Case Stud A.- Oral Dehydration Therapy for Diarrheal Diseases

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Summary

In the living conditions prevalent in the less developed world, characterized by a lack of potable water, sanitation, and refrigeration, the bacteria and other pathogens that cause diarrheal diseases are easily transmitted to young children by contaminated water, hands, and food. As a result, infants in less developed countries suffer on the average six to eight separate episodes of diarrheal disease per child.

The two major consequences of infant diarrhea are dehydration and malnutrition. Diarrhea causes a loss of body water and salts (electrolytes), which, if sufficiently copious and not adequately replaced, may result in dehydration. Approximately 1 of every 150 to 200 episodes of infant diarrhea results in severe, life-threatening dehydration. In the last decade, diarrheal dehydration was one of the major causes of infant mortality in virtually all less developed countries,

All episodes of infant diarrhea have nutritional consequences, in part because ill infants eat less and in part because the pathogens that cause diarrhea often diminish the ability of the small intestine to absorb nutrients. Repeated diarrheal infections within a short period of time can lead to clinically overt malnutrition.

Irrespective of the specific infectious agent causing diarrhea, the treatment of diarrheal dehydration is the same and involves the replacement of body water and electrolytes (salts in solution). In the 1950s and 1960s, this treatment was accomplished by intravenous rehydration—i.e., infusion of sterile water and electrolytes into the vein of an infant. Although intravenous therapy is very effective, it was poorly suited to use in the less developed world where it was most needed. The drawbacks of intravenous dehydration include its expense; the need for sterility of the fluids, tubing, and needles; the requirement for relatively sophisticated health workers to administer the infusion; and the difficulties of distribution and supply of all the materials.

In recent years, thanks to important contributions by a number of laboratory scientists, clinicians, epidemiologists, and health delivery experts, a simple, efficacious, technologically appropriate alternative to intravenous dehydration has become available—namely, oral dehydration therapy (ORT) using sugar / electrolyte solutions. An application of ORT other than for treating dehydration involves its use *early in* the course of infant diarrhea to *prevent* dehydration. The ingredients used in oral dehydration solutions are widely available, easily transported, and need not be sterile. Furthermore, sophisticated health workers are not required to administer ORT.

The efficacy of an oral glucose / electrolyte solution to promote sodium and water absorption was demonstrated in clinical intestinal balance studies by U.S. investigators in the Philippines in the early 1960s. By the end of that decade, clinical studies by U.S. physicians and their Bangladeshi and Indian collaborators had established that ORT could diminish by 80 percent the intravenous fluid requirements of adults with severe cholera. Similar studies were carried out in children with cholera and adults and older children with severe diarrhea not due to cholera.

Since 1977, investigators have carried out a number of clinical studies perfecting the use of ORT in noncholera infant diarrhea in many less developed areas of the world. These studies have examined modifications in oral dehydration formulas including the sugar, base, sodium, and potassium content; they have resulted in practical regimens for health workers to follow in orally dehydrating infants; they have demonstrated the efficacy of oral dehydration, irrespective of the etiology of the diarrhea; and they have defined the limitations of ORT.

Several methods have been devised for the preparation of simple sugar / salt solutions that are safe and can be prepared in the home. These simple solutions are just as effective as more complex balanced glucose / electrolyte solutions in stimulating sodium and water absorption by the intestine, though infants treated with such solutions have inadequate potassium replacement and can become potassium depleted, a state with adverse clinical consequences.

ORT has been perfected in recent years to the point where it represents one of the most powerful weapons in the armamentarium against disease in the less developed world. Increasingly, less developed countries are undertaking national diarrheal disease control programs in which ORT constitutes the keystone.

Many U.S. pediatricians were initially somewhat resistant to ORT. Through a series of recent seminars, reviews, and publications in American pediatric journals, however, information on the efficacy and advantages of oral dehydration has been widely disseminated,

The development of ORT illustrates how basic physiological and biochemical research can lead to a highly effective therapeutic modality and practical public health tool. Specifically, the observation that during diarrhea, the intestine maintains its ability to absorb glucose and that sodium and water absorption accompany glucose absorption provided the physiologic basis for ORT as a clinical tool.

Introduction

More than one-half of the world's population lives in less developed areas that are characterized by a lack of potable water, inadequate means for disposal of human fecal waste, and intense crowding in rudimentary housing. Under such conditions of poverty, underdevelopment and lack of education, the pathogenic bacteria, viruses, and protozoa capable of causing diarrheal disease in humans are readily transmitted to young children. Indeed, under such conditions, the hands that touch infants, the weaning foods that are fed to infants, and the water that infants drink are heavily contaminated with fecal material, and therefore with diarrhea-causing pathogens. As a consequence, in the first 2 years of life, young children in the less developed countries bear an enormous burden of diarrheal diseases.

This case study examines the causes of infant diarrhea, its consequences, the magnitude of the problem, and the interrelationship between infant diarrhea and other major public health problems of the less developed world. The primary focus of the case study is on ORT. The discussion that follows reviews basic scientific contributions that provide a physiologic basis for this therapy, obstacles that had to be overcome to give it widespread acceptance, and hurdles that are now having to be passed in order to realize implementation of ORT on a global scale.

Definitions of Infant Diarrhea and Dehydration

The term diarrhea stems from the Greek word meaning "to flow through" and denotes an increased number of stools per day which are in an unformed or liquid state. Since the daily stool patterns of infants vary greatly owing to diet, feeding frequency, etc., the most useful operational definition of infant diarrhea is when the mother (who best knows her baby's stool pattern) states that her child has diarrhea (71). Typically, a state of diarrhea is characterized by at least three loose stools within a 24-hour period. Since infancy in American pediatric terms refers to the first 12 months of life, strictly speaking, infant diarrhea would refer to illness within that period only. However, since diarrheal diseases remain an important cause of morbidity and mortality for at least the first 24 months of life in less developed areas, the term "infant diarrhea" in common usage has come to refer to the illness in children up to 2 years of age (71),

Seventy percent of the human body, by weight, consists of water. Approximately 55 percent of the body water is located inside tissue cells and is associated with potassium ion (K ‘); the remaining 45 percent is extracellular and is associated with sodium ion (Na^+). Irrespective of the specific infectious cause of an episode of diarrhea, the common denominator from the pathophysiologic point of view is the loss of body water and salts (electrolytes) in the diarrheal stool. Diarrhea represents mainly loss of extracellular water and Na^+, but K^+ is also lost in significant quantities.

In the older child or adult, diarrhea is usually a nuisance rather than a mortal danger (although the copious purging that occurs with cholera can dehydrate even adults). In children under 2 years of age, however, diarrhea of any etiology is potentially life-threatening if stool losses are copious. The reason is that the losses of body water and electrolytes resulting from loose stools can lead to significant dehydration, which, in the face of continuing unreplenished losses, can result in acidosis, shock, and death. In virtually all the less developed countries of the world, diarrheal dehydration is either the first, second, or third most common cause of infant deaths (22,48,71, 121,159).

Infants are at enhanced risk of development of severe dehydration for several reasons:

- Per kilogram of body weight, an infant each day requires 2% times more water than an older child or adult (67). This requirement is mainly due to the greater surface area of the infant per kilogram of body weight, which results in proportionally more water loss by transpiration through the infant's skin.
- An infant cannot talk to specifically communicate thirst and request fluids.
- An infant cannot walk to a source of water or fluids to help himself or herself quench thirst. The infant is thus totally dependent on its mother or caretaker. In many cultures across the world, mothers actually decrease the amount of fluids (and breast milk) offered to infants with diarrhea

in the incorrect belief that this will benefit the infant by "resting the gut."

- Certain homeostatic mechanisms of the kidney may be less efficient in the young infant, thereby diminishing the body's capacity to adjust successfully to physiologic derangements (3,6).

Etiology of Infant Diarrhea

Prior to the early 1970s, the etiology of most episodes of infant diarrhea was largely unknown, either in industrialized societies or in less developed areas (59,62,88,111,124,125,163,164,165). Since the early 1970s, however, there has been a veritable explosion of knowledge on the causes of infant diarrhea with many new agents being discovered.

The most important infectious agents that cause infant diarrhea are listed in table A-1. Currently, an etiologic agent can be identified in approximately 65 to 75 percent of the cases of infant diarrhea that occur in less developed countries if comprehensive microbiologic techniques are used (11,12,83,148).

Black and colleagues, working in Bangladesh, noted that two etiologic agents, rotavirus and enterotoxigenic Escherichia coli, were found in approximately 60 percent of the cases of diarrhea] dehydration severe enough to be seen in a dehydration center (11). Black and colleagues also followed a cohort of infants prospectively in a rural Bangladeshi village (9). This more intensive surveillance detected mild as well as more severe cases of diarrhea, including cases that would not usually be seen in a treatment center because of their mildness. Enterotoxigenic ***E. coli*** was found to be the most common cause of diarrhea, accounting for three episodes per child per year. One-fourth of the episodes of E. coli diarrhea lasted longer than 10 days (9).

Magnitude of the Problem of Infant Diarrhea

In the United States, the infant mortality rate is 11 per 1,000 live births (i.e., 11 of every 1,000 babies born live fail to survive to their first birthday) (161), and diarrheal dehydration is an uncommon cause of death. In contrast, in less developed countries, infant mortality rates typically range between 100 to almost 250 deaths per 1,000 live births, and diarrheal diseases are almost everywhere 1 of the three major causes of infant deaths. In general, when the infant mortality rate exceeds 100 per 1,000 live births, at least one-third of all infant deaths are attributable to diarrheal diseases (32,101).

