause of death for children under one year, the cause has been assigned in the International Classification of Diseases (sixth revision) to the group, " ill-defined diseases peculiar to early infancy "; and for those one year and over it has been coded to " ill-defined and unknown causes ". Thus, reported death-rates from diarrhoeal disease have been greatly influenced by the use of the term toxicosis. When to this confusion are added the facts that diarrhoea has been extensively attributed to the presence of intestinal parasites, and that in most parts of the world it is associated with severe malnutrition, it is clear that deaths due to or significantly associated with diarrhoeal disease may appear in many categories in the International Classification.

It must be appreciated that although, as has been pointed out, certain difficulties are encountered, a standard framework like the International List is necessary for world-wide study. The list is subject to continuous study, and regular revisions at 10-year intervals permit changes in accordance with medical progress.

The national mortality statistics to be cited consist of the categories designated gastritis, duodenitis, enteritis, and colitis (code numbers 543, 571 and 572 of the 1948 revision), since these constitute the great bulk of cases, are most frequently used throughout the world, and are most nearly comparable to categories 119 and 120, diarrhoea and enteritis, in the 1938 revision of the International List. While this group does not include diarrhoea of the newborn (764), diarrhoea of children two years of age and over (785.6), or deaths due to *Salmonella* (042) or *Shigella* (045), the omissions do not seriously affect the conclusions.

MAGNITUDE OF THE PROBLEM OF DIARRHOEAL DISEASE

Incompleteness and inaccuracy of statistics

National statistics, while showing that the problem of diarrhoeal disease is world-wide, none the less probably minimize the true magnitude of mortality from diarrhoeal disease, for there is gross under-reporting.

Under-reporting of births and deaths is common in most of the world. As an example, but 60 000 births of an estimated 308 000 were registered in Morocco in 1955.[1] Reporting of births and deaths was found to be grossly inaccurate by Weir et al. (1952) in Egyptian villages in 1948-49: " In the first year at Sindbis an infant mortality rate of 325.8 deaths under 1 year of age per 1000 live births and a crude death rate of 32 per 1000 population were reported. This contrasted sharply with infant death rates ranging from 80 to 161 and crude death rates from 12 to 23 in the other four villages . . . which were remote from the health center." While the reported birth-rate ranged from 44 to 50 births per 1000 population, the true birth-rate ranged from 56 to 61 per 1000.

A more recent detailed study of Egyptian communities in which registration is required by law revealed failure to register up to 71% of births, 77% of deaths, and 91% of infant deaths.[2] The degree of under-registration increased with the distance from the local health centre, at the most but a little over three kilometres. These Egyptian data, compiled in areas of high diarrhoea morbidity and mortality, show the inevitable concomitants: high birth-rate, high over-all mortality, and high infant mortality.

Duly reported deaths may be incorrectly certified as to cause. A major potential source of inaccuracy is the certification of deaths in many countries of the world by non-medical registrars. Of 25 countries in the Americas supplying statistical information for the XV Pan American Sanitary Conference (Pan American Sanitary Bureau, 1958), 13 reported medical certification of fewer than 60% of deaths in 1955 or 1956; the percentages of medical certification ranged as low as 12.1% in El Salvador and 13.0% in Guatemala.

Some of the possible errors in non-medical certification are illustrated by data from the Institute of Nutrition of Central America and Panama (INCAP) showing the discrepancies in a series of 222 deaths between causes of death reported by lay registrars and by a trained visitor who interviewed the dead child's family within two days of demise (Béhar et al., 1958). The official statistics showed 21 deaths due to disease of the digestive system, 58 to intestinal parasites, none to kwashiorkor, and 41 to ill-defined and unknown causes. After investigation, 37 deaths were considered due to diseases of the digestive system, none to intestinal parasites, 40 to kwashiorkor, and 17 to ill-defined causes. Thus, the diarrhoeal diseases and deficiency states would appear to be much more important causes of mortality than is apparent from official statistics, with intestinal parasites grossly overstated.

Even death certification by physicians does not ensure accuracy. The reported percentage of infant deaths in Warsaw attributed to diarrhoea rose abruptly from 19% in 1949 and 1950 to 39% in 1951, following a review by W. Winnicka [3] of the records of all infant deaths in 1951 (Bielicka et al., 1956).

Mortality

Notwithstanding difficulties in classification, under-reporting, and inaccuracies in certification of cause of death, statistics from all over the world document the pre-eminent position of diarrhoea as a killer of infants and young children. Indeed, in the light of the foregoing discussions, the reported statistics are all the more impressive. Representative data follow.

Latin America. The magnitude of the problem in the western hemisphere has been clearly presented by Verhoestraete & Puffer (1958). Diarrhoeal disease was found to be the leading cause of death in eight of the 17 countries forwarding data for the XIV Pan American Sanitary Conference in 1954, and among the five principal causes in four other countries of the Americas. Additional evidence regarding the importance of diarrhoeal disease was presented in an analysis of the principal causes of death in infancy (under one year) and in early childhood (one to four years) in ten selected countries. Diarrhoea was noted to be the principal or a major cause of death in most, with rates as high as 150 times the comparable rates in the USA.

The staggering toll of lives claimed by diarrhoea in Latin America is vividly illustrated by reports from small communities. In the " house-to-house "

[1] Youssef ben Abbes—unpublished information.

[2] Poulton, E. M. (1957) *The status of maternal and child health in the Eastern Mediterranean and adjacent areas* (unpublished working document of the WHO Regional Office for the Eastern Mediterranean).

[3] Personal communication, 1958.

TABLE 1
MORTALITY FROM DIARRHOEA IN JOHANNESBURG, 1951 [a]

Population		Crude mortality		Diarrhoea deaths			
		No. of deaths	Rate per 1000	Total	Under 1 month	Under 1 year	Under 2 years
African	355 000	5 658	15.6	1 152	84	829	1 064
European	311 000	2 715	8.15	29	—	—	24

[a] Based on data from Kahn (1957).

death investigation by INCAP mentioned above (Béhar et al., 1958), diarrhoea was found to account for at least one-sixth of the deaths in children under 15 years of age in a restricted Central American area. In a small town in Chile, in 1956, there were 100 infant deaths, of which 37 were due to diarrhoea (Brand & del Villar, 1957).

South Africa. Table 1 shows that diarrhoea accounted for one-fifth of all deaths in the socio-economically less favoured population at Johannesburg. In this city one African infant in 10 succumbed to a diarrhoeal disorder in the first year of life. In Cape Town, in 1954-55, 45% of the total non-European infant deaths were due to diarrhoea (Truswell, 1957). The vast majority of all deaths due to diarrhoea, in both African and European populations, occurred before two years of age.

Eastern Mediterranean countries. In Egyptian districts with health bureaux, in 1949, an infant mortality rate of 134 per 1000 was registered (Higgins et al., 1955a). Of 64 914 deaths with recorded causes (58% of the total reported deaths), 35 083, over half, were due to " diarrhoea and enteritis ".

The importance of diarrhoea, as compared with other leading causes of death in infancy and childhood, is illustrated by statistics summarized in Table 2, gathered for the Seminar on Maternal and Child Health in the Eastern Mediterranean Region held in Cairo, November-December, 1957, under the sponsorship of the WHO Regional Office for the Eastern Mediterranean in collaboration with the Egyptian Government and UNICEF.

Relation of mortality to age. Reported hospital statistics for children admitted with diarrhoea in areas of high morbidity show the mortality to be inversely rated to age. In Ceylon, in 1950-51, the case fatality rate was 37% in children under two years of age and 25% in older children (De Silva et al., 1953). In Mexico, in 1948-50, the case fatality rate for infants under one month of age was 60% as opposed to an over-all rate of 28.3% in children under two (De la Torre, 1956). In Chile, in 1955-56, the case-fatality rate for infants less than a month old was five times that of older infants (Costa & Arcayo, 1956).

Morbidity

Where mortality from diarrhoea is high, morbidity will, of course, also be high. As mortality becomes lower, morbidity figures assume progressively greater importance in evaluation of the problem of diarrhoeal disease.

Hospital statistics. To a certain extent hospital statistics reflect the relative importance of diarrhoea in a community. Representative reports from

TABLE 2
LEADING CAUSES OF DEATH IN CHILDREN IN TWO EASTERN MEDITERRANEAN AREAS [a]

Area and year	Age-group	Causes of death		
		Digestive	Infectious	Respiratory
Thessaly, Greece 1950-55	0-30 days	8.3%	4.2%	16.1%
	1-12 months	32.7%	11.9%	27.1%
	1-5 years	25.1%	26.0% [b]	27.6%
Tunis 1953-55	Under 1 year	38%	9%	19%
	1-2 years	44%	23%	22%
	2-9 years	17%	38%	16%

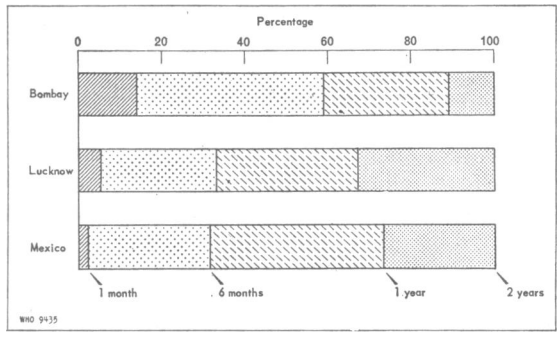
[a] Based on information made available to the WHO Regional Office for the Eastern Mediterranean by C. Saroglou in respect of Thessaly and M. Slim in respect of Tunis.
[b] Includes some digestive disturbances.

individual hospitals show almost half the admissions of children in Colombo, Ceylon, in 1950-51 to have been for intestinal parasitism or diarrhoea (De Silva et al., 1953); in Beirut, in 1954-55, one-third were for diarrhoea.[1] Also in Beirut, of over 60 000 sick children seen at polyclinics, 18%-35% complained of diarrhoea, the higher percentages during the summer months. In the municipal hospitals of New York City, in 1952, by way of contrast, fewer than 2% of children's admissions were for diarrhoea (Fraenkel & Erhardt, 1955).

Hospital statistics show that of all children admitted with diarrhoea, 70%-85% are under two years of age. Actually the peak incidence of diarrhoea morbidity as measured in this way is within the first year of life. Fig. 1 illustrates this in statistics reported from various parts of the world, from which one may conclude that, of hospitalized children under two years of age with diarrhoea, three-fourths are less than one year old, more than one-third are less than six months old, and even the newborn period has appreciable representation.

FIG. 1

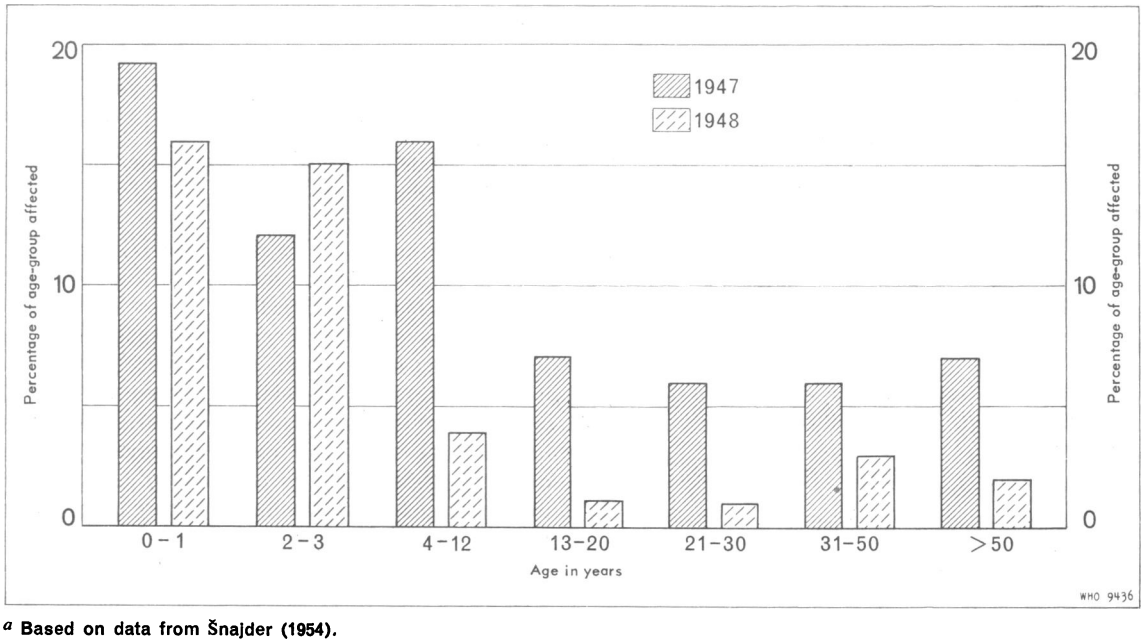
AGE DISTRIBUTION OF DIARRHOEA CASES IN HOSPITALIZED CHILDREN UNDER TWO YEARS OLD IN BOMBAY,[a] LUCKNOW[b] AND MEXICO[c]



[a] Data from Pavri (1953).
[b] Data from Sharma & Gupta (1954).
[c] Data from De la Torre (1956).

