Worldwide, the impact of acute diarrheal disease is immense and is particularly important in infants and young children. It has been estimated that each child experiences six to eight episodes of diarrhea per year in developing countries (1) and that this represents an annual mortality of up to 18 million children under 5 in those countries (2). Severe dehydration resulting from diarrhea occurs more readily in infants as a result of their higher basal fluid requirements compared to adults, their relative inability to gain access to fluids when thirsty, the immaturity of tubular reabsorption processes, and the popular misconception that fluids should be withheld in infants with diarrhea.

In 1831, O'Shaughnessy (3) and Latta (4) first described the biochemical changes occurring in the blood and the use of parenteral fluid replacement, respectively, in patients with cholera. However, the use of oral electrolyte solutions in children with acute diarrhea was not formally advocated for over another hundred years (5,6). In fact, in the West, parenteral rehydration has remained the cornerstone of the management of acute diarrhea in all but mild cases (7,8).

Glucose was included in early oral electrolyte solutions solely as a source of calories, and the high carbohydrate content of these early formulas may well have increased stool volumes by an osmotic effect (9). However, incorporation of carbohydrate into such solutions was shown to be effective in rehydrating even severely dehydrated infants (10), and it is now realized that glucose and certain other organic solutes also have a very important noncaloric role in stimulating transport at the brush border of the enterocyte.

GLUCOSE-COUPLED SODIUM TRANSPORT AND ENTERIC INFECTION

The rational use of glucose electrolyte therapy arose from the fundamental observation that glucose and sodium transport at the brush border is coupled (11-14) and that this coupling remains intact during infections with enterotoxigenic organisms.
Enteropathogenic bacteria may be broadly divided into two main but overlapping groups: those that are not mucosally invasive but produce diarrhea by the elaboration at the mucosal surface of enterotoxins that induce secretion, and those whose effect depends on mucosal invasion and disruption (15,16).

_Vibrio cholerae_ and enterotoxigenic _E. coli (ETEC)_ are classic examples of the first type of noninvasive organism. Cholera toxin activates enterocyte adenylate cyclase, resulting in raised intracellular cyclic adenosine 3′,5′-monophosphate (cyclic AMP), which is associated with net electrolyte secretion by crypt cells and impaired absorption from villous tip cells (17–19). Despite a massive net secretory state in cholera, coupled absorption of glucose and sodium remains intact (20–22). Thus, solutions containing glucose and sodium are capable of markedly reducing this secretory state and form the basis of practical and successful oral rehydration (23,24). Similarly, _ETEC_ can elaborate a heat-labile toxin (LT) and/or a heat-stable toxin (ST), which produce secretion in association with raised enterocytic cyclic AMP (25) and cyclic GMP (26), respectively. Despite the production of a massive secretory state by these “second messengers,” glucose-coupled sodium transport remains intact (20,21,27), and glucose-electrolyte solutions have been spectacularly successful in the management of these infections (23,28–31).

Of the invasive organisms, _Shigella_ and certain strains of _E. coli_ produce mucosal ulceration in the distal ileum and colon as a result of invasion of proliferation in and subsequent death of the enterocyte (15,32,32a,33). In contrast, _Salmonella_ pass in most instances through the enterocyte without destruction to reach the lamina propria. Enteropathogenic _E. coli (EPEC)_ of classic serotypes associated with infant diarrhea (such as 0111, 055, and 0127) appear to induce diarrhea by a combination of enteroadhesiveness (which results in a characteristic histopathological lesion seen on electron microscopy) (34–36) and production of an enterotoxin/cytotoxin apparently identical to _Shigella_ toxin (37).

Rotavirus accounts for about 50% of episodes of acute diarrhea in children under 2 years of age in temperate climates, but its incidence in the tropics appears to be much more variable (38). Recent evidence suggests that rotavirus infection in the tropics may commonly be subclinical (39) but that when associated with diarrhea it is a potent cause of dehydration (1). By analogy with porcine transmissible gastroenteritis virus, a remarkably similar organism, it seems likely that human rotavirus infection is associated with a morphological abnormality of the jejunal mucosa, the replacement of mature villous tip cells by immature crypt-type cells, reduction in mucosal Na⁺–K⁺ ATPase activity, and diminished glucose-coupled sodium transport (40–45).

