Symposium Proceedings
Cereal-Based Oral Rehydration Therapy:
Theory and Practice
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RESULTS

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Introduction and Background:
Symposium on Oral Rehydration Therapies

Recent developments in solutions for Oral Rehydration Therapy (ORT) and recognition that the existing glucose-based solution could be improved led to holding a symposium on ORT at the National Academy of Sciences in Washington, D.C. in early 1987. Discussion included the history of ORT development and how it works, examination of some of the newer solutions for treating diarrheal disease, what effects alternate ORT therapies might have, and an examination of ways to promote greater use and acceptance of ORT in the United States. Speakers included scientists who developed the original oral rehydration therapy and those who have been actively involved in programs for its use in developing countries; participants represented U.S. hospitals and clinics, government institutions, universities, private voluntary agencies working both in the United States and abroad, and corporations with health interests.

Diarrheal disease remains the number one killer of children in developing countries and a major cause of illness in the United States and other developed countries. Since its discovery in the early 1960s, Oral Rehydration Solution (ORS), made from glucose (or sugar), salt and water, has been a miraculously simple and low-cost treatment for people with life-threatening diarrheal disease. UNICEF and the World Health Organization (WHO) have been working diligently within developing countries, through governmental agencies and private institutions and organizations, both to distribute ORS and to provide education on ORS and ORT.

Oral Rehydration Therapy (ORT), as distinguished from the specific WHO/UNICEF solution for rehydration known as “ORS”, includes the use of other solutions made with effective and safe salt concentrations and cereals (available now only as home-made preparations). Other interventions such as breastfeeding for babies or early feeding for older children and adults, during the first few hours of a diarrheal attack, are included under the general term, “ORT.” By 1987, nearly 25 per cent of the world’s children were able to benefit from ORS and ORT through the increasingly successful education and communication efforts of UNICEF, WHO and others. Although it is estimated that already 500,000 children are saved each year through ORT, increased use of ORT could improve the survival rate among the more than five million still dying each year from dehydrating diarrheas.

The use of ORT by United States physicians and institutions, rather than the currently more popular intravenous therapy and non-rehydrating remedies to treat diarrheal disease, would help in furthering its acceptance and use in developing countries, where infant and child mortality from dehydration is far greater. Many developing country doctors, health agencies, and others look to the United States and other developed countries for the latest health technologies and systems.

Physicians agree that while glucose ORS successfully replaces fluid loss, it does not decrease, and may slightly increase, the patients’ diarrhea and vomiting. This can be frightening and discouraging to mothers and even to doctors and nurses unfamiliar with ORT and compromises the value of ORT in the mind of the user, who expects treatment to decrease liquid stools. Glucose-based ORS can cause increased diarrhea and hypernatremia if too much salt is added to a standard volume of water; glucose-based ORS provides little caloric benefit (approximately 80 calories per liter of fluid) and, therefore, this therapy alone does not prevent continued negative nitrogen balance. Other problems with glucose ORS include its sweet taste to those with severe nausea, and, in the case of home-prepared solutions in homes of the very poor or in remote rural areas, the lack of sugar availability (due to seasonal availability and cost).

Theoretical considerations suggested that using glucose polymers and proteins might improve the efficacy of ORT. Cereal-based formulas, combined with the appropriate amounts of salts now have been shown not only to rehydrate patients as well as glucose-based formulas, but also to considerably decrease vomiting and diarrhea. Cereals are most often available in even the very poorest homes and the taste appears to be more acceptable than the sweet taste of glucose-ORS, to children and adults alike. Distribution problems for packeted (not yet available commercially) cereal-based ORT would be
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similar to those of glucose ORT; storage life for cereal-based packets is being investigated, with results of initial studies of developing country conditions expected in late 1987 or early 1988.

Cereal-based ORT and glucose-based ORT have an identical physiologic basis. Glucose molecules facilitate sodium transport across the small intestine allowing absorption of fluid as fast or faster than the small intestine is expelling the fluids caused by the enteric infection. Starch, the dominant component in cereals (rice, corn, wheat, potato, sorghum, millet or plantain), is digested into smaller polymers when exposed to amylase in the intestine. The smaller polymers are then split by maltase into glucose at the intestinal brush border. This digestive process supplies larger numbers of glucose molecules to transport sodium ions from the lumen into the blood stream with minimal luminal osmotic “back drag” in comparison to an equivalent amount of simple glucose. One molecule of glucose has the same osmotic equivalent as one molecule of starch containing hundreds of glucose molecules. Thus, cereal-based solutions provide many hundreds of molecules of glucose to move precious salt and water back into the body through the intestine, thereby decreasing diarrhea losses.

Cereal proteins also provide amino acids and small peptides. Through independent cotransport pathways, these amino acids and small peptides facilitate absorption of additional sodium ions. A key to polymer-based solutions is that there must be sufficient digestive enzymes to split the polymers rapidly and to generate the least possible luminal osmoles during the transport process. Adequate starch-degrading and proteolytic enzymes are present, however, in the vast majority of even the most severe diarrheal illnesses except in young neonates, premature infants, and those with chronic pancreatic insufficiency.

Cereal solutions have another advantage over glucose-based ORT: they provide more calories (up to 400 kcal/liter) even during the acute phase of diarrhea when the patient is unable to consume foods. Addition of specific proteins may yield an optimal mix of co-transporting amino acids and peptides to increase the nutritional value of the solutions and to improve the sodium absorption. Further research is recommended to develop such an optimized solution for use in all kinds of diarrheas for most patients, regardless of age or source of diarrheal illness.

The cereal-based approach to oral rehydration therapy has several intrinsic advantages over glucose-based rehydration fluids. Several times more co-transporting molecules of glucose, amino acids and peptides can be ingested into the gut without osmotic penalty, due to the low osmotic property of large food polymers in solution. The cereal-based solutions can decrease intestinal fluid loss, because of greater enhancement of solute-linked sodium cotransport processes. Cereal-based ORT also provides additional needed calories and essential nutrients to patients at a critical time, the onset, of their illness. Rapid recovery of the intestinal lining during and after diarrhea may be very important in the early return of normal digestion and to more favorable growth curves for children following diarrheal episodes.

Major questions raised at the ICHF Symposium included whether it is appropriate to promulgate an improved form of ORT (based on the same physiologic principles as glucose-based ORS) when such rapid progress has been made in worldwide efforts by the World Health Organization, UNICEF and others toward acceptance and use of a standardized glucose-based ORS. There is great appeal in the concept of a single, standardized solution and packaged formula. Cereal-based solutions, food polymers of starches and proteins, would need to be adapted to the availability and dietary preferences of each country and region; the components, then, will not be as widely standardized or readily susceptible to pharmaceutical quality control. There would be considerable diversity in food polymer components and in the standard amounts of salts in oral rehydration solutions. However, properly constituted home solutions may perform better than standardized glucose ORS because they take advantage of natural starches and proteins (polymers) in foods.

Questions on whether cereal-based therapies should be introduced on a wide scale must be answered by further scientific and social research before it will be clear if the potential advantages outweigh the possible problems. In the meantime, symposium speakers and participants recommended strong continued support to make the present glucose-based ORS available as widely as possible to those in need. They also recommended that concepts on ORT be communicated clearly and that programs for ORT education be continually promoted and expanded. All people should be provided the knowledge that enables them to prepare appropriate solutions when standard glucose-based packets are not available. Other recommendations included further basic research to increase knowledge about the potential advantages of polymeric oral rehydration solutions, and rapid establishing of clinical trials to prepare and evaluate
solutions which could be optimal for each region.

In the United States dehydration, associated with a number of illnesses, results in the hospitalization of many thousands of patients each year. Despite its proven simplicity, effectiveness and low cost, ORT is not a popular form of treatment in U.S. medical institutions. American doctors often ignore oral therapy, preferring to hospitalize their patients and give them intravenous fluids. Many hospitals in the United States not only avoid ORT but continue to recommend starvation for the first days of an illness, or suggest consumption of colas or juices which do not provide the needed salts for adequate rehydration. Approved packets of glucose-based, WHO and UNICEF approved ORS therapy, are not available to the U.S. public, though they are available in many of the remotest areas in developing countries. Symposium speakers and participants agreed that efforts should be committed to promoting greater acceptance and use of ORT within the United States, not only because it would save lives, reduce costs and suffering, but also because United States' therapies would be widely accepted in developing countries where diarrheas are the major killers.

Finally, although cereals and salts, the essential components of an effective oral rehydration solution to treat diarrheas, exist in nearly every household in the world, the knowledge of how to use them is missing. The formidable challenge is to stop the tragic death tolls each year from diarrheal disease among children, the elderly and others, and to reduce needless hospitalizations and related costs, enabling precious health care dollars to be used in other ways.

REFERENCES
ACKNOWLEDGEMENTS

The symposium at the National Academy of Sciences was possible only by the co-sponsorship of the National Council for International Health in Washington, D.C. and because each of the speakers volunteered his time not only to come to the symposium but also to help prepare their talks for this publication. Many, many hours of volunteer time thus were provided by these dedicated individuals to bring attention to the importance of Oral Rehydration Therapy in both the United States and developing countries.

Special thanks also must go to the World Health Organization and to UNICEF for sending Dr. Dilip Mahalanabis and Dr. Roger Goodall; each contributed importantly to the presentations and discussion sessions.

The Johns Hopkins University Medical Institutions and RESULTS, a grassroots citizens lobby working to end hunger, malnutrition and related social and medical problems, provided press and media assistance; Technologies for Primary Health Care (PRITECH) helped develop the bibliography of articles related to cereal-based oral rehydration therapy (ORT); and Nestles Corporation provided funds toward symposium communications. Staff and volunteers of these organizations who deserve special recognition include Geoffrey Drucker of RESULTS, who wrote press releases and helped organize volunteers to telephone participants in the Maryland, Virginia and Washington, D.C. areas; Sally Coghlan, who not only helped in developing the invitation lists, and the logistics of the conference, but also helped proofread the symposium proceedings; Jacey Rosen and Kathleen Kirwan of NCIH, for their tireless work in logistics and organization of the conference and taping of the proceedings; Marion Glick, of Johns Hopkins Medical Institutions Public Relations Office for her press relations; Liz Jennings of PRITECH, who compiled much of the bibliography for participants at the symposium; Professor Shirley Lindenbaum for her editing of some of the papers in this publication; Celine Reagan, who typed the papers from very rough recorded tapes; and Robert Russell, who advised on design, scheduling, and arranged for printing at much reduced rates. Mr. Russell provided a considerable amount of his personal time toward publishing these symposium proceedings at no cost.

Finally, great thanks must go also to those at Management Sciences for Health, PRITECH, and to the Office of Science and Technology at the United States Agency for International Development for making this publication possible through a grant and for their guidance in the preparation of the publication. We are grateful to all those who helped make the symposium and this publication possible, and for their commitment to increasing the use of ORT and early feeding to reduce deaths, minimize the length of recovery from diarrheal illnesses, and cut costs for treatment — in the United States as well as in developing countries.

Charlene B. Dale
Executive Officer
International Child Health Foundation
Welcome. On behalf of the National Council for International Health (NCIH), a dynamic institution that brings together all those people in the United States interested in international health and links them with their foreign counterparts, and the International Child Health Foundation, a new institution working to develop simple health technologies for saving children’s lives both in the developing and the developed world, I’d like to welcome you to this conference.

In 1980, NCIH sponsored a conference on oral rehydration, which helped many of the voluntary agencies in the United States that are working in third world countries to understand the scientific as well as the problematic issues related to implementing oral rehydration therapy or ORT, as it is widely known. Since then there has been a wide emphasis on ORT, as one of the major thrusts in all the various international agency activities.

In 1987, we are now looking at the issue of cereal-based oral rehydration, described by some as going back to “chicken soup,” or to home remedies used for centuries by mothers and grandmothers. Many of us are excited about this for a number of reasons. Not only does such an approach provide new technology, but it utilizes the common sense approach of traditional methods.

I think one of the other very important things for all of us who are committed to international health in the United States is the fact that oral rehydration therapy is a very practical example of how our foreign assistance funds have come back to have repayment here in the United States as well as dividends for improving health overseas. Part of the emphasis of this program is not only going to be to update you with the scientific knowledge of cereal-based oral rehydration, but also to show its potential for use in three major areas that have applications both here in the United States and overseas: children, the elderly and AIDS patients.

I would like to reemphasize that we all need to be aware that there is a political issue in getting needed continued commitments for foreign assistance, and those of us who are committed for foreign aid will need to be able to translate the benefits in practical ways to constituents around the United States and seek their support.

I am pleased to start this conference by introducing Dr. Charles Carpenter, one of the original researchers involved in development of oral rehydration therapy.
This morning, I will give a brief overview of the evolution of treatment of dehydrating diarrheas over the last quarter century.

To start back where we were in 1962, I show this slide which illustrates the characteristic features of severe dehydrating diarrheal illness. The man, who many of you may recognize, is stuporous; his skin is tightly pinched, and he has the characteristic "wahmerman's fingers" of severe dehydrating diarrhea. Dehydrating diarrhea kills by dehydration, pure and simple, and all of our therapeutic efforts essentially: directed toward correcting and preventing this severe dehydration. (Slide 1)

This second slide demonstrates perhaps a more pertinent picture, a child with severe dehydrating diarrheal illness. Acute diarrheas primarily kill children, roughly 5 to 8 million per year throughout the world. You can see the terrible turgor of the skin, where it looks like that of a very elderly individual. (Slide 2)

What we did know by 1962 was that we could salvage all patients with dehydrating diarrhea simply by giving intravenous fluids. Although a variety of intravenous fluid preparations are effective, they share the characteristics of being nearly isotonic, slightly hypotonic in some cases, but having constituents very close to that of blood plasma. But the problem with intravenous fluid treatment, as is illustrated by the slide of this man surrounded by the vials of fluids which were required for him to survive, is one of logistics. In many areas of the world, it is just impossible to get a sufficient quantity of sterile intravenous fluid to treat as many as 300 patients a day, which, for example, was often the number that came to the Infectious Disease Hospital in Bellaghatta, India, in 1962 and 1963. (Slide 3)

The same thing happened in Taiwan and in the Philippines, wherever cholera occurred. The incredible numbers of bottles of fluid required to insure...
someone's survival were impossible to manage logistically in improverished areas where dehydrating diarrheas occurred.

By 1962 or 1963, it became clear that patient's fluid losses could be dramatically decreased (by 60 per cent) by giving a single antibiotic, tetracycline. However, the average stool loss in this group of patients was still ten liters, and that's a terrible problem to manage logistically in most of the areas where severe dehydrating diarrheas occur. Antibiotics helped, but certainly were not the total answer.

This slide (Slide 4) simply emphasizes the conditions under which the people are brought to the treatment centers in areas where dehydrating diarrheas occur. A patient, who had been perfectly healthy a few hours before, developed dehydrating diarrhea with total collapse, was brought by the best transportation available, her husband's feet. Transportation is another limiting logistic factor. We needed a treatment that could be given in the home and that was not available in 1962, or 1963, or 1964.

All of the current efforts at oral rehydration are based on a simple fact: cholera and other dehydrating diarrheas do not destroy the gut. This is a photomicrograph of gut mucosa in a dog, similar to that in man (Slide 5). The left panel shows the normal gut, the right panel shows the mucosa during a time when the dog was losing about 10 per cent of his body weight per hour as stool. The toxins in these diarrhea-producing microorganisms do not destroy the mucosa of the gut. The gut is therefore, able to respond to orally administered glucose-containing solutions in a very dramatic way.

