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A Historical and Physiological Perspective

Norbert Hirschhorn, M. D.

INTERNATIONAL CENTRE FOR
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Norbert Hirschhorn, M.D.
John Snow Public Health Group, Inc.
141 Tremont Street
Boston, Massachusetts 02111

INTERNATIONAL CENTRE FOR
DIARRHOEAL DISEASE RESEARCH, BANGLADESH
G.P.O. Box 128, Dacca - 2
Bangladesh

PREFACE

The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) is an autonomous, international, philanthropic and non-profit centre for research, education and training as well as clinical service. The Centre is derived from the Cholera Research Laboratory (CRL). The activities of the institution are to undertake and promote study, research and dissemination of knowledge in diarrhoeal diseases and directly related subjects of nutrition and fertility with a view to develop improved methods of health care and for the prevention and control of diarrhoeal diseases and improvement of public health programmes with special relevance to developing countries. ICDDR,B issues two types of papers: scientific reports and working papers which demonstrate the type of research activity currently in progress at ICDDR,B. The views expressed in these papers are those of authors and do not necessarily represent views of International Centre for Diarrhoeal Disease Research, Bangladesh. They should not be quoted without the permission of the authors.

ABSTRACT

This review examines the historical, physiologic, clinical and epidemiologic evidence to support a method of therapy for children's diarrhoea that may be recommended for general acceptance.

The understanding and use of fluid and nutritional therapy of acute diarrhoea in childhood have progressed over the years to a point where acute mortality can be reduced to nearly zero. At the same time, the ill effects on electrolyte balance and nutrition may be reduced to a minimum. Through use of an oral glucose electrolyte solution with a carefully designed composition, physiologically correct treatment may now be so simplified and inexpensive as to be readily available to the remote, underserved areas of the world where most of the morbidity exists; and be useful as well to more sophisticated settings.

The method of therapy recommended in this paper has several important departures from traditional teaching. It advocates rapid restoration of extracellular fluid with a polyelectrolyte solution containing sodium, base and potassium; use of an oral glucose electrolyte solution for repletion of those not in shock and for maintenance; use of a single oral glucose electrolyte solution for all age groups, regardless of diagnosis; and quite early feeding with tolerated foods. Sodium loads given are generally higher than advocated by standard pediatric teaching. The origins of that teaching and support for the newer approach come from a detailed analysis of current knowledge in the epidemiological, clinical and physiological aspects of diarrhoeal illness.

"Copying from one book, it is said, is plagiarism, while copying from two books is research." (1)

INTRODUCTION

Acute diarrhoea affects nearly 500 million children annually worldwide (2), is the leading cause of death in children under four years old (3), and is a substantial cause of undernutrition (4). This is the grim situation now in the poor underserved parts of the world, but it was the same in the West 70 years ago (5). Since then, sanitation, protected water supplies and better medical therapy have dramatically reduced the incidence of acute diarrhoea, with a nearly hundred fold drop in mortality (6).

Nontheless, in the West, diarrhoea still ranks second to respiratory diseases as the cause of non-surgical pediatric admissions (6); approximately one-half the children receive intravenous therapy (7). Diarrhoea causes one-fourth of the avoidable deaths in hospitalized children (8).

Over the past three decades the study of acute diarrhoea in children (and adults) has led to important knowledge of the physiology of body fluids and the intestine, and of therapy. Table 1 suggests how this knowledge relates to the falling mortality rate. The essential elements, known since Darrow's work (18-20) are adequate replacement of sodium chloride, base, potassium and volume losses, and maintenance of nutrition. Workers at clinical centres in Asia, Africa, and Latin America recognized the need to translate these elements into a rational treatment that was simultaneously simple, cheap and applicable under the adverse conditions and shortages of the developing world.

The key elements of the method developed are: rapid restoration of salt and water depletion with simultaneous correction of acidosis, and administration of potassium; use of an oral glucose electrolyte solution for repletion[1] of those not in shock, and for maintenance; use of a single polyelectrolyte intravenous fluid and a single oral glucose electrolyte solution, for all age groups; and early feeding with tolerated foods. This approach has been successful both in well supplied hospitals (31-33), and, spectacularly, in Bangladesh refugee camps under the worst of conditions (35).