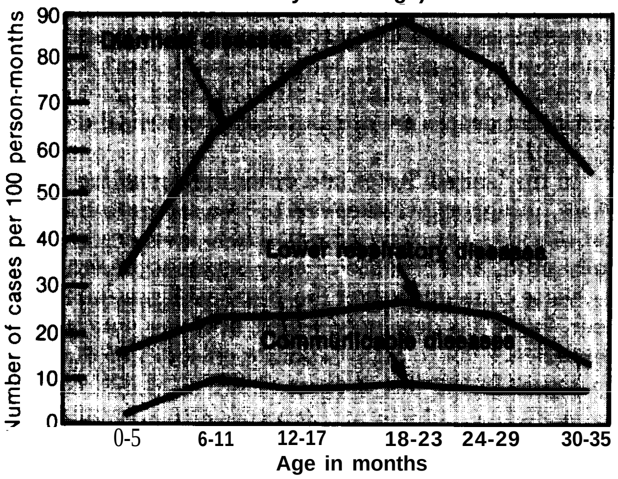
In the United States and other industrialized countries, infants experience one to two separate episodes of diarrhea per year (58,68). These episodes are usually mild, and because of easy access to health care, adverse consequences of the diarrheal illness rarely occur. In the less developed world, however, infants may experience six to eight separate episodes of diarrhea per year in the first 2 years of life (7,81,82). Results of a study of infectious disease incidence among children in less developed countries are summarized in figure A-1, showing the incidence of diarrhea] disease to be much higher than rates for the other major causes of morbidity. Since each separate episode of clinical diarrhea lasts for several days, one calculates that infants in less developed countries spend approximately 15 percent of their entire life experience in the first 2 years, when rates are highest, suffering with diarrhea.

The World Health Organization (WHO) undertook to quantitate the magnitude of the problem of infant diarrhea in the less developed world by reviewing the published literature to determine the incidence rates of infant diarrhea and applying the calculated rates to the 1980 estimates for the population of children under 5 years of age (145). In an extremely conservative estimate, the investigators calculated that there are at least 750 million to 1 billion episodes of diarrhea and 4.6 million deaths each year due to diarrhea in children less than 5 years of age in Africa, Asia (excluding the People's Republic of China), and Latin America. They also estimated that approximately 1 in every 167 episodes of diarrhea in young children results in death.

Table A-1 .—Infectious Agents That Cause Infant Diarrhea

Type of agent	Major importance	Lesser importance
Bacteria.	Enterotoxigenic *Escherichia coli* *Carnpylobacter jejuni* Enteropathogenic *E. co/i* *Shigella*	*Salmonella* *Aeromonas hydrophila* *Vibrio cholerae*
Viruses	*Rotavirus* Atypical adenoviruses	27NM Gastroenteritis viruses Astroviruses Calciviruses
Protozoa	*Giardia lamblia*	*Cryptosporidium* *Entameba histolytica*

Figure A.1.—Incidence of the Main Groups of Infectious Diseases Among Children During the First 3 Years of Life in Less Developed Countries (data from a cohort of 45 children observed from birth to 3 years of age)



SOURCE: Adapted from L. J. Mata, R. A. Kronmal, and H. Villegas, "Diarrheal Diseases: A Leading World Health Problem," in *Cholera and Related Diarrheas*, O. Ouchtertony and J. Holmgren (eds.) (Basel: S. Karger, 1980).

Nutritional Consequences of Infant Diarrhea

Besides dehydration, the other major consequence of infant diarrhea is malnutrition. Virtually every infectious agent that causes acute diarrhea results in a temporary state of intestinal malabsorption that may last up to several weeks, during which time ingested nutrients are not properly digested and absorbed (14,63,74,76,129). Furthermore, each episode of diarrhea has other nutritional consequences. The diarrheal infection itself, particularly if associated with fever, results in increased catabolism (i.e., increased breakdown of body mass to provide energy sources). Studies in Guatemala by Mata and colleagues (81,82) showed that infants and toddlers readily consumed the recommended daily caloric intake during periods when they were not ill. However, young children ill with diarrheal or respiratory infections simply did not consume the recommended intake of calories during the episode of illness. When episodes of illness occurred one after the other, children would fall off the normal growth curve and malnutrition would become evident. Another problem faced in many parts of the world is that mothers in many cultures will decrease offerings of food to infants with diarrhea.

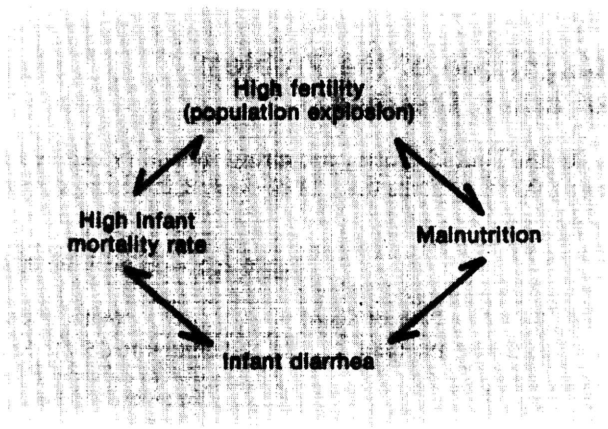
The Interrelationship of Infant Diarrhea With Other Major Public Health Problems of the Less Developed World

Certain health problems are common to all less developed countries. These include high infant mortality, diarrheal disease as a major cause of infant morbidity and mortality, high fertility (manifested as high population growth), and malnutrition (see fig. A-2). Because of interrelationships among these various health problems, control of some of them can have an important ameliorating effect on others. The interrelationships and the critical points of intervention are briefly discussed below.

The fertility rate of a country refers to the average annual number of live births per 1,000 women of childbearing age (15 to 49 years). High fertility leads to rapid population growth. One school of thought contends that high fertility is in great part the consequence of high infant mortality, since the latter creates compelling pressures for parents to produce more children in order to ensure survival to adulthood of some children (16,82,84). For example, in a particular culture, if two sons are believed to be required for the well-being and perpetuation of an agrarian family, the parents aim to produce a sufficient number of "insurance" children to ensure the survival of the desired number.

Multiple infant deaths and multiple pregnancies lead to the maternal deprivation syndrome—the poorly nourished, anemic, exhausted, women ubiquitously

Figure A.2.—Interrelationship of Factors Perpetuating Diarrheal Disease



SOURCE: Office of Technology Assessment, 1985.

encountered throughout the less developed world. The last infants of such women have even less chance of survival because of their mothers' diminished lactational capacity.

High fertility can lead to extraordinary population growth and pressure on land resources and limited food supplies. Some less developed countries (e.g., Kenya) have annual population increases of more than **3** percent. Consequently, the population is young (about **40** percent are less than 15 years of age) and doubles in size every **20** to 25 years!

There is an intimate relation between infant diarrhea and malnutrition (9,10,29,71,80,81,102, 121,130, 143,152,154). Simply stated, multiple bouts of diarrhea lead to malnutrition. Malnutrition, in turn, predisposes to increased incidence, severity, and case fatality of diarrheal disease. Puffer and Serrano's (121) classic study of childhood mortality in the Americas documented the intimate correlation between malnutrition and death due to diarrheal disease.

There is evidence that the malnourished child has more frequent bouts and increased severity of diarrhea. Protein malnutrition leads to decreased stomach acid (49); stomach acid is perhaps the most important nonspecific defense mechanism against bacteria that cause diarrhea. Diminished stomach acid allows inordinately large numbers of pathogenic bacteria to reach the small intestine.

Points of Intervention

How is it possible to intervene effectively to diminish or break the vicious cycle portrayed in figure A-2 and described above? In the past, attempts were made via nutritional intervention and family planning programs. Nutritional programs by themselves have largely failed, and family planning is least successful where infant mortality rates are high.

Some countries have broken this cycle in the course of just **25** to **30** years as a consequence of rapid capital development, industrialization and striking improvement in the general socioeconomic level. Just how rapidly these changes can occur is demonstrated by the New York City's experience between **1900** and 1930. Figure A-3 shows that the infant mortality rate in New York City in **1900** was 140 deaths per 1,000 live births, a typical rate for a developing country. The single most important cause of infant mortaIity was infant diarrhea (referred to as "cholera infantum"). By 1930, New York's infant mortality rate had plummeted to approximately 50 per 1,000 live births. This extraordinary fall in the rate was almost entirely attributable to the decrease in infant deaths from diarrhea] disease. It is important to note that this decrease in New York's infant mortality from diarrheal disease occurred in the absence of modern treatments such as dehydration therapy or antibiotics and without the benefit of specific vaccines. Rather, the rapid improvement in living conditions (provision of potable water and sanitation systems) and in the educational level of the population resulted in a striking decrease in the incidence of diarrheal infections. As the population of New York City went from living conditions of underdevelopment to those of modern industrialized societies, the transmission of the micro-organisms that cause diarrhea in young children was sharply curtailed. Thus, both the incidence of diarrhea and mortality due to diarrhea] diseases sharply decreased. The epidemiologic changes described in New York City were also experienced in European countries (including England, France, and Germany) at approximately the same time.

Although fundamental changes in quality of living conditions represent the optimal mode of intervention, such changes are unlikely to occur in ***many less*** developed countries in the near future because the means for rapid capital development and industrialization simply are not available. Other more practical, simplified interventions must be employed if they are to have an expectation of success in the short term.