In spite of this widespread disruption of absorptive function, oral rehydration therapy (ORT) in acute diarrhea caused by rotavirus infection is, perhaps surprisingly, as effective as in diarrhea caused by toxigenic infection (31). Furthermore, ORT has proved as effective in the management of neonates with diarrhea (46) as it has in older patients.
CLINICAL APPLICATION OF ORAL REHYDRATION THERAPY

The remarkable effectiveness of ORT was initially demonstrated in the management of that most devastatingly dehydrating infection, cholera (20,21). Adults so treated required 80% less parenteral fluid than controls, and in the majority it was possible not only to replace fluid and electrolyte losses but also to maintain them in positive balance by the oral route alone. Using a solution containing rather less sodium (90 mM) to take into account the lower stool sodium concentration seen in choleric children (47), it was possible to repeat these successes in children suffering from cholera (29,30,48). As a result, an "ideal" oral rehydration solution (ORS) was suggested (28), comprising $Na^{+}$ 90, $K^{+}$ 20, $HCO_3^{-}$ 30, $Cl^{-}$ 80, and glucose 110 mM, and this has been adopted by the World Health Organization (UNICEF/WHO oral rehydration solution) for the management of acute diarrhea in children, irrespective of geographical locality.

The efficacy of this glucose-electrolyte solution (29,30,49–54) is now well established not only as a rehydrating agent but also as a means of reducing mortality by preventing dehydration caused by diarrheal disease in developing countries (55). Its low cost, lack of need for sophisticated sterile equipment, and simplicity compared to parenteral therapy make ORT ideally suited to developing areas. Vomiting may occur in up to 65% of children treated with ORT, but is usually infrequent and low in volume and does not preclude a successful outcome (31,50–52).

It is important to differentiate between the use of ORT in patients with overt (5–10% acute loss of body weight) dehydration, using a solution containing a high sodium concentration (e.g., 90 mM), and its use with solutions containing lower sodium concentrations (e.g., 30–50 mM) to prevent dehydration. A longstanding debate has taken place regarding the wisdom of using a 90 mM sodium solution on a universal basis in the management of diarrhea (56–62). A view has been expressed (59) that the early advocates of ORT did not make clear either the need for concurrent administration of water with ORS or the importance of differentiating between rehydration and replacement of ongoing losses.

In the treatment of moderate and moderately severe dehydration in developing countries, WHO ORS is currently administered to infants in a volume of 100 ml/kg body weight over 4 hr followed by 50 ml/kg of water (or breast milk ad lib) over the next 2 hr (63). After the 6-hr course of therapy, the infant is reexamined (clinically and by weight gain). If complete rehydration has been achieved, the infant enters a maintenance phase of therapy. If dehydration is now mild (about 5%), WHO ORS is continued for 6 more hours with one-half the volume being offered (50 ml/kg), as for the moderately dehydrated state. This rehydration regimen is successful in over 95% of patients and is the treatment of choice in all but the shocked child, when intravenous fluids should be administered. Successful rehydration occurs in 50% of children by 6 hr, in 65% by 12 hr, and in 95% by 18 to 24 hr. Following rehydration, ORS is given
in maintenance amounts; 10 ml/kg over 24 hr. In addition, and very importantly, oral nutrients are now commenced in the form of breast milk ad lib or half-strength cow’s milk formula feed (120 ml/kg per day), both of which provide free water with which to handle the sodium load given during the maintenance period of rehydration. Plain water or an alternative low-solute fluid is also offered during this phase, to provide more free water if necessary. The child is regraded back onto a normal diet as soon as dehydration is corrected and vomiting has stopped. In the malnourished child this should be supplemented with locally available high-calorie feeds wherever possible.