In the normal mucosa of the gut, sodium and chlo-
a great net secretion of isotonic fluid. However, during dehydrating diarrhea, cholera is the example here, the gut secretes a lot more fluid than it absorbs. Because the gut wall is still intact, it continues to absorb fluid at close to a normal rate.

We knew in the mid-60s that adding glucose to the normal gut tremendously enhanced the absorption of sodium and chloride and, in a series of studies in Dacca and Calcutta in 1965, 1966, 1967, and 1968, it was found that by giving an oral solution containing glucose as well as sodium chloride, the intestinal losses of fluids could be counterbalanced by fluid given orally if glucose were added to oral fluid.

Even in cholera, where there is a tremendous loss of intestinal fluid, the absorption more than counterbalances the losses, so the patient can be restored to adequate fluid balance and can survive. This is a tremendously important clinical finding based on the very simple physiologic principle that glucose in the gut improves the absorption of salt and water.

Pertinent to further discussion is that orally administered glucos-based fluids do not decrease the duration or the volume of diarrhea. If anything, they may increase it. Losses are matched by absorption, so the patient does well physically, but the diarrhea continues. This is sometimes troubling to the people treating the individual. The solution developed for oral rehydration which has been promulgated by WHO and UNICEF can be very simply prepared in every environment. It consists of sodium chloride (table salt), sodium bicarbonate (baking soda), potassium chloride and glucose. Sucrose can be substituted for glucose. It is known as “ORS”.

ORS is very effective and, even in the most adverse circumstances with very severe diarrheal diseases, survival of 98 percent of the patients can be achieved with this oral rehydration solution alone.

Patients with E. coli and rotavirus respond equally well to oral rehydration with the glucose-electrolyte solutions. It was an important step to demonstrate this as cholera accounts for only a small amount of diarrheal disease in the world. Diarrhea caused by enterotoxigenic E. coli, physiologically very similar to cholera, accounts for a major proportion of diarrheal disease worldwide; rotavirus, which has a different mechanism of action than cholera, is responsible for much of the diarrheal illness of children under age two.

Throughout the world, we can now identify the etiologic agent in most diarrheal disease. And to the surprise of many, the same oral rehydration solutions works equally well in virtually every kind of dehydrating diarrhea.

Although oral rehydration is a tremendous advance and is now available in most of the world, there are still some problems with it: the volume of diarrhea is not diminished, it continues and may even increase. As I said before, that is perplexing to the family of patients who have the illness; a second problem is that is doesn’t provide adequate calories, so children with diarrhea do not get sufficient nutrition from oral rehydration alone; finally, a third problem is that ORS has to be prepared properly. If twice the required amount of salt is added to the solution, the diarrhea is aggravated.

These problems are not insurmountable but they are significant. Recognition of these problems led to the development of cereal-based oral rehydration therapy in the last few years. Glucose-based oral rehydration therapy is limited by the number of molecules of glucose that can be given: too high a glucose concentration increases the diarrhea. The cereal, or starch-based, oral rehydration does not have that problem. With up to eighty grams of rice starch or up to sixty grams of maize, there is a very small osmotic effect. Starch molecules are large polymers and, as the polymers are broken down by the gut enzymes, they gradually release glucose and enhance sodium absorption, thus avoiding the problem of giving a big solute load and enhancing diarrhea. Also, through this process, more sugar is available per gram of ingested material, so that absorption can be enhanced to the extent of reducing the rate of diarrhea. With rice-starch ORS, the actual volume of diarrhea has been decreased by 30 to 40 per cent. The cereal-based oral rehydration solutions do not have the potential disadvantage of aggravating diarrhea if too large a volume were given. They provide a great deal more nutrition than sugar-based solutions and, in fact, provide some proteins and amino acids and up to four times the calories, all important to a child with diarrheal disease.

So we have now the new concept of starch-based or cereal-based oral rehydration; rice starch, maize, wheat, and soya have been shown to be effective. The availability of these solutions has led to some questions which I hope will be addressed today.

One is whether or not the cereal-based oral rehydration therapies are consistently effective. We have a lot of data on sugar-based oral rehydration. If it’s in the right concentration, it’s almost invariably effective in virtually every type of diarrheal disease.
don't have as much data on the cereal-based oral rehydration. We need to be sure that it is consistently effective with dehydrating diarrheas.

Secondly, is cereal-based ORT safe? We think it’s safer, because we think the chance of error in making the solution is very small. Again, if you add too much of rice or wheat soya, the solution becomes non-drinkable and it is virtually impossible to give the patient too large an osmotic load. Do we have enough data on that?

Cereal-based oral rehydration is of greater nutritional value, but we should have some discussion on this issue. We'd like to know if rice, starch, wheat and maize are equally effective in all rehydration therapy. We now have a lot of information about rice starch, some about wheat, and very little about maize.

And finally, what additional studies do we need to answer these questions? Because if we are going to move from ORT II, sugar-based oral rehydration, to ORT III, cereal-based oral rehydration, on a worldwide scale, we've got to be absolutely sure we are right and absolutely sure that the cereal-based solutions are consistently effective, and whether rice, wheat, maize, soya or other starches are all equally effective in oral rehydration therapies. Those are the critical questions.

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A HISTORY OF THE DEVELOPMENT OF ORAL REHYDRATION THERAPY (ORT)

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This discussion is very much a personal observation and interpretation of events in which colleagues and I were involved. In this discussion of the history of the development of oral rehydration therapy (ORT) in the 1960s, three points will be emphasized: 1) the importance of the scientific method in developing ORT and in creating support for its use; 2) the importance of conducting this research where the problem of life-threatening diarrheas exists; 3) the fact that the process of developing new medical therapies is both competitive and complementary.

Oral rehydration therapy has two components: 1) the use of fluid and electrolytes (oral rehydration solution or "ORS") to correct the dehydration and replace the continuing fluid loss of acute watery diarrhea; and 2) nutritional therapy to minimize weight losses and even shorten the duration of illness. Time today permits me to discuss only the historical development of oral fluid and electrolyte therapy.

Contrary to popular belief, the development of most technologies does not follow a clean linear progression. There are starts and stops, serendipity, and missed opportunities. The development of ORT demonstrates this sequence. An early documented use of ORT was discussed by O'Shaughnessy in The Lancet in 1832: an oral salt solution that was given to an adult cholera patient actually worsened diarrhea. In 1832, Lewis suggested that small amounts of oral alkali be given though he did not demonstrate the effectiveness of this regimen. Sellards (1910) did, in fact, demonstrate that oral alkali could alkalinize the acid urine of some patients indicating some degree of absorption.

In the 1940s, Harrison at Johns Hopkins Medical School used electrolyte solutions with glucose added to treat mild diarrhea and dehydration chiefly during late convalescence. The glucose was intended as a source of calories; its role as the substrate necessary to move sodium and water across the intestinal mucosa was not yet known. These were not balance studies, so input and output measurements were not precisely recorded. In 1953, Chatterjee, working in Calcutta, reported on the use of an antemetic and an herbal medicine in the treatment of cholera; fluid losses of patients receiving antemetics were replaced both orally and rectally with a solution containing salt, water, and glucose, but no bicarbonate. He did not use oral therapy in severe cases, although the level of dehydration is not well-described; he also did not report any balance studies or provide a clear treatment regimen. Like some other early workers, he reported favorable results, but it would appear that these reports were regarded as anecdotal since they failed to gain acceptance or even attract rigorous investigators to follow up the apparent leads. The absence of data on dehydration severity, diarrhea rates, net fluid balance or control groups may have been unconvincing. In the 1950s a renewal of scientific interest in intestinal absorption of sugars and amino acids laid down many of the scientific principles later tested on diarrhea patients. These principles later provided an understanding of why oral therapy works during diarrhea. Fisher and Parsons (1953), for example, demonstrated that there was increased intestinal absorption in the presence of glucose; Allfrey et al (1956-57) showed an association between sodium movement and amino acid uptake in thymic nuclei, a phenomena later seen in intestinal cells. Mechanisms for these models were developed by a number of investigators by the early 1960s.

The first clear scientific demonstration of the use of oral therapy was made by Captain Robert Phillips and his colleagues at the Naval Medical Research Unit (NAMRU) in Taiwan between 1962-1964. Dr. Phillips, a physiologist who had earlier directed the NAMRU Laboratory in Cairo, was given the Lasker award for studies he had conducted on cholera in Egypt, Taiwan, and Thailand. Many of us still have the image of Dr. Phillips in our minds: arriving at the Dacca airport, cigarette holder in hand, a blue Navy cape draped over his shoulders. In a series of intestinal balance studies conducted at the San Lazaro Hospital in Manila, Phillips added substrates, including glucose, to electrolyte solutions to examine intestinal absorption in adult cholera patients. It is unclear whether he chose to study glucose in cholera...
because of any familiarity with publications demonstrating that it increased sodium and water absorption by the non-diseased intestinal mucosa. In fact, he steadfastly claimed that he chose it as a safe non-electrolyte useful for adjusting intestinal perfusion solution osmolarity, and that he was not aware, at the time, of any other reason to choose it. He did not reference the work of the absorption studies noted earlier of Riklis and Quastel, Schultz, Curran, or others that demonstrated that glucose enhanced the movement of sodium across an isolated intestinal membrane. After demonstrating that glucose promoted net absorption and decreased net stool losses in cholera patients, Phillips moved immediately to a clinical trial, though Craig Wallace, who was working with him at the time, urged caution. These studies were purposefully carried out under less than ideal conditions because Phillips wanted a method to approximate actual physical facilities then present in much of the world. A solution with a high sodium concentration (190 mEq/L) was used, the idea being that the higher sodium concentration would move more sodium across the intestinal mucosa and thus overcome the paralyzed sodium pump, as it was then conceived, to further enhance water absorption. Unfortunately, there were some deaths in these early studies. It appears that many of the patients developed congestive heart failure, which resulted from a combination of increased sodium and water absorption and continuing intravenous infusions. The latter he continued, in part, because of a fear of inadequate intestinal absorption. This was the opinion, at least, of Dr. Graham Bull, Director of the British Medical Research Council, who was visiting Dr. Phillips and his group at the time of these studies. Many feel that this experience had a lasting negative effect on Phillips' view of the safety and usefulness of oral therapy.

The next major breakthrough on the road to developing ORT occurred in 1965, when David Sachar, Jim Taylor and others at the Pakistan-SEATO Cholera Research Laboratory (PSCRL) demonstrated an increase in intestinal transmural potential when glucose was added to the electrolyte solution bathing the small intestine. This clearly demonstrated that there was movement of electrolytes across the intestinal lumen, even during cholera, when glucose was added to the solution. Norbert Hirschhorn, a colleague of Sachar's, wanted to follow up on this observation and the earlier studies of Phillips and went to Dr. Phillips (then Director of the PSCRL) to see about carrying out intestinal flux studies and possibly clinical studies using the oral glucose-electrolyte solution. Hirschhorn recalled how Phillips discouraged him and produced charts of some who had died in the Philippine studies. Hirschhorn then agreed to carry out only the intestinal net flux studies, deferring any clinical work to a later time. Hirschhorn and his colleagues then carried out a study which ultimately confirmed Phillips' earlier observations that a cholera patient whose intestine was lavaged with a glucose-electrolyte solution went from negative to positive fluid balance. They published their results in the New England Journal of Medicine in 1968. A group of investigators at the Johns Hopkins University International Centre for Medical Research and Training (ICMRT) in Calcutta followed up on these studies after visiting Dacca and learning of Hirschhorn's study. The ICMRT study, also in 1968, confirmed Phillips' observations and they published their results at almost the same time as Hirschhorn.

In July 1967, David Nalin and I arrived in Dacca, East Pakistan (now Dhaka, Bangladesh). Oral therapy was not being used in Dacca since no treatment method had been developed. It was also clear that most clinicians thought that trying to treat a heavily purging cholera patient with an oral solution was just too heroic and impractical. Vomiting is a salient characteristic of this disease. A two page proposal examining the clinical effectiveness of ORS had been given to the Pakistani ward doctors to carry out; however, these physicians had had very limited research training and limited clinical guidance was provided. It was generally felt by Phillips and others, I believe, that clinical studies were of less importance than laboratory studies, and that if a treatment that was supposed to be simple enough to be given orally in the field did not work in the hands of ordinary doctors, it was impractical. The way that clinical studies were initially handled reflects these attitudes.

There was no cholera in Dacca in the fall of 1967 and all studies were put on hold. Then, a cholera outbreak was reported to be occurring in Malumghat, a small town in the south between Chittagong and Cox's Bazaar. The Christian Mission Hospital there informed us of this outbreak and requested PSCRL assistance. PSCRL responded by moving a large group of nurses, doctors, and support personnel to Malumghat. Tents were set up at the hospital to assist with the outbreak and provide extra study space. David Nalin was assigned to oversee the ORS studies that were to be based on the brief protocol which had been developed before we arrived.

These first ORS studies, all in adults, were a dismal failure. A significant number of patients (over 50 per cent) received intravenous therapy (IV) after ORT was started. ORT was considered to have failed, either because it was started too early or vomiting occurred.
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(early vomiting was then considered a reason for stopping ORT and for beginning IV, or purging rates exceeded oral intake. In reviewing data on the first few patients, Nalir recognized that the problem lay in the treatment method being utilized. We were giving a fixed amount of oral therapy solution to the adult cases, regardless of stool output. What was needed was a treatment method derived from balance techniques. Input and output measurements would be made, stool and vomitus losses would be measured; ORT would then replace these losses along with insensible losses, and urine volume and specific gravity would serve as measures of hydration along with the traditional method (at PSCRL) of measuring plasma specific gravity. Slight modifications of the formula previously used (especially increasing potassium concentration) were also important. During the next outbreak of cholera in Dacca in the late winter and spring of 1967-68, clinical studies on the use of ORT in adult cholera patients were conducted using the new treatment method. Unsure as to how effective and safe the ORT would be and determined to put patients at no increased risk of recurrent shock should ORT fail, we stayed with the patients twenty-four hours a day, measuring serum stool and urine electrolytes in addition to closely following the patients' clinical status, ready to restart IV therapy if needed. Twenty-nine adult patients were studied; all were admitted with severe dehydration and were rehydrated with oral (or nasogastrically administered) solution, and all proved to be heavy purgers. Serial cholera patients admitted in shock were alternately assigned to control IV or oral therapy groups. There were ten controls, ten were given oral therapy by nasogastric tube and nine drank the solution. It was demonstrated that 80 per cent of the IV could be saved in those patients treated with oral therapy solution after initial dehydration was corrected with 5:4:1 IV solution (Dacca solution, or 5:4:1, had, in grams per liter NaC1 - 5 grams, NaHCO3 - 4 grams, KCL - 1 gram).

Shortly after our initial clinical studies, David Nalin traveled to Calcutta and informed the group at the ICMRT of our results using glucose and the clinical methods we developed. After Dr. Nalin's visit, the ICMRT group discontinued the current studies on maltose and began to enter patients into a study of a practical ORT regimen, a design similar to that which Dr. Nalin had discussed with the ICMRT scientists during his visit. When I visited Calcutta a number of weeks later, they were well on their way to duplicating the results we at PSCRL had achieved in Dacca.