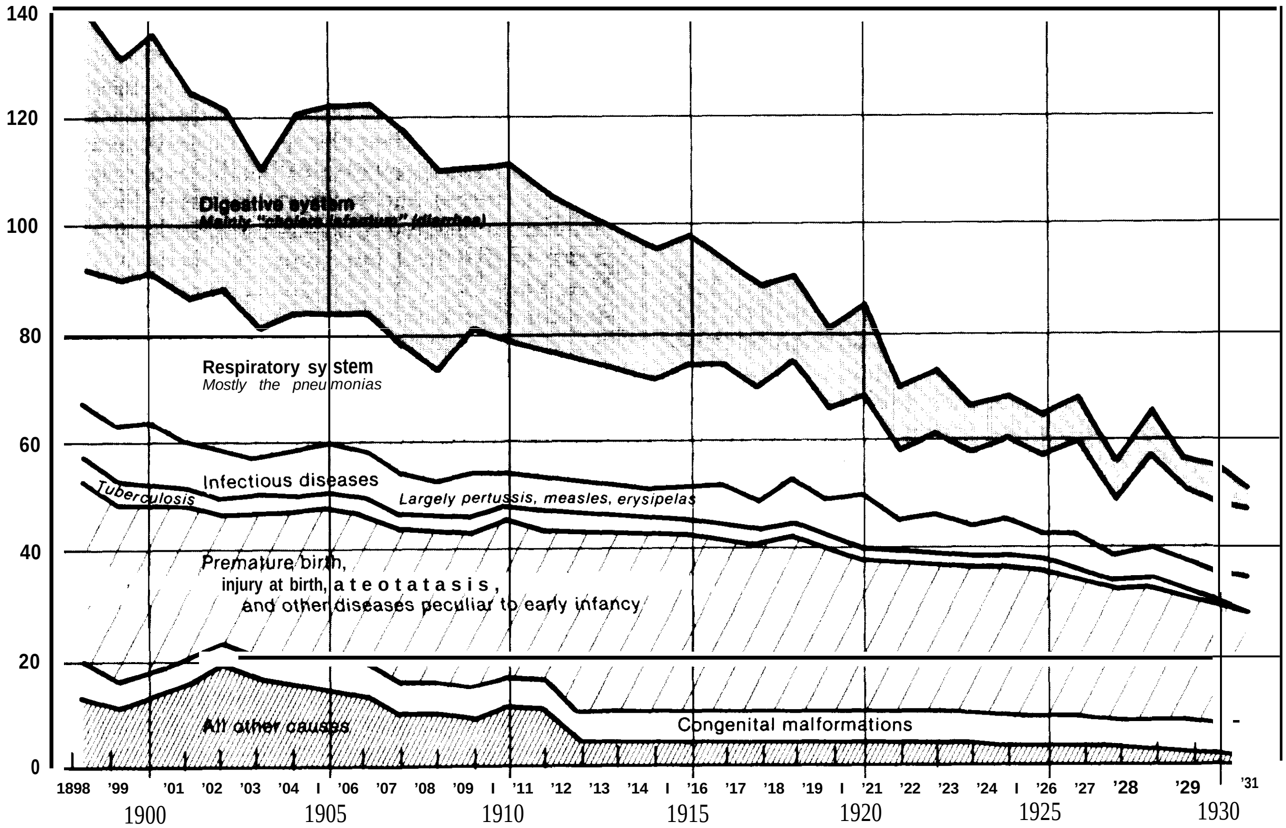
Up to the last decade, there was no simple and effective intervention to attack the vicious cycle in figure A-2 at the point involving infant diarrhea. However, such an intervention now exists: ORT. This is an inexpensive, highly effective means of replacing the deficits of body water and electrolytes in dehydrated infants,) that is technologically appropriate for use in less developed countries. ORT constitutes a revolutionary innovation in the treatment of diarrheal disease that has the potential to greatly diminish infant mortality throughout the world.

History of the Development of ORT

Intravenous Dehydration

Dehydration is the most important complication of diarrhea; untreated it can lead to death. An important therapeutic advance in pediatrics was the demonstration in the first half of the 20th century that deaths from diarrheal dehydration could be prevented if the dehydrated infant's deficits in body water and electrolytes were replaced by infusions into a vein of sterile electrolyte-containing solutions (54).

Figure A.3.—Infant Mortality by Prominent Causes in New York City, 1898-1930 (rates **per** 1,000 births)



SOURCE: W. McDermott, "Modern Medicine and the Demographic-Disease of Overly Traditional Societies: A Technologic Misfit," J. *Med. Educat. 41* (Sept. Suppl.): 137-162, 1966, used by permission from the *Journal of Medical Education*

This life-saving intravenous therapy gained widespread use in the United States in the 1940s, 1950s, and 1960s for the treatment of diarrheal dehydration in infants (54). Intravenous dehydration used by U.S. Navy physicians during large outbreaks of cholera in Egypt in 1947, in Thailand in 1958-60, and in the Philippines in 1962 dropped the case fatality rate for severe cholera from 20 to 50 percent down to 1 percent (108, 158,160).

Intravenous dehydration for the treatment of dehydrated infants also became increasingly popular in less developed countries in the 1950s and 1960s. However, its impact was limited because availability was generally restricted to hospitals in cities. Even in those facilities where it was used, it represented a significant drain on financial and personnel resources.

The disadvantages of intravenous dehydration include the following:

- Intravenous dehydration is expensive.
- The intravenous fluids and needles and plastic tubing required to administer them must be sterile; often these materials must be imported with hard currency.
- In general, a specially trained person is required to start the intravenous infusion, select the appropriate fluid, and supervise the volume and rate of administration.
- Use of the same needles and tubing in more than one patient without proper sterilization (a common practice in less developed areas) in an effort to decrease costs encourages the transmission of infections such as hepatitis from one patient to another.
- The mother is not directly involved in care of the infant.
- There are logistical problems in ensuring the delivery of supplies of intravenous fluids, tubing, needles, etc., to rural and less accessible areas.

Oral Rehydration—An Alternative

During the past 20 years, there has evolved an alternative form of therapy, ORT, that has multiple advantages over intravenous dehydration and is well-suited for use in less developed countries. This new therapy involves rehydration by the oral route using solutions containing glucose or sucrose (sugars) and electrolytes (salts in solution). The advantages of ORT include the following:

- ORT is inexpensive.
- The basic ingredients are found within most less developed countries.
- Sterile materials are not necessary.
- Highly specialized personnel are not directly required to administer the therapy.
- While therapy is in progress, the patient does not require the same degree of vigilance as a patient receiving intravenous rehydration.
- The mother can be directlv involved in treatment by administering the oral rehydration solution to the infant.

Physiologic Basis of Oral Dehydration

The normal intestine has tremendous absorptive capacity. In the normal state in the healthy adult, 7 to **8** liters of endogenous fluids (including saliva, bile, stomach fluid, intestinal juice, pancreatic juice) are secreted into the intestine. In addition, approximately 2 to 3 liters of exogenous fluids are consumed each day. Yet at most, only 200 ml of water are lost each day in normal feces. The normal intestine absorbs 98 percent of the fluid that enters it in the normal state. In contrast, during diarrhea, the intestine exhibits net secretion.

The physiologic rationale for the efficacy of glucose/electrolyte oral rehydration solution is the fact that even during diarrhea, the simple sugar glucose continues to be absorbed by the upper small intestine (the jejunum) via an active transport mechanism (56,107,109). As molecules of glucose are actively absorbed, molecules of water and sodium (Na^+) are also absorbed; bicarbonate (HCO_3^-) and potassium (K+) are absorbed during diarrhea even without glucose.

The first clinical balance studies documenting the importance of glucose as an actively transported substrate that promotes water and Na^+ absorption during diarrhea were carried out in 1962 in the San Lazaro Hospital in Manila, Philippines by Phillips and coworkers (108) of the U.S. Naval Medical Research Unit—2 (NAMRU-2), Taipei.

Prior to that time, several clinical investigators had published reports describing the use of glucose/electrolyte mixtures in oral rehydration of patients with diarrhea, but none of these investigators was aware of the critical importance of glucose in the absorption of Na^+ and water during diarrhea. Rather these workers had included glucose merely as a source of calories for the child with diarrhea. Darrow (34) and Harrison (44,52) used such solutions to treat infants with mild dehydration. Chatterjee (21) treated mild cholera patients with oral dehydration. The most extensive and impressive experience was reported by Menenghello and colleagues (86) from Santiago, Chile. Each summer during the 1950s, epidemics of infant summer diarrhea in Santiago overwhelmed the available health services. These Chilean workers set up oral rehydration units and rehydrated infants with a glucose/saline solution administered into the stomach through a nasogastric tube. In a comparative study, these Chilean workers noted that oral rehydration with their glucose/saline solution was as effective as intravenous fluids in rehydrating moderately dehydrated infants and was much more practical, simple, and economical. Menenghello and colleagues' experience was reported in the American pediatric literature in 1960 in the annual publication ***Advances in Pediatrics,*** but little notice was given to it.

Prior to 1962, there also had been several publications in the scientific literature establishing that in animal intestine glucose is actively absorbed and promotes the absorption of Na^+. Fisher and Parsons (45) are credited with being the first to show that glucose is actively absorbed by rat intestine and that its absorption promotes water absorption. Riklis and Quastel (127) in 1958, and Curran (31) in 1960, demonstrated that glucose also promoted the transport of Na^+ and Cl^- ions. Finally, Schedl and Clifton (140) as early as 1963, reported that glucose exhibited a stimulator effect on the absorption of Na^+ and water by normal human intestine.