But the approach deviates considerably from conventional pediatric teaching. Table 2 contrasts the differences in methods. Much of current pediatric teaching emphasizes slow repletion of fluid losses; great concern over the sodium load, especially for infants; tailoring of fluid therapy to each

TABLE 1

CHANGES IN HOSPITAL MORTALITY OF CHILDREN'S DIARRHOEA

Year	Event	Hospital Mortality
1832	Latta (9) uses intermittent intravenous saline and alkali in cholera. Most relapse when drip ceased.	Over 75%
1912	Sellards (10) describes acidosis in cholera and uses alkali.	
	Howland and Marriot (11) describe acidosis in infantile diarrhea and give small doses of alkali, with brief improvement.	86%
1926	Powers (12) uses intermittent blood, glucose, saline and bicarbonate infusions, and prescribes prolonged fasting.	33%
1928-1938	Hartmann (13) uses sodium lactate to relieve acidosis; recurrent dehydration, however, causes high mortality.	51%
1931-1933	Karelitz and Schick (14-16) use continuous saline dextrose infusions and recommend a 3-day fast.	12 - 33%
1945	Mortality at Harriet Lane Home (Johns Hopkins) still quite high on regimen without potassium (17).	32%
1946-1949	Darrow, at Hopkins, (17-20) does balance studies to measure salt-H_2O deficits in diarrhea; emphasizes use of potassium in addition to saline, base and water. Prescribes 1-5 day fast.	6%
1948	Chung (21) urges continued feeding in spite of diarrhea; mortality unaffected, disease not prolonged, nutrition enhanced, but fluid balance more difficult to achieve.	10%
1947-1958	Rapoport (22), Finberg and Harrison (23) and others (24) describe hypernatremic dehydration.	12-24% for hypernatremi

TABLE 1 (Continued)

Year	Event	Hospital Mortality
1958	1/2 Darrow's solution (in mEq/L: Na^+61, K^+18, base 27) as sole intravenous fluid in tropics (25, 26).	10%
1959	Phillips and co-workers (27) measure water and electrolyte loss in cholera.	
1950's-1960's	In the West, better understanding of hypernatremia (28, 29), careful tailoring of intake, and laboratory monitoring (30) put treatment of diarrhea on a scientific footing.	0-5%
1960's-1970's	In Asia, simplified methods of treatment of cholera and non-cholera diarrheas developed at cholera research laboratories, based on physiologic studies (31, 32) emphasize speed and large fluid volume for rehydration; simultaneous use of salt, potassium, base; and early feeding.	2-3%
1966-1979	Increasing use of oral glucose-electrolyte solutions in cholera and non-cholera enteritis (33, 34).	0-2%

TABLE 2

COMPARISON OF TWO APPROACHES TO TREATMENT OF DEHYDRATING DIARRHEA

	Traditional Teaching	Recently Developed
The Physiological Models	Varying degrees of dehydration and tonicity require careful tailoring of fluid therapy.	Within broad limits a simple and unified therapeutic approach may be taken.
Speed of Rehydration	24-48 hours	4-6 hours
Choice of Initial Rehydrating Solution	Hypotonic with sodium content 30-60 mEq/L, especially for infants.	Polyelectrolyte solution with sodium content 80-130 mEq/L for all age.
Use of Potassium	Only after urination commences.	In polyelectrolyte solution.
Use of Base	Only for severe acidosis.	In polyelectrolyte solution (bicarbonate, lactate or acetate).
Use of Oral Fluids	Small, infrequent sips of H_2O in first 24 hours.	Ad-libitum intake of glucose-electrolyte solutions for those able to drink (in mM/L:Na^+90, K^+ HCO_3-30, glucose 111). Need for intravenous fluid can often be eliminated.
Feeding	Fasting for 24-48 hours; careful re-introduction of food.	Tolerated feeds as soon as appetite restored (usually within 6-24 hours) in small frequent amounts.
Principal Concerns	Overhydration, Hypernatremia, persisting loose stools.	Under hydration, Hyponatremia, Under-nutrition.

individual; and the need to "rest the bowel" for several days. A classic presentation of this approach was written in 1974 by Blair and Fitzgerald (36). Given these differences, this paper has been prepared with several aims in mind: to review the historical development of current pediatric teaching about treatment of acute diarrhoeal disease; to collect and synthesize in one review the epidemiologic, clinical and physiologic data that explain both successful and unsuccessful treatment regimens; and on the strength of the synthesis, to reevaluate the hypotheses upon which these different treatment regimens are based.

REGIMENS AND PATIENTS' CHARACTERISTICS

The death rate in hospitals from acute diarrhoea can and should be 2% or less, whether in a sophisticated urban hospital or in a makeshift tent ward in a rural area. Most of the excessive mortality that occurred in the past (Table 1) came soon after admission and was due mostly to uncorrected volume depletion or electrolyte imbalance (31, 37-40).