FIG. 2

INCIDENCE OF DYSENTERY BY AGE IN SERBIAN EPIDEMICS [a]



[a] Based on data from Šnajder (1954).

Physicians' reports. Reporting of " dysentery " by physicians is obviously less complete and reliable than hospital studies. In Serbia (Šnajder, 1954), in 1947 and 1948, a public health team discovered 231 cases of dysentery in epidemics from which but 49 cases had been reported. The Serbian experience illustrates the importance of the house-to-house survey in the acquisition of valid morbidity data.

[1] C. J. Ross-Smith—personal communication, 1955

The results of this particular survey are summarized in Fig. 2. They illustrate, as do mortality figures, that diarrhoeal disease chiefly affects children.

Home visits. The best morbidity data are derived from weekly or bi-weekly visits to all homes in an area for a period of many months or years. This technique, extensively applied in the USA (Watt & Hardy, 1945; Hardy & Watt, 1948), has more recently been employed in Egypt, Israel, and Guatemala. There follows a summary of some of the data from these areas of high diarrhoea morbidity.

In a group of 82 Egyptian village children under five years of age appraised clinically weekly for one year in 1953-54, the average number of episodes of diarrhoea experienced per child progressively decreased from 3.6 for children in the first year of life to 1.7 for children in the fifth year (Table 3) (Higgins et al., 1955a). One child had seven episodes during the year, while only five children were free of diarrhoea.

In a similar study of four months' duration in 1954, in Israel, the average child less than three years of age was found to be ill with diarrhoea about one-tenth of the time (Yekutiel et al., 1958). The data, showing a lower incidence of diarrhoea in infants than the Egyptian study, are seen in Table 4.

According to unpublished information from the Pan American Sanitary Bureau, home visits made every two weeks for one year in 1956-57 in two villages in Guatemala with a combined population of 1159 disclosed 469 cases of diarrhoea in the total population, an incidence of 40.5%. Incidence was highest in the 6-11 months age-group (five cases per child) and in the 12-23 months age-group (three cases per child); 69% of the total cases occurred in children less than five years of age. Only 17% of children less than two years of age were free of diarrhoea during the year, while 54% of the 2-4 year age-group had no diarrhoea.

TABLE 3

INCIDENCE OF DIARRHOEA IN EGYPTIAN CHILDREN, BY AGE, DURING A 12-MONTH PERIOD IN 1953-54 [a]

Age (months)	Number of children	Average number of diarrhoeal episodes per child
0-12	13	3.6
13-24	24	3.0
25-36	16	2.6
37-48	22	2.6
Over 48	7	1.7
All ages	82	2.8

[a] Reproduced, by permission, from Higgins et al. (1955a).

TABLE 4

INCIDENCE OF DIARRHOEA IN ISRAELI CHILDREN, BY AGE, DURING FOUR SUMMER MONTHS IN 1954 [a]

Age	Number of children	Average number of diarrhoeal episodes per child
0-5 months	130	0.95
6-11 months	109	2.38
1-2 years	226	2.08
2-3 years	180	1.05
Exact age unknown	4	
All ages	649	1.62

[a] Reproduced, by permission, from Yekutiel et al. (1958).

ETIOLOGY

Basic considerations

From epidemiological considerations there can be little doubt that the great majority of cases of diarrhoea are due to infectious agents. Aside from relatively infrequent cases of "parenteral" infection, to be discussed later, the agents of disease infect the gastro-intestinal tract directly.

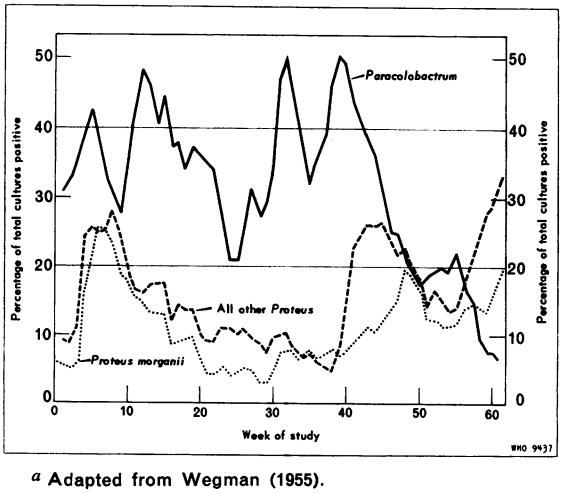
Classically, establishment of an etiological relationship between an organism and disease is based on fulfilling Koch's postulates. Properly applied epidemiological studies may, however, be equally useful. One may thus suspect an organism as a cause of disease if it is consistently found more often among persons ill with the disease than among well persons of the same age living under the same conditions. A variant of this principle was used by Watt & Walton (1949) in a study to evaluate the importance of the organism formerly designated *Shigella alkalescens*. In a prolonged survey with weekly observations, the prevalence of various organisms in rectal swab cultures of children was related to the presence or absence of acute diarrhoeal disease in their families. It was shown that diarrhoeal disease occurred no more frequently in families from which *Sh. alkalescens* was isolated than in

families with intestinal flora containing no known pathogens. By contrast, the attack rates were twice as great or more in families from which *Sh. paradysenteriae* Flexner sp., *Sh. sonnei*, or *Salmonella* species were cultured. It was concluded that *Sh. alkalescens* could not be incriminated as a cause of diarrhoea any more than organisms normally considered saprophytic.

Stool cultures taken from a population in which diarrhoea is prevalent demonstrate the characteristic flora of the moment, but may have in themselves little further significance. Studies in a large nursery for premature infants in New Orleans (Wegman, 1955) showed that the pattern of intestinal flora was constantly changing—now one organism predominating, now another. The changing prevalence rates of paracolon bacilli and *Proteus* over a 60-week period are illustrated in Fig. 3. During this time the prevalence rate of *Pseudomonas* fluctuated in a manner similar to those of the other organisms, although it did not exceed 15%. There were cases of diarrhoea from time to time throughout the study, never, however, in epidemic proportions. In the absence of mass epidemiological data, the assumption might be made at a time of high prevalence of one of these organisms that cases of diarrhoea were due to infection with that organism. The data show, however, that such an assumption, while not excluded, would have little validity.

FIG. 3

THREE-WEEK MOVING AVERAGE PERCENTAGE OF ANAL CULTURES FROM PREMATURE INFANTS POSITIVE FOR *PROTEUS* SPECIES AND PARACOLON BACILLI, NEW ORLEANS, SEPTEMBER 1948 TO DECEMBER 1949 [a]



[a] Adapted from Wegman (1955).

Recently, sensitive immunological techniques have been developed and used to demonstrate, through rise in antibody titre, that persons have been infected by certain organisms recovered from the stool during a clinical attack of diarrhoea (Neter & Suskind, 1958). The incrimination of an infecting agent does not necessarily prove its causative role in the concomitant clinical illness, however, without application of the epidemiological principle enunciated above. Insistence on the identity of immunological response and clinical illness in the case of organisms from the complex and immunologically interrelated group of the *Enterobacteriaciae* is particularly apt to be misleading.

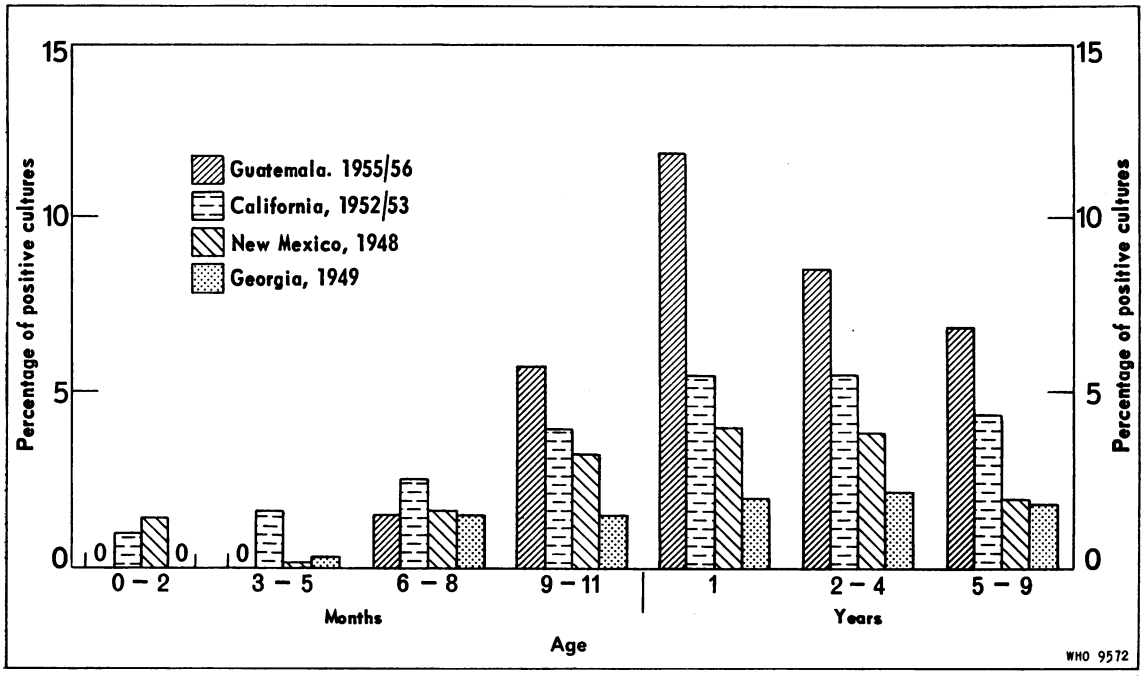
Bacterial agents of diarrhoeal disease

Shigella. Since *Vibrio comma*, formerly widespread, is now limited to relatively few areas, *Shigella* has been recognized as the chief pathogenic agent in areas of high diarrhoea morbidity. Seventy-three of 75 Egyptian children were shown to be infected in the course of the year 1951-52, on the basis of rectal swab cultures made at weekly intervals (Floyd, 1954). The average number of new infections during the year was 2.5 per child. About one-third of the infections were associated with diarrhoea, and the prevalence of positive cultures closely paralleled the prevalence of diarrhoea. This close association is generally recognized, and as a consequence the determination of *Shigella* prevalence has been widely employed as an indicator in studies of the epidemiology of diarrhoea.

Infection with *Shigella* is uncommon in the first six months of life, after which prevalence of the organism in rectal swab cultures rises rapidly to a peak in the second year of life, thereafter falling gradually. This trend is shown in Fig. 4, which summarizes observations in communities in the USA and Guatemala. The apparent resistance of young infants to infection with *Shigella*, even in an area of high prevalence of the organism, is shown in Fig. 5 (Floyd et al., 1956). Over 60% of children over six months of age had become infected with *Shigella* in a 32-week period of study in an Egyptian community before the first recovery was made in the "1-6 month" group, in which all infants had actually become older than six months when *Shigella* was first recovered.

In contrast to the low incidence of *Shigella* infection in Egyptian infants under six months, that of diarrhoeal disease was actually higher than in older children (Table 5) (Floyd et al., 1956).

FIG. 4
PREVALENCE OF *SHIGELLA* IN RECTAL SWAB CULTURES OF CHILDREN IN AREAS OF MODERATE AND MODERATELY SEVERE DIARRHOEA MORBIDITY [a]



[a] Based on data from Beck et al. (1957).