It is not clear whether Phillips and associates were aware of the above reports when they commenced their studies in Manila in 1962. Van Heynigan and Seal discusses this question in their book ***Cholera—The American Scientific*** *Experience 1947-1980* (155). They quote one associate of Phillips, Craig Wallace (p. 229), as believing that Phillips was indeed aware of these early physiologic studies reporting the effect of glucose on Na^+ and water absorption. In contrast, they point out that another friend and collaborator of Phillips, Sir Graham Bull (p. 229-230), was convinced that Phillips was unaware of the importance of glucose in stimulating absorption of Na^+ and that his inclusion of glucose in solutions given to certain patients in Manila in 1962 was "purely to make the solution isosmolar,"

Whether Phillips did or did not know of the earlier studies is probably irrelevant in the historical context. What is important is that he carried out elegant and precise clinical balance studies on adult patients with cholera who ingested various solutions. In the course of these studies, he demonstrated for the first time the salutary effect of glucose on absorption of both Na^+ and water in patients with severe diarrhea.

Phillips first published his observations in 1964 (107). In these balance studies, Phillips measured diarrheal stool output (in ml/kg/hr) and quantitated the electrolyte content of the cholera stools. He also carefully measured the volume and rate of administration of the various oral solutions that he tested. By subtracting the hourly oral intake from the hourly stool output, Phillips was able to gauge the effects of various oral solutions on stool output.

In this way, Phillips clearly documented that pure distilled water, devoid of any electrolytes or other solutes, was readily absorbed by an adult cholera patient and was able to replace the water losses in moderate cholera. Phillips reported that the patient with cholera drank two glasses of water (500 ml) each hour without difficulty. However, choleraic stools of adults contain considerable Na^+ (approximately 13s mMol/1) as well as other electrolytes. Since plain water does not replace the Na^+ losses, patients with moderate cholera rapidly become deficient in Na^+. The Na^+ deficits must be repaired or the patient's life would soon be endangered.

Phillips had cholera patients drink a balanced oral solution that contained concentrations of electrolytes closely resembling those found in the stools of an adult with cholera. Phillips noted that in contrast to plain water, the electrolyte solution resulted in no absorption whatsoever of water or Na^+ even with the patient drinking **700** ml each hour. Only K^+ was readily absorbed. Phillips next demonstrated that when a healthy adult without diarrhea drank the same electrolyte solution at the same rate, no diarrhea occurred. This showed that the healthy intestine could easily absorb the water and electrolytes in the large volumes of the solution ingested.

In the next step, Phillips gave an electrolyte solution containing a much higher concentration of Na^+ **(230** mMol/1) than cholera stool (135 mMol/1) or serum (140 mMol/1). Under these circumstances, as well, water and Na^+ losses increased in the stool.

Phillips next decided to "investigate the effect of oral solutions supplemented with nonelectrolytes such as D-glucose." The solution he used included **95** mMol/1 of Na^+ and 100 mM/1 of glucose. The patient drank the solution at the rate of 500 ml/hr. Phillips found that glucose was absorbed during cholera, and along with it water, Na^+, Cl^-, HCO_3^-, and K^+. Phillips exact words in the **1964** report are of interest (107):

> Furthermore, it was found that the glucose was absorbed, indicating that the glucose transport mechanism was not inactivated in cholera.

The use of the term "glucose transport mechanism" strongly implies that at least at the time of preparation of his 1964 manuscript, Phillips was aware of studies showing intestinal absorption of glucose by an active transport mechanism.

The last clinical experiment described by Phillips involved the evaluation of increasing concentrations of glucose from so to 400 mMol/1 with the electrolyte concentrations remaining the same. As the glucose concentration increased, Na^+ losses in the stool decreased (i.e., Na^+ absorption increased).

Phillips' closing statement is prescient and worth noting in its entirety (107):

> Oral therapy in cholera. From the above studies it is evident that oral solutions can replace the H_2O, K+, and some of the HC03– losses in cholera. This means that the only intravenous requirement is the replacement of the Na^+ and Cl^- losses. We have further evidence which suggests that by incorporation of glucose in an oral solution that one may be able to develop an oral treatment regimen which in the average case might completely eliminate the requirement for intravenous fluids. I would like to urge caution on this particular point. Such a regimen can only be validated by careful balance studies of the type reported here. The literature on cholera abounds with treatment regimens which had been enthusiastically urged by their proponents in whose hands there has been great success. When the same treatment was tried by others, it appeared to be useless, I am sure this audience will readily understand why we believe it is necessary to carefully document any new therapeutic regimens suggested for the treatment of cholera.

Further Studies of Intestinal Absorption

In the 5 years following Phillips' 1964 report on the effect of glucose on intestinal absorption of Na^+ and water in patients with cholera, important research proceeded rapidly in two independent but mutually related areas. First, physiologists and gastroenterologists began to study intensively the precise mechanisms by which glucose enhanced Na^+ and water absorption in the intestine of healthy humans and animals (5,40,46,47,128,141,144). Second, concomitantly, Americans and Bangladeshis in Dhaka, East Pakistan (now Dacca, Bangladesh), and American and Indian investigators in Calcutta, India, carried out clinical intestinal flux studies to expand on and confirm Phillips' observations in the Philippines, again establishing the feasibility of using oral dehydration in the treatment of cholera (56,109).

Schultz and Zalusky (141) suggested that the enhancement of Na+ transport by glucose is due to an interaction with the sugar transport per se, i.e., there occurs a glucose-coupled Na^+ transport. Sladen and

Dawson (144) came to the same conclusion from studies of intestinal absorption in humans. Fordtran and coworkers (47), who also studied glucose and Na^+ absorption in humans, concluded in 1968 that while a small fraction of Na^+ absorption occurs by active transport coupled to glucose, most Na^+ absorption occurs in the osmotic flow of water molecules created by the active absorption of glucose. (This means that as glucose molecules are actively absorbed, osmosis results in absorption of water molecules as well. And as the water molecules are absorbed, Na^+ is dragged along.) In a 1975 publication, Fordtran (46) reiterated that both active and passive sodium transport occurs in the jejunum and that the relative importance of each depends on the glucose and Na^+ concentrations in the jejunal lumen. Fordtran again concluded that solvent drag, rather than active cotransport, is the most important mechanism by which glucose stimulates net Na^+ absorption in the human jejunum.

Other investigators showed that substrates other than glucose, including certain amino acids, also promote the absorption of Na^+ and water as they are actively transported (50,128,142,147,151). This finding raises the possibility of including more than one actively absorbed substrate in an oral dehydration solution to stimulate absorption of water and Na^+.

Hirschhorn and colleagues (56), working at the Pakistan Southeast Asia Treaty Organization Cholera Research Laboratory (CRL) in Dacca, and Pierce and colleagues (109), working at the Johns Hopkins International Center for Medical Research and Training (ICMRT) at the Infectious Disease Hospital in Calcutta, carried out elegant clinical balance studies to expand the preliminary work initiated by Phillips (107) in patients with cholera. These clinical studies provided a sound physiologic basis in humans for proceeding with clinical trials of oral glucose / electrolyte therapy in cholera and other diarrheal diseases.

Hirschhorn and colleagues (56) infused various sugar / electrolyte solutions into the stomach or small intestine of eight patients with cholera. The electrolyte concentration of the solution was fixed (and included 134 mMol / 1 of Na^+), but varying concentrations of glucose, galactose, or fructose were added. Hirschhorn's group confirmed that glucose caused enhanced Na^+ and water absorption. Fructose, in contrast, was shown to have no enhancing effect.

Pierce and colleagues (109) carried out balance studies in 14 adults with cholera who were divided into three groups to receive one of three solutions by nasogastric tube. All three solutions contained approximately the same concentrations of K^+ and HCO_3^-, while the Na^+ and glucose concentrations varied. These investigators confirmed that the intestine's ability to absorb glucose remained intact during cholera and that glucose stimulated absorption of Na^+ and water. They reported that raising the glucose concentration of the solution infused into the stomach from 40 to 160 mMol / 1 doubled the absorption of water and Na^+. However, further raising the glucose concentration from 160 to 220 mMol / 1 did not further enhance water and Na^+ absorption.

Progression of Clinical Research Studies Leading to ORT as It Is Practiced Today

Early Studies in Adults With Cholera

The first publication investigating the therapeutic efficacy of an oral glucose / electrolyte solution was reported by Nalin and coworkers (95) from the CRL in Dacca and involved adults with moderately severe cholera. After receiving intravenous fluids to treat shock, 29 patients were randomly assigned to one of three groups. The first group of 10 patients continued to receive intravenous fluids, the standard therapy for cholera; the second group of 10 patients received a glucose / electrolyte solution by stomach tube after they were treated for shock with intravenous fluids; and the third group of 9 patients drank the glucose / electrolyte solution after they were successfully treated for shock.

Nalin's group (95) demonstrated for the first time that the intravenous fluid requirements of patients with severe cholera could be diminished by 80 percent if they either drank a glucose / electrolyte solution or had it infused through a stomach tube. The composition of the oral glucose / electrolyte solution used in this study contained 120 mMol / 1 of Na^+ and 110 mMol / 1 of glucose. Cholera patients drank 400 to 1,050 ml each hour without difficulty, and vomiting was not a problem.

In 1969, Pierce and coworkers (110) in Calcutta reported a similar favorable experience using an oral glucose / electrolyte solution in 20 adult patients with cholera. The solution contained 120 mMol / 1 of glucose but had a somewhat lower Na^+ concentration (100 mMol / 1) than the solution used by the CRL group (95). Only one patient in the oral therapy group required some additional intravenous fluids to recover. The results of the Calcutta group corroborated the report from CRL,

In 1979, Cash and coworkers (17) reported from the CRL in Dacca that adults with moderate cholera and dehydration short of overt shock could be entirely treated by oral dehydration using a solution that contained 120 mMol / 1 Na^+ and 110 mMol / 1 glucose, completely obviating the need for intravenous fluids.