Given the importance of the first day in the fluid treatment of severe dehydration, the ranges of a first 24-hour fluid regimen associated with improved survival should be defined. It is unlikely that such data will ever be generated prospectively, but a retrospective analysis of reported experience may provide clues. A literature search followed these rules for inclusion in the analysis: a study had to specify clearly the first 24-hour volume and electrolyte regimen (intravenous and oral) planned or actually received; the children had to have been visibly dehydrated, requiring at least some intravenous fluid; given the known adverse effects of omitting potassium (Table 1) and acidosis (41), regimens analyzed had to specify inclusion of potassium and base at levels of at least one mEq per kilogram body weight respectively; and mortality reported had to be related to the diarrhoeal illness. Fifteen studies reporting 20 regimens met these criteria (20, 25, 31, 32, 37, 38, 40, 42-49). All were published after 1945. When ordered in terms of mortality, both higher and lower rates were described from Western and tropical countries, in urban and rural settings, among infants and toddlers, and in children well or poorly nourished.

Five independent variables were analyzed against mortality: sodium load, total volume, "free water" volume, sodium load x total volume, and sodium concentration. All variables were expressed as ml or mEq per kilogram of body weight as appropriate. Total volume and sodium load included all intravenous and oral fluid and sodium intake in the first 24 hours of hospitalization. "Free water" was calculated as that component of fluid not bound to salt in terms of extracellular fluid sodium concentration (at

a sodium concentration of 140 mEq/L, a liter of solution has no "free water", while one at 70 mEq/L has 500 ml "free water"); calculations for "free water" were further corrected for the potassium given. A composite index, sodium load x total volume, was derived to examine any augmenting effect of one on the other. Finally, the effective sodium concentration (in mEq/L) was calculated by $\frac{\text{sodium load}}{\text{total volume}} \times 1000$.

The first four variables were plotted against mortality. Since mortality cannot be less than 0%, computer-calculated hyperbolic curves rather than linear regressions were fitted to the data (Figure 1). This analysis is susceptible to the hazards of a retrospective review of multiply disparate studies, and randomness' cannot be guaranteed since most outcomes are not published. Statistically significant negative correlations with mortality were present for sodium load and the composite index, sodium load x total volume. A negative correlation of borderline significance was found for total volume. A weakly positive correlation between "free water" volume and mortality was also found. The effective sodium concentration of regimens associated with 6% mortality or greater averaged 60 mEq/L; the effective sodium concentration of regimens associated with 3% mortality or less averaged 77 mEq/L; the difference, however, is statistically insignificant. At a minimum it can be said that, along with potassium and base, the higher levels of sodium-containing fluid administered were compatible with improved survival, and may have contributed to it.

Although the successful regimens, higher in volume and sodium than generally advocated, have been used both in the West and the tropics, it is often said that children from the tropics, or disadvantaged groups such as American Indian children, represent a "different type of infant" than the Western child (51-53); and that egimens developed for the former are inappropriate for children generally seen in U.S. hospitals. Specifically, it is supposed that certain attributes render Western children less tolerant of fluid and salt overload, or these other children more tolerant.

In an attempt to test this hypothesis, the clinical and biochemical attributes reported for Western and tropical children hospitalized were examined. Table 3 reviews 71 reports written in the past three decades; from the West (generally from urban teaching hospitals); from tropical areas (urban and rural); and, for comparison, studies of children presenting exclusively with hypernatremia (including four from the tropics). For each of the attributes listed - dealing with clinical, biochemical and

TABLE 3

CLINICAL AND BIOCHEMICAL ATTRIBUTES OF CHILDREN WITH DIARRHOEA FROM DIFFERENT PARTS OF THE WORLD[a]

	Western	Tropical	Hypernatremic
# of Studies	18	21	16
# of Children	2,764	5,607	323
(median/series)	79	100	20
Attribute			
1. Mean age (months)			
median	7	10	7
IQR	4-10	6-14	6-9
2. Malnutrition, % with weight <75% normal	5,30,38		26,37
median		59	
IQR		51-68	
3. Volume depletion, % with 5-15% loss body weight			
median	57	84	90
IQR	45-100	72-100	66-100
4. Mean % weight loss when clinically "severe"	4,8,10,13		7,9,9,10+
median		8	
IQR	8-10	8-10	

.../9/

TABLE 3 (Continued)