Obviously the diarrhoea of the infants must have been in large part due to other agents or factors.

When an infant does become infected with *Shigella*, the likelihood of his having clinical disease is great. Observations made by Watt & Hardy (1945) suggest a ratio of clinical disease to infection of at least 0.9 in infants; the ratio gradually falls, becoming about 0.4 after two years of age and about 0.25 in older children and adults.

Data from reported epidemics of diarrhoeal

TABLE 5
RELATION BETWEEN *SHIGELLA* INFECTION, DIARRHOEA, AND AGE DURING 32 WEEKS OF OBSERVATION; EGYPT, 1953 AND 1954 [a]

Year	Infants under six months of age				Older children			
	Number observed throughout study	*Shigella* isolations/ total cultures		Incidence of diarrhoea (cases per 100)	Number observed throughout study	Age range	*Shigella* isolations/ total cultures	Incidence of diarrhoea (cases per 100)
		1 month old	1-5 months old					
1953	21	0/75	1/294	—	189	6 months to 5 years	204/3 230	—
1954	36	0/105	1/324	10.1	102	1-6 years	70/1 553	7.4

[a] Based on data from Floyd et al. (1956).

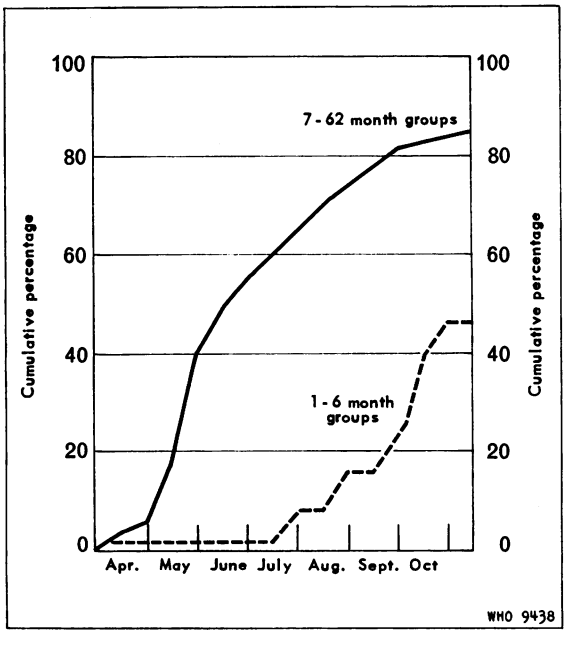
TABLE 6
RELATIONSHIP OF BACTERIAL FLORA TO AGE IN SPORADICALLY OCCURRING DIARRHOEA

Area, year and source	Characteristics of population	Number of cases	Age-group	Percentage of recoveries of		
				Shigella	*Salmonella*	Enteropathogenic *E. coli*
Mexico, 1957 (Olarte et al., 1957)	Brought to out-patient department	107	Less than 1 month	0	1	19
		277	2-6 months	11	3	19
		282	7-12 months	23	5	8
		136	13-24 months	30	4	8
London, 1952-54 (Thomas & Charter, 1956)	Children taken ill at home	306	0-1 year	6.2	3.3	13.1
		371	1-2 years	7.5	2.7	10.2
		270	2-3 years	14.4	3.7	3.7
		188	3-4 years	21.2	3.7	1.6

disease reviewed by Watt et al. (1953) indicate that about two-thirds of cases can be attributed to infection with *Shigella*. Undoubtedly the incidence of *Shigella* infection is even higher, but the organism soon dies once it has left the body and even the best of bacteriological techniques, employing cultures from rectal swabs rather than stools, will fail to recover it from all infected persons.

In sporadically occurring cases of diarrhoea *Shigella* is recovered less frequently (Table 6).

FIG. 5
CUMULATIVE PERCENTAGE OF CHILDREN INITIALLY INFECTED WITH *SHIGELLA*; EGYPT, 1953 [a]



[a] Reproduced, by permission, from Floyd et al. (1956).

Salmonella. *Salmonella* is distinctly second in importance to *Shigella* as a cause of human diarrhoeal disease (Tables 6 and 7). Numerous species are involved, with *S. typhimurium* predominating throughout the world. In contrast to *Shigella*, the rate of infection is highest in young infants. The data of Fig. 6 show infection with *Salmonella* to have been twice that with *Shigella* in Texas infants, whereas *Shigella* prevalence led by 7 to 1 in children one year of age and older. Clinical disease due to *Salmonella* is also encountered chiefly in infants. In a 21-year study of 100 cases seen in a southern United States hospital (Clyde, 1957), 92 were found to be under six years of age, 69 under one year, and 46 under six months. The peak age incidence was four months. In a study of 40 cases of salmonellosis in children in Jamaica (Jelliffe et al., 1954), in 1952-53, all cases were found to lie between two and 28 months of age, the average age being 9-10 months. The clinical expression of a *Salmonella* infection is usually gastro-enteritis, but typhoid-like infections occur with some frequency and there are rare illnesses such as meningitis and osteomyelitis.

Typhoid fever, caused by *S. typhosa*, occasionally presents with diarrhoea as a sign, but just as fre-

quently with constipation. It is a disease of lower mortality than diarrhoeal disease and affects chiefly older children. Of 205 cases of typhoid fever in children up to 12 years of age (Taneja & Ghai, 1957), there were but 18 under three years of age, the youngest of whom was nine months old; about two-thirds of the children were over six years of age.

Enteropathogenic Escherichia coli. A large number of hitherto unexplained hospital epidemics of infantile diarrhoea have in the past decade been shown to be due to a variety of types of *Escherichia coli*. In nurseries, the presence of enteropathogenic *E. coli* in an infant's stool is usually associated with diarrhoea, and it is infrequently recovered from well infants. It is distinctly less prevalent in older infants,

TABLE 7

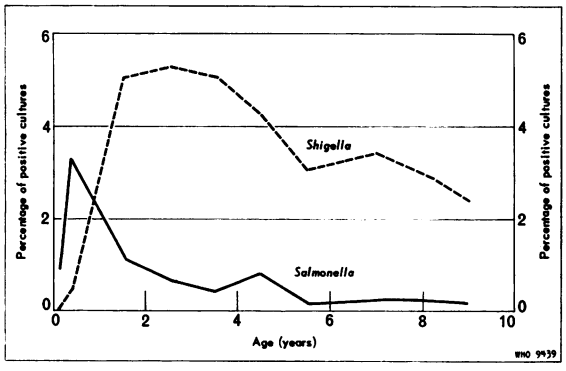
ISOLATION OF INTESTINAL BACTERIAL PATHOGENS FROM CHILDREN BY HOSPITAL LABORATORIES

Area and year	No. of cultures	Age and characteristics of population	Percentage of recoveries of			
			Shigella	*Salmonella*		Enteropathogenic *E. coli*
				Other than *typhosa*	*typhosa*	
Northern France, 1952-56 [a]	380	Hospitalized children with diarrhoea, 1 day-4 years old	2.6	3.9		52.6 (203/216 under 1 year)
Morocco, 1956 [b]	109	Out-patients with diarrhoea; 78 hospitalized	2	5.5		50
Uganda, 1957 [c]	187	100 hospitalized children with diarrhoea, age 10 days-4 years, 67% 5-18 months	13	3		1.6
Tunisia, 1956 [d]	400 420	Cases of diarrhoea in summer Cases of diarrhoea in winter	12 5.5	3.3 4	0.25 1.75	0.25 0
Ceylon, 1950-51 [e]	510	Hospitalized children with diarrhoea	0	22.8	8.6	—
Chile, 1955-56 [f]	more than 134	134 hospitalized children with diarrhoea, age 1-2 years, 86% less than 1 year old	9.3	0		36
Venezuela, before 1955 [g]	95	Sporadic cases of diarrhoea less than 1 year old	4	4		7
Guatemala, 1956-57 [h]	102	Children with diarrhoea attending municipal clinics	16	2		12 (" in the very young infants and children ")
Mexico, 1950-54 [i]	13 545	In- and out-patients with various illnesses, 55% less than 2 years old	10.7	4.1	1.6	5.4
Mexico, 1955-56 [j]	497	Hospitalized children with severe diarrhoea	12.9	1.8		30
USA, 1955-56 [k]	153	Out-patients with diarrhoea, age 1-4 years, 73% less than 1 year; 53% hospitalized	9			30

[a] Buttiaux et al. (1956).
[b] Drieux & Raynaud de Fitte (1957).
[c] Wilson & Luder (1957).
[d] Huet (1957).
[e] De Silva et al. (1953).
[f] Costa & Arcayo (1956).
[g] Briceño Iragorry (1955).
[h] Information made available by the Pan American Sanitary Bureau in 1958.
[i] Olarte & Joachin (1957).
[j] Valenzuela (1956).
[k] Ramos-Alvarez & Sabin (1958).

FIG. 6

RELATIVE PREVALENCE OF *SHIGELLA* AND *SALMONELLA* IN RECTAL SWAB CULTURES OF TEXAS CHILDREN, BY AGE [a]



[a] Based on data from J. Watt—personal communication, 1948.

infection of whom is less likely to be associated with diarrhoea. The observations in Table 8, made in Stockholm hospitals and children's institutions, are typical (Laurell, 1956).

While the causative role of *E. coli* types has been established beyond reasonable doubt in institutional outbreaks, their importance in the community remains to be established. Their association with sporadic cases of diarrhoeal disease has been reported from all over the world (Table 7) and their prevalence is greatest in young infants (Table 6). The earlier-cited epidemiological criterion of their relevance to the clinical illness is, however, yet to be satisfied. Present observations are in conflict. A Finnish community study (Hallman et al., 1954) revealed enteropathogenic *E. coli* types in 21 of 116 infants with mild diarrhoea and but two of 100 healthy controls. In contrast, in the USA *E. coli* types were recovered in 30% of 153 cases of diarrhoea and in 20% of concurrent controls (Ramos-Alvarez & Sabin, 1958). Serotype O111 was, to be sure, six times as frequent in the group with diarrhoea. In a South African study (Coetzee & Pretorius, 1956), the frequency of recovery was 19% in 108 children with kwashiorkor, most of whom had diarrhoea, and 17% in 69 controls.

Recognition of enteropathogenic strains of *E. coli* is complicated by the fact that there is no simple way to identify suspected colonies of the strains under study. The percentage of positives increases as the number of colonies picked for study increases up to 10. Thus, large-scale studies involve a great many laboratory examinations.

TABLE 8

RELATION BETWEEN INFECTION WITH ENTEROPATHOGENIC *E. COLI*, DIARRHOEA, AND AGE; STOCKHOLM, 1949-52 [a]

Age (months)	Number of infants harbouring *E. coli* O111:B4	
	Healthy carriers	Infants with diarrhoea
0-3	4	40
3-6	5	28
6-12	6	21
12-18	10	10
Over 18	10	5

[a] Reproduced, by permission, from Laurell (1956).

Staphylococci. Staphylococci may cause diarrhoea in hospitalized persons along with other serious manifestations of infection, and in nurseries for the newborn this may take on the appearance of an epidemic (Smith, 1956). The emergence of *Staphylococcus* as a pathogen may be related to the use of antibiotic agents to which it is resistant, so that the population of competing sensitive bacterial flora is greatly diminished (Dearing, 1956). From the community standpoint, *Staphylococcus* would appear to have little importance as an agent responsible for diarrhoeal disease.

Distribution of bacterial agents of diarrhoeal disease. *Shigella*, *Salmonella*, and enteropathogenic *E. coli* are prevalent throughout the world (Table 7). Comparison of their relative importance in different areas is not possible because of variation among laboratories and of the tendency of investigators to concentrate on the recovery of but one organism.

Intestinal parasites and diarrhoea

Intestinal parasites are an important cause of morbidity in the world, but do not play an important role in the causation of diarrhoea. In areas of high morbidity, such as Egypt, where, for instance,[1] 363 of 367 single examinations of stools from children in a community were positive for at least one parasite, no relation could be detected—in contrast to *Shigella*—between the prevalence of parasitic infection and that of diarrhoeal disease.