OPTIMAL FORMULATION OF AN ORAL REHYDRATION SOLUTION

Despite geographical differences in stool electrolyte composition [depending on the infecting organism, age of patient, and rate of purge (47,64,65,65a) and biochemical disturbance (66,67)], most clinically dehydrated infants are iso-natremic. Further, all children with diarrhea incur body deficits of sodium, potassium, and water, suggesting that a single solution may be appropriate world wide.

Sodium Concentration

The presence of increased insensible losses, an immature renal concentrating capacity, and an impaired natriuretic response all predispose to the development of hypernatremia in young children. As a result of this and experience in the 1950s, concern has been expressed (56,57,59) about the use of WHO ORS (90 mM sodium) in mildly dehydrated children, particularly when not used in accordance with WHO guidelines (63).

Although mild periorbital edema has occasionally accompanied the use of WHO ORS (69–71), significantly greater sodium absorption occurs with this solution than with a solution containing 60 mM sodium so that hyponatremia is prevented (71). Until recently, most studies with a 90 mM sodium ORS had been performed in children in developing countries, and little information has been available on which to base a recommendation for the use of WHO ORS in well-nourished infants and children, many of whom may be bottle fed. Santosham et al. (72), in a controlled, randomized trial, have shown 90 mM sodium ORS to be effective and safe in treating moderate to severe dehydration in well-nourished patients in hospital in Panama and the United States. Hyper- and hyponatremia returned to normal after 8 hr of therapy, and ORT appeared to be safer than conventional intravenous therapy. Uncontrolled evidence suggests similar conclusions in well-nourished outpatients (73) treated with a 90 mM Na⁺ ORS.

It seems likely, therefore, that solutions containing 90 mM sodium are safe and effective in the management of overt dehydration (5% or greater) in well-
nourished bottle-fed children in industrialized countries irrespective of the serum sodium concentration at presentation. Patients who are shocked on admission must be resuscitated intravenously; water should be administered in addition to ORS in a ratio of 2 ORS to 1 water except perhaps in those patients who are severely hyponatremic. It is imperative that a differentiation be made between the use of ORT to rehydrate overtly dehydrated children on one hand and the use of ORT in the maintenance phase after rehydration or in the prevention of dehydration early in the course of a diarrheal illness on the other. In the latter instances, considerable free water should be administered along with a 90 mM sodium solution (1:1); alternatively, and perhaps ideally, a solution containing 30 to 50 mM sodium should be available, which circumvents the need for extra water.

**Potassium and Bicarbonate Concentrations**

The WHO ORS currently contains 20 mM potassium, and there is evidence to suggest that, at least in the tropics, this may be too low. Potassium absorption from an ORS containing 35 mM $K^+$ by a group of dehydrated Jamaican infants was significantly greater than from an ORS containing 20 mM $K^+$ (71). Furthermore, the higher concentration (35 mM $K^+$) prevented the hypokalemia commonly seen with the lower (20 mM $K^+$) (71).

The inclusion of bicarbonate in ORS is important in reversing the metabolic acidosis that is almost invariable during acute infective diarrhea. In addition, bicarbonate within the jejunal lumen also enhances sodium and water absorption (74). The inclusion of acetate in ORS instead of bicarbonate circumvents the discoloration on storage that occurs with bicarbonate and has been shown to be as effective as bicarbonate in correcting acidosis (75).

**Carbohydrate**

Sucrose has been shown to be almost as effective as glucose in electrolyte solutions in correcting diarrheal dehydration caused by differing pathogens and occurring in a variety of geographical settings (31,54,76–79) and has been shown to correct cholera-toxin-induced secretion in the rat *in vivo* (80). Treatment with sucrose electrolyte solutions may be associated with increased vomiting and slower return to normal of electrolyte disturbances, although these differences do not reach statistical significance. Compared to glucose, sucrose is more widely available, is cheaper and more palatable, and, on an equimolar basis, has a higher caloric content than glucose.

Starch, in the form of rice powder, is an alternative carbohydrate that is currently attracting interest. Starch is hydrolyzed into its component glucose subunits in the intestinal lumen and at the brush border and in its polymeric form imposes a considerably reduced osmotic load. Rice powder also contains 7 to 10% protein, a source of nitrogen for the malnourished child, and its
constituent amino acids, notably glycine, enhance sodium and water absorption (81). Two recent reports (82,83) suggest that rice electrolyte solution is as effective as more conventional solutions and, in addition, cheaper and widely available.