	Western	Tropical	Hypernatremic
5. Mean sodium loss, mEq/kg, in severe dehydration	10,10,13	11	13*, 8-14*
6. Acidosis, % with pH < 7.3, or CO_2 < 15			
Median	50	78	81
IQR	28-85	61-95	59-99
7. Hypokalemia, % with K^+ <3.5 (corrected for acidosis)			
median	5	51	50
IQR	0-14	34-66	22-63
8. ECF sodium on admission: % hypertonic (Na^+>150)			
median	14	7	100
IQR	7-29	2-18	
% Hypotonic (Na^+<130)			
median	12	41	0
IQR	4-21	17-59	
9. Mean evaporative loss, ml/kg/day	64*,70	44,44,51*,70*	50
10. % Children with parenteral infection		19,19,40	
median	17		20
IQR	4-20		17-47
11. Mean stool sodium, mEq/L (non-cholera, acute)	60,71	46,56,91	20

.../10/

TABLE 3 (Continued)

	Western	Tropical	Hypernatremic
12. % children with carbohydrate intolerance	6,25,50+*	24,25,77	-
13. % children with enteric bacterial pathogen			0,0,18
median	14	36	
IQR	3-17	21-59	
14. % children with rotavirus			
median	42	40*	-
IQR	35-55	38-55	

[a]Notes to Table:

1. Median values and interquartile range (IQR) underlined.
2. Single values, not underlined, are means from individual studies and insufficient for calculation of median.
3. Values with an asterix indicate data from studies not otherwise included in total analysis.
4. Reference numbers of studies included in this table:

   Western: 7, 18-20, 24, 37, 41, 45, 47, 50, 54-61

   Tropical: 32, 40, 44, 48, 62-78

   Hypernatremic: 22, 24, 45, 62, 66, 71, 79-87

   Asterixed: 88-103

bacteriologic measurements - the mean values reported by each study were ranked. Where five or more reports characterized an average attribute in the group under study, a median value and the interquartile range (IQR) were calculated.[2] Although differences in reporting exist between series, this method of comparing means should reveal different tendencies between the three groups.

Several findings are of interest. First, contrary to accepted teaching, children with hypernatremia are, on the whole, neither younger nor better nourished than the population with diarrhoea from which they were drawn. Second, hypertonic dehydration does occur in tropical children, though not as commonly as in the West. The incidence of hypotonicity is several times greater in tropical children with diarrhoea. The differences, however, are unlikely to be explained by differences in evaporative water loss, the incidence of parenteral infection, carbohydrate intolerance, or sodium loss in the stool. Third, the severe consequences of diarrhoea - marked volume depletion, acidosis, and hypokalemia - are seen with nearly equal prevalence in the tropical and hypernatremic series, and more often than in the Western series. But, once severe volume depletion occurs, as indicated by clinical shock, the mean weight loss in all the groups is approximately 10%; and accumulated sodium losses on admission, as measured by net retention studies, were approximately the same in the few Western, tropical and hypernatremia studies recording these data. Traditional bacterial pathogens (shigella, salmonella, enteropathogenic *E.coli*) were more often isolated from children hospitalized in the tropics, but reovirus-like agents seem to be equally distributed worldwide. The diagnosis of enterotoxigenic *E.coli* has been confused by a variety of assay techniques; they are unlikely to be common pathogens in Western children (104, 105), but cause 10-20% of episodes in tropical and American Indian children (102, 106). In two studies of Apache children where the newer approach to treatment outlined in Table 2 was used exclusively (33, 107), their clinical and biochemical attributes resembled both Western and tropical children: nutritional status and severity of illness like the Western children, hypotonicity like the tropical children; evaporative loss, stool sodium concentration and carbohydrate intolerance like both.

None of the attributes examined, therefore, compel one to believe that tropical (or Apache) children should be more tolerant of sodium loads than Western children. Traditional teaching has often dwelt on the differences in these attributes

- especially tonicity - as the basis for regimens tailored to each category. This review will advance the hypothesis that, within broad limits, a simpler, unified approach is not only possible, but physiologically correct. The support for such an hypothesis must be built on the resolution of four apparent paradoxes in the pathophysiology of diarrhoeal dehydration.

The first seeming paradox is that despite the fact that fluid losses in stool, sweat and expired air contain considerably more water and less sodium than does the extracellular fluid (ECF), most children with diarrhoea present with a serum sodium concentration equal to or less than normal.

The second paradox has to do with the source of fluid loss. Darrow in the U.S. (19) and Mahalanabis in India (70) measured the retention of electrolyte and water during the recovery phase. Both showed that the estimated deficits of sodium and potassium on admission were roughly equivalent (total ion loss 318-53 mEq per liter water loss), which indicated that intracellular (ICF) and ECF fluid compartments are equally depleted in diarrhoea. Yet measurements of the ECF compartment by the chloride-space (18, 19, 70) or with inulin (54) show mostly ECF depletion.