[1] Information taken from Research Report NM 005 050.51.02 of United States Medical Research Unit No. 3, Cairo, United Arab Republic (W. H. Wells & W. Blagg).

To the extent that heavy parasitism may be associated with malnutrition, however (see below), it may have an indirect relation to diarrhoeal disease.

Diarrhoea due to viruses

In view of the fact that with the best of bacteriological techniques about two-thirds of cases of diarrhoea fail to have evidence of a bacterial causal agent, the possible etiological role of viruses has been suspected for many years. Support was first found in institutional outbreaks caused by filtrable agents, studied by Light & Hodes in 1943 and by Buddingh & Dodd in the following year. Since then four filtrable agents have been recovered in the USA (Reimann et al., 1945; Gordon et al., 1947; Jordan et al., 1953) and Japan (Kojima et al., 1948) from patients in institutional and widespread community epidemics of gastro-enteritis and diarrhoea, which have been in general mild but associated at times with dehydration in infants. These four agents have reproduced the disease in human volunteers, with production of immunity.

Since the development and improvement of tissue culture techniques, interest has naturally focused on the group of enteroviruses, including poliomyelitis, Coxsackie, and ECHO viruses.

In the USA, Eichenwald et al. (1958) have reported an epidemic of diarrhoea due to ECHO virus type 18 in a nursery for the premature, followed by an epidemic due to the same virus in a nursery occupied by older children. The virus was not present in the nurseries before or after the epidemic. During the epidemic it was present only in the stools of affected infants, all of whom showed a rise in antibody. The data conclusively support the hypothesis that ECHO type 18 caused this nosocomial epidemic, but leave unanswered the question whether enteroviruses are of importance in the community.

More recently, Ramos-Alvarez & Sabin (1958) have reported the isolation of pathogenic bacteria and a variety of enteroviruses from infants and children with diarrhoeal disease studied during the summers of 1955 and 1956. Of the total patients 73% were less than one year of age, the rest between one and four years; 53% were hospitalized. ECHO viruses were recovered six times as frequently in the children with diarrhoea as in 100 concurrent control children. Coxsackie viruses and polioviruses were similar in prevalence in both groups. All children exhibited a rise in antibody titre to the viruses they harboured. *Salmonella* and *Shigella* were also isolated, at times in conjunction with viruses. While it is likely that ECHO viruses caused diarrhoea in some of these infants, proof of their pathogenicity must await more detailed epidemiological study.

" Parenteral diarrhoea "

The possible role of infections elsewhere than in the intestinal tract in the production of diarrhoea is not well understood. It is undoubtedly an overrated clinical concept. In areas of high over-all morbidity the patient with diarrhoea frequently suffers from an infection elsewhere in his body at the time the symptom, diarrhoea, brings him to the hospital.

Short of careful epidemiological observations, the best support for the concept of parenteral diarrhoea is found in a South African study (Kahn, 1957) in which 200 cases of diarrhoea of varying severity, treated in a hospital out-patient department during the summer months, were compared with the same number receiving treatment during the winter months. In the summer *Shigella* and *Salmonella* were isolated 45 times and there were but 64 instances of concurrent respiratory infection. In the winter, on the other hand, there were but 16 isolations of *Salmonella* and *Shigella*, while in 164 patients there was an associated respiratory infection which usually started before the onset of the diarrhoea. It is not unreasonable to assume, however, that " respiratory infection " and diarrhoea may both have been signs of the same systemic illness.

Whatever the relationship may be between infection elsewhere in the body and diarrhoea, the prognosis for doubly afflicted children is understandably poor. De la Torre (1956), in reporting an over-all mortality of 25.3% from diarrhoea in hospitalized infants under two years of age, noted the mortality of 189 infants with accompanying bronchopneumonia to be 62.4%.

EPIDEMIOLOGY

Anal-oral spread

The mechanism of propagation of intestinal pathogens may be summed up in the expression, " anal-oral spread ". The opportunities for humans to ingest faeces are, of course, greatly facilitated by close personal contact, lack of knowledge of personal hygiene, faulty preparation of food, contaminated water supply, intimate association with animals, and lack of protection against flies.

In areas with poor environmental sanitation, diarrhoeal disease and prevalence of *Shigella* are at

a peak during the summer months. Under good environmental sanitary conditions, the summer-time increase in prevalence of diarrhoeal disease disappears. Indeed, in a long-term United States family epidemiological study the peak incidence of gastro-intestinal upsets has been observed to be in November (Dingle et al., 1953). In England a slight winter-time increase in the frequency of shigellosis has been attributed in part to the longer survival of *Shigella* in public places during cold weather, for instance, on toilet seats (Hutchinson, 1956).

The role of hand-to-mouth contact becomes relatively more crucial as community sanitary measures improve. In Southampton, England, *Shigella* was cultured from toilet seats and pupils' hands in school epidemics (Hutchinson, 1956). Studies indicated the probable mechanisms of contamination of toilet seats, demonstrated the lack of protection to the hands afforded by toilet tissue, and called attention to the frequency with which children would suck their fingers, even before their dutiful hand-washing following use of the toilet. A Scottish report of an institutional epidemic due to drug-susceptible *Shigella* notes that failure was most common in infants under one year of age. "Frequent reinfection from faeces, contaminated hands or linen, is considered to have been an important factor in failure of cure in this age group" (Johnson & Landsman, 1957).

Intimate personal contact enhances the spread of enteric infection despite adequate community health protection. Watt et al. (1953) noticed in their California study a distinctly higher incidence of *Shigella* infections in infants with infected siblings than in only children. In a United States family epidemiological study (Hodges et al., 1956), gastro-intestinal symptoms were more than twice as frequent in the late pre-school and early school years as in infancy and adulthood, presumably reflecting the effects of closer and more frequent exposure to other children.

Size of infecting dose

In addition to *qualitative* environmental factors, the importance of *quantity* of the infecting dose of organisms deserves particular emphasis. The application of this concept is well illustrated in the contrast between the violent reaction of adults, a relatively insusceptible population, to large doses of *Salmonella* in episodes of poisoning by contaminated foods, and the lack of diarrhoeal disease observed in a highly susceptible population, premature infants in a nursery in New Orleans into which *Salmonella tennessee* was introduced by six premature infants transferred from another hospital (Watt et al., 1958). In the ensuing many weeks more than 30 subsequent isolations were made from other infants, nursery personnel, and facilities, such as weighing scales and even a freshly prepared bassinet. During this entire period no infected infant had diarrhoea. The numbers of organisms were never large and most of the recoveries would not have been made unless special cultural techniques had been used. Presumably, thanks to constant precautions on the part of nursing personnel—notably scrupulous attention to careful hand-washing—the infants were infected with numbers of organisms so small that clinical disease did not appear.

Animal reservoirs of enteric pathogens

A word is in order about the special epidemiological characteristics of *Salmonella*. In contrast to *Shigella*, this is basically an animal pathogen and, with the exception of *S. typhosa*, infection of the human organism may be considered accidentally related to our association with animals and animal food products. It thus tends to be prevalent in food handlers and in persons living in association with domestic animals. It has been recovered from all animal species cultured, including a pet armadillo (Watt & DeCapito, 1950) and a pet tortoise (Thomas 1957); the last is known to have initiated outbreaks of diarrhoeal disease in human contacts.

Once introduced into the human population, *Salmonella* is spread by the same mechanisms as *Shigella*, as illustrated by numerous reported hospital nursery outbreaks of diarrhoea due to *Salmonella*.

Though enteropathogenic *E. coli* types are widely prevalent in cattle, an animal reservoir appears not to be of epidemiological importance for this pathogen.

Comment on relation between pathogenic agents and diarrhoeal disease

Shigella is presumably the agent chiefly responsible for diarrhoeal disease in children and adults in areas of moderate to severe diarrhoea morbidity, and is, under these conditions, a sensitive indicator both of personal and community sanitation and of the prevalence of diarrhoeal disease. Information concerning the agents responsible for diarrhoea in infants, particularly in the first six months of life, is incomplete. Presumably diarrhoeal episodes in this

age-group are of infectious origin and come about through the same epidemiological means as *Shigella* infections, since the frequency of diarrhoea in young infants parallels the incidence of diarrhoea in the community. The infecting agents most likely to be causative, on the basis of present information, are *E. coli* types and viruses.

RELATION OF MALNUTRITION TO DIARRHOEAL DISEASE

The world's literature emphasizes the almost universal association of malnutrition, frequently severe, with diarrhoeal disease. Typical is a South African analysis of 100 consecutive cases of diarrhoea: 12 of 17 undernourished children over five months of age had had previous attacks of diarrhoea, as opposed to but nine of 47 adequately nourished patients in the same age-group (Truswell, 1957). The reported experience in communities in Egypt (Higgins et al., 1955a), however, where diarrhoea is rampant and malnutrition is not common, shows that malnutrition is not an obligatory concomitant of diarrhoea and suggests the desirability of attempting to define their interrelationships in an effort to view them as separate problems. Answers may be sought to the following questions: 1. Does malnutrition predispose to gastro-intestinal infection? 2. Is diarrhoea a sign of severe malnutrition? 3. Does diarrhoea lead to malnutrition?

Does malnutrition predispose to gastro-intestinal infection?

On theoretical grounds, malnutrition should indeed greatly lower the resistance of the host to infection (Chandler, 1957). This is most easily illustrated in consideration of deficiency of protein, which is necessary for tissue repair, antibody production, and leucocyte production. Since the parasite is in competition with the host for food, lack of protein may react adversely on the parasite as well. While the parasite may suffer more than the host when a specific dietary essential, such as a vitamin, is lacking, the net balance in malnutrition is usually distinctly to the disadvantage of the host. Well nourished animals tend to have relatively few ectoparasites. Malnourished dogs have been observed to deliver hookworms promptly on being given an adequate diet. Chandler (1953b) comments: " One may go so far as to say that severe chronic intestinal nematode infections are unusual, if not impossible, in an otherwise normal host on an adequate diet."

Despite plausible theoretical preconceptions, however, there is as yet no evidence to support the thesis that enteric infection occurs with increased frequency in malnourished persons in areas in which both malnutrition and diarrhoeal disease are prevalent. On the contrary, in patients with the most extreme form of protein malnutrition—kwashiorkor—enteric infection with bacteria and parasites has been encountered no more frequently than in better nourished subjects (Scrimshaw et al., 1956). Observations by Coetzee & Pretorius (1956) in a South African hospital are typical: a search was made for enteric bacterial pathogens in 108 out-patients with kwashiorkor aged six months to four years, most of whom had diarrhoea of short duration, and 69 concurrent controls, without gastro-intestinal complaints, in the same age-group. The percentage of pathogens isolated was 28 in the kwashiorkor group and 21 in the controls.

A sociologist's observation [1] of the common ingestion of dirt from the household floor by children in Guatemala leads one to wonder what the relative frequency of *pica*, a potential mode of infection, may be in malnourished, as compared with well nourished, children.

Is diarrhoea a sign of severe malnutrition?

The data reported by Coetzee & Pretorius, cited above, can logically lead one to conclude, with the authors, that bacterial pathogens did not play an important causative role in the diarrhoea of their patients with kwashiorkor. Indeed, it is generally accepted—without adequate epidemiological evidence, however—that recurrent and chronic diarrhoea is a *sign* of this syndrome. Diarrhoea has been observed by Jelliffe, Bras & Stuart (1954) to occur with comparable frequency in kwashiorkor (protein malnutrition) and marasmus (general caloric under-nutrition).

Since morbidity and mortality from diarrhoea are at their peak at an earlier age than that at which kwashiorkor occurs with greatest frequency, conclusions based on observations of the older group do not necessarily apply to younger subjects, most of whom present less striking evidences of malnutrition. Interesting light has been shed on this and other problems by the recently published report of a 15-months' clinical, bacteriological, and

[1] Unpublished report (1957) by J. D. Freedman on social factors in the etiology of infantile *pluricarencial* syndrome (kwashiorkor) in Guatemala.

epidemiological study of children in immigrants' camps in Israel (Yekutiel, 1959).