In other studies at this time, Nalin and Cash (93) compared glucose/electrolyte solutions containing 2 percent glucose (110 mMol/1) and 4 percent glucose (220 mMol/1), and found that net water balance was equally good with the lower concentration. Since Pierce and colleagues (109) had earlier shown that a solution containing 5 percent glucose offered no advantage over a 3 percent glucose solution, this combined experience led to the general acceptance of 2 percent glucose as the concentration in all future clinical studies with oral dehydration solutions.

Studies in Children With Cholera

Nalin's group at the CRL in Dacca next examined oral dehydration in children with cholera (94,96). In the early 1970s, the CRL investigators were routinely using an oral glucose/electrolyte solution containing 120 mMol/1 of Na^+ and 110 mMol/1 of glucose. The results in children were as good as those obtained in adults with cholera. The intravenous fluid requirements of children with severe cholera were reduced by 80 percent, and children with mild or moderate cholera could be dehydrated entirely by the oral route. Evidence was rapidly accumulating showing the efficacy of oral glucose/electrolyte solutions in treatment of patients of any age with cholera.

Studies in Patients With Noncholera Diarrhea

The next major contribution of clinical investigators working in the Indian subcontinent was the demonstration that oral glucose/electrolyte solution was effective in treating adults and older children with diarrheal dehydration of etiology other than cholera (92,136). Most of these adult patients were later found to be infected with enterotoxigenic E. coli (137).

Preliminary Use of ORT in Field Dehydration Centers

Although experience with ORT in Dacca and Calcutta was rapidly increasing and the scope of its use was being expanded, ORT was at first used only in clinical research studies under carefully controlled conditions. Beginning in 1970, however, reports of evaluations of ORT under field conditions in rural treatment centers began to appear (18,78). Cash and coworkers (18) showed that ORT could be used successfully under field conditions in rural East Pakistan during an epidemic of cholera. As in the controlled environment, the requirement for intravenous fluids was decreased by 70 percent.

In 1975, a notable report by Bangladeshi researchers showed the promise of ORT (78) by describing its use in a crowded camp for Bangladesh refugees during a cholera epidemic. Polyethylene packets of glucose and salts were prepared by hand. When mixed in 1 liter of water, the solution yielded 90 mMol/1 of Na^+ and 121 mMol/1 of glucose. No potassium was included since K^+ salts were unavailable. Under extremely adverse, primitive conditions, 3,703 patients with clinical cholera were treated with oral glucose/electrolyte solution and only a small supply of intravenous fluids. The case fatality rate was only 3.6 percent in this epidemic, largely because of the availability of ORT.

Early Reports of ORT in Infants With Diarrheal Dehydration

Despite the expanding use of ORT in Dacca and in Calcutta in the mid-1970s, there were few reports of its use in infants and young children outside of the Indian subcontinent. This represented a problem since the greatest need for oral dehydration worldwide was in the treatment and prevention of dehydration in infants and young children with noncholera diarrhea rather than in the treatment of adults with cholera.

Up through 1977, almost all of the reports describing oral dehydration of pediatric patients originated from Asia (almost all from the Indian subcontinent) and often included children with cholera. Thus, a false perception was perpetuated elsewhere in the world that oral therapy was mainly for cholera.

The earliest reports of the use of oral glucose/electrolyte solution outside Asia were those of Hirschhorn and coworkers (55,57), who treated moderately dehydrated Apache infants with oral dehydration in Arizona. In these pioneer efforts, the investigators clearly demonstrated ORT'S efficacy by means of monitoring body weights, stool volume, and plasma protein concentration. The method of dehydration Hirschorn and colleagues described was referred to as "ad Iibitum" treatment, implying that when glucose/electrolyte solution is offered to an infant, the homeostatic mechanisms of the infant would lead the infant to drink until dehydration was established.

The "ad libitum" treatment regimen was not readily adopted by pediatricians or other health workers for three reasons:

1. The "ad libitum" treatment does not make use of the concept of estimation of fluid deficits and replacement of the calculated deficit. This is the fundamental physiologic concept on which all rational dehydration therapy, oral or parenteral, should be-based (79). -
2. The treatment is not easy to teach to unsophisticated health workers.

3. A small percent of overtly dehydrated infants do not readily drink oral dehydration solutions and must be actively coaxed. The fluid needs of such infants would not be recognized if a pure "ad libitum" method were followed.

Clinical Studies of ORT in Infant Diarrhea Since 1977

Since 1977, there has been a veritable explosion of information on the use of ORT in infants in many areas of the world including Central and South America, Africa, Southeast Asia, and the Caribbean basin. In careful clinical research studies, the remaining voids of knowledge were filled and obstacles impeding widespread acceptance of ORT were overcome. Much of this research was carried out by five groups: from the University of Maryland School of Medicine; the National Children's Hospital, San Jose, Costa Rica; the International Center for Diarrheal Diseases Research, Bangladesh (ICDDR, B); the Baltimore City Hospital; and the Kothari Pediatric Gastroenterology Center, Calcutta. Most of these studies in infants and children used the glucose/electrolyte solution recommended by WHO (shown in table A-2) or a very similar solution. These clinical studies established the efficacy of ORT in infants, identified its limitations, examined efficacy in relation to etiology, and evaluated modifications in the sugar and base content, and Na^+ and K^+ concentration in oral dehydration solutions. These studies are summarized below.

Clinical Indications, Regimens, and Limitations of ORT

Development of Practical Methods To Rehydrate Dehydrated Infants

Several groups of researchers have described regimens of ORT that were highly successful in dehydrating dehydrated infants (except those in overt shock) (24,28,100,114,139). These methods used the concepts of percent dehydration and fluid deficit estimations. Three methods (28,100,114) included offerings of plain water to infants, in addition to sugar/electrolyte solutions, to prevent the development of hypernatremia (a condition in which the serum Na^+ concentration exceeds 1.50 mMol/1).

Two groups (24,139) have demonstrated that dehydrated infants can be safely rehydrated with sugar/electrolyte solution alone without hypernatremia developing. Other investigators (113,132) have corroborated these findings.

Table A.2.—WHO Glucose/Electrolytes Solution

Ingredients:	
NaCl	3.5 gm
NaHCOs	2.5 gm
KCI	1.5 gm
Glucose	20 gm
HzO	1.0 liters

Electrolytes in resulting solution (mMol/liter):

Na^+		cl-	$HCO3^-$	Glucose
90	20	80	30	111

Acceptability of Oral Solutions and Intestinal Water Absorption

Many researchers have documented that the vast majority of overtly dehydrated infants, despite fever, malaise, and lethargy, avidly drink sugar/electrolyte solutions (19,20,24,26,28,73,100,113,114,118,132,139), even though the taste is described as unpleasant by healthy adults. These overtly dehydrated infants gain weight from absorption of water and electrolytes (19, 20,24,26,28,73,100,113,114,118,132,139). Approximately 95 percent of dehydrated infants, even those 10 to 12 percent dehydrated (but not in shock) can be successfully rehydrated with oral sugar/electrolyte solutions. (Dehydration with loss of more than 10 to 12 percent of body weight is almost always accompanied by clinical shock. Mild dehydration refers to up to 5 percent loss of body weight; moderate dehydration means loss of 6 to 9 percent; 10 percent or greater loss of body weight represents severe dehydration.) The demonstration that infants with 8 to 12 percent dehydration could be orally rehydrated was important, because it dispelled the contention of some pediatricians (101) that oral dehydration alone was incapable of dehydrating infants with moderate and severe dehydration short of shock.

ORT'S Efficacy in Relation to the Etiology of Diarrhea

Studies from Costa Rica (100) and those of investigators in other parts of the world, including Dacca (13,134,150), have shown that ORT is effective in 95 percent of cases of diarrheal dehydration, irrespective of etiology. ORT is equally efficacious whether diarrhea is due enterotoxigenic bacteria (e. g., enterotoxigenic E. coli. ***Vibrio cholerae),*** invasive bacteria (e.g., ***Shigella*** spp., ***Campylobacter jejuni),*** enteropathogenic E. ***coli,*** or viruses.

Of particular interest is ORT'S efficacy in rotaviral infection. Davidson and coworkers (35) showed that in isolated loops of piglet small intestine heavily infected with human rotavirus, there was no evidence for glucose-coupled Na^+ absorption. On the basis of these observations, they inferred that oral glucose/electrolyte solutions might be ineffective in infants with rotavirus infection. In fact, however, ORT is as effective in infants with rotavirus infection as it is in non-rotavirus infection (13,100,134,150).

The pathophysiologic explanation is that rotavirus causes patchy involvement of the small bowel with islands of denuded intestinal surface surrounded by normal or minimally affected areas. While the severely affected areas undoubtedly are defective in active glucose absorption, the nonaffected surface of the bowel absorbs sufficient glucose to permit excellent clinical results. When Nalin and coworkers (100) measured stool glucose concentration during oral therapy in infants with rotaviral diarrhea and infants with non-rotaviral diarrhea, the concentration was significantly higher in the former, demonstrating that indeed glucose absorption was somewhat impaired. Nevertheless, sufficient active transport of glucose occurred to allow 92 percent of rotavirus-infected infants to be successfully treated with ORT. In Costa Rica, rotavirus is by far the major single cause of diarrheal dehydration in infants (83), and ORT is the mainstay of therapy in the Emergency Room Service of the National Children's Hospital. Similar success in the treatment of dehydration due to rotavirus has been reported in Bangladeshi infants (13,150).