The third paradox relates to the second: fluid regimens were designed to correct both ICF and ECF ion and water loss with approximately equal concentrations of sodium and potassium (limited by considerations of safety to about 40 mEq per liter each). Yet children regularly respond well, perhaps better, to solutions closer in composition to the ECF (Figure 1).

A fourth seeming paradox is that children from the tropics with diarrhoea are predominantly hyponatremic; yet their attributes closely resemble those of hypernatremic children in severity of volume depletion, acidosis and hypokalemia.

To resolve the paradoxes requires an overview of the pathophysiology of diarrhoeal dehydration.

THE PATHOPHYSIOLOGY OF DIARRHOEAL DEHYDRATION

Figure 2 represents a synthesis of a wide variety of data on the effects of and the body responses to diarrhoeal dehydration. Some caveats are in order. The events depicted do not represent all the possible effects; neither is any weight assigned to predominant effects, or to the likelihood of interactions; and not all of the events have been investigated specifically in children's diarrhoea. But the formulation is a

reasonable synthesis of the known and the likely responses to diarrhoeal fluid loss.

In the overall formulation (the top portion), diarrhoea first induces a major effect on the body through salt and water depletion, with compensatory responses by the vascular, renal, and hormonal systems. The second major effect is on the intestine, inducing malabsorption and (iatrogenically) fasting or improper intake; various metabolic, evaporative and intestinal events follow. The first effect leads generally to hypotonic or isotonic dehydration. This response may be considered "normal" or compensatory in a more helpful, homeostatic fashion. The second effect tends generally toward hypertonicity. This response may be considered "pathologic" or a more harmful compensation.

Throughout the discussions that follow, the reader will be assisted by referring back to Figure 2.

Hyponatremic Dehydration

Let us first consider the normal compensatory events that follow quickly upon the loss of water, sodium, potassium and bicarbonate in the stool (mid portion of Figure 2). (References 18, 19, 78, 107a-121 contain data providing the basis for the following ideas.)

With the loss of potassium from the ECF to the stool, a chemical gradient is created that facilitates potassium (and water) movement from the ICF to the ECF. Facilitated by aldosterone, sodium (and water) tend to move into the ICF. Protons (which accumulate in the ECF following bicarbonate loss in the stool, during tissue hypoperfusion, and with ketosis of catabolism) also tend to displace ICF potassium. Since an effect of aldosterone is to promote sodium retention and potassium excretion via the kidney, a substantial proportion of the potassium deficit in diarrhoeal disease may be accounted for in this way. The effect of aldosterone may account for the observations of Darrow (19), and Mann and colleagues (78), that potassium retention is inversely related to the volume of stool loss, even though potassium loss in the stool cannot account for the total deficit.

With even minimal ECF volume contraction (loss of 2% of body weight or less), renin, angiotensin, aldosterone and antidiuretic hormone (ADH) secretions are increased, and the

glomerular filtration rate (GFR) is decreased or redistributed. As GFR falls, acidification of the urine is also blunted and accumulating protons tend to be retained, which in turn may further promote tubular secretion of potassium.

These actions lead to a compensatory retention of salt and water, but proportionately more of the latter. The first palpable response to ECF contraction is thirst. If water is taken, it will be mostly retained as ADH increases distal tubule and collecting duct permeability to free water, facilitating its reabsorption. Even without much intake, water may be generated internally, and retained, in the response to stress by steroids and catechol amines which promote catabolism of body tissue.

We may now suggest resolutions for three of the four apparent paradoxes. First, the tendency to hypernatremia, due to loss of more water than sodium, is counteracted by avid retention of water (ingested or internally generated).

The second paradox is also explained: fluid deficits in acute diarrhoea, as measured by net retention studies, combine both ECF and ICF losses in roughly equal proportions; but the predominant contraction measured by chloride and inulin space takes place in the ECF because sodium and hydrogen ions (and water) replace ICF potassium (and water). In other words, ECF space contracts in two directions: out in the stool, and into the cell; so that the net measured loss of volume appears to come mostly from the ECF.