**Amino Acids and Dipeptides**

In a similar fashion to glucose, some amino acids and di- and tripeptides are also cotransported with sodium at the brush border membrane (84). Furthermore, the rates of absorption of amino acids from dipeptide solutions are considerably greater than from the corresponding free amino acid solutions (68,85). In patients with cholera, an ORS solution containing glycine will promote a positive water balance, and when glucose and glycine are combined, the effect is additive (81), suggesting that such a combination may form the basis for a second generation of "super" ORS.

**SIMPLE SALT AND SUCROSE MIXTURES**

Because prepackaged mixtures of sugar and electrolytes are not universally available, attention has turned to the use of simpler mixtures made up with household equipment. Although a method employing finger pinches of salt and finger scoops of sugar may produce widely varying results (86), safe concentrations of sugar and salt are obtained by the use of special double-ended plastic spoons (87) or a 5-ml teaspoon and a 1-liter bottle (88). When compared to WHO ORS, a simple sucrose/salt ORS has been shown to be an acceptable alternative, although vomiting and prolonged hypokalemia were greater problems with the simple mixture (50).

**ORAL REHYDRATION AND NUTRITION**

Evidence is beginning to emerge that ORT with early refeeding may have a beneficial effect on nutritional status following an episode of acute diarrhea. Two studies, performed in the Philippines (89) and in Iran (90), suggest that the provision of ORT during episodes of acute diarrhea may result in a significantly greater weight gain in the months following recovery, compared to those children who do not receive ORT. Although the maintenance of appetite may contribute to the beneficial effect of ORT on nutrition, the provision of sound nutritional advice at the time of distribution of ORS is likely to play an important role in the provision of additional nutrients at the time of acute diarrhea. Many mothers adhere to the popular misconception that it is necessary to starve a child with diarrhea, and they do not appreciate the importance of early reintroduction of breast milk or half-strength formula feeds as soon as rehydration is complete. When protracted diarrhea follows an acute episode it is likely to be associated with multiple dietary intolerances. In these circumstances a diet that is free of cow's milk protein, gluten, and disaccharides and that is based
on comminuted chicken, Caloreen®, and long-chain triglyceride emulsion (91) may be successful in improving nutrition and stool output. A modification of this diet is possible, making it suitable for use in developing countries (92).

PROTRACTED DIARRHEA

Although the use of oral electrolyte solutions has made a dramatic impact on the management of acute diarrhea, similar solutions used differently may also be useful in protracted diarrhea. In acute diarrhea, the principal aim of treatment is to correct dehydration, whereas in protracted diarrhea it is the long-term replacement of ongoing stool losses. Provided oral input (possibly by nasogastric tube) is matched to fluid and electrolyte losses in the stools, it may be possible to maintain children in a positive balance, even with profuse protracted diarrhea (Fig. 1), without recourse to intravenous therapy.

It has been shown that a net secretory state exists in the jejunum of infants with severe protracted diarrhea of infancy (SPDI) (93), and this is associated with impaired jejunal glucose and fructose (less so) absorption, normal mucosal adenylate cyclase activity, and diminished Na⁺-K⁺ ATPase activity (93). Thus, in contrast to enterotoxigenic diarrheal states, coupled sodium and glucose transport is impaired and is associated with a defective “sodium pump.” Oral glucose electrolyte solutions would not therefore be expected to be as successful in maintaining patients with SPDI in positive water and electrolyte balance as in acute diarrheal states. As fructose is absorbed by an alternative carrier to glucose (94), electrolyte solutions containing both fructose and glucose may be more successful, particularly as each may enhance the absorption of the other.

FIG. 1. Twenty-four-hour stool output (6.9 liters) of a 22-month-old girl with severe protracted diarrhea of infancy.
Nevertheless, luminal glucose at an optimal concentration can still be expected to enhance sodium and water transport.

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