If, indeed, the gastro-intestinal tract of young infants is vulnerable to a variety of adverse influences elsewhere in the body, it is not unreasonable to assume that diarrhoea might be a sign of malnutrition at this age. Malnutrition might at least aggravate the severity of diarrhoea due to a variety of primary etiologies, whether or not it produces it directly.

Diarrhoea as a sign of severe vitamin A deficiency in children 2½ to 9 years of age has been observed by Ramalingaswami (1948). The diarrhoea promptly ceased on administration of vitamin A without other therapy.

Diarrhoeal disease, whatever its etiology, is a more serious disturbance in the presence of malnutrition. In a South African study (Truswell, 1957), 47% of severe cases were malnourished, as opposed to 6% of mild cases. The mortality rate ncreases with the severity of malnutrition (Table 9). In Japan, where the diet of children after weaning s low in calcium, shigellosis in this older age-group may present itself in the form of the grave clinical picture called *ekiri*, in which violent diarrhoea with high fever is accompanied by convulsions related to hypocalcaemia (Dodd et al., 1949). Recent studies from Mexico (Frenk et al., 1957; Metcoff et al., 1957) call attention to the presence in severe malnutrition of a marked disturbance of body fluids characterized by hypo-osmolarity and expansion of extracellular space, a situation frequently associated with diarrhoea and responding relatively poorly to the generally accepted modern methods of intravenous fluid therapy. The Mexican observations perhaps shed some light on the concept of the old German school that dehydration and acidosis may develop readily in states of severe malnutrition in the absence of clinically significant diarrhoea. Finally, it has been held by Dean (1956) that the treatment of kwashiorkor with skimmed milk may lead to diarrhoea due to the sensitivity of the intestinal tract of the malnourished subject to lactose; this concept is, however, not accepted by most experts in the field of kwashiorkor.[1]

TABLE 9

MORTALITY FROM INFANTILE DIARRHOEA RELATED TO NUTRITIONAL STATUS; MEXICO, 1948-50 [a]

Nutritional status [b]	Number of patients	Mortality (%)
Normal	67	14.9
First degree malnutrition	149	14.1
Second degree malnutrition	488	29.1
Third degree malnutrition	370	51.6

[a] Based on data from De la Torre (1956).

[b] Normal = Body-weight no more than 10% below standard for age.

First degree malnutrition = Body-weight 11%-25% below standard for age.

Second degree malnutrition = Body-weight 26%-40% below standard for age.

Third degree malnutrition = Body-weight over 40% below standard for age.

Does diarrhoea lead to malnutrition ?

The view that diarrhoea plays an important role in the production of malnutrition has a firm basis. Verhoestraete & Puffer (1958) have observed in certain Central American statistics that the peak incidence of kwashiorkor follows that of diarrhoea by two to three months. Identical observations have been made in Beirut by Majaj,[2] who noted that 54% of children with kwashiorkor entering the hospital in one year were admitted in the four-month period, October through January. The reasons for this relationship are easy to comprehend. With the onset of diarrhoea there is prompt reduction of pancreatic enzymatic activity (Bozkowa, 1956). In young children well on the road to recovery from kwashiorkor, the appearance of diarrhoea is associated with great increase in faecal loss of nitrogen and fat, together with marked decrease in absorption (Robinson et al., 1959). Waste of dietary nitrogen has also been demonstrated in ascariasis; in children with ascariasis and without diarrhoea faecal nitrogen was high and fell promptly following worming (Venkatachalam & Patwardhan, 1953). Similar direct interference with intestinal absorptive function by bacterial pathogens has not been demonstrated. If now to recurrent acute caloric loss from diarrhoea and chronic loss from ascariasis one adds prolonged therapeutic restriction of caloric intake as carried out by lay persons in many parts of the world, and unfortunately widely endorsed by physicians, the successive steps leading to malnutrition in an area of high diarrhoea morbidity are apparent, quite apart from considerations as to whether this may actually be a vicious cycle in which malnutrition in turn predisposes to enteric infection or diarrhoea or both.

[1] Personal communication (1958) from J. Sénécal, indicating opinions of Maeyer, Béhar, Scrimshaw and Jenz.

[2] C. J. Ross-Smith—personal communication, 1955.

RELATION OF DIARRHOEAL DISEASE TO SOCIO-ECONOMIC STATUS

Three basic factors are emphasized in virtually all discussions of diarrhoeal disease: age (infants and young children), malnutrition, and low socio-economic status. The last two are obviously inextricably interrelated. The last, already implicated in the discussion of epidemiology, will now be briefly considered with emphasis on sociological factors.

Mortality and morbidity statistics

Nowhere is the influence of local contrasts in socio-economic status more strikingly illustrated than in South Africa. In Johannesburg, in 1951, the infant mortality rate from diarrhoea was 35 times higher in the African than in the European population (Table 1) (Kahn, 1957). In 1954-55, diarrhoea caused 45% of 1069 non-European infant deaths in Cape Town as opposed to but 8% of 72 deaths in European infants (Truswell, 1957).

In an area of low diarrhoea mortality, Yekutiel et al. (1958) have shown an inverse relationship between adequacy of socio-economic status and diarrhoea morbidity in young children (Table 10). In the Israeli camps in which these observations were made, diarrhoea was more frequent among children of Iraqi refugees than among those from Egypt or Morocco. These differences were not related to such obvious factors as crowding.

The failure of individual and group habits of hygiene to keep pace with medical progress and public health improvements is implied in a variety of statistics. Although improved housing and an energetic maternal and child health programme in Israel resulted in a fall in infant mortality from diarrhoeal disease from 7-8 per 1000 in 1950-52 to 4-5 per 1000 in 1954-56, the reported morbidity rate in older children and adults remained steady at 50-60 per 10 000 (Yekutiel, 1959). A report from an English hospital is similar; deaths from diarrhoea in children fell from 48 in 1948 to two in 1955, but admissions for diarrhoea remained the same, about 250 yearly (Jamieson, 1956).

TABLE 10

DIARRHOEA MORBIDITY IN ISRAELI CHILDREN RELATED TO SOCIO-ECONOMIC CLASS [a]

Occupation of father	Average duration of diarrhoea per child
Fully employed skilled worker	6.65 days
Fully employed unskilled worker	10.19 days
Partly employed worker	11.47 days
Unemployed	13.11 days

[a] Reproduced, by permission, from Yekutiel et al. (1958).

Hardy (1954), citing data from two United States cities, has called attention to the fact that the installation of safe public water systems failed to bring about the same prompt decline in mortality from diarrhoeal diseases that it did in the water-borne disease, typhoid fever. Verhoestrate & Puffer (1958) have extended these observations to include 16 United States cities and show that during a period of 91% reduction in typhoid fever mortality there was but a 44% reduction in that from diarrhoeal disease. The implication is that full advantage of the improved water was not taken for purposes of personal cleanliness. Hardy (1954) has further pointed out that the mortality rate from diarrhoeal disease among infants and young children has fallen more slowly than the diarrhoea mortality rate for all ages, suggesting that hygienic precautions have been less well carried out with the younger age-group.

Areas of need for health education

The observations of the preceding paragraphs suggest that much of the morbidity and mortality from diarrhoeal disease could be avoided through improvement of the health practices of individuals and groups. Three of the many areas in which health education is needed may be designated health awareness, sense of cleanliness, and "mother efficiency".

Lack of health awareness, rather than the admitted inadequacy of numbers of physicians and health services, is the major factor in the failure of parents to seek out continuing health supervision for their children. Many reports emphasize the fact that the majority of infants have never had medical attention prior to the attack of diarrhoea that brings them to the physician. Failure of parents to appreciate the seriousness of diarrhoea leads to delay in seeking medical aid, and delay makes the prognosis still graver. De la Torre (1956) reported a mortality rate of 15% for those infants whose diarrhoea was less than two days in duration but 42.4% for those who had been sick for more than a month.

Lack of a sense of cleanliness, implied in official statistics cited above, is apparent in published observations of smaller groups. Watt et al. (1953)

noted—to be sure, in observations too few for statistical significance—that *Shigella* was six times as prevalent in rectal swab cultures of children of low income as of those of moderate income families living in homes with adequate inside plumbing. Tables 11 and 12 show the contrast in incidence of diarrhoeal disease between Finnish and Israeli infants given formulae prepared from fresh cow's milk and reconstituted milk powder. Obviously, by comparison with the incidence of diarrhoea among breast-fed infants in both countries, the preparation of the formulae was faulty, but equally clearly the manipulations entering into the preparation of a formula from powdered milk was accompanied by more hazards of contamination in the Israeli group than among the Finns.

"*Mother efficiency*"—the ability of a mother to care for her family and protect her children from disease—is an important, less tangible factor difficult to measure objectively. It has been emphasized by Spence et al. (1954) in their survey of 1000 families in England as one of the predisposing factors to a variety of childhood illnesses. Inadequacy of this maternal factor has been cited as being of importance in the incidence of infantile diarrhoea in Jewish refugees in Israel (Yekutiel et al., 1958) and in late deaths from diarrhoea in non-European children in Cape Town (Truswell, 1957).

RELATION OF DIARRHOEA AND MALNUTRITION TO BREAST-FEEDING

While it is reasonable to assume that breast-feeding may protect infants from diarrhoeal disease in a variety of ways, it is difficult to substantiate this impression objectively. Reports stating percentages of non-breast-fed infants with diarrhoea fail to indicate the incidence of breast-feeding among infants of the same age in the community. There are indeed few exact data on the prevalence and duration of breast-feeding in the world. In general, breast-feeding tends to be carried out longer in less well developed countries. Among the Eastern Mediterranean countries, its duration is reported to vary from a minimum of a few months in Aden, in which but 2% of infants are said still to be nourished at the breast at one year of age, to a maximum in Ethiopia, in which over half of the children are said to nurse at the breast up to three years of age.[1] While most countries in this area first offer solids at about six months of age, a little liquid butter is given in Ethiopia from birth on, and in Tunisia millet and chick-pea purées are started at one month. From these last observations it can be seen that while breast-feeding affords the infant his chief source of calories, many opportunities are present before weaning for ingestion of contaminated food.

The most obvious advantage of breast-feeding would seem to be reduced exposure of the infant to infectious agents, in view of direct delivery from the source to the infant's mouth, whereas there are many opportunities for infection in improperly prepared human milk substitutes. Presumably this explains the absence of *Salmonella* infection in breast-fed infants noted in a recent report of a summer epidemic of diarrhoea in Poland (Chwalibogowski et al., 1956).

TABLE 11

DIARRHOEA MORBIDITY AMONG CHILDREN IN FOUR FINNISH TOWNS, RELATED TO TYPE OF MILK FEEDING, DURING TWO SUMMER MONTHS, 1948 [a]

	Breast milk	Powdered milk	Fresh cow's milk
Number of children surveyed	1 256	1 208	1 294
Cases of diarrhoea	57	104	233

[a] Based on information communicated by A. Ylppö to the World Health Organization, 1949.

TABLE 12

DIARRHOEA MORBIDITY AMONG CHILDREN IN ISRAELI REFUGEE CAMPS, RELATED TO MILK FEEDING AND AGE, DURING FOUR SUMMER MONTHS, 1954 [a]

	Infants 0-5 months old		Children 1-2 years old	
	Breast milk	Powdered milk [b]	Powdered milk [b]	Fresh cow's milk
Number of children surveyed	83	45	170	54
Average total days of diarrhoea per child	4.22	9.08	15.01	8.3

[a] Based on data from Yekutiel et al. (1958).
[b] With or without breast milk.

[1] Poulton, E. M. (1957) *The status of maternal and child health in the Eastern Mediterranean and adjacent areas* (unpublished working document of the WHO Regional Office for the Eastern Mediterranean).

The low prevalence of enteropathogenic *E. coli* infection reported in breast-fed infants may rest in part on more complex factors. The proved protective action of cow's colostrum against fatal *E. coli* infection of newborn calves and the demonstrated presence of antibodies against enteropathogenic *E. coli* in human colostrum (Lindberg & Hunter, 1957) suggest that passive immunity may be of importance. The alleged protective action of breast-milk has also been attributed to the acid colonic contents of breast-fed babies (Ross & Dawes, 1954), due in part to the presence of *Lactobacillus bifidus*. Enteropathogenic *E. coli* flourishes better in the more alkaline stools of artificially fed babies. Neither of these explanations appears fully satisfactory, however, in the face of observations that the incidence of diarrhoea due to *E. coli* is higher in infants fed bottled breast-milk than in those fed directly at the breast (Kirby et al., 1950).