A resolution to the third paradox follows: since it is continued ECF contraction that is at the root of these physiologic changes, reversion to normal is more readily accomplished by solutions more nearly approximating the composition of ECF than ICF. The more hypotonic a fluid is with respect to sodium, the less well it can quickly correct ECF contraction, unless proportionately more of that fluid is given (see Figure 1B). It should be noted that hypotonic dehydration, once initiated, tends to be self-perpetuating, since vascular collapse and all the physiologic responses thereto occur with less fluid loss than seen in isotonic or hypertonic dehydration (122). Pre-existing, or uncorrected potassium deficit may also perpetuate hypotonicity by several possible mechanisms. There is evidence that potassium depletion causes an increased secretion of renin (123), and promotes catabolism by impairment of insuling secretion (124). Also, with potassium depletion but normal hydration, sodium (and water) may replace potassium (and water) in the cell causing ECF contraction and then ADH secretion (117). The rational treatment then should reverse these events by

restoring volume quickly, correcting acidosis and reducing the potassium deficit with solutions approximating the composition of the ECF. Under-replacement of ECF fluid can perpetuate all the events listed above. This has been shown empirically by studies comparing regimens higher and lower in sodium (41, 44, 93).

It must be acknowledged that solutions more closely approximating ICF in composition have been used in rehydration therapy for years. Their apparent success, however, derives in part from the avid retention of "maintenance" fluids over several days, and from the unproved view that severely dehydrated children have lost, and therefore should be given, 15% or more of their weight in fluid (compare reference 30, Table 3). The use of hypotonic solutions more nearly approximating the ICF, however, explains the necessity of the traditional practice to allow rehydration to proceed slowly over 24-48 hours; a rehydrating fluid more nearly approximating the ECF can be given more rapidly.

A hypothetical profile of a child most susceptible to hyponatremia may now be drawn. It is a child with repeated bouts of diarrhoea; with chronic potassium depletion; with perhaps slight, continued ECF volume contraction; who is fasted; and who gets only salt-poor fluids once diarrhoea starts. Many children in the tropics are found to suffer from chronic or relapsing diarrhoea at any time surveyed (125, 126), and are predictably potassium depleted (76). Malnourished children, with diarrhoea much of the time, have chronically elevated levels of renin (127). And finally, the usual fluids given children in the tropics (as well as to Apache children) are hypocaloric and virtually salt-free: tea, barley-water, rice-water, jello-water or soft drinks. Clearly, not all of these features need be present simultaneously to cause hyponatremia in any one child.

A solution to the fourth paradox posed - how hyponatremic children in the tropics and hypernatremic children come to share several critical biochemical attributes - is yet to be supplied. This will require a more intensive analysis of how hypernatremia originates.

Hypernatremic Dehydration

The dessication of the ICF in hypernatremia (128) can lead to serious neurological consequences; therefore, hypernatremia is a matter of great concern. Since the regimen this review has recommended contains more sodium than traditionally used, it is also necessary to examine the pathogenesis of hypernatre-

mia to determine if the newer regimen is as safe, from a theoretical point of view, as it seems to be in practice. We may analyze the predisposing events by means of three categories: The epidemiology of hypernatremia, augmenting mechanisms, and abnormal water loss.

Epidemiology: Hypernatremia complicating diarrhoea is a condition of infants and toddlers of either sex. The median age in 16 reported series is seven months. But the median age of the general group of children hospitalized with diarrhoea in the West is also seven months (Table 3). Hypernatremia has been reported both to have winter (28, 103, 129, 130) as well as summer peaks (131, 132), suggesting that it reflects only the dominant diarrhoeal seasonal pattern in a particular locale. Hypernatremia occurs both in the tropics and in temperate zones, but is more common in the latter (50, 66, 71, 73, 83, 84, 133, 134). It is said that better-nourished children are more susceptible to hypernatremia (53). Data presented in two large series of hypernatremia from the U.S., however, found these children to suffer mild to severe malnutrition, not different from the larger group at risk (22, 28). In the tropics, hypernatremia is more common in large, bottle-fed infants (73, 75, 83). The most important epidemiologic clue, however, is that while hypernatremia has been recognized for decades (23), there appears to have been a two-decade epidemic, starting in the 1950's and only now abating (129, 133, 135, 137). If the documentation is valid, it must mean that certain physiologic mechanisms reputed to cause hypernatremia can only be predisposing, augmenting, or perpetuating, but not initiating.

Augmenting Mechanisms: Commonly cited predisposing events include the large ratio of surface area to weight in children (138), and the normally increased metabolic rate in children 6-15 kg (139), both of which dictate a more rapid turnover of water. Small children are especially susceptible to metabolic water loss, especially under heat stress and fever (72, 84). But these phenomena only serve to confirm that hypernatremia more commonly affects infants and toddlers.