Oral Dehydration and Vomiting

Infants with diarrhea commonly manifest vomiting. Pediatricians and nurses unfamiliar with ORT often conclude that ORT cannot be instituted or that it will not be effective in those cases. This is a fallacy. In carefully monitored clinical studies in Costa Rica and Honduras (28,100,114), most of the infants had a history of vomiting on admission and most also experienced one or more episodes during ORT. However, careful balance studies in which the volume of vomitus was carefully recorded showed that with rare exceptions, the volume vomited was only a small fraction of the total volume of glucose/electrolyte solution ingested (28,73,100,114). From the perspective of the fluid and electrolyte status of the patient, it is not the frequency of vomiting that is of importance but the net balance of intake versus emesis (vomitus) and stool volume.

Studies in Costa Rica (114) have shown that vomiting tends to be more frequent during the early hours of ORT and diminishes thereafter. This observation suggests that emesis in some infants may be the consequence of electrolyte imbalance and acidosis.

The rate of emesis is also related to the sugar in the solution and to the method of administration. In comparative trials between glucose/electrolyte and sucrose/electrolyte solutions, children who received the sucrose/electrolyte solution had higher rates of vomiting (13,28). In summary, careful balance studies have provided the evidence to demonstrate that vomiting is rarely an obstacle to successful ORT.

ORT of Hypernatremic and Hyponatremic Dehydration

In approximately 70 percent of cases of diarrheal dehydration in infants, the concentration of Na^+ in serum remains normal (131 to 149 mMol/1). In a minority of cases, the serum Na^+ may be elevated (hypernatremia, ≥150 mMol/1) or abnormally low (hyponatremia, < 130 mMol/1).

Hypernatremic diarrheal dehydration represents a serious complication. It usually occurs in young infants and can be accompanied by seizures, cerebral hemorrhages, and death. Hypernatremia is notoriously difficult to treat because of the propensity of infants to convulse during therapy. In the 1950s and 1960, hypernatremia was encountered in approximately 20 percent of infants with diarrheal dehydration seen in North America and Western Europe. Older American and European pediatricians and family practitioners, therefore, have great respect for this complication of infant diarrhea, consequent to their experiences several decades ago. In general, hypernatremia has been uncommon in infants in the tropics.

Some pediatricians have expressed concern that oral glucose/electrolyte solutions of the type recommended by WHO contain a Na^+ concentration (90 mMol/1) that is too high for infants, particularly those in industrialized countries (6,9,64,153,156,157). They suggest that in these well-nourished, predominantly formula-fed infants, who suffer mainly from rotavirus diarrhea, glucose/electrolyte solutions with Na^+ concentrations of 90 mMol/1 are potentially unsafe and could lead to or exacerbate hypernatremia.

Considerable confusion has resulted from discussions on this point because of the failure to differentiate clearly between the use of oral glucose/electrolyte solution to ***replace*** fluid deficits in overtly dehydrated infants versus administration of glucose/electrolyte solution early in the course of diarrhea to ***prevent*** dehydration. The use of solutions with Na^+ concentrations of 90 mMol/1 in nondehydrated infants with diarrhea must be accompanied by equal volumes of low solute fluids or plain water to allow the kidneys to handle Na^+ loads which are greater than the stool N_a+ losses. However, in the overtly dehydrated infant, even if hypernatremia is already present, there exists a total body deficit of Na^+ as well as water. In overtly dehydrated infants, a glucose/electrolyte solution containing 90 mMol/I is physiologically sound and clinically safe; indeed, it is an ideal dehydration solution to replace deficits (26,113,115,119).

Pizarro and coworkers have carried out several studies (113,115,119) in Costa Rica clearly establishing the safety of ORT of infants with hypernatremic dehydration. The problem with treatment of hypernatremic dehydration, intravenous or oral, is the occurrence of seizures (15,42,65,75,119). The last report by Pizarro and coworkers (113) described the use of slow oral dehydration in 35 infants with no episodes of seizures during therapy.

ORT also has been shown successful in treating infants with hyponatremia (serum Na^+ concentration <130 mMol/1) (113,119,139).

Experience With ORT in Neonates

At the National Children's Hospital in Costa Rica, the use of ORT in neonates has been exhaustively studied by Pizarro and colleagues (116,117). An extraordinary collective experience involving several hundred newborns documents that ORT is as safe and effective in this age group as in older infants. Furthermore, neonates with hypernatremic and hyponatremic dehydration can be as successfully rehydrated as older children (116,117).

Rapidity of Oral Dehydration

Complete replacement of the water and electrolyte deficit, accompanied by clinical signs of normal hydration and weight gain, is complete by 6 hours after beginning ORT in approximately 60 percent of cases; by 12 hours in 90 percent; and in 95 to 98 percent of instances by 18 hours (24,28,73,100,114,118). At the point of successful dehydration, infants are switched to the maintenance phase of dehydration, which includes the introduction of soft foods. Depending on social factors, the infant may be sent home at this point after the mother has been instructed in how to provide maintenance fluids at home and has been given packets to prepare the solution (118).

Limitations of ORT

Even in highly experienced units such as those in Costa Rica, Honduras, Bangladesh, and India, 2 to 5 percent of overtly dehydrated infants will fail on ORT alone. The most frequent causes of failure include the following:

- **Glucose or sucrose intolerance.** Overtly dehydrated infants often are severely malnourished and have intestinal bacterial infections. When given sugar/electrolyte solutions, these infants greatly increase their purge rates. This situation is seen in perhaps 1 percent of cases in less developed areas.
- **Intractable vomiting.** Occasionally, a dehydrated infant will simply be unable to drink without vomiting virtually the entire fluid volume that was just ingested. Such instances are rare.
- **Continuing high purge rates.** Most infants with diarrheal dehydration have diminished purge rates following replacement of fluid deficits or purge at rates that can be adequately replaced orally. Some infants, however, particularly those with cholera, continue to purge copiously at rates that cannot be easily replaced with ORT.
- **Abdominal distention.** Paralytic ileus or abdominal distention occasionally occurs, precluding continued ORT.

ORT is labor-intensive. Someone must continue to administer the fluids to the infant. If the mother or another guardian is not available, this requirement becomes a limitation. ORT units are dependent on the full cooperation of the infant's mother or a surrogate.

Composition of Oral Dehydration Solutions

Comparison of Glucose and Sucrose

Because of the lesser expense and greater availability of sucrose (table sugar), trials have been carried out to compare the efficacy of sucrose/electrolyte versus glucose/electrolyte solutions (13,99,103,134, 135). Sucrose molecules are "double sugars" twice the size of glucose molecules. For sucrose to be effective, it must be broken down by intestinal enzymes to its single sugar constituents, glucose and fructose, whereupon the actively absorbed glucose molecules promote water and glucose-coupled Na^+ transport. Fructose, in contrast, is not avidly absorbed and thus exerts a "solute drag" osmotic effect (56). In summary, the comparisons show that glucose/electrolyte solutions are slightly superior to sucrose/electrolyte solutions. However, the differences in overall efficacy are minimal so that if economic or logistic considerations are paramount, sucrose-based solutions can be routinely used with expectation of excellent clinical results.

Comparison of "Low" and "High" Sodium Dehydration Solutions

Several controlled studies have been carried out in which dehydrated children were rehydrated orally with either "high" Na^+ (90 mMol/1) or "low" Na (50 to 60 mMol/1) glucose/electrolyte solutions (4,20, 98,133,138,139). High- and low-sodium rehydration solutions appeared equally efficacious in replacing fluid deficits.

In a study in Jamaica (98), Nalin and coworkers detected transient hypernatremia in 4 of 25 minimally dehydrated infants who were given the WHO glucose/electrolyte solution without free water. The hypernatremia was mild (150 to 156 mMol/1) and was not associated with any adverse clinical signs or symptoms. Chatterjee and colleagues (20) in India reported similar results. Two of their dehydrated infants who had normal serum Na^+ concentrations on admission developed asymptomatic mild hypernatremia during ORT with a glucose/electrolyte solution containing 90 mMol/1. In contrast, Santosham and colleagues working in Panama and in the United States did not encounter hypernatremia (138,139) in their orally rehydrated infants who also received the solution without free water.

In the study in Jamaica (98), net Na^+ absorption was significantly less in the infants who received the low Na^+ (60 mMol/1) solution and hyponatremia developed in 3 of 31 infants. Furthermore, several infants who were hyponatremic on admission remained so during oral rehydration with the low Na^+ concentration solution. A comparison of "high" and "low" Na^+ sucrose/electrolyte solutions by Saberi and Assaee (133) in Iran gave comparable results as seen in the glucose/electrolyte comparisons.

In summary, while in "low" and "high" Na^+ oral glucose/electrolyte solutions give equivalent results in most dehydrated infants, the high Na + solution is safer for hyponatremic and hypernatremic infants.

Optimal Potassium Concentrations

Losses of potassium ions (K^+) in diarrheal stool can be significant, particularly in infants in less developed countries who have repeated episodes of diarrhea. In such infants, insufficient replacement of K^+ losses can lead to total body K^+ depletion, accompanied clinically by muscle weakness, ileus, cardiac arrhythmias, and hypokalemic kidney disease. Nalin and colleagues (98) compared K^+ balance in mildly dehydrated infants treated with the WHO oral dehydration solution (which contains 20 mMol/1 K+) versus a modified solution containing 35 mMol/1 K+. Net K^+ absorption at 24 hours was more than twice as high in the infants that received the solution containing the higher K^+ concentration (35 mMol/1), and none of these infants had abnormally low or high potassium blood levels at 6 or 24 hours after beginning ORT. In contrast, low potassium levels were detected in about one-fifth of the infants treated with the low K^+ solution. Based on these studies in Jamaica, the formula of the oral rehydration solution used in Costa Rica was modified to provide more K^+.