A cogent argument for the desirability of breast-feeding is to be found in the satisfactory nutritional status of breast-fed infants, at least during the first half of the first year of life. It is significant that in countries in which severe malnutrition and kwashiorkor are problems, these make their appearance in the late breast-feeding period and at weaning—that is, during or after the second half of the first year of life. Up until this time children in these countries are comparable in their growth and development to children in Europe and the USA (Davies, 1954; Scrimshaw et al., 1955).

In areas of great poverty and primitive hygienic conditions, breast-feeding does not in itself offer protection against diarrhoeal disease. In a report of diarrhoea among Bombay children (Pavri, 1953) it is noted that of 150 ill children less than two years of age approximately one-third were exclusively breast-fed, and that of 21 infants less than one month old, 13 were breast-fed.

The foregoing paragraphs do not minimize the importance of the promotion of breast-feeding as a measure to reduce the incidence of diarrhoea. On the contrary, "doing what comes naturally" continues to make good sense even if it is difficult to prove its benefits objectively. Two studies already cited (Tables 11 and 12), carried out in areas of moderate diarrhoea morbidity, do indeed document the protection against diarrhoea afforded to breast-fed infants. Both in Finland and in Israel the incidence of diarrhoeal disease was twice or more as high in children fed artificial formulae as in those nursed at the breast.

ATTEMPTS AT ENVIRONMENTAL CONTROL OF DIARRHOEAL DISEASE

Pointing out the gratifying fall in mortality from diarrhoeal disease that has been seen in the past many decades in the better-developed countries of the world, Verhoestrate & Puffer (1958) have related the decline to gradual improvement in public health facilities in these countries. The most important features in public health improvement have been the provision of abundant water of high quality, the sanitary disposal of excreta and wastes, and the control of flies and other insects.

A programme of partial sanitary improvement was carried out by Weir et al. (1952) nine years ago in poor, rural, Egyptian-delta communities with high total morbidity and mortality. The measures included improvement of public water supply through centrally located drilled wells, provision of a bored-hole privy in each of the crowded houses, and control of flies by insecticides. With the exception of a temporary reduction in mortality from diarrhoea brought about by fly control, the health status of the communities was unimproved, though in a follow-up study two years later Chandler (1953a, 1954) attached significance to a decrease in the *Ascaris* infection rate from 62% to 50%.

The Weir experiment cannot validly be cited as an example of failure to improve the health standards of a community through improved sanitation, since significant improvement in sanitation was in effect never achieved. On the basis of an arbitrary score of 106.5 points for adequate minimum sanitation, the average scores in the Egyptian communities before improvement were 19.1-23.8, rising after improvement to but 31.1-46.1.

In happy contrast to the Egyptian failure, specific attention to any one of the three important public health improvements has in itself, in populations with initially higher standards of public health and personal hygiene, resulted in reduction of enteric infections. The published pertinent experiments and observations are summarized in the following paragraphs.

Excreta disposal

Excreta disposal was recently studied as a single problem in a southern rural community in the United States (McCabe & Haines, 1957). All unsanitary privies in the town were changed to sanitary structures. The frequency of diarrhoeal disease and the prevalence of infection with *Shigella* were studied

by monthly clinical historical appraisal and rectal swab cultures from over 300 children under ten years of age, in this community and in neighbouring control communities, before and for eighteen months after the installation of the sanitary privies. Following the installations, the *Shigella* infection rate fell from 4.7% to 2.8%, while in the same period the rate rose from 3.3% to 5.7% in the unimproved towns. The improved town also experienced a 50% reduction in morbidity from diarrhoea. The reduction in infection is believed to have been brought about through the removal of faeces from contact with flies. Although the total fly population of the village was unchanged, the number of flies breeding in privies or visiting privies was greatly reduced.

Fly control

The importance of flies as carriers of enteric organisms was demonstrated by Floyd & Cook (1953) in Egypt. These workers trapped flies in various areas and cultured 156 " pools " of 25 flies each. All but one pool were positive for *Escherichia coli* species. Eighteen pools were positive for *Shigella* or *Salmonella* in a ratio of two to one, while *S. typhosa* was found four times. Further study showed that a fly may carry *Shigella* up to 12 days and *Salmonella* up to 28 days. The organisms were demonstrated to multiply while in the fly's intestinal tract. Eggs deposited in infected faeces produced infected adult flies.

Fly control by insecticides has been significantly but only temporarily effective in reducing the incidence of diarrhoeal disease. In carefully controlled studies in southern United States communities with moderate (Lindsay et al., 1953) and moderately high (Watt & Lindsay, 1948) diarrhoea morbidity and high fly populations, the incidence of both *Shigella* infection and diarrhoea fell during fly control; *Salmonella* infections were found not to be significantly affected. Fly control was noted above to have been the only one of several partial sanitary improvements in Egyptian-delta communities that resulted in lowered mortality from diarrhoeal disease (Weir et al., 1952).

Fly control by larvicides and insecticides is at best but a temporary measure, however, since resistance develops within a few months (Weir et al., 1952; Lindsay et al., 1953). The only permanently effective fly control is sanitary control of breeding-places. Screening is, of course, of local benefit.

Abundance and availability of water

In recognizing the value of water of high *quality* for *internal* consumption one must emphasize as well the importance of adequate *quantity* for *external* purposes: for instance, loosening of infected material from hands, bodies, clothing, utensils, and the environment with the aid of soap and removal of most of it through copious rinsing, coupled with sanitary removal of excreta and wastes through water-borne sewage disposal systems. Pathogenic organisms can be so reduced in number through hand-washing as not to produce infection when they are carried, directly or indirectly, to the mouth; or, if infection does result, it may be so mild as not to be expressed as clinical disease.

Frequent, thorough hand-washing, which, as several cited observations have implied, is a health habit carried out more or less effectively depending on the individual's training and experience in the family or cultural group, requires water which is not only in adequate supply but *readily available*. The importance of this was demonstrated in two separate studies carried out by Watt and collaborators in migrant workers' camps in California (Watt et al., 1953; Hollister et al., 1955). Prevalence of *Shigella* infection and frequency of diarrhoeal disease were directly related to the distance of the source of water from the house. A similar study by Stewart et al. (1955) carried out later in a southern United States community in homes without inside plumbing showed that the prevalence of *Shigella* in rectal swab cultures of families was 42% higher when the source of water was relatively far from the house than when it was close by. Of particular interest is the observation that *proximity* of the water was of greater importance than its *quality*. Prevalence of infection was approximately the same whether municipal water was piped to the area or whether the source was an open dug well subject to pollution.

MEDICAL PROPHYLAXIS OF DIARRHOEAL DISEASE

There is no safe or effective immunological or chemoprophylactic method of protecting the individual exposed to enteric pathogens. A controlled experiment among Egyptian children in an area of high diarrhoea morbidity showed that *Shigella flexneri 3* vaccine was ineffective in preventing infection due to this or any other *Shigella* species (Higgins et al., 1955b). As part of the same experiment prophylaxis of shigellosis with sulfadiazine,

streptomycin, and oxytetracycline was attempted and found to be neither practical nor effective in the dosages used (Higgins et al., 1955c). Attempts to prevent diarrhoea and other infections in nurseries for premature and full-term newborn infants have proved uniformly unsatisfactory and complicated by the appearance of a variety of clinical infections, including diarrhoea, due to the emergence of resistant organisms such as fungi or *Staphylococci*, or the appearance of diarrhoea as a sign of intolerance of the antibiotic agent used.

TREATMENT OF DIARRHOEAL DISEASE

Treatment of the patient with diarrhoeal disease falls into three categories, listed in order of importance:

1. Fluid therapy:
   (*a*) restoration of deficits of body water and electrolytes;
   (*b*) provision of fluids to offset normal and abnormal fluid losses, together with provision of at least minimal caloric requirements.
2. In so far as practical and practicable prevention or reduction of further abnormal losses of fluid from the body (symptomatic treatment).
3. Destruction of the infecting agent.

Fluid therapy

Proper management with water and electrolytes is by all odds the most important feature in the treatment of the patient with diarrhoea. The marked reduction of mortality from diarrhoeal disease universally achieved in hospital practice during the past twenty years has been almost entirely due to the application of principles derived from better understanding of the disturbed physiology of dehydration. In short, modern therapy amounts to the rapid restoration of most of the child's deficit of water and sodium chloride, followed by further provision of more modest amounts of water and salt, together with the addition of potassium and at least sufficient carbohydrate to minimize the breakdown of body protein during the necessary period of diminished caloric intake. While the principles are simple enough, their practical application may be unsatisfactory owing to failure to recognize the severity of dehydration in small infants, failure to carry out therapy with requisite vigour initially, technical difficulties in the parenteral administration of fluids to small infants, and perhaps above all the overwhelming clinical pressures imposed on inadequate numbers of inadequately equipped professional personnel in areas of high diarrhoea morbidity.

While it is generally accepted that rapid intravenous administration of fluids is the most effective therapy for severely dehydrated infants, for reasons cited above resort has been successfully made in many rehydration centres to either of two simpler techniques: hypodermoclysis and slow intragastric drip through a nasogastric tube. The success of these forms of therapy is intimately related to the effectiveness of patient follow-up and will be discussed below in a section devoted to rehydration centres.

Quite obviously the simplest means of administering fluids is by mouth. *Repair* of dehydration by the oral route is ordinarily not practicable in the severely dehydrated baby, because of vomiting, anorexia, fatigue, or drowsiness on the part of the infant, or fear on the part of the physician of aggravating the severity of the diarrhoea. *Prevention* of dehydration, on the other hand—that is, maintenance of hydration—by adequate administration of fluids by mouth, is accepted by all physicians as being of great value. In practice the baby's milk feedings are temporarily suspended and electrolyte solutions are given by mouth in their place. While this sort of treatment seems eminently sensible, no critical objective data are available to indicate that dehydration appears in a significantly lower percentage of these infants than in babies not so managed. An ever-present danger lies in the fact that fluids useful and desirable for successful oral hydration are inadequate nutritionally. When use of these fluids is unnecessarily prolonged, malnutrition may be produced or aggravated, as noted in an earlier section. A further danger is that of improper dilution of powders or liquid concentrates, resulting in administration to the patient of a solution too high in electrolyte content. The widespread promotion of oral hydration as a public health measure would require greatly expanded maternal and child health activities, including large numbers of trained home visitors.

A cogent medical criticism of almost all recommended regimens for rehydration—parenteral and oral alike—is that the electrolyte content of the special fluids prescribed is excessively high. This is probably due to two factors: (*a*) adherence to recommendations of a few years ago, which in the light of recent knowledge are not satisfactory; and

(*b*), probably more importantly, widespread confusion based on failure of physicians to distinguish between requirements for *repair of dehydration* and for *maintenance* of the patient during the phase of recovery, whether or not accompanied by the passage of liquid stools. The electrolyte content of fluids for the latter purpose should be considerably lower than for the initial repair.

A satisfactory maintenance solution will contain approximately equivalent amounts of sodium and potassium, will have an over-all electrolyte concentration of about 100 milliosmoles per litre, that is, about one-third the osmotic pressure of normal body fluids, and will contain carbohydrate in approximately 5% concentration. The simplest possible solution, prepared from the chloride salts of sodium and potassium, is the following, to which attention was called some years ago (Hardy, 1954):

Sodium chloride	1.5 g
Potassium chloride	2.0 g
Syrup of raspberry	60 ml
Water to make	1000 ml

This solution may be offered to infants *ad libitum* in place of milk mixtures. Dextrose may be substituted for the syrup in amounts of 35 (isotonic) to 100 g, in order to make a preparation suitable for parenteral use (Ordway, 1956). Some authorities prefer to replace up to half the chloride with phosphate and bicarbonate; the bicarbonate commonly takes the form of lactate.