After this exciting development, we were enthusiastic about moving ahead to test ORS in other clinical settings, especially at the field hospital in Matlab. Dr. Phillips, however, was reluctant to go ahead, possibly because he was still very disturbed by those earlier studies in the Philippines. Through a cable from Dr. John Seal, the Director of the PSCRL program at the NIAID of the National Institutes of Health (NIH), we (as officers in the Public Health Service) were ordered to discontinue any further studies on ORS until otherwise notified. We suspected that Dr. Phillips had initiated the cable, although this was never definitively determined. Convinced of the efficacy, safety and potentially great impact of ORT on diarrhea morbidity and mortality, we then proceeded to develop a plan to get around this restriction. The strongest encouragement we received to carry on further work was first from Dr. W. Henry Mosley, Director of the Epidemiology Section at the PSCRL, and then from Dr. Alexander Langmuir, then Director of the Epidemiology Intelligence Service (EIS) at the Centers for Disease Control (CDC), who very early on recognized the importance of these studies, and Dr. Kendric Hare, Deputy Director of the PSCRL. We arranged for Dr. Mosley, who had been a former EIS officer under Dr. Langmuir, to send two additional sets of EIS officers to Dacca for one month each, ostensibly to work in the epidemiology unit under Dr. Mosley. Using protocols developed by David Nalin and myself and working under our direction, these EIS officers assisted in carrying out two field studies in Matlab on the clinical use of ORT. As Dr. Phillips knew little about the epidemiology unit and, frankly, did not seem interested in its work, we knew it was unlikely that he would review all the studies being conducted in Matlab. We carried out the field studies uninterrupted and they were extremely successful.

In the first of these field studies at Matlab, 135 adult male cholera patients admitted to the Matlab hospital with severe dehydration were given ORS; there was a savings of 70% of the IV fluid used in a similar group of patients in the previous year. In the second study, severe acidosis (mean venous blood pH 7.14) was rapidly corrected with ORS alone.

The clinical facilities at Matlab were similar to government treatment facilities throughout the country. Nurses and physicians at Matlab, however, were clearly superior in their clinical skills though government health care workers could easily be taught these skills if there was an interest. The field studies, then, were a true test of the effectiveness of oral rehydration therapy. After reviewing the results of these field trials, Dr. Phillips became an enthusiastic supporter of ORT.

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Shortly after our initial clinical studies, David Nalin traveled to Calcutta and informed the group at the ICMRT of our results using glucose and the clinical methods we developed. The ICMRT group switched from using other sugars to glucose and, when I visited Calcutta a number of weeks later, they were well on their way to duplicating the results we at PSCRL had achieved in Dacca and Matlab. Oral therapy was given to children (both in Dacca and Calcutta) and was used on non-cholera cases. The non-cholera diarrhea cases most likely included patients with enterotoxigenic E. coli, campylobacter, and rotavirus, but these organisms had not yet been identified as causative agents.

The dramatic effectiveness of ORS in the treatment of cholera outbreaks among Bangladesh refugees in 1971, as demonstrated by Mahalanabis and colleagues, went beyond the ordinary difficulties overcome in the earlier Matlab field trials and experience with ORS to include disaster conditions, thereby strengthening the complementary nature of ORS and further extending its credibility. In those early years, the confirmatory work of the two laboratories, PSCRL and ICMRT, did much to strengthen the scientific basis of ORT.

A few words about glycine and other substrates: In late 1968, glycine and the combination of glycine and glucose were used instead of just glucose in the oral rehydration solution. Glycine was as effective a substrate as glucose, but the two together significantly reduced both the duration and the volume of diarrhea. There was a transient rise in blood-urea-nitrogen (BUN). During a period of normalization of plasma, protein concentrations were used as the indicator of glycine absorption and conversion to urea, and this was confirmed. Though there may not be a commercially prepared glycine-based ORS, these observations formed the basis for the next generation of oral rehydration solutions.

Since those early studies, a great deal of work has been carried out testing ORS solutions with different electrolyte compositions in diarrhea of different etiologies, in different clinical environments, using a variety of training and marketing techniques. Now, the most exciting area of research, however, is that of the cereal-based solutions. This work was pioneered by Molla and his co-workers at the ICDDR,B in Dhaka (the latest reincarnation of the PSCRL, which was, from 1971 to 1979, the CRL). Discussions on these studies will be described later in this symposium.

Let me return to the three points I made at the beginning of my talk. First, I would like to reiterate the importance of "scientific method." The early efforts to develop an oral rehydration solution for diarrhea failed, or did not lead to the use of ORT, because study designs were flawed and well-defined treatment regimens were not established. Balance studies had not been adequately carried out. When advocates of ORT have to deal with the resistance of drug companies or with that of clinicians, especially pediatricians, the results of well-designed studies are extremely important.

Secondly, the context in which the research was carried out was critical. Individuals who were involved in the early field trials were living next to the problem. They saw people dying in villages because they could not get to a treatment facility. Even if these villagers did reach a clinic, there often was no IV fluid or equipment. Researchers were highly motivated to develop methods that extended access and reduced costs. Investigators moved quickly from balance studies to the field application of ORT. Science was taken to where the problem was. Individuals working in a Bangladesh environment were often, though not always, sensitive to the needs of the people in the area. The search for better home-based solutions through the use of cereals is clearly an outgrowth of the proximity of "scientist to problem."

And, lastly, the issue of competition and complementarity. There will always be competition in science. We are certainly seeing this in AIDS research today. This competition can sometimes be unhealthy, leading to premature publication, deception, and so forth, by failing to disclose all the methods in a paper.

A number of individuals and events did much to popularize oral therapy and they should be recognized. Many a scientific idea has remained dormant for want of a patron or political commitment. High on the list of those who should be specially recognized is Dr. Dhiman Barua, who, as Director of the Diarrhoeal Control Programme at the World Health Organization, was a champion of oral rehydration therapy. The resolutions at Alma Ata, which called for an emphasis on primary care, was the political stimulus needed to legitimize the use of oral therapy throughout the world. Oral rehydration therapy, after all, is the quintessential example of a primary care intervention: It is a simple technology; it can be made available in the home so families can be more empowered to provide effective care; it is inexpensive; and it effectively treats a common problem.
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or just plain lying. On the other hand, healthy competition can lead to exciting interchanges and collaboration. When I left Dacca in 1970, I don’t believe there were more than two dozen researchers involved in diarrhea work and even fewer were involved in developing related therapies. However, the subsequent research that was generated from this relatively small investment in people and money has been enormous. One reason for this has been the frequent scientific exchanges and cooperative studies that have taken place on this topic.

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Thank you. In the next few minutes, I would like to give a global view of oral rehydration solution (ORS), its composition and our understanding of how it works. I am not going to discuss the implementation of ORS therapy, which will be covered by Dr. Northrup. However, first, I do want to make a few comments regarding some of the historical aspects of ORS development that I think bear reemphasizing.

The first one, as I am sure you are all aware, is that this fluid was originally developed specifically as a treatment for cholera. (1) Certainly, those of us in Calcutta had no idea at that time that ORS would have the potential for being an essentially universal diarrhea treatment solution.

The second is to point out the one person, at least in my mind, who was very influential in having this occur was Dr. Dhiman Barua. I think he, more than any of us, saw early on that ORS was more than just a cholera treatment and he was the one who kept pushing us to expand its use, first implementing it in children's diarrheas and in diarrheas of other etiologies. I think it was his push that encouraged all of us to continue expanding the horizons of ORS.

The third small point is that the World Health Organization (WHO) ORS composition comes in very nice round numbers: 3.5, 2.5, 1.5. This sounds like something that came out of a committee decision, and indeed it was. It came out of a WHO meeting in Jaipur, India, of primarily Indian pediatricians who were there discussing oral therapy for pediatric diarrhea. This was one of the earliest meetings regarding the use of oral therapy for infantile diarrheas of all kinds, not just cholera. It was in this series of meetings that this very convenient formula for ORS was proposed and then later adopted by WHO.

Prior to discussing the composition of ORS, I would like to note that the expectations for oral rehydration therapy on a global basis have now been primarily realized (in specific areas) and these experiences have been well-documented: 1) decreased mortality comes with appropriate use, 2) decreased hospital admissions are now seen because children can be treated as outpatients (the closing of many diarrheal wards in developing country hospitals has occurred because they are no longer needed), and 3) improved nutritional status is effected, not from the calories included in the ORS, but because children's appetites return sooner and they can eat earlier.

Clearly, oral therapy does not decrease the number of episodes of diarrhea because it is only a physiologic replacement fluid. Also, in the last few years it has been clearly demonstrated that ORS does have the potential for actually causing childhood deaths when used incorrectly. If the sodium is increased to high levels or decreased to low levels, the solution can be potentially lethal. Or, if the potassium concentration in ORS is increased to high levels, death can occur, as has recently been reported. So, even though in most situations we think of ORS as a very benign solution, it does have the potential to be lethal if it is not used correctly.

Now, for some of the major issues that I think have been studied and resolved regarding the composition. First of all, I think studies now are in agreement that in areas of the world where there is no cholera, all diarrheas can be adequately treated with ORS containing 50 to 90 milliequivalents (mEq/L) of sodium per litre. (2)

However, in those parts of the world where there is cholera, anything less than 90 mEq/L would be inadequate because of the large stool volumes lost during cholera. Therefore, WHO has adopted the 90 milliounivalent of sodium concentration as the universal solution. It has been suggested that the potassium concentration, which is now at 20 mEq/L could be increased; I think this is a reasonable suggestion. However, as I will discuss a bit later, with early feeding one can easily get potassium supplementation in foods and therefore it would not be necessary to include it in ORS.

The present ORS composition has been adequate in preventing clinical potassium problems, as measured by serum potassium. The base composition has been changed in the last year; citrate has replaced bicarbonate. Citrate has been shown to be equally effective in correcting acidosis, and most importantly, it is stable and increases the shelf life of the salts. (3)
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Table 1
Defined Organic Substrates for ORS
- Carbohydrates
  - Glucose
  - Sucrose
  - Glucose Polymers (Maltodextrins)
- Amino Acids
  - Glycine
  - Alanine
- Dipeptides
  - Glycyl Glycine

Poorly Defined Substrates for ORS
- Hydrolyzed Lactalbumin
  - Cereals
  - Rice
  - Maize
  - Wheat
  - Green Gram
  - Others

Food - Given Early During Treatment

been studied, and I would also like to discuss these. (Table 1) Glucose was the original organic substrate and is still the standard, being used universally in ORS packets. Sucrose, which is a disaccharide (glucose and fructose), also can be substituted, but is needed in twice the amounts; the gut has adequate sucrase enzymes to hydrolyze sucrose. The use of sucrose has expanded the possibility of oral therapy to include household sugar, which is sucrose. Glucose polymers also have been studied; maltooligos of various chain lengths of glucose, or synthetic glucose polymers have been used. These formulations offer some of the same advantages (osmotic, primarily) of cereal-based ORS, except that they are more expensive and have to be manufactured.

The amino acid glycine has been studied extensively. Unfortunately, the initial favorable published results using glycine have not been borne out in more recent studies done in the United States and Europe. These later studies have shown that glycine, at least in the way it has been studied, has no significant advantage over the glucose solutions and it may have some disadvantages. Aline, another amino acid, is also undergoing testing but no human studies have yet been published. Physiologically, it may have the same difficulties as glycine. By increasing the absorption of sodium in children who do not absorb glucose well, it may predispose to hyponatremia. (4)

Dipeptides have been studied because they seem to be absorbed through a different mechanism than either amino acids or carbohydrates, and may add significantly to the absorption of sodium.

The less well-defined substrates (Table 2) that you are going to be hearing about more today have also been the subject of considerable study. Protein hydrolysates would provide a combination of various amino acids and di- and tri-peptides which may improve the absorption of sodium.

A large number of cereals have now also been studied. Rice is one that has had the most study; rice ORS is as effective as glucose in replacing fluid losses and, in some studies, it has resulted in a decreased stool output, thereby shortening the duration of illness. All studies have confirmed the fact that it is useful as glucose, but not all have uniformly shown the effect of significantly diminishing stool volume. Two additional cereals have been recently studied: maize in Kenya and green gram in India. Both studies have shown these cereals to be as effective as glucose in oral rehydration solution, but neither showed a significant decrease in stool output. Wheat also is being studied, however, in the form of noodle soup. Wheat noodles and rice soup are widely used in Peruvian populations. Other cereals have been studied in Bangladesh, but have not received wide study elsewhere. There is clearly a large group of cereals that all have potential for use in ORS. Rice is the one that has received the largest attention because of its availability and its widespread use in much of the developing world.

Another aspect of oral rehydration therapy that I would like to discuss is early feeding. This is a very important part of oral rehydration therapy, because if one begins feeding at four hours, one is adding organic substrates (protein, carbohydrate, etc.), which can then provide additional mechanisms for
absorption of sodium and water. The expectation we have from improved oral rehydration therapy, or “Super ORS”, as it was originally called, is that of decreased morbidity, due to a shortened and less severe diarrheal illness. This would be the only reason for changing from glucose ORS, which we know is adequate.

There have been a number of published studies that show distinct nutritional advantages to early feeding. I think this should be no surprise. In order for a child to grow and not to lose weight during an episode of diarrhea, he has to have adequate caloric intake. The calories we are talking about in cereal-based ORS, however, are not the calories that we are talking about in early feeding. I think it should be very clear that the cereal in cereal-based ORS is only an important mechanism for sodium and water absorption; it is not a significant source of calories. These have to come from another source: early feeding. Early feeding also provide an advantage in fluid and electrolyte absorption. This has been shown in one of the studies of Dr. Santosham[5]. The presumed mechanism is that by giving these additional organic substrates within four hours, you are essentially producing an “improved” ORS, simply by adding the food. What is not yet known, and needs to be determined, is whether there is an advantage of any improved ORS over early feeding alone in decreasing stool output, or in the shortening of illness.

To briefly summarize a point that Dr. Mahalanabis from the World Health Organization is going to expand on later, WHO is supporting a large number of clinical trials using various formulations of “improved” oral rehydration solutions. Approximately 25 such studies are either underway or about to begin. Most of them involve ORS supplemented with amino acids (glycine or alanine), dipeptides, maltodextrins of various chain lengths, and cereals, including rice. These studies probably will be completed within the year and, hopefully, all of this information will then be widely available. We can then make a more rational determination of which of these oral rehydration solutions is a “super” ORS, which has problems and which should be used. Another basic question is: will children take more or less oral fluid based on the flavoring? This may be a minor consideration, but, from a practical standpoint, deserves to be answered.

In closing, I would like to point out that in spite of these advances in the formulation of ORS, there are still problems. ORS is still not widely accepted by the medical profession in some developed countries, including the United States. As you are aware, there is relatively limited use of ORS in the United States, although this is changing. Perhaps a conference like this will lead to better acceptability. There is still a need for inclusion of oral rehydration therapy in all medical texts. Information on ORT in texts is less than optimal: because of this there still remains some resistance to the use of oral therapy in a few developing countries. The argument in these countries is that because ORS is not widely used in the United States and not widely discussed by well-known U.S. pediatricians, it must not be the preferred therapy for diarrhea. So it is not just a matter of putting out the word on ORS and having people automatically accept it. We still need to educate professionals in this country about its usefulness.

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Speaking from an implementor's point of view leads me to suggest a subtitle for this talk. We read a lot about ORS and ORT as "the simple solution" but from our experiences as implementors, we might better call ORT the "not so simple solution".