Acetate or Citrate in Place of Bicarbonate

The shelf life of optimally prepared glucose/electrolyte packets containing HCO_3^- is 3 years. However, the shelf life of poorly made porous packets is limited because of the discoloration and caramelization that occurs when moist glucose and bicarbonate mix. Sodium acetate and sodium citrate are being studied as substitutes for sodium bicarbonate to see whether they prolong the shelf-life. In the body, acetate and citrate are converted to bicarbonate. Pizarro and colleagues (112) and Patra and colleagues (105) recently have carried out double-blind randomized comparisons of glucose/electrolyte solutions containing citrate or acetate, respectively, versus the standard solution containing bicarbonate. The solutions with citrate or acetate were equally efficacious.

"Super Solutions"

In 1970, Nalin and colleagues (97) reported results of a clinical study in which a glucose/electrolyte solution was compared with an electrolyte solution that contained the amino acid glycine as well as glucose. Both glucose and glycine molecules are actively transported, but by different mechanisms. The objective of this study was to determine if a solution containing two distinct actively transported substances would result in faster and increased water and electrolyte absorption than a solution containing only glucose and electrolytes. Nalin and coworkers observed that the glucose/glycine/electrolyte solution was superior to the glucose/electrolyte solution in promoting water and Na^+ absorption in patients with severe diarrhea. In fact, the glucose/glycine/electrolyte solution was so much better that the duration of diarrhea and total stool volume were significantly diminished in patients who received the solution as compared to the group who received glucose/electrolyte solution.

The implications of this important observation were not widely appreciated at the time. Many public health authorities believed that the lesser availability of glycine and the increased cost of solutions having both glucose and glycine ruled against widespread use of such solutions. Since 1982, however, the concept of "super solutions" with more than one substance actively transported by the gut has reappeared with increased popularity (2,77,144). Patra and coworkers (144) in Calcutta compared glucose/electrolyte and glucose/glycine /electrolyte solutions in oral dehydration of infants with diarrheal dehydration. Their results corroborated those in adults with cholera 15 years earlier. The duration of diarrhea and the total stool volume significantly diminished in infants given the solution containing both glucose and glycine.

Work is under way to carry these investigations further. The goal is to develop a "super solution" containing up to three actively transported substrates that not only replaces water and electrolytes but actually diminishes diarrheal stool volume to the point where losses are no longer clinically relevant (2).

Some groups of investigators have been examining naturally occurring complex substrates as opposed to pharmaceutically prepared formulas in making of "super solutions" (90,106,162). They hope in this way to accomplish the same goals at lesser cost and with greater availability. Most work in this area uses rice powder (30 to 50 gm per liter) with the same electrolyte concentrations as in the WHO soIution. Rice contains polymers of glucose (glucose molecules strung together in a chain) which can be broken down in the small intestine to single glucose molecules (90). Rice also contains glycine (30 to 36 mg/100 gm of rice). Clinical studies have shown rice powder/electrolyte solutions to be at least as effective as glucose/electrolyte solutions in oral dehydration of infants with diarrheal dehydration (90,106). Some studies in infants (106) demonstrate a clear superiority of a 5-percent rice powder/electrolyte solution over the glucose/electrolyte solution, with the former significantly lowering stool output, duration of diarrhea, and intake of oral dehydration fluid.

ORT To Prevent Dehydration

Up to this point, ORT has been discussed in this case study as a substitute for intravenous dehydration to treat 95 percent of infants with overt clinical dehydration. Used this way, ORT is practiced by health care providers in health care facilities.

The second major use of ORT is to initiate the use of oral sugar/electrolyte solutions early in the course of diarrhea in an attempt to prevent dehydration. Ideally, this intervention is carried out with a balanced, physiologically sound solution containing appropriate concentrations of K^+ and HCO_3^- (or other base) in addition to Na^+ and Cl^-. In infants, stool Na^+ concentrations in noncholera diarrhea usually range from 25 to 70 mMol/1, with a mean of approximately 45 to 50 mMol/1 (89,100,101,149). Thus, a glucose (or sucrose) /electrolyte solution containing 40 to 50 mMol/1 of Na^+ is ideal to replace ongoing diarrheal losses early in the course of diarrhea in young children (43,44). The WHO solution can also be utilized to replenish ongoing diarrheal losses in infants but in this instance, an equal volume of low solute fluids (or plain water) is given following each volume of glucose/electrolyte solution to provide free water to handle Na^+ loads.

Simple Sugar/Salt Solutions

It is not possible economically or logistically to provide a packet of balanced sugar/electrolyte powder to treat every episode of diarrhea in all young children in developing countries, For that reason, some observers have advocated the use of simple dehydration solutions of table salt and sugar, prepared and administered in the home (15,53,66,70,85,91,120). Depending on the purity of the sugar and salt, simple solutions may contain only Na^+, Cl^-, and sucrose.

Two major obstacles had to be overcome before the use of home-made simple sugar/salt solutions could be advocated with confidence. First, it was necessary to identify simple, technologically appropriate methods for producin solutions containing safe and effective levels of Na^+ and sucrose. This was regarded as critical by many authorities who feared that improper mixing could result in solutions with unacceptably high Na^+ and sucrose concentrations, which could conceivably induce hypernatremic dehydration, accompanied by convulsions, intracerebral hemorrhage, and high case fatality. Second, it had to be shown to what degree simple sugar/salt solutions promoted water and Na^+ absorption, how well they combatted acidosis (since they lacked base), and what clinical and biochemical problems might accrue from the lack of K^+ in the fluids.

Many methods for measuring sugar and salt in preparation of simple sugar/salt solutions have been described. Some methods, such as the "finger pinch of salt and fistful scoop of sugar" technique, use the human hand for measurement (25,91). Other methods make use of a teaspoon or bottle cap, ***and*** a glass or a 750 ml or 1.0 liter bottle (30,38,69,70,72). Some authorities favor the use of a special double-ended plastic spoon with one trough for measuring salt and another for sugar (79,53). There is great controversy over the reliability of some of these methods (8,23,25, 30,32,33,38,51,53,66,69, 70,72,85,91,120,126, 146). Many health workers consider certain methods such as the "pinch and scoop" inherently so variable that they are unacceptable (32,69,72). Others disagree and believe that the simplicity of the pinch and scoop method justifies its use (25,91,146). A large rural ORT program in Bangladesh (Bangladesh Rural Advancement Committee) makes use of the pinch and scoop method (33).

Despite controversy over particular methods of preparation of simple sugar/salt solutions, all involved parties appear to agree on two fundamental points.

The first is that one must adapt methods of preparation of simple sugar / salt solutions to local conditions using local utensils. The second is that the more supervision and teaching involved, the greater the reliability of the method and the greater the safety of the resultant solutions.

Simple Sugar/Salt vs. Glucose/Electrolyte Oral Dehydration Solutions

Although many health authorities avidly supported the use of simple sugar / salt solutions and many national diarrheal disease control programs relied heavily on them, prior to clinical studies in Honduras (28), there were no physiological data to support their efficacy or show their limitations. Clements and coworkers (28) treated 61 Honduran infants 3 to 18 months of age with diarrheal dehydration with either a simple sugar / salt solution (60 mMol / 1 Na^+, 3.0 gm percent sucrose, no K^+ or HCO_3^-) or with the WHO glucose / electrolyte solution. The simple sugar / salt solution was found to be equal to the glucose / electrolyte solution in stimulating Na^+ and water absorption and almost as good in combatting acidosis. However, because of the lack of K^+ in the simple sugar / salt solution, significantly more infants treated with this solution developed abnormally low serum K+ concentrations. Small amounts of banana puree were unable to replace sufficient K+. It would require at least 320 ml of banana puree (280 ml of mashed banana, 2 to 3 whole bananas) to provide as much K^+ as contained in the amount of WHO glucose / electrolyte solution given over 24 hours to an infant with diarrhea (27).

In summary, properly prepared simple sugar / salt solutions are highly effective in promoting water and Na^+ absorption, thereby restoring a normal blood volume and blood flow through the kidneys which combat metabolic acidosis. However, the lack of K^+ in most simple sugar / salt solutions represents a critical drawback which can lead to abnormally low serum K^+ concentrations. Until the problem of adequate K^+ replacement can be resolved, simple sugar / salt solutions must be regarded as suboptimal alternatives for use only where a balanced sugar / electrolyte solution is unavailable.

Effect of ORT on Nutritional Status

A study in the Philippines showed that children who received ORT with glucose / electrolyte solution during bouts of diarrhea gained significantly more weight in ensuing months than matched control children who did not receive ORT (60,61). Studies in two other countries (Turkey and Iran) had similar results (7,39). Field workers, in the Gambia, however, have not been able to corroborate the results (131). One possibility is that ORT stimulates the appetite of children with diarrhea, and this accounts for the increased weight gain. Since early reintroduction of feeding is part of the ORT intervention, it is difficult to determine what role ORT per se plays with respect to food consumption. More information about ORT'S effect on food consumption and nutritional states is needed.