It has been suggested by several authors that immature renal function in infants is an important contributing factor to hypernatremia (53, 140). If body surface area is used as the basis for comparison of renal functions, particularly for GFR and urinary excretion of sodium, infants reach levels seen in young adults by anywhere from four to thirteen months (141, 142); but if GFR per unit of total body water, or per unit extracellular fluid volume, or per unit kidney weight are

calculated, values equivalent to those in adults are reached by one to two months of age (143, 144). McCance, who first called attention to the maturation question in 1941, decided by 1957 that the latter method of comparison was more rational (143). Finally, maximal concentrating ability reaches at least 85% of adult levels by the second month of life (143, 145, 146, 147) in the majority of children, and certainly by ten to twelve months in all. Any remaining difference between adults and children would permit conservation of only trivial amounts of water. So it would not seem that immature renal function plays an important role in the incidence of hypernatremia, where the median age of occurrence is seven months (Table 3).

A number of distinctly pathologic renal and metabolic events do occur that, once hypernatremia is initiated, serve to perpetuate it. Renal concentrating ability (i.e., the ability to conserve water and excrete solute) does not keep pace with the hypertonicity, especially as persisting volume depletion causes decreased delivery of sodium to the distal tubule, and free water is thus not generated for retention. Potassium depletion (148) and hypertonicity itself (149) also affect the kidney's ability to excrete salt.

Potassium depletion is generally not appreciated as a perpetuating factor in hypernatremia. Yet the tendency to retain sodium and develop edema in the face of body potassium deficiency has been described for nearly three decades by Darrow and others (20, 41, 54, 150). The effects are multiple: on the renal (148, 151), hormonal (123), and cellular levels (152, 113). Ramirez and colleagues (153) have demonstrated in children that a potassium-free diet is associated with cumulative weight gain and sodium retention beginning on the first day.

Severe acidosis is commonly found with hypernatremia (Table 3) and is a likely perpetuating factor. Acidemia stimulates the release of non-extracellular sodium (154). With continued water loss, hypernatremia may ensue. Hyperosmolarity, in turn, induces further hydrogen ion secretion from cells (155). With dehydration, the kidneys are less able to excrete acid (156). The burden of compensation on the lungs is then increased; but with increased respiration, unfortunately, water loss also increases. Moreover, as acidosis becomes severe, (pH less than 7.1), blood is shunted from the peripheral vessels to the lungs causing pulmonary congestion (157). If carbohydrates are poorly absorbed, additional protons are generated during bacterial fermentation of the sugars in the gut and are either transferred to the body fluids or remove bicarbonate already secreted into the lumen (158, 159). Both

acidosis and hyperosmolarity cause hyperglycemia (86, 160-163) which, by an osmotic diuresis, can further force renal water loss.

We come back to our fourth, as yet unresolved, paradox. Since many children in the tropics with diarrhoea are seriously potassium depleted and acidotic, why is hypernatremia not more common? Or, how can hypokalemia predispose both to hypo and hypernatremia? In fact, the known intolerance of malnourished children to sodium (164), as evidenced by the development of edema or congestive failure, may have its roots in potassium deficiency (165). But the latter develops over some time, allowing for compensatory water retention. Hypernatremia, on the other hand, happens quickly (66, 84). Some event causing rapid and excessive water and potassium loss, in addition to sodium retention, is necessary. The next section examines this point.

Abnormal Water Loss: A search for a likely initiating cause of hypernatremia must start with some of the early clinical observations. That drinking milk during diarrhoea often causes clinical deterioration is quite an old observation. Howland, in 1921, noted that " . . . it is now generally appreciated that sugars initiate and perpetuate diarrhoea. . . " (166). Infantile diarrhoea, with profuse stools, dehydration and shock, was often called "alimentary intoxication" and it was recognized that cow's milk initiated or worsened the condition (12, 14, 164). When hypernatremia occurs in the tropics it is related to cow's milk feeding (71). Hypernatremia has been described in association with high-solute or hyperosmolar feeds such as boiled skim milk (82), hypertonic (10-20%) glucose solution (168), tinned milk formulas (133, 134, 137), or commercial glucose-electrolyte solutions containing dextrose polymers in high concentration (10%) (169, 129). An interesting concomittant clue to the pathogenesis of hypernatremia is the tendency of hypernatremic children to produce voluminous, watery stool low in sodium (28, 169). Normally, as stool rate rises, so does the stool sodium concentration, approaching plasma levels; this occurs in adults with cholera (170) as well as in infants with non-cholera enteritis (calculation of data presented by Darrow (18, 19). Since stool fluid is rarely hypoosmotic to plasma, voluminous stool low in sodium must contain other solutes such as organic metabolites. Such metabolites are generated in the gut during malabsorption of carbohydrates (171). Intestinal bacteria degrade undigested carbohydrates into many osmotically active fragments which draw water into the lumen in the upper intestine. This may cause the production of gas, distension and ileus and impair colonic absorption of salt and water (172). Voluminous,