It might be also important at this point to note that the perspective from which I will be speaking is that of rational diarrheal disease control or ORT programs in developing countries. In this discussion on implementation I will not be referring to the use of ORT in the United States with AIDS or with elderly patients, but rather to its use for children with diarrhea in developing countries. The perceptions presented will have been gained from experiences of the PRITECH project, an AID funded project to assist some 25 developing countries to implement national ORT programs and diarrheal disease control, in close collaboration with similar efforts by the World Health Organization. Our perspective as implementors is certainly somewhat different than usual. Our patient is not the individual diarrhea case with active purging, like the ones presented on my colleagues' slides, but rather the country, the CDD program, the Ministry of Health, and, through them, all the patients with diarrhea taken together as a population, both those at home and those who come to the hospitals, those with no dehydration as well as those in shock who need 98 bottles of IV fluid.

How far have we come in implementation of ORT programs? WHO statistics from their last Technical Advisory Group (TAG) meeting in April 1986 indicated that out of 125 target countries, 104 (83%) have Control of Diarrheal Disease (CDD) program plans. Of those 82 (79%) have actually operationalized their national programs. By "operationalized" I mean that the national program is based on CDD unit, or has at least a manager, that it has some kind of monitoring system, that there is implementation of some kind of planned activities, and that ORS is available in at least some services. Importance is placed on ORS here because this conference is about cereal-based ORT, a form of ORS.

What is implementation, or more specifically, what are ORT programs? In general, they are made up of six components, plus one. The objective of such programs is effective case management for diarrhea, in the home as well as in health services. Sometimes this is interpreted as the establishment of oral rehydration units, but national programs generally are concerned with much broader concerns than that alone. In fact, it is important to recognize that national programs are predominantly concerned with behavior change, not with what happens in the intestine. Enhanced absorption in the intestine occurs only as the result of behavior change on the part of mothers and other care providers.

Planning and Policies
The first component of a national program is a plan and some policies. For example, should we start with a communication program aimed at the public or with a national diarrhea training unit aimed at doctors? Should we plan to work stepwise, by region, or should we take on the whole country at once? Is the program going to be primarily packet oriented, or is there going to be a greater emphasis on home treatment? Egypt, for example, has a strongly packet-oriented program, which encourages mothers to use ORS packets as a first action when diarrhea occurs.

Policies are critical to program success. What has the country decided that the mother should do at home when her child's diarrhea begins? What should be the role of sugar/salt solution? What particular home solutions should be recommended? What are the indicators of dehydration that should be used by mothers to know when to take children to health workers and, for peripheral health workers, when to refer the children to more central locations? And when should a national program introduce preventive concepts and efforts to prevent diarrhea illness in addition to its promotion of ORT to reduce deaths?

Training
The second component in a national plan is a major training effort aimed at better case management of diarrhea by health workers. This is most often in-service training, but recently there is more attention being paid to pre-service education in medical schools and nursing schools. Training must cover not only case management, but also logistics, super-
vision, trainers' training and so forth. A part of the training component is the establishment of diarrhea training units, which are often at the national hospital where clinical studies of cereal-based ORS can be carried out.

Communication
The third component in a national plan is a communication and health education program. If training deals with the health workers, the communication component is aimed at the public, and primarily at mothers. It involves both mass media efforts and direct interpersonal communication from doctor or nurse or health worker directly to the patient and his or her mother. Communication activities involve message design, with initial research into what mothers are currently doing and what they might be willing to do, related to what we might want them to do. This is aimed at determining what messages will be the most effective in inducing mothers to change their personal behavior. This research leads to materials production, placement of materials, monitoring, evaluation, and redesign — the cycle of replanning and problem solving.

Logistics, Manufacture and Distribution
The fourth component in national plan development is logistics, manufacturing and distribution of ORS. This is certainly implied in the stress on ORS availability mentioned earlier. Should ORS be manufactured locally or should it be imported? We find that many countries take pride in manufacturing their own packets of ORS. Other aspects of this component are ordering, stock supply, and inventory management. Then come the complications and challenges of distributing ORS to the village level and resupplying millions of health workers who may run out at any time. A critical factor which is often neglected is private sector sales and distribution of ORS beyond the Ministry of Health operations. How will cereal-based ORS affect that component?

Information
The fifth component is the information system for control of diarrheal disease, including monitoring and evaluation of activities. I include supervision in this component as well. How does the manager find out what is actually going on in order to improve it? This involves the choice of indicators. What is the best indicator, one which is both convenient and inexpensive to collect and also gives an accurate picture of the success of the program? Can we depend on following the number of ORS packets distributed? Should we look at the number and proportion of severely dehydrated patients who come into the health center?

Management
The sixth and last component is management, the process of making it all happen, setting policies, coordinating, trying to integrate the public sector and the various elements within the private sector. Planning and budgeting are particular challenges. For example, finding the money for ORS, for training, gasoline, and so forth, requires resources and creativity. Management is solving problems, replanning, in essence responding to what's going on in the field. A responsive management system is the goal of this component.

Research
The "plus one" I wanted to mention is research. Often, research is not considered as part of a national plan. In fact, however, research, particularly operational research, is required where data is needed to solve problems that arise. The goal of this component is to have decisions by program managers based on objective rather than subjective data as often as possible.

So, the implemenor of ORT programs has to deal with planning, policy, training, communications campaigns, logistics, manufacturing, information systems, management — a collection of activities very different from the process of diagnosis and treatment. These different demands raise some issues from the implementor's perspective. The question, from that point of view, is what the role of cereal-based ORT should be today in developing country CDD programs, particularly in relation to a few common problems that we experience with their implementation.

First of all, every country is different and needs different approaches and different messages; they may have different foods or cereals in the basic diet, and there are different diarrhea patterns. Some countries have cholera, others do not, and some have more chronic diarrhea or more benign diarrhea. Do we know enough, today, about cereal-based ORT to recommend it broadly in all of these countries, in all these situations?

As justification for answering "yes" to use of cereal-based ORT, we have some quite positive studies with acutely purging patients, given the particular causes of their diarrhea, with particular cereals and other substrates. Other studies have not been nearly so positive. And some cereals, prominent foods in some countries, have not been shown to be effective substrates. There is also concern over the ability of children under the age of six months to digest starch because of a relative deficiency of amylase at that
Thus, at the present time, it seems inappropriate to draw general conclusions about cereal-based ORT. We should, rather, confine our conclusions to specific situations about which we have substantial data defining what cereal, at what concentration, in what sort of preparation, and with what kind of patient. Conclusions from that situation, those data, should be applied to that specific situation, but may not apply to other situations.

A second common problem is that mothers want something to stop the diarrhea, which ordinary standard ORS does not do. Will adoption of cereal-based ORT improve the levels of appropriate case management by mothers? On the basis of the positive studies of cereal-based ORT, this would be one desirable effect of a shift to cereal-based ORT, since it does reduce volume and duration of diarrhea. Studies in milder cases, the majority of diarrhea cases, are not quite so clear, however, and these constitute the majority of diarrhea cases — just the cases that mothers see most. If cereal-based ORT had no better effect than standard ORS in such cases, its adoption would do us no good.

On the other hand, mothers have been clamoring for anti-diarrheal drugs for years, while many studies have shown that such drugs have little or no effect on volume or duration of diarrhea. Thus, it is probably the case that the mother's judgment is not based on actual observation, but rather on what they are told will be the effect of a particular drug or of ORT. Since the usual case of mild diarrhea probably will respond exactly the same to no treatment, treatment with drugs, treatment with standard formula ORT, or treatment with cereal-based ORT, what may be more important, then, is the image which cereal-based ORT has among the medical and pharmacy professions, or among drug store clerks. If this image is derived from doctors' or pharmacists' opinions, and if, in turn, their opinions are determined by the demonstrated effectiveness of rice polymer-based and cereal-based ORT in severe diarrhea, it may be unimportant that it has little effect in mild diarrhea. We can promote it enthusiastically based on its demonstrated effectiveness in severe diarrhea, even though we know it has little real effect on duration or volume of stooling in milder cases. All this raises the further question, should we be at all concerned about the ethical aspects of how we promote cereal-based ORT, about following the principles of "truth in labeling"?

A related aspect concerns the taste of ORS. Some preparations of cereal-based ORS taste better than standard formula ORS. Usually, however, it is the mother who tastes the ORS, not the child who will actually receive it. The child may think both types of ORS taste equally good. Or, the "better tasting" ORS may lead the child to drink more than he needs. Should we then promote cereal-based ORT because it tastes better?

A third problem is the reluctance of physicians and health workers, and particularly pharmacists, to accept ORT. A major challenge facing program implementors the world over is to bring about greater adoption of ORT by this group. We certainly look to cereal-based ORT and its better results in severe diarrhea as better ammunition for us and for program managers to use in convincing doctors and pharmacists to adopt ORT in general. This would potentially be a major benefit from adoption of cereal-based ORT, and it represents a real advantage of cereal-based ORT over the standard ORS formula. The same concerns about "truth in labeling" I expressed earlier, however, apply here, too.

A fourth problem is the extra work potentially needed to use the treatment, potentially at least. Does cereal-based ORS have to be cooked? Can it be supplied in easily dissolved packets, or are we talking about a home prepared solution? These questions will lead to big differences in considerations and use rates for mothers.

Kielman in Egypt (1) showed that mothers there were more likely to use a prepared packet which required only mixing with water than to use sugar/salt solutions which required more effort, at least that was his interpretation. D'Aulaire reported from Nepal (2) that Tibetan refugees preferred home prepared solutions because they seemed more like natural foods and liquids and less like Western medicine in aluminum packets. The diarrhea training unit in Lahore, Pakistan, is currently teaching mothers to cook a mixture of rice and dhal (legumes) as their home ORS, a "super ORS," and reports anecdotally that mothers like the idea of that being a more powerful solution enough to do the work to prepare it. That needs testing in the field, however. The conclusion should probably be that each cultural setting and each set of promotional messages will lead to different results. Again, cereal-based ORT appears not to be a single entity, but rather a range of possibilities, among which program managers and technical consultants must choose.

A fifth problem is the initial response to diarrhea. What should the mother's response be to the first
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evidence of diarrhea in her child? Should we recommend the use of cereal-based ORT for the first loose movement? Or should we recommend the use of specially prepared home solutions like sugar/salt or the Pakistani rice and dhal ORS I just mentioned, or chicken soup as we heard about earlier? The Indonesian CDD program is currently concerned that its promotional efforts may have gone too far, as mothers are requesting ORS packets for even mild diarrhea in their children. Health workers feel they can not refuse to give packets when they are requested, and the Ministry of Health budget may not be able to take the strain of the many packets required. In the Egyptian program, mothers were apparently induced by the public promotion program to use packets, many of which they purchased themselves, for 70% of all diarrhea episodes. But few developing countries are comparable economically to Egypt. Will greater adoption of cereal-based ORT contribute to a clearer approach relative to early diarrhea and the mother's initial response?

A sixth problem is manufacturing. As I mentioned, many countries want to manufacture their own ORS. Will the desired formulations of cereal-based ORS lend themselves to manufacture in developing countries? Present formulations of cereal-based ORS will not dissolve directly in the same manner as standard glucose-based ORS. They either require cooking or making a suspension which must be actively mixed at the time of administration to insure delivery of the substrate. The mixtures may not also look clear and clean like current ORS. The use of artificial carbohydrate polymers with various chain links is customary in making artificial baby formulas, but require some chemical manipulation. If such substrates are adopted, will developing country pharmaceutical manufacturers be capable of effectively carrying out the chemical procedures effectively that are necessary? How much will this factor of the appearance of the solution influence adoption and use by mothers? Clearly, the ultimate evaluation criterion by which to judge cereal-based ORT must be its role in stimulating effective use by mothers and by health workers in the population at large, not only its clinical effect in a research study with ward diarrhea patients. If standard ORS packets lead to higher rates of use and to more effective use than cereal-based ORT, either in packets or home made, then the clinical advantages of cereal-based ORS become irrelevant.

The seventh aspect relates to the nutritional damage caused by diarrhea. Dealing with this effect of diarrhea is certainly a major challenge to program implementors. Jon Rohde presented the rationale for more attention to feeding during and after diarrhea and closer links between CDD programs and growth monitoring at ICORT II (3). Working out the operational approach to this in each country, however, is a problem. Diarrhea is often accompanied by mother-produced starvation, food withholding, as well as anorexia and malabsorption, which makes the effectiveness of any case management technique in preventing this effect of considerable importance. Cereal-based ORT certainly has more calories than standard WHO formula ORS, from 30 to 60 more grams of substrate, or 120 to 240 additional calories per liter. Food, however, is much better than cereal-based ORT. Breast milk or cow's milk has some 680 calories per liter, and rice or other cereals taken directly, as well as fruits and other weaning foods are even denser in calories. Standard case management guidelines for diarrhea have now universally accepted the principle of continued feeding during diarrhea. Perhaps the improved nutritional status that Dr. R. Bradley Sack mentioned here earlier may be due in large part to patients getting food, not to the type of ORS actually used.

Why, then, is there the tremendous concern over incorporating a cereal carbohydrate or other caloric source into the rehydration solution for its nutritional benefit? When I think of the simple approach used in Dacca at the Cholera Research Laboratory in the 1960s, how much of the success of that treatment was due to the chicken curry, rice and dhal which we gave the patients sometimes within minutes of their arrival on the ward. Given the difficulties in packaging cereal-based ORS, or even artificial long polymer carbohydrate, we might have greater impact in the long run by shifting the attention of the ORT research group more toward developing better techniques to get mothers to feed their children during and after diarrhea while using the current standard solutions, and away from the seductions of trying to develop a single solution which will both feed and rehydrate. Is anyone proposing that we should not feed during rehydration therapy? Unless someone is, the results of the nutrition-oriented research on cereal-based ORT may be primarily academic, rather than of practical value.

Conclusion

At first blush, better tools always seem desirable to make work more effective or easier. But if a better tool requires increased work to use it, or is more difficult to manufacture, more expensive, or harder to obtain, its better quality from one particular perspective may prove less important in the light of such other practical aspects of its implementation.

I remember a provocative article in The New England
Journal a number of years ago which showed the effect of a hypothetical new test for pancreatic carcinoma, a test which was better, but still not quite perfect. The calculations reported that adding such a test, in fact, would lead to an increase in mortality "related" to pancreatic carcinoma, due to the increased number of laparotomies for false positive test results and for disagreements of the new test with existing tests. Cardiac bypass, another new tool, has proven over time to relieve the symptoms in many patients. Its effectiveness in getting heart disease patients back to work, however, has been much less than was hoped.

I have been tremendously excited by the improved absorption and decreased morbidity seen in clinical studies of certain types of cereal-based ORT. And I look forward to learning more today about the results of additional such studies. I certainly hope that cereal-based ORT will turn out to be the answer to the implementor's prayer — the "simple solution" we all are looking for. I hope, however, that the conference today can keep its perspective and its recommendations broad enough to include the potential drawbacks which may appear when this new tool is put into the hands of mothers, general practitioners, pharmacists, and national ORT program managers.