Effect of ORT on Infant Mortality

Implementation of ORT programs in less developed countries would be expected to diminish diarrhea-related infant mortality. Unfortunately, however, few epidemiologic data are available to demonstrate this effect. Reports from India, Bangladesh, and Egypt provide some insights, but none is completely convincing because of methodologic problems (1,66,123). More data on this important question need to be gathered,

Dissemination of ORT

Many international, national, religious, and private agencies are involved in disseminating the use of ORT throughout the world. The most important agencies are the following:

1. World Health Organization (WHO),
2. Pan American Health Organization (PAHO),
3. U.N, International Children's Emergency Fund (UNICEF), and
4. U.S. Agency for International Development (AID).

World Health Organization

ORT is the keystone in WHO models for national diarrheal disease control programs.

WHO's Diarrheal Disease Control Program has played a pivotal role worldwide in stimulating the use of ORT. This has involved:

- provision of treatment guides, manuals, etc., in several languages;
- provision of technical consultants to countries;
- assistance in organization of national and regional workshops on ORT and diarrheal disease control; and
- provision of research grants to support basic, clinical, and operational research related to ORT.

Pan American Health Organization

PAHO is both the WHO regional office for the Americas and the Pan American Sanitary Bureau. Both independently and in conjunction with WHO, PAHO has pursued dissemination of ORT. This has involved:

- provision of technical consultants;
- support of national and regional meetings. PAHO has been active in promoting workshops on diarrheal diseases and ORT; and
- provision of research grants, equipment, and materials to clinical and public health investigators.

In the late **1970s,** the first generation of PAHO ORT consultants were mainly North Americans. These consultants trained a second generation of PAHO ORT consultants from Latin America and the Caribbean who have since become internationally recognized authorities.

U.N. International Children's Emergency Fund

UNICEF has been a major supplier of packets of glucose/electrolyte powders to allow countries to start national pilot programs. UNICEF also has supplied some countries with machines to package their own ORT powders. ORT is an integral part of "GOBI/FF" program (growth chart, oral therapy, breast feeding, immunizations/family planning, female literacy).

U.S. Agency for International Development

AID has made major contributions to the dissemination of ORT. Some of the most important contributions include:

- provision of technical consultant support.
- support for meetings and workshops, and
- special projects.

The AID-supported international meeting on ORT in Washington, DC, in June 1982 was an important instrument to disseminate ORT. One of AID's special projects is the Mass Media Diarrhea Project, which has pilot programs in Honduras and the Gambia. Mass communications techniques (mainly radio) are being used to spread health information about diarrhea, dehydration, and ORT. The effectiveness of this program in Honduras is very impressive. Another special AID project has been direct financial support for the International Center for Diarrheal Diseases Research, Bangladesh. This is the offspring of the CRL (Cholera Research Laboratory), which has played an important role carrying out basic, clinical, and operational research on ORT.

Attitudes of U.S. Pediatricians Toward ORT

The vast majority of pediatricians practicing in the United States were trained in programs where the following attitudes were fostered:

- ORT helps to prevent dehydration and is useful in treatment of mild dehydration.
- ORT solutions for U.S. children should not contain more than 60 mMol/1 of sodium in order to preclude the development of hypematremia (a much feared complication).
- Children with moderate or more severe dehydration must be given intravenous dehydration.
- If a child is sufficiently dehydrated to receive intravenous fluids, nothing further should be given by mouth for 24 hours. The bowel should be "rested."

These have been the fundamentals of diarrhea therapy taught to two generations of American pediatricians.

Because of the large number of reports on ORT that have been published in recent years in the most prestigious pediatric journals in the United States (Journal ***of Pediatrics, Pediatrics,*** and the ***American Journal of Diseases*** *of Children)* and Britain ***(Archives*** *of Disease in childhood),* most U.S. pediatricians are aware of the expanded use of ORT. Most are also cognizant of the composition of the WHO oral dehydration solution and accept its use as an important advance for the treatment of diarrhea in the less developed world. Some pediatric training programs in the United States have adopted ORT and use the WHO (as well as other) dehydration solutions. Throughout the United States, however, there remain many pediatricians who are skeptical of ORT and who are particularly resistant to use of a formula like the WHO glucose/electrolyte solution which contains 90 mMol/1 of sodium.

The American Academy of Pediatrics has played an important role in fostering information on ORT and in attempting to forge agreement on the role of solutions containing 90 mMol/1 of sodium in treatment of diarrhea in the United States. At its autumn national meeting in New York City in October 1982, the Academy convened a workshop on ORT. Other presentations on oral dehydration were made at American Academy of Pediatric meetings in May **1983,** in Philadelphia, and in October 1983, in San Francisco.

In February 1983, the Academy convened a task force on ORT which met in New York. The assignment of the task force was to prepare recommendations on the following issue:

> the advantages and disadvantages of Oralyte, a high electrolyte solution (distributed worldwide by UNICEF/WHO) in the treatment of infants with diarrhea and dehydration.

Initially, the task force was not able to come to an agreement. Most of the task force members wanted to make Oralyte (the WHO solution) a prescription drug in the United States for fear that some infants would develop hypematremia (abnormally high serum Na + concentrations) if it were used without medical supervision. One dissenter argued that Oralyte had been proved safe worldwide and was safer than aspirin (which is sold without prescription). Some task force members believed that adopting a prescription requirement for Oralyte in the United States could have serious repercussions internationally, perhaps impeding the dissemination of in less developed countries.

A compromise was accepted for the task force to prepare recommendations, which were sent to the Academy Committee on Nutrition and then transmitted to the Food and Drug Administration to assist that agency in developing policy and regulations. The major points of the compromise include the following (28a):

- There is a role for two different sugar / electrolyte solutions in the treatment of diarrhea in the United States. The solutions would differ in sodium concentration. A solution for deficit replacement should contain 61 to 90 mMol / 1 of Na^+. A solution for maintenance should contain 40 to 60 mMol / 1 of **Na^+.**
- The solution for deficit replacement should be used preferably in a fixed health care facility (physician's office, emergency room, etc.) in overtly dehydrated children.
- The higher sodium solution also may be used in prevention of dehydration or maintenance of hydration but must be accompanied by provision of ample additional low-solute fluids to provide free water.
- A preferred maintenance solution is the lower (40 to 60 mMol / 1) sodium solution.
- All the dehydration solutions should be considered "medical foods. " (Distribution of medical foods does not require a prescription, but such foods are accompanied by explicit instructions.)

The Economy of ORT

ORT makes the treatment of diarrheal disease more economical in two ways: 1) by diminishing the cost of the dehydration fluids, and 2) by shortening the hospital stay of the pediatric patient admitted for the treatment of dehydration.

The costs of treatment for two hypothetical patients treated by ORT versus intravenous dehydration are compared below.

The first patient is a 10 kg American infant admitted to a large Eastern municipal hospital with 10 percent dehydration, In typical pediatric care in the 1970s, this infant would have a hospital stay of approximately 3 days and would receive intravenous fluids. Typically, he or she would be given nothing by mouth for the first 24 hours and then would have slow introduction of clear fluids and dilute formula over the subsequent 2 days. Some of the costs of treating this infant intravenously would include: sterile intravenous fluids at $1.50 / liter (approximately 3 liters might be used in this patient over 2 days); sterile plastic intravenous tubing ($2.62); and at least one sterile butterfly needle ($0.40). The relevant cost of intravenous therapy for the infant would be $4.50 for intravenous fluids, plus $3.02 for sterile tubing and needle and $600 for 3 days of hospitalization.

In the 1980s, this same infant could be treated with ORT and early reintroduction of feeding with a probable hospital stay of only 24 hours. The cost of ORT would be $0.25 per liter for WHO oral dehydration solution. The infant might require 3 liters ($0.75) of the solution, but no sterile tubing or needles would be needed. So the relevant cost of ORT for the infant would be $0.75 for oral dehydration solution, plus $200 for 1 day of hospitalization.

The second hypothetical patient is a 16-year-old, 70 kg east African male who presents with severe cholera during a cholera outbreak. He arrives at the hospital in a severely dehydrated state and in shock. Treated with intravenous fluids, this patient might typically require 20 liters for treatment. This would cost $30 in fluids alone ($1.50 per liter) plus at least $2.00 for sterile tubing and needles. Thus, the total cost for intravenous therapy for this patient would be $32.00.

With ORT, this patient's intravenous fluid requirement could be reduced to 3 liters ($4.50). The patient would also require approximately 26 liters of oral dehydration solution (at $0.15 per liter in east Africa). So the total cost of treating this patient with ORT would be $3.90 for 26 liters of oral glucose / electrolyte solution, $6.50 for 3 liters of intravenous solution, infusion tubing, and a sterile needle to treat shock; the relevant costs total $10.40.

The comparative costs for purely intravenous treatment of a patient with severe cholera in shock, $32.00, versus the use of ORT, $10.40, are notable. Many patients with somewhat less severe cholera can be treated entirely with ORT alone, further reducing the costs. Savings of this magnitude in therapy of diarrheal diseases are of critical importance to less developed countries where financial resources are severely limited in comparison with health care needs.

Conclusion

Diarrheal disease is one of the most important causes of morbidity and mortality in infants and young children in the less developed world. Dehydration is the most common precipitating cause of death in infant diarrhea, and malnutrition is the most important chronic consequence of such diarrhea.

Even during diarrheal infection, the intestine maintains its ability to absorb glucose and many amino acids; as glucose is absorbed, sodium and water also are absorbed. This observation has allowed the development of ORT—a highly efficacious form of therapy for diarrheal dehydration that is technologically appropriate for use in less developed countries.

ORT, which involves oral dehydration with solutions containing glucose or sucrose and electrolytes, now is in use worldwide, in programs sponsored by international agencies and national governments. Although the basic breakthrough has been made, efforts to improve the solutions and to increase the accessibility to ORT by those in greatest need are continuing.

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