Prevention of further fluid loss

The first energetic intravenous efforts to combat dehydration are usually attended by rapid reduction in the number and volume of stools. From this point on the continued suppression of diarrhoea as a sign is best effected by the further provision of fluids to the body by some parenteral route. Continued interdiction of oral feeding, however, not only imposes the technical difficulties already cited but is inevitably accompanied by the provision of inadequate calories. For a short period this is of no great import to the patient but one hesitates to continue to starve the malnourished subject for more than a day or two. While some authorities are quite apprehensive over the dangers from temporary under-provision of adequate nutritional needs and are overly zealous for early re-establishment of full oral feeding, others are so concerned over the character of the stools that they are willing to neglect the infant's nutritional needs until watery stools have completely disappeared. Each point of view is logical, and fortunately in the vast majority of instances treatment can be so designed as partially to satisfy both.

Aside from suppression of oral intake no treatment has been shown to be effective in reducing loss of water and electrolytes from the body. Various pharmaceutical agents, such as opium derivatives, are notably ineffectual. Great interest has attached to a variety of preparations and special formulae containing pectin, hemicellulose, and other hygroscopic agents. Essentially these absorb the water and electrolytes excreted into the bowel, where to all intents and purposes they are already outside the body. It remains to be shown that these agents are in any way effective in reducing loss of water from the body, even though they may alter the appearance of the stool and perhaps result in retention of stools in the colon for more prolonged periods so that they cannot be seen. The most generally used preparation of this sort in Europe is carrot purée, which appears to be well tolerated, provides needed calories and electrolytes, and leaves physician and mother alike with the feeling that something beneficial is being done for the baby. Certain proprietary infant feeding preparations appear to be equally satisfactory.

The use of acid milks such as yoghourt, lactic acid milk, vinegar milk, and " acidophilus " milk has been recommended in the belief that through alteration of bacterial flora in the intestinal tract they will favourably alter the clinical course of diarrhoea. It is likely that the greater virtue of these preparations lies in their resistance to bacterial contamination in situations of inadequate refrigeration.

Antimicrobial therapy

Shigella. While *Shigella* may be eliminated from the gastro-intestinal tract by a variety of drugs, the patient's clinical illness is not likely to be greatly altered, although its duration may be a day or two less than in the untreated subject. In view of the magnitude of the disturbance of gastro-enteric physiology and metabolic balance in diarrhoeal disease, the lack of striking clinical response to chemotherapy is not surprising. Since the chief effectiveness of antibacterial drugs thus lies in termination of the infection rather than of the diarrhoea, their use is, in a sense, more important for the person in the next bed than for the patient himself.

Sulfadiazine in relatively small dosage has been the drug of choice in *Shigella* infections in the United States since 1943, when Hardy et al. (1943) demonstrated its superiority over insoluble sulfa preparations. Only a year later, however, Hardy (1946) observed the emergence of a resistant strain during the course of an institutional epidemic, and recently the emergence of resistance in the USA has again been reported (Wentworth & Wentworth, 1957). The ineffectiveness of sulfadiazine was reported in Japan in 1947 (Tateno, 1950), and since then increasing resistance to this drug has been documented in many parts of the world.

Fortunately many antibiotics, particularly the tetracyclines and chloramphenicol (Garfinkel et al., 1953), have proved to be effective against *Shigella*, but again resistant strains are emerging. The pattern is illustrated in a recent report from Israel (Marberg et al., 1958), where sulfadiazine resistance was first recognized in 1951. By 1956 half the *Shigella* strains tested were resistant to sulfadiazine and in the same year for the first time, 19 of 100 strains were resistant also to chloramphenicol. Fortunately, the strains resistant to sulfadiazine were susceptible to chloramphenicol. Resistance to tetracycline paralleled in general that to chloramphenicol.

Salmonella. Despite the bacteriostatic action of chloramphenicol in *Salmonella* infections and the apparent clinical importance of this drug in typhoid fever, results have been disappointing with this or any other drug in cases of diarrhoea due to *Salmonella*. Although the number of organisms in the stools can be diminished, the organism promptly reappears after cessation of therapy and the clinical course of the illness is uninfluenced.

Escherichia coli. Nursery epidemics of diarrhoeal disease due to enteropathogenic *E. coli* have been characterized by high morbidity, along with high case fatality despite adequate fluid therapy. In contradistinction to the experience in shigellosis, successful management of the diarrhoea appears to rest in overcoming the infection as well as restoring and maintaining normal hydration and acid-base balance. Several drugs have been reported to be effective in eliminating the organisms. The best of these has been neomycin, but resistance to this drug has already been encountered.

Unknown agents. Two careful studies have been carried out in an attempt to evaluate the effectiveness of antibacterial agents in the therapy of cases of diarrhoea not due to *Salmonella* or *Shigella*. One study was carried out in a Johannesburg hospital on 170 severely ill children under two years of age, 20% of whom died (Stein, 1955). No benefit was discernible in these cases from the use of sulfadiazine, chloramphenicol, or oxytetracycline, all of which had perhaps some benefit in the management of concurrently observed cases from which *Shigella* or *Salmonella* were cultured. In a study of 1168 cases of infantile diarrhoea in ten different hospitals in Britain (Great Britain, Medical Research Council, 1953), the usefulness of very high doses of chlortetracycline, chloramphenicol, and sulfadiazine was evaluated in infants with stool cultures negative for *Shigella* and *Salmonella*. The over-all mortality in this study was 2.8%. Statistically significant therapeutic effectiveness of chloramphenicol and sulfadiazine was shown by shorter duration of the diarrhoea (one to three days less than in untreated controls), shorter period of total illness (two to four days less), and less likelihood that cases first seen as mild would become severe. The effectiveness of the drugs in this last category is most striking from a clinical standpoint: 14.5% of the control patients became more severely ill in the course of their disease, as compared with 3.7% of those who were treated—a fourfold difference.

The reasons for the divergent results of the South African and British studies perhaps lie in differences in severity of disease and in doses of the drugs. If bias due to more assiduous medical and nursing supervision of treated patients can be eliminated—a not uncommon inadvertence in studies of this sort—the apparent effectiveness of potentially dangerous amounts of drugs in the British study is presumably to be attributed either to the elimination of unrecognized pathogens or to some non-specific benefit related to alteration of the intestinal flora. Such therapy is costly and presupposes hospitalization of patients and close medical supervision.

Antibacterial therapy in institutional outbreaks of diarrhoeal disease. In view of the possibility of complete elimination of a susceptible agent in limited environmental situations, antibacterial therapy may have public health significance. Shigellosis endemic in institutions and nursery outbreaks of *E. coli* diarrhoea have been effectively controlled by chemotherapy. In all such institutional situations it is ordinarily necessary to treat all persons, sick and well alike, in order to eradicate the responsible organism. All reports of institutional infections

emphasize the necessity of concurrent strict application of sanitary precautions in order effectively to limit the spread of infection (cf. quotation from Johnson & Landsman on page 85). Among these measures hand-washing by all personnel before and after each contact with a patient is of paramount importance.

SPECIAL OUT-PATIENT PROGRAMMES FOR TREATMENT OF CHILDREN WITH DIARRHOEA

The institution of out-patient programmes for the therapy of children severely ill with diarrhoea has been a necessity in many parts of the world with overcrowded hospital wards. As recently as 1955 one-third of children with diarrhoea and severe dehydration coming to a Chilean hospital were turned away for lack of beds (Meneghello et al., 1957).

Out-patient rehydration centres

Chilean "semi-ambulatory" centres. Centres for the care of non-hospitalized patients have taken the form of separate wards attached to the out-patient department, where babies may remain for hydration, chemotherapy, dietary advice, and observation for periods up to two days. While those services which admit babies for a day or two have nursing supervision at night, therapy is carried out during the day only.

In a centre with 12 cribs (de la Maza & Agliati, 1957) infants are observed for two days and then either discharged home or, in about 25% of the cases, sent to the infants' ward for further therapy. This centre routinely gives fluids intravenously. Over a three-year period, of 1100 infants treated, including about one-third with "toxicosis", the immediate mortality was 1.5%. Of 489 infants seen in 1956-57, 55% could be followed for six months following discharge from the centre. Of these, 10.3% had to be rehospitalized within 15 days, in general because of poor home care rather than for strictly medical reasons.

In another large Chilean out-patient centre with 20 beds (Meneghello et al., 1958), daytime care only is given. While the intention is to admit all infants with "toxicosis" or severe malnutrition to the hospital, the pressure of cases during the summer months has been such that 22% of cases treated in the centre have had "toxicosis". In the year 1956-57, 1158 infants were treated in this unit as compared with 269 hospital admissions with diarrhoea. Most of the infants are rehydrated by gastroclysis. Of 2268 infants treated in the period 1955-57, 3.3% died of acute disease, 20.4% were hospitalized, and the remaining three-fourths were followed on an ambulatory basis. The follow-up of these patients proved to be the most difficult problem, owing to inadequacy of personnel and lack of close coordination with other health services for children. In 1955-56, 78% of the discharges could be followed for one month; 14% of these died.

A South African centre. In a Cape Town hospital, six cots have been set up for the out-patient therapy of children with diarrhoea (Truswell, 1957). Rehydration is carried out by the subcutaneous route over a period of a few hours, following which the children are sent home on a regimen of oral electrolyte solutions, gradually replaced by increasing quantities of milk. Adequate follow-up has been a major problem. In order to gather information as to the fate of these patients, 100 consecutive cases coming into the centre in the late fall and winter of 1955 were studied. Three were admitted directly to the hospital and three were referred to the hospital on subsequent out-patient visits. Of the remaining 94, all but six could be located and it is assumed that these survived because their names did not appear in public mortality records. Only 49 of the 94 were thought to have had adequate out-patient supervision. Twelve died: one in the out-patient department on the initial visit shortly after the hypodermoclysis, seven within five days of the last out-patient visit, and four between two and six weeks after the last out-patient visit under circumstances of parental neglect.

Polish extranosocomial centres. The experience with seven out-patient rehydration centres in the city of Warsaw led to their closing seven years ago after two or three years of operation.[1] These centres were set up to operate at hours during which hospital out-patient departments and infant welfare stations were closed—namely, from 6 p.m. to 9 p.m. daily and 9 a.m. to 11 a.m. on Sundays. They were adequately equipped and staffed, dietary advice was carefully given, and medical follow-up in the homes after discharge was satisfactory. Dehydrated babies were treated by hypodermoclysis. Careful evaluation of the fate of all infants treated revealed that many had to be admitted to hospitals one or two

[1] W. Winnicka—personal communication, 1958.

days later in more critical condition than when they were first treated. Some of these died. All dehydrated infants are now admitted to hospitals for treatment, even if wards are overcrowded.

Comment. While the Polish experience illustrates the desirability of hospitalization of all children with serious diarrhoeal disease, the Chilean and South African centres represent important expedients when admission to a hospital is not possible. Indeed, both Chilean and South African workers urge the establishment of additional, outlying rehydration centres under the supervision of a State public health programme, in order better to care for the appreciable numbers of patients who must come considerable distances to the present hospital centres. The small number of acute deaths reported from existing centres, even though initial intravenous therapy is not usually employed, testifies to the effectiveness of intragastric and subcutaneous rehydration in the great majority of subjects.

Attention is called to the lack of adequate follow-up emphasized in the South African and Chilean reports, eloquently attested by the number of late deaths. Extension of maternal and child health services would seem to be an essential concomitant of—indeed, a prerequisite to—the establishment of additional rehydration centres.

UNRWA health centre programme of oral hydration [1]

The use of oral hydration in health centres, supplemented with adequate follow-up in home and centre and with careful attention to nutritional factors, has been extensively attempted among Palestine-Arab refugees in Jordan under UNRWA supervision. Infants not requiring hospitalization are offered electrolyte solutions by mouth in health centres, followed at home by restriction of milk for from 12 to 24 hours and administration of salted rice water or sweetened weak tea. Mothers of nursing babies are then urged to return the baby to the breast. Other babies, as well as breast-fed babies needing supplement, then embark on a rigid and complex dietary programme consisting of carrot purée and mashed bananas prepared at the centre, *labaneh* with olive oil on bread at home, and liberal amounts of a specially prescribed oral electrolyte solution prepared at home by dissolving in water packaged powders supplied by the centre. *Labaneh* is a local Arab food very much like cottage cheese, made from *laban*, a fermented milk similar to yoghourt, prepared with the aid of a locally available culture. In the refugee camps the *laban* is made from powdered skimmed milk.