One means for doing this would be to include an agenda for the operational research and field based studies which will be required to demonstrate definitively that the benefits of this tool are greater than the range of potential and perhaps unforeseen costs which may be incurred when it is put into implementation. Some of the questions or topics which might be on that agenda are as follows:

1. Is the locally available starch effective as a substrate for ORT?
2. Is it more work to prepare than standard ORS or sugar-salt solution?
3. Is it more acceptable to mothers, in taste, in appearance, in packaging?
4. Is it easier to teach cereal-based ORT to mothers?
5. Is it more feasible to manufacture a cereal-based ORS in developing countries than the standard ORS? Is it more difficult?
6. Is it more expensive to make?
7. Will packets of cereal-based ORS be stable under storage conditions of high humidity and heat?
8. What will be the effectiveness of cereal-based ORT on mild diarrhea as well as on severe diarrhea?
9. Does cereal-based ORT work any better than merely giving food plus glucose-based ORS or even food plus a plain electrolyte solution without glucose?
10. Do mothers and doctors actually use cereal-based ORS more frequently and more correctly than standard-formula ORS?

Knowing the answers to these questions, in addition to knowing that cereal-based ORS is more effective in reducing stool volume and duration in heavily purging diarrhea patients studied on a clinical research ward, would help us to make recommendations about cereal-based ORT more useful to implementors of diarrhea disease control programs.

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NUTRITIONAL ASPECTS OF ORT

Dr. Mathuram Santosham
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It is not a surprise to those of us who have worked in developing countries that children have several episodes of diarrhea each year. Children in Bangladesh, for example, suffer anywhere from four to eight episodes of diarrhea each year.

In each of these episodes, the child has a nutritional setback. This is true not only in developing countries, but also true in certain parts of United States.

An example of this includes data generated by work that Dr. R. Bradley Sack and I have done in Arizona among Apache Indians. The rate in this population also ranges anywhere from four to seven episodes per year. Moreover, Dr. Robert Black has been able to show that young infants under two years of age can spend about 16% to 17% of their life having diarrhea, which is a very significant proportion of their life. Assuming that during this period (during a diarrheal episode), the child at the very minimum is not getting adequate nutrition, and then takes another week or so to recover from this reduced nutritional intake, this child may spend 25% of his life not eating an adequate diet. As a result of that phenomenon we see this typical graph that was generated by Dr. Leonardo Mata, who is very familiar to many of you (slide 1). Children usually don't suffer many episodes of diarrhea during the first six months of life, depending on the country situation, but after that age suffer many episodes of diarrhea. With each diarrheal episode, the child loses weight and slowly recovers. Every time he catches up, he suffers another episode of diarrhea. Our hope is, in the next few years, to change this curve so that with each diarrheal episode the child does not drop weight, but can maintain it close to normal.

What is the reason for this weight loss? Part of the reason is the child is anorexic during the diarrheal episode, another is the vomiting during the diarrheal episode. Mothers in many countries still believe that food should be withheld during diarrhea. In the few countries I have visited, I have asked many parents why they withhold food when their child has diarrhea. Very often their response is, “My doctor told me not to feed my child when he has diarrhea.” Why do physicians give such advice? We will talk about that in a few minutes. There are also catabolic losses due to tissue breakdown and diversion of nutrients. The child is expending a lot of energy during a diarrheal episode to build up nutrients that have been lost.

Let us return to the reasons behind physicians withholding food during a diarrheal episode. Traditionally it has been said that food should be withheld during an acute diarrheal episode. There are studies going back to the 1950s and 1960s which show that children who are fed a lactose containing formula during diarrheal episodes can have increased stool output. Based on those studies, American pediatricians for the last couple of decades have withheld lactose containing formulas, but what in fact happens is all food is withheld during a diarrheal episode. The recommendations are to withhold lactose containing formulas, but what in fact happens is all food is withheld during a diarrheal episode. Dr. Brad Sack earlier talked about the importance of incorporating the right recommendations into textbooks of pediatrics. Here is a quotation from a very popular textbook of pediatrics which is read all over the world, on diarrhea treatment, “...Frequency and volume of stools usually subside rapidly in forty-eight hours. When this occurs oral feeding of one of the carbohydrate electrolyte solutions may be initiated. (Until then you should keep them on IV therapy, after that you can start with ORS)....return to the normal diet in seven to eight days...” Such a recommendation would be catastrophic for a child in Bangladesh.
or many other developing countries, who is already spending such a large percentage of his life not eating — and you would add another seven to eight days of starvation with each one of his annual episodes? These textbooks are read not only in the U.S., but in many parts of the world. I want again to emphasize that it is not only important to publish data, but also to make sure that it gets into the right textbooks. Unfortunately, the malnourished child is at a considerable disadvantage. It has been shown that the diarrhea mortality rate increases about four fold in children who are in less than the 65th percentile weight for age. Dr. Black was able to show, and others have now shown, that the incidence of all diarrheas do not really change much according to nutritional status, but the duration of diarrhea does increase in undernourished children when all diarrheal episodes are compared, regardless of etiology. If one looks at specific etiologies, the effect is much more dramatic. For example, in E.coli diarrhea the duration of diarrhea is increased two and a half fold in undernourished children, compared to well-nourished children. In shigella diarrhea, again there is a three fold increase in duration of diarrhea. People have also shown this for cholera and some of the other etiological agents.

One really important fact that we must keep in mind is that even if a child has diarrhea and he loses weight, he does gain it back. Let me explain this slide for a minute.

This is a child who had normal growth before his diarrheal episode. This is the extrapolated weight. This is his actual weight. But you see here, he loses a considerable amount of weight, but he gains it back in about two to three weeks. With appropriate intervention, i.e., introduction of a proper diet, we should be able to change this growth pattern considerably so that infants do not dip down in their nutritional status with each diarrheal episode. A number of us now are interested in this aspect of the management of diarrhea. Dr. Kenneth Brown and I are conducting studies in Nigeria and Peru to look at the dietary management of diarrhea. The purpose of these studies is to evaluate the use of different locally available and culturally acceptable diets during an acute diarrheal episode.

What about ORT? In the 1960s and 1970s, there was a lot of enthusiasm about community-wide use of ORT. Can ORT itself improve nutritional status among children? In a study in Iran, where ORT was introduced into one community and not in another, it was shown six months later that the children in the community with the ORT intervention had significantly better weight gain compared to the infants in the community that did not receive ORT. As Dr. Northrup pointed out, this is not a big surprise because when you introduce ORT, you also introduce feeding to educate parents. There have been a number of programs that have looked at this issue. Some have shown a positive nutritional effect and others have not shown any nutritional effects. If one looks at these studies carefully, it was not the ORT that made the difference, but the dietary advice given along with the ORT. I think the bottom line is that if one introduces ORT properly, by incorporating health education, proper feeding practices, etc., one should be able to demonstrate a positive nutritional effect as a result of the intervention.

We all agree that there are at least three phases to the treatment of acute watery diarrhea: rehydration, maintenance (feeding), and replacement of ongoing stool losses. Many studies have been done in the past two decades on the rehydration aspects and issues related to replacement of ongoing losses during diarrhea; Unfortunately, few careful studies have been done to evaluate the dietary management of diarrhea.

Fortunately there have been at least two or three well controlled studies which have looked at introducing food during the early phase of diarrheal disease immediately after rehydration. One of the first controlled studies, published back in 1946 was by, I believe, Dr. Chung, when he looked at one group which was fed and another group that was starved. Both groups received IV therapy initially. Chung was able to show that you do not increase the duration of diarrhea by introducing feeding immediately after rehydration. The big concern those days was that if you introduced food, you would increase the duration of diarrhea. Chung showed that both groups tended to lose a little weight in the first 48 hours, mainly because both groups were not receiving any nutrition in the first forty-eight hours; they only received intravenous therapy. There was no difference in weight gain between the groups. However, he did not have enough patients to show any nutritional advantage. His important contribution was to show that it was not dangerous to feed infants during an acute diarrheal episode. This was a very important contribution, but was somehow lost in the literature for about 30 years.

This is a study that we did in Arizona (slide 2). We gave early feeding to one group and to a control group. We gave ORS only for a 48 hour period and gave them a half-strength formula after 48 hours for an additional 24 hours, then a full-strength formula.
This may seem outrageous to you now, but this is still common practice in many US hospitals (IV therapy alone for 24 to 48 hours, then a glucose ORS, and then a half-strength formula). The treatment group was given rehydration therapy for four hours and then given a full strength soy-based, lactose free, formula. We were able to show that within 24 hours there was a reduction in stool output in the group that was fed the soy-based formula compared to the group that was receiving only ORS. At the end of the illness, there was quite a dramatic difference: Less than 50% stool output in the group that was fed (slide 3). We were also able to show the same thing for the duration of diarrhea: there was about a 40-50% reduction in duration of diarrhea in the group that was fed (slide 4).

A similar study was done by Dr. Khin Maung U from Burma, who looked at children who were breast fed immediately after rehydration, compared to infants who were given only ORS for a 48 hour period. He was able to show that if you breast feed infants immediately after rehydration, stool output is reduced. We can say now that soy-based, lactose free, formula and breast milk can be introduced safely during a diarrheal episode and both seem to have an advantage.

Another very important study that has not yet been published was done by Dr. Ken Brown in Lima, Peru, on four different groups. He fed one group a casein hydrolysate-based formula, without any dilution, immediately after rehydration. Another group was given a half strength formula which was then increased to full strength after 24 hours. The third group received oral rehydration solution only for 24 hours and then a half strength formula and then a full strength formula. The fourth group received intravenous (IV) solution, then a glucose solution, and then a half strength formula followed by a full strength formula. It is important to remember that the first group was fed full strength formula immediately after rehydration. He did not find any difference in total stool output among the four groups during the entire course of the illness. There was some difference during the first 24 hours, the IV group had a slightly less stool output during this period. These were all acute diarrheas of less than five days duration. They ranged from mild to severe diarrheas; about 30% of them were mild dehydration, about 10% had severe dehydration; the remaining had moderate to mild dehydration at the time they entered the study. After eight days the groups that were fed early clearly had better weight gain. This advantage seems to be maintained on day 15, but the difference is not statistically significant. Dr. Brown also was able to show that the arm circumference and the skinfold thickness was increased in the groups that were fed immediately after rehydration.
The children who were fed have better arm circumference and skinfold thickness on day eight. There was also much better absorption of energy in the groups that were fed in the first 24 to 48 hours compared to the two groups that did not get any feeding during the first 24 hours. In addition, he was able to show better absorption of protein and fat in the groups that were fed early.

These studies on the dietary management of diarrhea can be summarized as follows: (slide 5) a) Studies in native American populations, using a lactose free soy-based formula have shown that the duration of diarrhea and stool output is reduced when this formula is introduced immediately after the rehydration period. b) Infants have better weight gain, better nutritional status and better absorption of nutrients when feeding is introduced immediately after rehydration. c) If breast milk is introduced immediately after rehydration, stool output decreases. Feeding the appropriate food during diarrhea certainly seems to be advantageous. However, there are many more questions that need to be answered. What kind of diets can be used in countries where formulas are not available? When can lactose containing formulas be used? Can cow's milk be introduced? How soon can cow's milk be introduced? Does cow's milk have to be diluted?

The last point I would like to make is to reemphasize a point made by Dr. Northrup earlier today: We have to very carefully think about the advantages (if any) of using cereal-based ORT. Is it going to offer us something more than the glucose-based ORS during rehydration therapy combined with early feeding? If so, those advantages should be clearly outlined because we must not lose the momentum we have gained over the last 10 to 15 years with all the work that many people in this room have done in teaching parents, doctors, and health workers about the use of glucose-based ORS. If indeed feeding can achieve the same results, perhaps we should be spending our resources and our energy in the next few years looking at different feeding practices. Thank you.

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Feeding is essential in treating diarrheal illness and, as such, rehydration must be linked to it since oral hydration is an essential prerequisite for nourishment. The Baltimore Sun, February 17, 1987, announced that, "Research Backs Grandma on Chicken Soup for the Ill", indicating the successful use of oral rehydration therapy and nutrition has been in use for thousands of years, and cites one reference at least three thousand years old. If this is so, why does diarrhea continue to take a large toll of lives? The answer lies both in the composition of the solution and how it is given. Science has been able to define how ORT works and the safe and optimum composition needed. In its earlier use as a folk remedy, the concept of replacement of fluid and nutritional loss was not clearly articulated nor was the importance of salt well understood. Both are critical for effective use.

If an oral rehydration solution is to be based on locally available food, then dietary preferences are critical. Modifications to accommodate preferences, however, must never violate the established principles which make ORT so effective. In addition, the correct amount needed to replace losses, must be kept clearly in mind. Moreover, each different solution needs to be studied carefully before its dissemination and use.

We must constantly remind ourselves that, except under famine conditions, every household in the world has the necessary ingredients for providing effective oral rehydration solutions. What is missing is knowing how to use what is available to prepare a solution of the correct composition, and how to give it at the right time and in the right quantity. Resorting mainly to manufactured products and distribution systems created by commercial organizations and professionals to an important extent dodges the challenge of imparting the needed knowledge to the poor in urban and rural households around the world.

Since we are discussing ORT, we should examine the "ORT" closely (figure 1). It has a watery body with salts and carrier legs, legs that are composed of the critical co-transporting substances that move salt and water from the lumen of the intestine to the blood stream in order to avert dehydration and death. Several legs are made of smaller molecules, glucose and amino acids, which, if linked together form polymers of varying sizes, the largest being proteins and cereal starches.

Dr. Michael Field, now at the College of Physicians and Surgeons of Columbia University, in an editorial in The New England Journal of Medicine in 1978, pointed to the likely importance of polymers of glucose and amino acids in optimal transport of sodium and water from the gut lumen into the blood stream. Using a children's rhyme by Maurice Sendak to make his point: "Sipping once, sipping twice, sipping chicken soup with rice," he noted that biophysical considerations and transport studies had indicated a significant advantage in using larger co-transporting substrates to maximize the absorption of salt and water during diarrhea. Let us clearly understand what is behind this idea.

The intestinal lining is a very leaky and complex membrane. Small molecules such as glucose, which may ultimately transport fluid from the lumen into the blood, will initially, by osmotic force, do the reverse and draw water out of the bloodstream into
the gut lumen. Tangible evidence of this process is seen when a dehydrated, sweating tennis player or runner, on a very hot day, drinks several hypertonic sugar-based sodas in rapid succession. Initially, the athlete becomes faint, as the concentrated sucrose in the soft drink draws fluid into the gut lumen before it is subsequently reabsorbed. In a similar way, the small co-transport molecule of glucose exerts an osmotic penalty (Fig 2). This limits the efficacy of the current ORT solution. No additional small molecules can be added without paying the penalty of increasing shock and diarrhea, which can produce increased concentrations of sodium in the blood and further complications or death.

Starches from natural foods such as rice are long, elegantly branched chains of chemically linked glucose molecules. (Fig 3) Each starch molecule has the same osmotic activity for its hundreds of linked glucose molecules as does a single glucose molecule, and thus there is no osmotic penalty incurred if higher concentrations of starch are employed. A solution with a large concentration of a starch and a protein which, during digestion, releases large numbers of the salt and water-transporting small molecules of glucose and amino acids can be prepared without excess osmolarity. Fortunately, the human digestive system is designed to split starch into glucose and proteins into amino acids. These are the “business end” of oral rehydration solutions carrying sodium and, with it, water across the lining of the gut into the blood stream. The pancreatic starch digesting enzyme, amylase, is present in excess in diarrheal disease.

Natural food products are principally polymers (starches and proteins). Only special items such as honey or sugar cane are made up of small molecules. Our digestive system has been designed to process these polymers and absorb efficiently the split products of the digestive process. Foods high in sugars and amino acids are characteristic of the processed products in developed countries. People with mild absorptive defects, may actually develop diarrhea in response to such diets. Food polymers are broken down by secretions such as amylase, and enzymes that digest proteins. After the initial splitting into fairly large polymers, processing into individual molecules with high osmotic activity, such as glucose and amino acids, occurs at the brush border of the intestinal cells of the gut. Digestion thus minimizes excess luminal osmole and the accompanying osmotic penalty. Thus, feeding cereals which contain glucose in the form of a starch polymer, during diarrhea, can accelerate the transport of salt and water in oral hydration solutions without any penalty. Their use is based on sound physiologic principles. In the 1960s Dr. John Fordtran clearly showed that a high osmotic load can produce diarrhea and delayed absorption.

Figure 2

In diarrhea we have seen from studies by Dr. A. M. Molla that carbohydrate absorption is little compromised but absorption of fat and proteins is more vulnerable. That polymeric substrates, for oral hydration, reduce stool volume was first demonstrated by Dr. F. C. Patra and Dr. D. Mahalanabis in 1982. They also showed that glycine and glucose, when consumed, also reduce losses. Subsequent studies have not confirmed this latter observation, however. Earlier, in Dacca, Dr. Molla and his colleagues showed that rice-based oral rehydration solution was, at least, equally as effective as the sugar-based solutions. Shortly thereafter, he showed that in comparison to the World Health Organization/UNICEF glucose based solution there was a striking reduction in vomiting and in stool output. Most of the cereal grains have now been studied to date as well as plantain, green banana and some starchy roots. So far, all starches used in ORT solu-
tions perform at least as well as the current glucose based solution and usually much better (Fig 4). The cereal solution we are currently working with uses fifty grams of rice powder per liter. Since we know we can eat dry rice without ill effects, there is no hazard in preparing a solution as thick as is drinkable. Thus, in telling mothers how to prepare a rice solution, it is safe to instruct them to make a solution that someone can drink. Salt concentration remains critical, however, and must be made explicit so that it does not exceed limits and make a dangerous solution. Cereal solutions differ in appearance. They all have pleasant tastes to people used to eating the particular grain chosen. For instance, the rice solution in Bangladesh certainly is most acceptable to mothers and children and others with diarrhea. Dr. Northrup has pointed to some of the disadvantages and complexities in using cereal solutions, but let us look at some of the advantages.

Certainly, cereal grains are widely available in most households of the world, except during famine. Bread is considered “the staff of life” and that is also true of rice and of other cereals. They are also familiar. Many dishes are made from cereals in every culture. They have greater nutritional value than sugar and, furthermore, the recipe for a soup-oral hydration easily translates into a pudding or a soft cereal that can achieve greater caloric density by adding oil or fat for post-diarrhea feeding. The fundamental principle is to use the patient’s digestive enzymes, rather than the factories in developed countries, to process the product. This has greater physiologic merit and also saves costs.

The proper role of proteins has not been addressed in ORT. Obviously, if the optimal solution for oral hydration would include proteins which would release a maximum amount of co-transporting amino acids, the protein would need to be mixed in the highest concentration possible. This has not been done yet to my knowledge, and is an area of needed research.

In an English translation of Vedic texts derived from the oral traditions of Indian medicine, which is at least three thousand years old, specific statements are made about the use of rock salt with cooked soft rice in a thick gruel. The texts also state that copious quantities should be used, indicating that there was some conception of replacement or use to repair dehydration. As asked earlier, why have these observations not been taken up and used effectively? Many useless things may be added to genuine remedies resulting in something that is ineffective, and sometimes genuine remedies are ignored while nonsense gets recycled. For example, observations in the 1940s by Dr. Chung showing that feeding shortened diarrhea and lessened fluid losses were overlooked for forty years by “modern” medicine while the myth of “resting the bowel” was propagated. This concept probably killed many children in the world.

The advantage of using food-based solutions for ORT in developing countries is that they may have no glucose industry. To secure glucose for a product, indigenous starchy foods must therefore be processed in a developed country and sold back as glucose and added to ORT locally. This seems irrational unless local substances are less effective in the treatment of diarrhea. This bears careful thought, particularly by people in developing countries who may not have the industries to process local foods. Rice, wheat, sorghum, millet, and plantain are widely available and are cooked every day in village homes throughout the world. Their adaptation is thus only a problem for those who come from foreign places. What we need to provide are reasonable formulas for the salt, and reasonable instructions for preparation that match what different populations like to eat and drink. This is the challenge. We should focus on oral hydration at this level, even if we feel we must be concerned about the logistics and international transport of packets. I would like to see palatable solutions prepared in all homes.

In a developed country such as the United States, an appropriate cereal or solution to use in diarrhea at home can be purchased in the supermarket. Diarrhea, which is still a considerable problem in the United States, does not cost us as many lives as in poor countries, but it is very expensive in hospitalizations and a great waste of health resources. Thus both the ingredients for standard glucose-based and cereal-based solutions are readily available in most food stores in wealthy countries.
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GLOBAL TRAINING NEEDS:
U.S. PERSPECTIVE

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There are three questions that I would like to consider this morning to help us to focus on the topic of oral therapy education in the United States. The first question is: Is diarrhea a problem in the United States? The second question is: What are the practices that are already in place in the United States? Since the United States is often regarded as a leader in health care, perhaps what is already being done is appropriate and correct and educational programs may not be needed. The third question is: If improvements or changes are needed in the United States, what can be done to alter people's attitudes?

The first question deals with the magnitude of the problem of diarrhea. In the developing world, as many as five million children under five years of age die each year from diarrhea (1). In our country, the risk of dying from diarrhea is much less. However, the morbidity of diarrheal diseases is considerable: currently 14 per 1,000 children under one year of age are hospitalized each year in the United States because of acute diarrhea and the average stay is four and one-half days (2). The average hospitalization costs between $1,000 and $3,000, an expensive proposition both in terms of money and disruption to family life. So diarrhea is an important problem in our country, although it does not have the impact seen in developing countries.

The second question was whether educational efforts concerning treatment of diarrheal disease are needed in the United States, which is regarded by many as providing the standard for optimal care in health. Since oral therapy for diarrhea concerns both fluid and electrolyte management and feeding, a review of the practices concerning these therapies will help

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<th>Composition of oral rehydration fluids commonly used in the US and Canadian medical school emergency rooms</th>
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Table 1
answer the first half of this question. In 1980, I was asked to look at what was done in our country to treat a child with acute diarrhea in an outpatient setting and did a survey on oral rehydration practices. Table 1 summarizes the data obtained from departments of pediatrics at U.S. and Canadian schools of medicine (3). We found a great deal of variability in the responses and no single focused approach to oral treatment of acute diarrhea. If the child was seriously ill, he was given intravenous fluids. If he was not seriously ill, any of a great variety of different fluids might be given. As can be seen from Table 1, many of these fluids were not optimal fluids.

As an example, carbonated beverages, which are still quite popular in 1987, contain a high sugar concentration, little salt, and have a high osmolarity which makes them very poor rehydration solutions (2). Fruit juices, which are also commonly used, also have high sugar concentrations, little sodium and high osmolarities. The commercially produced sugar-salt solutions available in 1980 were not ideal solutions either. Fortunately, in the last few years, there have been improvements in the composition of commercial sugar-salt solutions (Table 2), which now more closely approach a solution based on physiologic principles and studies. A number of studies in the United States have proven these solutions to be safe and effective. However, despite the availability of more physiologically sound solutions, a great variety of oral fluids, including carbonated beverages and fruit juices, are still used to treat acute diarrhea. So we still need to educate our practicing pediatricians about the composition and use of oral rehydration solutions.

Oral therapy for diarrhea also should include the reinstitution of feeding. A 1984 review of literature on studies of feeding during diarrhea documented that relatively little data were available to answer whether feeding was a safe and efficacious therapy (4). Fortunately, in the last few years there have been studies which have provided increased evidence that feeding is a helpful therapy for a child with diarrhea. At Children's Hospital, we teach that therapy includes replacement of deficits and ongoing losses and that maintenance fluids and electrolytes must be provided and that, in addition, feeding will prevent energy and protein deficits, allowing the body to repair itself. However, many U.S. pediatricians are still concerned about the potential of feeding causing malabsorption with fluid loss and acidosis, and the data on the potential for decreased morbidity from diarrhea in children receiving appropriate feeding has not yet met with widespread support in this country.

The answers to our first two questions indicate that diarrheal diseases are indeed a problem in the United States and the general U.S. approach to oral therapy is still not optimal. How can attitudes and practices be changed to incorporate the proven benefits of oral therapy?

To be able to change practices, an understanding of the concerns of practitioners would be helpful. Among the most frequently voiced reservations about oral therapy are the potential risk of causing hypernatremia and the efficacy of oral therapy in a vomiting child. When a child starts to vomit, many pediatricians start IV therapy. I have already mentioned concerns about malabsorption with diarrhea. Most pediatricians in this country feel that if a child with

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Some Oral Electrolyte Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration When Diluted (mEq/l)</td>
</tr>
<tr>
<td>Product</td>
<td>Na</td>
</tr>
<tr>
<td>Rehydration WHO Oral Rehydration Salts</td>
<td>90</td>
</tr>
<tr>
<td>Rehydralyte (Ross)</td>
<td>75</td>
</tr>
<tr>
<td>Maintenance Prevention Infalyte (Pennwalt)</td>
<td>50</td>
</tr>
<tr>
<td>Lyten (Mead Johnson)</td>
<td>50</td>
</tr>
<tr>
<td>Pedialyte (Ross)</td>
<td>45</td>
</tr>
<tr>
<td>Resol (Wyeth)</td>
<td>50</td>
</tr>
</tbody>
</table>

1. HCO₃ or derived from citrate
2. Cost to the pharmacist, based on Average Wholesale Price, Drug Topics Red Book 1987 and June 1987 Update
3. Available in the USA only from Jannas Brothers Packaging, 2533 SW Blvd., Kansas City, MO 64106
4. Also contains 4 mEq each of Ca and Mg, and 5 mEq of PO₄
diarrhea is starved, the diarrhea will be decreased. This teaching is still found in medical textbooks of pediatrics even in the early 1980s (4). Now, however, we have many studies showing us the benefits of introducing early feeding to children with diarrhea.

A final concern, often not voiced, is whether a therapy which is not “high technology” can be effective. Oral therapy has a major hurdle to overcome in this regard because it is a simpler form of therapy which is attempting to supplant a “higher” technology.

To summarize, in our country there is not a focused, single approach. Most pediatricians use fluids, but not the sugar-electrolyte solution that has been proven to be effective in many parts of the world. And the common practice for feeding is still to starve children in that first twenty-four to forty-eight hours in an acute episode of diarrhea.

So what can we do to change these attitudes and practices? There are several things that can be done and some of these principles have been incorporated into our program at Children’s Hospital in Boston. The first is to create an awareness of both in the general public and in the medical community. A forum like this, which includes physicians and other health care providers and members of the lay community, is a very positive way to create an awareness of what is appropriate in treating acute diarrhea.

Secondly, although scientific studies and presentations can be helpful, there already is a large body of literature showing the effectiveness of oral fluid and electrolyte therapy; there also is now beginning to be a sizeable body of literature on feeding during diarrhea indicating how very effective feeding can be. However, no matter how eloquent the speaker or persuasive the study, these methods often are not enough to change practice habits. The essential element which we in Boston have found to change attitudes is to provide practical experience in using oral therapy. This is as true in the United States as it is in developing countries. To change attitudes, and thereby practice, the program we developed includes what we consider to be the five important factors for creating a successful “hands on” program.

At Children’s Hospital, our program in oral rehydration therapy has incorporated these five principles, and we emphasize education of both the professional staff and the families about ORT. One further point is that we have incorporated ORT without creating more work. We are using an emergency room sheet which includes space on the form to objectively assess a child’s state of hydration, based on the child’s history and physical examination. This has helped our staff a great deal in matching their previously subjective impressions with objective criteria.

In closing, I would like to say that Oral Rehydration Therapy is still vastly underutilized in this country but can have an important impact on the treatment of diarrhea. We are hopeful that more practical “hands on” programs for the use of oral rehydration therapy will be developed in the United States to provide experience in its use. In this way, a new generation of practitioners will learn that technology does not necessarily have to be “high” to be effective.
References:


A major goal of research and development for oral therapy for diarrheal diseases is to devise oral solution formulations or dietary regimens leading to absorptive efficiency exceeding that of current solutions, thereby diminishing the duration and volume of diarrhea while enhancing nutritional benefits. (Table 1). Balance studies are essential in testing for appropriate ingredients and selecting among regionally available foodstuffs, and large-scale field trials are essential to confirm practical applicability and to identify and overcome potential safety hazards. The critical importance of particular solution ingredients is reflected by the fact that plain oral salt water severely aggravates acute diarrhea [1,2], whereas glucose added to salt water provides an absorbable and life-saving solution [3, 4].

Disease severity influences the outcomes of such studies of new solutions and foodstuffs. Since the majority of patients have mild self-limited diarrhea, prevention of starvation therapy is more important for their management than choice of particular oral solution. Most patients have mild, brief disease and relatively small acute intestinal absorptive defect. These patients easily absorb a wide variety of oral solutions and foods. They present an ideal opportunity to teach mothers and other health workers not to use starvation as therapy, how to make up an oral solution properly, and how to distinguish signs of improvement from signs of progressive dehydration warranting referral, should diarrhea continue (Figure 1). It matters little if the oral solution used for such patients has, for example, 30, 60 or 90 mEq/L of sodium [5] unless an amount is given in excess of actual needs, because the episode is brief and the absorbable menu is large. In such patients it is more important to avoid counterproductive excess therapy; since they absorb so much so well, they are not ideal
subjects for detecting subtle but important clinical differences between solutions or regimens of different compositions.

In contrast, relatively few patients have profuse, potentially fatal fluid losses with severe dehydration (Figure 2). Their intestinal absorptive impairment is severe, and water and electrolyte shifts are massive. Even small differences in solution composition can mean positive or negative balance, benign or complicated course, and sometimes life or death. It is in this group that enhanced oral therapy efficacy and efficiency can be pivotal to program success by improving therapeutic results in critically ill patients. If an innovation works better in such patients, it is likely to be adaptable to milder cases. Patients with the highest purging rates have the highest failure rates: they provide for the most rigorous tests of potentially improved therapies.

Certain methodological details are essential for comparing oral solutions. Prestratification by initial diarrhea rates, that is, entering study patients with known and equal initial rates into planned comparison groups, is ideal for ensuring intergroup comparability. If mean initial diarrhea rate is higher in one group than in the other, the chance of failure and of inferior overall results will be greater in the more severely purging group.

Valid comparisons of oral solutions in severely purging patients require prompt correction of initial deficits; lag in rehydration or inadequate intake, can confound results by comparing inadequate methodologies rather than solution absorbability. Patients with concurrent disorders like glucose-galactose malabsorption or severe disaccharidase deficiency should be excluded, since their underlying disorders themselves increase failure rates, further clouding interpretation of comparative solution efficacy (Table 2).

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In confirmed bacterial diarrheas of the enterotoxigenic type, continued bacterial enterotoxin production should be abrogated when possible by appropriate concurrent antibiotics [6]; otherwise continued enterotoxin production is highly variable and can confound detection of oral solution effects on duration of diarrhea. After the bacteria are eradicated, disease duration is determined chiefly by the rate at which sick cells bound to enterotoxin are shed and replaced by healthy cells, i.e., the rate of intestinal mucosal cell turnover.