The organization of this programme is such that objective appraisal of its effectiveness is difficult. Various unpublished evaluations of it [2] make clear, however, that its success depends to a considerable extent on its acceptance by and the enthusiasm of the persons responsible for its execution. Some of its shortcomings lie in failure of this acceptance and enthusiasm to carry on down the line through doctors and nurses, lack of adequate personnel to follow up the effective carrying out of the programme in the homes of the patients, unwillingness of mothers of sick babies to conform to the rigid 10-day pattern of relatively unpalatable diet, and the necessity for mothers to come to the centre twice daily—once for a supervised meal (more older children are brought to these meals than infants, presumably because the latter have to be carried) and again to pick up a diet for home use. A major contribution of the programme is its recognition of local acceptance of such foods as tea, which incidentally is always boiled, and *labaneh*, which is a poor culture medium for bacteria and despite the heat of the summer keeps in good condition for at least 24 hours although unrefrigerated.

Shortcomings of out-patient programmes

The difficulties confronting programmes designed to prevent and treat diarrhoeal disease and improve nutrition seem to fall into two main categories:

1. Inadequacy of personnel and follow-up. This is the most crucial area of difficulty. Hospitals and health centres are crowded and inadequately staffed. The importance of carrying medical supervision to homes is generally realized, but the number of persons at present available to carry out this task is hopelessly inadequate. Consider the impossible task imposed in an Egyptian health centre on one doctor, whose daily duties included care of 90 new out-patients, follow-up care of many children and pre-natal cases, routine bilharziasis treatment of the local populace, examination of all dead bodies in five villages, and supervision of the sanitary programme of the area (Weir et al., 1952).

[1] Khuri-Otaqui, S. (1957) *Some aspects of the management of infantile diarrhoeas among Palestine Arab refugees in Jordan* (unpublished working document of the WHO Regional Office for the Eastern Mediterranean). See also: WHO Regional Office for the Eastern Mediterranean (1958) pp. 21-23.

[2] By R. F. A. Dean, S. H. Guirguis, S. Khuri-Otaqui and J. S. McKenzie Pollock.

2. Lack of acceptance of hygienic methods. This is usually the result of cultural blocks and inadequate health education. It is clear, for instance, that not all the dietary inadequacies of the world are due to poverty alone. The resistance to health progress imposed by ingrained cultural habits has been emphasized by many observers (Jelliffe, 1957; Solien & Scrimshaw, 1957; Freedman [1]) but appears not to be generally appreciated. Resistance to alteration of established dietary habits is illustrated by the widespread lack of acceptance of powdered milk in the area to which it is supplied by UNRWA. Only about 40% of the mothers in this area take the skimmed milk ration to which they are entitled.[2] A sociologist (Freedman [1]), reporting on the impact of the programme of study and prevention of malnutrition in Guatemala, points out that the collection of blood samples has caused such misunderstanding and resentment that it threatens to compromise effective relationship between populace and health personnel. In the treatment of kwashiorkor, in which it is important that local dietary customs be radically changed, some Guatemalan hospitals have not provided parents with the opportunity to visit at meal-times so that they may see their child improve on a diet interdicted at home, or at a time when they may talk with the physician in charge of the child's treatment.

FUTURE ACTION

General objectives and suggested specific measures

Enough is known from what has already been done to make it possible for future programmes to be effective in the prevention of diarrhoea morbidity and mortality. Acquisition of further important epidemiological and etiological data is secondary to this primary objective.

Obviously programmes of public health improvement, particularly in environmental sanitation, must be carried forward vigorously. Physicians in all countries must be educated to the desirability of employing more precise nomenclature in the description of diarrhoeal disease. Nations must increasingly recognize the importance of complete and accurate classification of causes of disease and death.

Short of these general and long-term objectives, the foregoing review has pointed up several more limited measures that hold considerable promise of reducing morbidity and mortality from diarrhoeal disease within present frameworks of socio-economic under-development. These measures are:

1. Limited sanitary improvements in selected environments:

   (*a*) provision of abundant water in or immediately adjacent to homes;

   (*b*) installation of facilities for the sanitary disposal of human excreta.

2. Attempted prevention of dehydration by early oral administration of sugar-electrolyte solutions to infants and children with diarrhoea.

3. Treatment of dehydration in " semi-ambulatory " rehydration centres in areas of high diarrhoea morbidity and inadequate hospital services.

Provision of water

The first of the above measures, representing a preventive rather than a therapeutic approach, merits further discussion.

There is urgent need to demonstrate whether the United States experience of reduced incidence of diarrhoea and *Shigella* infection in environments with readily available water can be duplicated in less well developed areas of the world, among peoples unfamiliar with running water and with little or no conception of the rudimentary principles of personal hygiene. Such a study is at present under way in Brazil (Penido, 1959).

The importance of developing municipal water systems was stressed by the Advisory Committee on Environmental Sanitation of the Pan American Sanitary Bureau at its first meeting in April 1958. The following paragraphs appear in the summary and recommendations of the committee's report (unpublished):

" Sanitary control of the environment is one of the principal means for the prevention of [diarrhoeal and other communicable] diseases, involving chiefly provision of safe and abundant water, sanitary waste disposal, clean milk and other foods, and adequate housing.

" A program to carry out large-scale improvement in all of these phases, simultaneously, does not appear practicable now or in the immediate future. The Committee believes therefore that a concerted effort should be initiated as soon as possible on one function which is most certain to give positive results within a minimum time at a relatively low per capita cost. Installation of

[1] *Op. cit.* (see p. 86).

[2] R. C. Burgess—personal communication, 1956.

piper water systems throughout populated communities, whether urban or scattered, meets best these criteria.

" Besides direct benefit to health, a water program will also result in improved and more rapid development of community housing, industrial and commercial growth and tourist trade—all of which are of great economic importance to [the Latin American] countries. . .

" The Committee unanimously recommends that the Pan American Sanitary Bureau look to the early initiation of a program for the full-scale, concerted promotion of public water supply systems in the Americas. Such a program should envisage:

" 1. Provision of safe and ample water directly into the homes in concentrated populated areas, by construction of new systems or by the extension and improvement of existing ones. . .

" 8. Accomplishment of a substantial part of the program within a 10-year period with an overall expenditure of about $50 per capita. Based on serving an estimated population of 80 million persons, the total capital investment is estimated at $4 000 000 000. This amount may seem startling at first sight, but it is reasonable considering the area involved, the time for full development, the size of the immediate and future benefits and the dormant resources in many of the countries."

Need for further epidemiological knowledge

Programmes can be designed to yield information, in addition to the effectiveness of the control measures being tested, on the following unsolved problems:

1. The importance of *E. coli* types as enteropathogenic agents in the community at large;

2. The etiological significance of viruses;

3. The relation in the first year of life between diarrhoea and *E. coli*, viruses, and other microbiological agents;

4. The relation of malnutrition to diarrhoea;

5. The relation of breast-feeding to diarrhoea and malnutrition;

6. More precise definition of sociological factors such as " mother efficiency ".

Need for trained personnel

The great need for additional personnel, including physicians, nurses, and engineers, has been repeatedly pointed out in this review. Of basic importance are the strengthening of existing maternal and child health organizations and the development of new ones. The shortage of trained public health nurses can be met in part by " nursing auxiliaries ", of whom considerable and growing use is being made in Latin America (Ripley & Verhoestraete, 1958). These are persons of limited general educational background who can be well trained to assume limited, clearly defined responsibilities in the field of maternal and child health. It is not unlikely that such persons, under the guidance of health educators as well as nurses and doctors, may be particularly effective in promoting acceptance of health programmes by lay persons and communities.

The counsel of sociologists might be sought with profit in adapting programmes to communities and in evaluating their effectiveness as experiments in health education. In other words, it is suggested that the value of epidemiological observations will be enhanced by sociological appraisal, and that the effectiveness of programmes themselves will be abetted by such review.

RÉSUMÉ

Malgré la confusion de la nomenclature, la complexité de la classification et l'insuffisance notoire du nombre des déclarations, il est incontestable que les maladies diarrhéiques à étiologie infectieuse sont une cause majeure de morbidité dans le monde entier et la cause principale des décès chez les nourrissons et les jeunes enfants.

L'infection à *Shigella* sévit parmi les nourrissons du deuxième âge, les enfants et les adultes, dans les zones à morbidité diarrhéiques moyenne et élevée. Les *Salmonellae* présentent une importance tout à fait secondaire, bien qu'elles soient plus répandues que les *Shigellae* parmi les nourrissons. On sait qu'il faut imputer à des *Escherichia coli* et à certains virus encore insuffisamment étudiés les flambées de diarrhée survenues dans des établissements collectifs. Il n'est guère probable que les parasites intestinaux soient par eux-mêmes une cause fréquente de maladie diarrhéique.

Les agents pathogènes sont propagés par la contamination fécale des aliments. On a démontré le rôle joué par les mains dans la dissémination du matériel contaminé au cours des épidémies qui éclatent dans les hôpitaux, les crèches et les établissements scolaires. Le tableau clinique de l'infection est directement en rapport avec la quantité de germes infectants.

Dans les zones à forte morbidité diarrhéique, la maladie est presque toujours associée à la malnutrition. S'il est évident que la diarrhée et le parasitisme intestinal qui l'accompagne le plus souvent peuvent aboutir à la mal-

nutrition, aucun indice convaincant ne nous permet de conclure que la malnutrition prédispose aux infections gastro-intestinales. Le fait que la diarrhée puisse être par elle-même un signe de malnutrition grave doit retenir l'attention, mais ce n'est pas un argument inattaquable. L'allaitement au sein est susceptible d'assurer un état de nutrition convenable pendant les six premiers mois et de réduire les risques de contamination.

La régression de la morbidité et de la mortalité diarrhéiques dans les pays avancés est étroitement en rapport avec l'amélioration générale des services de santé publique. Il a été démontré que la distribution d'eau potable et l'installation de lieux d'aisance contribuaient à réduire la fréquence des cas nouveaux de maladies diarrhéiques et la fréquence globale des infections à *Shigella*, dans les zones bénéficiant déjà, il est vrai, d'assez bonnes conditions de salubrité. La lutte contre les mouches au moyen d'insecticides a été certes universellement efficace, mais de façon temporaire seulement.

La prophylaxie des maladies diarrhéiques par vaccination ou médicaments s'est révélée inefficace en tant que mesure de santé publique.

Le traitement des maladies diarrhéiques réside principalement dans la réhydratation. La prévention de la déshydratation par consommation de liquide est très répandue. Quoiqu'elle paraisse évidente, l'efficacité de cette pratique appelle une démonstration objective. Le traitement de la déshydratation, par voie intraveineuse est théoriquement le meilleur. Néanmoins, on a obtenu de bons résultats par la gastroclyse ou l'hypodermoclyse en traitement ambulatoire dans des centres chiliens et sud-africains où tous les lits étaient occupés par des enfants déshydratés. Ces succès ont été limités surtout par l'insuffisance de la postcure et par des résistances d'ordre culturel à l'adoption de méthodes d'hygiène modernes et d'un régime alimentaire approprié.

Il conviendrait qu'à l'avenir les programmes de lutte contre les maladies diarrhéiques fassent passer au premier plan certaines mesures de caractère limité qui pourraient donner de bons résultats même dans les pays dont le développement socio-économique est retardé: amener à domicile une quantité suffisante d'eau saine dans certaines zones à population très dense, installer des lieux d'aisance hygiéniques, prévenir la déshydratation en administrant précocement par voie buccale aux enfants diarrhéiques des solutions d'électrolyte sucré et créer des centres de réhydratation en traitement ambulatoire dans les régions à forte morbidité diarrhéique où les services hospitaliers sont insuffisants.

Quoi qu'il en soit, le succès est subordonné essentiellement au développement de l'éducation sanitaire et des soins médicaux, grâce à une forte extension du réseau des services d'hygiène de la maternité et de l'enfance.

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