Gut net balance, or the difference between the volume of oral fluids imbibed and that of diarrhea and vomitus lost is a useful guide to net absorption, and can be calculated from basic intake and output data recorded on a simple bedside sheet (Figure 3). Net balance calculations should include not only oral solution volumes, but also volumes of water, milk, soy formulas, in short, all fluids taken by mouth (Table 3). Comparison groups should receive the same foods, but the choice of foods should avoid those whose ingredients might confound the comparison of the rehydration or maintenance solutions. For example, a comparison of glycine plus glucose vs glucose solutions becomes meaningless if both groups also receive soy milk formulas, since the latter also contain glycine and other amino acids. Effects of new solutions on electrolyte balance should be reported, along with average serum

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**ORT Proceedings**

**Essentials**

- Severe Purgers
- Prestratify: Dehydration, Diarrhea Rate, Age
- Rapidly Correct Shock & Dehydration I.V.
- Ensure Adequate Intake
- Measure Net Balance
- Measure Duration

Table 2

In confirmed bacterial diarrheas of the enterotoxigenic type, continued bacterial enterotoxin produc-
Electrolyte levels before, during, and after therapy. Duration of diarrhea should be precisely determined according to valid criteria defining the endpoint of clinical diarrhea.

Enhanced absorption, reduced duration and volume of diarrhea, and improved nutritional repair can be best tested for in controlled studies examining the effect on water and electrolyte balance (and on makers of nutritional improvement) of new substrates and new combinations of solution ingredients. Let us explore some exploitable mechanisms for achieving these goals through new solutions, some potential pitfalls and their implications of research methodology, and some new leads for future study (Table 4). In calculating net gut balance, intake of absorbable fluid and electrolyte intake can reduce net losses and ultimately this can lead to net gains (positive fluid balance) by promoting sufficient absorption of water and salts to exceed losses of fluid and electrolytes in diarrhea and vomitus. Adequate amounts of oral solutions of glucose and electrolytes can achieve positive balance, but solutions promoting even greater absorptive efficacy can more rapidly diminish net losses and, unlike glucose alone, can ultimately reduce gross losses and diarrhea duration as well.

Various solutions can change net losses into net gains and are effective in achieving positive net gut balance, but efficiency of effective solutions varies. Efficiency can be expressed as volume of net positive balance divided by volume of solution ingested, and in practice is best measured when vomiting has ceased and when the amount of solution imbibed during successive intake and output periods (four to eight hours) approximates measured diarrhea losses of the preceding period. For example, several solutions promote net positive gut balance, in which (due to net absorption of the solution) oral intake consistently exceeds fluid losses. However, some of these electrolyte solutions, like those with low substrate concentrations (i.e., 50 mM glucose) do this while consistently increasing gross diarrhea up to a new level, forcing patients to drink more in order to keep up [7]. This may raise failure rates, since fewer patients are capable of drinking the larger volumes demanded. Other solutions, like those with 110 mM glucose, are more efficiently absorbed without significantly increasing gross diarrhea rate [2,3,7], but do not reduce diarrhea duration.

Additional substrates further enhancing water and active sodium transport, like glycine, further enhance absorptive efficiency, thereby reducing net and gross diarrhea losses [2,8-10]. Combinations of certain sugars with levo amino acids by enhancing gut epithelial protein synthesis [11,12], may possibly accelerate gut mucosal cell turnover, thereby promoting earlier shedding of cells affected by diarrheagenic toxins. The potential exploitation of these mechanisms deserves careful study (Table 5).

<table>
<thead>
<tr>
<th>Reduction In:</th>
<th>Mechanism</th>
<th>Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net Losses</td>
<td>Promote Absorption of Water, Salts</td>
<td>Oral Glucose/ Electrolytes (GE)</td>
</tr>
<tr>
<td>Gross Losses</td>
<td>Further Enhance Absorption (Tail-End Effect)</td>
<td>Oral GE + Glycine</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Prevent Starvation And Supply Nutrients</td>
<td>Absorbable Diet And Vitamins</td>
</tr>
</tbody>
</table>

A third exploitable modality is dietary: the amelioration and prevention of malnutrition by preventing so-called starvation therapy, avoiding harmful dietary components and supplying adequate absorbable nutrients [13-15]. Proper nutritional rehabilitation can also reduce diarrhea morbidity and recurrence rates; but not all food components are of equal efficiency in promoting absorption. Furthermore, adequacy of nutritional rehabilitation may partly depend on adequacy of electrolyte replacement.

Starches, glucose polymers and maltose have been studied and found useful as substrates for enhancing salt and water absorption in healthy volunteers or in patients with relatively low diarrhea rates [16-18]; but in severe cholera, maltose was apparently not successful [19], and intolerance to such substrates has been reported in some infants with diarrhea [20]. Success or failure of solutions containing them may depend on whether there is concurrent amylase, glucosidase or maltase deficiency [21].

A number of mixed food products have potentially useful roles, but in the severely ill they have been studied chiefly after rehydration is well underway. The effect of fat in feeds on gastric transit time and on rehydration time deserves study, since fats are known to delay gastric emptying into the small bowel, the site of most absorption. Some patients have soy milk, casein or even chicken soup intolerance [20,22]. Some of these foods or formulas are
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relatively costly, and more study of their relative long-range benefits is needed.

Rice, maize, mung bean, and other grain and cereal formulas are less expensive and more widely available in some areas, and have been tested in various formulas. In some studies results matched glucose balance results closely [23-28], but other studies yielding results suggesting variable superiority of one or the other [29-31]. Until prestratified controlled studies are carried out, relative merits of these new substrate sources are hard to validly assess. Most appear less effective in diminishing diarrhea duration and volume than the combination of glucose with glycine, which was first shown in 1968-69 to produce significant reductions in diarrhea duration and volume compared to controls receiving oral glucose electrolytes alone, both in cholera and noncholera adult diarrhea patients [2,8]. Confirmatory studies in children and in animals have been published [9,32], and several reports document the success of glucose with glycine in veterinary practice as well [33-35].

Leads exist which suggest that glycine plus glucose combinations may act by more than one mechanism, and this also deserves further study. First, in secretory diarrheas, glycine and glucose together enhance net absorption more than either one alone [2,8,32]. This improved absorption of luminal contents can reduce diarrhea volume and duration by shortening the interval during which the load of fluid delivered to the colon exceeds colonic reabsorptive capacity. By crossing the threshold of colonic reabsorption earlier, the dwindling end of the clinical disease is foreshortened, a “tail-end” effect. How is the tail-end effect clinically recognized?

Hirschhorn showed that in cholera patients receiving I.V. therapy alone, initial diarrhea rates are closely correlated with overall duration and volume of gross diarrhea [36]. The groups with higher initial diarrhea rate had progressively longer durations and retained their “lead” throughout; their curves (Figure 4) are stacked above one another on the graph.

In contrast, Figure 5 compared gross diarrhea with oral intake and net gut balance obtained using glycine, glucose, or glycine plus glucose solutions in the most severely purging class of cholera patients (all receiving concomitant tetracycline). The “glycine alone” group had the highest initial diarrhea rate and lower initial positive balance. The “glucose plus glycine” group had an intermediate initial diarrhea rate which exceeded that of the “glycine alone” group, but balance data were similar in these two groups. Note that unlike the diarrhea curves of Hirschhorn’s intravenously treated patients (Figure 4), the glucose plus glycine curve, although starting out higher than the “glucose alone” curve, crossed the “glucose alone” curve; and diarrhea ended earlier in the “glucose-glycine group” than in the other groups, in which it continued on for a mean of 50 hours (not shown in figure). Based on Hirschhorn’s observations, diarrhea duration in the “glucose plus glycine” group should have exceeded that in the “glucose alone” group, due to the higher initial diarrhea rate in the “glucose plus glycine” group.

It is also possible, particularly in the malnourished, that the combination of glucose with glycine might speed up shedding of sick intestinal cells bound with enterotoxins, since amino acids enhance epithelial protein synthesis (Figure 6), an effect which may be potentiated by combinations of glucose with glycine [12].

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>FIRST PERIOD STOOL RATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (10)</td>
<td>&gt;600 ml/hr</td>
</tr>
<tr>
<td>II (15)</td>
<td>500-599 ml/hr</td>
</tr>
<tr>
<td>III (21)</td>
<td>400-499 ml/hr</td>
</tr>
<tr>
<td>IV (12)</td>
<td>300-399 ml/hr</td>
</tr>
<tr>
<td>V (17)</td>
<td>200-299 ml/hr</td>
</tr>
<tr>
<td>VI (8)</td>
<td>100-199 ml/hr</td>
</tr>
<tr>
<td>VII (10)</td>
<td>6-99 ml/hr</td>
</tr>
</tbody>
</table>

Figure 4. Course of Diarrhea in 93 Patients with Cholera Receiving Intravenous Fluid Replacement as the Only Treatment.

The 25 patients in Groups I and II represent the controls (not receiving perfusions) for this study. Groups III-VII are presented for purposes of comparison. The number of patients in each group is given in parentheses.
However, as with rice solution, contradictory reports also exist, based, however, on formulas and nutritional regimens quite different from those of the original glucose-glycine studies [37,38]. Several factors may explain such variations and the discrepancies deserve further study in the quest for supersolutions. For example, as shown in Table 6, many oral therapy studies purport to compare two oral solutions which, however, are altered so as to differ in more than one variable from the earlier solutions. Rice or glycine may be added, but sodium content, tonicity and nutritional regimens also are changed. Some of these changes may render the comparison invalid and biased or uncontrolled. For example, addition of certain amino acids (or foods containing them) may reduce absorbability due to the presence of D amino acids in the mixture along with active L amino forms, or to interference with substrate absorption through competition for transport sites, as shown by the 79% reduction in absorption of glycine in the presence of alanine [39], and by galactose-leucine competition [40], the latter being aggravated at low sodium concentrations.

A second factor confounding comparability is the lack of prestratification according to initial diarrhea rates, leading inadvertently to disparate initial rates and differing disease severity in (otherwise “randomized”) small series of patients used in most balance studies. For example, in a recent study [31] (Figure 7), results with boiled rice paralleled Hirschorn’s curves: the higher initial rate in the boiled rice group was maintained throughout the study, and there was no crossing of curves and no tail-end effect. This could

Figure 5. Average gross stool volume (A), gut balance (B), and oral intake (C) during successive eight-hour periods in three study groups. (A) The shortest duration of diarrhea occurred in the combined glucose-glycine group. (B) While duration was relatively short in the glycine group, mean net balance remained negative during the first eight hours. (C) Since diarrhea over 75 ml/hr persisted in the glucose group for a mean of 44 hours (not shown), oral therapy was necessary for a relatively long period when the glucose solution was used.

Figure 6

Protein synthesis (mg protein/g liver per h)

Perfusate amino acid concentration (multiple of normal plasma level)

For example, in a recent study [31] (Figure 7), results with boiled rice paralleled Hirschorn’s curves: the higher initial rate in the boiled rice group was maintained throughout the study, and there was no crossing of curves and no tail-end effect. This could
be due to better absorption of glucose, but here it is more likely due to the more severe disease in the rice group from the very beginning. A contradictory result was obtained in another similar study in which a boiled (powdered) rice group started out with lower diarrhea and its overall diarrhea rate was less [41], as predicted from Hirschhorn's graph. This indicates that re-stratification is essential for valid judgment of solution superiority vis-a-vis effects on duration and volume of diarrhea in small series. If randomization alone is used without stratifying by initial severity, results obtained in small series are often irreproducible. Randomized allocation in small series is no guarantee of comparability per se, particularly when patient-to-patient variability is high.

A third factor affecting comparison of different solutions is the striking effect on net absorption of different substrate to sodium ratios [42] (Figure 8). Since absorption of glucose and glycine in the small bowel is coupled to sodium absorption, the closer the luminal ratio is to the observed 1:1 stoichiometry of coabsorption, the better the enhancement of absorption. If the substrate to sodium ratio deviates too far from unity, it can cause serious deterioration in solution performance; but a 2:1 substrate:sodium ratio still yields acceptable results. Optimal ratios enhance jejunal glucose metabolism [43], reduce competitive inhibition between coexisting sugars and amino acids [40], and enhance acceleration of protein synthesis by luminal amino acids [44]. These

**Optimum Sodium:**

**Substrate Ratio (2:1)**

- Enhances Jejunal Glucose Metabolism
- Reduces Competitive Inhibition of Sugars, Amino Acids
- Enhances Protein Synthesis and Cell Turnover
- Effect Greatest In Malnourished
- Additional vs. Better Substrates (3D-3C Glucose)
Potassium Deficiency: Sequelae

Muscle Weakness
   Ileus
   ↓ Infant's Breast Manipulation and Sucking Strength
   ↓ Maternal-Child Interaction
   ? Anorexia

Renal Impairment

Cardiac Dysrhythmias

Table 8

Effects of substrate to sodium ratio are probably greatest in the malnourished [45] and are exceptionally important with certain novel substrates like 3D-3C glucose (Table 7).

Luminal pH in the small bowel is also an important factor, since it can influence absorption rates [46]. Supranormal absorption of substrates or of sodium can be induced by certain substances. Vitamin B-12 enhances intestinal glucose absorption under certain circumstances [47]. Hydrocortisone, glucagon or CCK, substances affecting calcium handling (low-dose verapamil), angiotensin, neurohypophyseal extracts and vagostimulatory agents can enhance intestinal absorptive capacity for substrates or for sodium, respectively above physiologic levels [48-55]. Such substances, and foods which may enhance their endogenous production, deserve more study as potential oral therapy ingredients, as do dietary constituents like serotonin derivatives [56], and perhaps additional amino acids [57] and other substances which may speed cell shedding.

The role of vitamins, minerals and dietary components of oral therapy regimens in providing long-range protection from malnutrition and from diarrhea beyond their caloric value also needs study [13] (Table 8), since adequate amounts of such factors might enhance feeding capacity of infants, reduce malabsorption in convalescence, and might help restore nutritional defects underlying the high prevalence of "tropical hypochlorhydria" in developing countries [58].

Post oral therapy potassium deficiency has been identified in small series as a problem [59-62], and studies have shown that it can be minimized by using oral solutions with potassium concentrations of 25 to 30 mEq/L, with excellent results [62,63]. If an oral therapy solution potassium concentration is such that its use leaves even 30 extra children out of 1000 significantly potassium depleted after therapy, does that leave those children at risk of greater morbidity? Are those the highest-risk children for severe malnutrition and death? What is the impact of post oral therapy residual potassium deficiency on frequency of ileus and muscle weakness, resulting in decreased vigor of breast feeding, reduced maternal child interaction and decrease in the mother's interest in the weak child? Can the ileus of potassium deficiency promote anorexia, or as the ileus of opiates does in guinea pigs, enhance susceptibility to diarrheal pathogens (Table 8)? Potassium also can

Potassium Deficiency After Oral Therapy:
Impact on Nutrition and Development?

Gut Epithelial Turnover:
Which Oral Therapy Ingredients Can Speed It Up?

Supranormal Substrate, Sodium or Water Absorption:
Which Substances Promote It?

Convalescent Normochlorhydria:
Which Ingredients Can Promote It?

Table 9

induce enterocyte amino acid transport [64]. Can higher oral solution potassium reduce adverse hydrotalonal and nutritional outcomes? These are among the efficacy questions which I would add to the previously mentioned potential research study candidates meriting priority (Table 9).

And what of safety? Hazards of oral therapy have yet to be subjected to the kind of postmarketing frequency surveillance of large series long familiar in industry. Issues like therapy-related hypernatremia have eclipsed equally important problems like hyponatremia [65] and hypokalemia [59-62]. But the debates have featured series of 20 to 30 patients, not the surveillance of thousands required. If Solution "A" yields 3% hypernatremia, and Solution "B" yields 10%, it takes a sample size of 200 patients per group to show the difference with any statistical validity at 80% power; but such studies have rarely been carried out. Nor have numbers been adequate to determine relative risk of such phenomena when additive
with other factors enhancing the risk of hypernatremia.

In conclusion, adequate methods, exploration of new mechanisms, comparison groups matched across key variables and selection of appropriate new substrates can lead to significant future improvements in oral therapy, both in the rehydration and maintenance phases and the nutritional rehabilitation phase. Careful evaluation of new ingredients for oral therapy can serve to better integrate these goals, and should include study of the physiological interrelationships of electrolyte and nutritional deficits and their impact on the therapeutic responses and on the comparative safety of new formulas.
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Thank you. It is a pleasure to be here. I am from the WHO Diarrhoeal Disease Control Program, with which many of you are familiar. There are two components to our programme: one is intervention and the other is research. The first, intervention, is taken up in various countries. You have already heard its objectives from Dr. Robert Northrup, who has very ably posed the questions which the intervention component poses to us on the research side. The job of the WHO research component is clearly to offer improved tools to the health component for their program implementation. It is within this limit that WHO promotes and supports research within various countries. WHO addresses selected questions and their priorities, and the research promoted by WHO and the research projects which are conducted with assistance of WHO may have a different set of priorities from those of academic institutions. As you are aware from the talks this morning, there is a tremendous interest in improving oral rehydration therapy.

The WHO CDD Programme is continuing to support research to develop an improved ORS formulation that will reduce volume and duration of diarrhea, correct dehydration and maintain hydration more effectively. Twenty-one studies to compare standard WHO ORS with formulations that may be more effective are underway or will soon be started.

Before summarizing the status of WHO supported ORS research projects, I should initially mention one important point so there will be no confusion about certain technology, in particular, that of “ORS” and “ORT.” WHO and UNICEF have tried very hard to prevent confusion on this. It is important and not a semantic issue. When you talk about “ORT,” you are talking about oral rehydration therapy, which includes home therapy as well as therapy of patients under hospital conditions. The therapies are very different in different settings. If you refer to the WHO red book (1) on oral rehydration therapy, a policy document, it defines these terms at the beginning, and ORS, meaning oral rehydration salts, is a complete formula. When the document discusses ORT, it includes fluid therapy at home. This could be home fluids based on cereal gruel or other home fluids such as soup, or any other drink used traditionally at home; it could be specially prepared containing specific amounts of salt and that issue is very different from treating, in the hospital, patients who are completely dehydrated and for whom we at WHO recommend the complete formula be used. These are important issues. Now, I will bring you up to date on the efforts which have been made by the research component of WHO. Let me focus first on the progress of some of the non-cereal-based ORS work WHO supports: (much of the following is quoted from the WHO Interim Programme Report, WHO/CDD/87.26:pp.21,22)

1) GLUCOSE WITH AMINO ACIDS AND/OR DIPEPTIDES: There are six studies ongoing based on a glucose and combination of amino acids and/or dipeptides, which has been talked about this morning. These are based on earlier studies in Bangladesh and India suggesting that the addition of glycine to glucose-ORS caused improved fluid absorption and reduced stool volume during acute diarrhoea. However, no clinical benefit was shown from adding glycine or glycyyl-glycine to glucose-ORS in recently completed studies in Finland and the USA, which were supported by sources other than WHO, and in the Philippines and Thailand, supported by WHO. These studies suggest that such formulations may be

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>No. Of Studies</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rice Powder</td>
<td>7</td>
<td>- Chile (Recooked)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Egypt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- India</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Madagascar (In malnourished)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Senegal (malnourished)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tunisia (&lt;4 months)</td>
</tr>
<tr>
<td>2. Sorghum Powder</td>
<td>1</td>
<td>- Rwanda</td>
</tr>
<tr>
<td>3. Maize</td>
<td>1</td>
<td>- Cameroon</td>
</tr>
</tbody>
</table>

Table 1
because, like rice starch, it provides a source of glucose without inflicting the osmotic penalty associated with glucose, especially when the concentration of glucose exceeds 20 g/l. Maltodextrins are inexpensive and readily soluble; the most starch-like maltodextrins (e.g., MD-02) also have the advantage of being highly stable for prolonged periods when stored under tropical conditions. These simple multidextrins, very hydrolysed, used in the various studies, were produced by hydrosis of starch and the final product is glucose. Manufacturers that produce glucose could also easily use this technology for new products. Producing simple glucose from maltodextrin does not require very high technology and could be done in less developed countries, although I do not think it has been produced by any local manufacturers in the last thirty years.

The results of many of the ORS multidextrin studies will be available later this year. We expect these results to make a significant contribution to further development of an improved, packageable ORS formulation.

2) MALTODEXTRIN STUDIES: Ten studies are underway of ORS solutions containing maltodextrin in place of glucose. Six involve solutions containing a moderately hydrolysed maltodextrin (MD 25; 20 g/l) combined with glycine, glycyglycine, or both; and four involve a minimally hydrolysed maltodextrin (MD-02; 50 g/l) without added amino acids. Maltodextrin is of particular interest for inclusion in ORS

Table 2

<table>
<thead>
<tr>
<th>Improved ORS Studies</th>
<th>No. Of Studies</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glucose &amp; amino acid and/or peptide</td>
<td>6</td>
<td>- Bangladesh - Costa Rica - Peru - Phillipines - Thailand</td>
</tr>
<tr>
<td>2. Maltodextrin &amp; Amino Acid and/or Peptide</td>
<td>6</td>
<td>- Burma - Egypt - India</td>
</tr>
<tr>
<td>3. Maltodextrin (minimally hydrolyzed)</td>
<td>4</td>
<td>- Bangladesh - Egypt - India - Phillipines</td>
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disappointing; we have tried seven or eight manufacturers' preparations that seem to settle in a half an hour to one hour, which is not convenient; they do not form a stable suspension in water and thus require frequent stirring. These are programmatic issues that need to be answered. As to the stability of cereal-based solutions, in many countries, once you make it you cannot keep it more than six to eight hours before it turns sour and is undrinkable.

4) FEEDING DURING DIARRHOEA: WHO is supporting studies on feeding during and following diarrhoea in Argentina, Burma, Egypt, India, Peru, and Sudan, with the hope of developing simple guidelines to prepare and provide optimally nutritious diets based on inexpensive, locally available ingredients. These studies, either underway or soon to start, follow research previously conducted by the WHO CDD Programme which has demonstrated that diarrhoea patients fed early during their illness have a better clinical and nutritional outcome than those fed intravenously. The final point, which has been mentioned, is the question of fear of giving food to those with severe diarrhea, whether cereal-based ORS is used or not. It is very important to continue feeding, as obviously there are not adequate calories available from ORS for feeding purposes.

5) ANTIDIARRHOEAL DRUGS: A study in Egypt has shown that oral chlorpromazine reduces stool output by 26% on average and ORS requirements by 15% in boys aged 3-24 months with moderate dehydration due to acute diarrhoea; the frequency of vomiting was also significantly reduced for 48 hours after admission. However, lethargy occurred in 40% of the cases, making the drug impractical for routine use as an antidiarrhoeal agent. Similar results had been reported in adults earlier. More promising are preliminary reports from Egypt and Finland suggesting that cholestyramine may reduce stool output by as much as 50% during acute diarrhoea without significant side effects. Detailed studies of antidiarrhoeal action of cholestyramine will begin shortly in Bangladesh and Egypt, and studies to evaluate the antidiarrhoeal activity of several modern and traditional drugs are underway or planned in Bangladesh, China, Egypt, Madagascar, Morocco, Philippines, and the USA.

6) PERSISTENT DIARRHOEA: A study in the United States has shown that children with persistent diarrhoea have small bowel colonization with enteropathogenic Escherichia coli belonging to classical pathogenic serogroups and that treatment with oral gentamicin causes improvement. A second study is underway in India to describe the small bowel microflora in children with persistent diarrhoea and to determine the effect of treatment with oral gentamicin (1).

I. SUMMARY OF WORKSHOP ON CEREAL-ORT AND CHILDREN

A common approach is needed that can be adopted to all countries and that includes therapies which can be used at home; there will be a need for other kinds of oral rehydration therapy that standard WHO/UNICEF ORS cannot meet.

Optimal solutions for the youngest children have not yet been worked out; intensified research is needed.

Standard ORS (WHO/UNICEF) has proven effective at all ages and should be used when available; every effort should be made to create its availability.

Early feeding during diarrhea reduces the severity and duration of illness, and should always be standard ORT.

Breastfeeding should always be encouraged and continued during diarrhea.

Cereal-ORT combines in one modality rehydration and early feeding. It is not sufficient for full nutritional requirements, however, and must be accompanied by early feeding.

Mothers have needed ingredients to make simplified ORS at home and should be taught how to do this now.

How to insure safe and effective use of salt in home solutions remains difficult. Packets do not resolve this problem of themselves. Proper education and monitoring of solutions are required. There are broader limits for salt concentrations when a child is well hydrated since the kidneys will function well in such circumstances.

Each country has problems unique to it which include ways to measure water, availability of salt, sugar, as sources of starch for cereal solutions.

Adequate volumes must be given whatever kind of solution is used. This can best be judged by an adequate flow of urine and lack of thirst.

In the United States, day care centers have a lot of diarrheal illness and ORT would be a very appropriate form of treatment in these settings.

II. SUMMARY OF WORKSHOP ON CEREAL-ORT AND THE ELDERLY

Diarrhea commonly afflicts the elderly.

A definition of diarrhea is three or more liquid stools per day or one liquid stool of large volume (>500 ml).

Early correction of loss of body fluids with ORT can prevent the serious complications such as strokes, heart attacks, and kidney failure.

Loss of body fluids from sweating can be replaced by sweat replacement solutions such as Gatorade.

These solutions are not adequate to replace diarrhea losses, but are very useful to prevent volume depletion with its serious consequences.

The signs and symptoms of volume loss are obscured by age.

Oral hydration solutions may be judged sufficient in quantity by good urine flow.

It is important to maintain feeding during diarrhea with complex carbohydrates, starches and proteins.
Cereal solutions are appropriate for older people so long as the salt concentration is correct and adequate volumes are given.

Many of the currently available food supplements in wide use can produce diarrhea.

Oral rehydration therapy is well adapted to use in nursing homes where diarrhea outbreaks are common. Proper education of nursing home staffs and administrations is needed.

It is important for travelers, particularly those traveling in areas where diarrheal diseases are endemic, to know how to make, use, and administer ORT.

III. SUMMARY OF WORKSHOP ON CEREAL-ORT AND AIDS PATIENTS

Diarrhea is a common problem in patients suffering from AIDS.

Malnutrition and severe weight loss often accompany AIDS. This occurs with and without diarrhea.

AIDS is worldwide now officially reported from 85 countries and unofficially from 100 countries.

There are 100,000 cases of AIDS and 300,000 to 500,000 cases of AIDS-related diseases. By 1991, 270,000 cases of AIDS are expected in the U.S. alone. There are 5 - 10 million people infected at present in the world.

There are many cases of diarrhea in AIDS. In careful studies, a cause can be found in about 50% of diarrhea cases. All such cases could benefit from ORT and the feeding methods currently in use for diarrhea.

Supplemental nutrition is critical in AIDS patients. Oral food supplements should be designed to give maximum absorption and minimum diarrhea. At present, commercial food supplements satisfying those needs are not available.

Anecdotal AIDS cases of diarrhea successfully treated by cereal-ORT have been reported but no controlled studies exist.

Anorexia makes both oral feeding and ORT very difficult. Orogastric tubes can be used to improve nutrition and hydration temporarily.

There is little knowledge of the causes of anorexia and malabsorption seen in AIDS.

Parenteral hyperalimentation is possible but expensive, invasive, and associated with complications.

Antibiotics can aggravate diarrhea.

Studies are needed to find the best kinds of ORT and nutritional supplements in AIDS.
ORT Proceedings

SYMPOSIUM SUMMARY
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The Lancet, the leading global medical journal, in 1978 hailed oral rehydration therapy (ORT) as one of the most important advances in medical science of this century (1). Potentially, the fullest application of ORT could avert 4 to 5 million deaths from diarrhea each year and prevent countless millions of visits to hospitals and health centers in all countries, wealthy and poor. Thus, this extraordinarily simple, inexpensive technology can save lives and millions of dollars of health expenditures. Therefore, the challenge to make this technology available to every patient needing it is enormous and the benefits with the present formulation of oral rehydration solution (ORS) are indisputable.

This symposium sought to emphasize the importance of this challenge. It also presented an opportunity for discussion about future approaches expected from continued scientific inquiry into improving solutions used for ORT. Important issues noted during the symposium were as follows:

- Evidence from the basic sciences and clinical trials of ORT indicate that substituting a polymeric form of glucose (starch) for the single molecule form results in solutions that perform at least as well and, in most studies, strikingly better than the current formulation of ORS;

- Advantages of cereal-based ORT (CEBORT) over glucose-based formulations:
  1) Greater effectiveness in many clinical trials, showing
     - less diarrhea fluid losses
     - shorter duration of diarrhea
     - less vomiting during treatment
  2) More rapid return of normal digestion and improved nutrition even if used without feeding;
  3) Availability of cereals and starchy vegetables in all countries and households;

- Obstacles to Immediate Adoption of CEBORT:
  1) Variations in composition of local food staples which may cause differences in solution effectiveness and difficulties in standardizing recommended solution preparation methods;

  2) Need for cooking home solutions requires fuel and effort, potential barriers to early use of CEBORT by the mother. Cooking, however, does insure killing of bacteria in contaminated water;

  3) Varying manufacturing methods to produce a starch powder which will dissolve readily without cooking;

  4) Lack of studies to show that CEBORT has clinical advantages over glucose-based ORS in the treatment of the predominant mild diarrheas; nutritional outcomes would be essential to assess this point.

  5) Lack of proof that CEBORT has clinical and nutritional advantages over the combination of glucose-based ORS and continued feeding;

- Oral rehydration therapy should be used more widely in the United States, not only because it is applicable for saving lives and reducing hospital costs, but also because the United States health services often serve as a model to many physicians in developing countries, where the use of ORT is critical to saving many millions of lives.

Polymers-based oral rehydration solutions (POLYBORT) thus have some clear theoretical and practical advantages and have been shown to be more effective in treating diarrhea in a number of clinical studies. Top priority should be given to dealing with the obstacles to wider adoption through the following recommended mechanisms:

  1) Studies of home-prepared CEBORT in field community settings comparing use rates and accuracy of solution preparation compared with packets of glucose-based ORS;

  2) Research into food processing methods needed to produce a readily dispersable glucose polymer powder;

  3) Comparison of the nutritional advantages in field use of the various approaches to ORT;

  4) Efforts to improve the effectiveness of teaching families the use of home solutions for early diarrhea treatment and the prevention of dehydration; Improved distribution of the current formulations of ORS and education in its use;
will provide the foundation for ready introduction of improved cereal-based formulations when proven advantages warrant this step. Given the existing demonstrations of the effectiveness of solutions based on home available food staples, however, efforts to make standard formulation ORS more widely available through commercial and health system channels should not be allowed to interfere with teaching families the immediate use of home solutions based on the best available knowledge.

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