low sodium stools are the result, in which potassium is also lost. Intestinal fermentation produces acidemia, while distension and ileus increase fluid loss and the accompanying nausea reduces total intake. If the incidence of hypernatremia has followed an epidemic curve between the 1950's and 1970's, perhaps it may be related to the common medical practice in that time which promoted boiled skim milk plus sugar, or dextrose polymer-salt solutions, as suitable therapy for diarrhoea. The hypothesis that carbohydrate intolerance is a principal initiating cause of hypernatremia awaits formal testing.

A hypothetical profile of a child most susceptible to hypernatremia from diarrhoea may now be drawn. It is a child under a year of age, with a brief history of diarrhoea, getting complex carbohydrates at high concentration, and with reduced intake or considerable insensible loss of water. Once initiated hypernatremia tends to be perpetuated by hypovolemia, hypokalemia, and acidemia. Rational treatment then should reverse these events by restoring volume, correcting acidosis, reducing the potassium deficit, and eliminating complex sugars from the diet (especially lactose). Some caution must be used in the speed with which serum sodium concentration is reduced, but this caution should not permit perpetuation of the hypernatremic biochemical complex. A recent paper (175) reported the use of a 0.18% sodium solution over 48 hours, with base given only for "severe clinical acidosis". The patients suffered a 13% death rate, slow rate of return to normal plasma osmolarity, and a high incidence of edema and thromboses. On the other hand, Finberg, who has studied hypernatremia for three decades, now recommends (87) a regimen for the severely dehydrated (over 10% weight loss or greater) that provides up to 50 ml per kilogram in the first 4 to 5 hours with a solution containing 80 mEq/L sodium and 25 mEq/L base. In his most recent series, only 2/67 (3%) died. The fluid and sodium load he recommends for hypernatremia is not remarkably different from what this review has suggested for all diarrhoea in children.

The regimen suggested in this review (Table 2) does not, in fact, fit into any of the contributing factors for hypernatremia. On the contrary, with early prevention or correction of volume depletion, acidosis and potassium loss, both hyponatremia and hypernatremia should be avoidable or easily corrected. Perhaps we are relearning Darrow's wisdom: "These patients with hypernatremia received the usual fluid therapy used in other cases of diarrhoea." (45)

It is now necessary to examine more closely some of the origins of current pediatric teaching which emphasize that an absolute ceiling for safe sodium intake exists, one regularly exceeded by the regimen recommended in this review.

SODIUM: STRIKING THE BALANCE

In the mid-1950's, Talbot, Butler and their colleagues presented an encompassing framework for fluid therapy of adults and children (88, 176-182) which established "floors and ceilings" for the amounts of water and electrolytes that could be safely administered. Their work came at the time when awareness of hypernatremia was most acute and formed much of the intellectual underpinning for traditional pediatric fluid therapy. Their basic concepts may be summarized as follows:

> There is a minimum and a maximum rate of administration of water and salt that can be given without disturbance of body fluid composition. The body's adjustment to fluid administered between the limits is by the usual neuro-endocrine and renal homeostatic mechanisms, but the fluid administered should be balanced as much as possible between minimal need and maximal tolerance (hence the original use and meaning of the term "balanced solutions"). "Stress due to injury, surgery, or illness lowers the ceiling for maximal tolerance. In treatment of dehydration, ICF and ECF losses are to be replaced simultaneously with equal amounts of sodium and potassium; it is unnecessary or undesirable to replace all deficits within a few hours, once shock is corrected.

Talbot and Butler suggested that the ceiling for daily sodium administration to acutely ill children would be 225 mEq per square meter surface area, with 150 mEq the "balanced" amount given, along with an equivalent amount of potassium, in no more than 3500 ml/m^2 fluid volume. In an eight kilogram child, this works out to a sodium load of 7.5 mEq to 11.3 mEq per kilogram in 175 ml/kilogram volume (sodium concentration 43-64 mEq/L). Such a child, if severely volume depleted, will have lost approximately 640-960 ml (80-120 ml/Kg) of fluid and approximately 90 mEq of sodium, or 11 mEq/kg (see Table 3). The volume of fluid and sodium thus recommended for rehydration is likely to be insufficient and only the "ceiling" approaches adequacy (see Figure 1). On the basis of his balance studies, Darrow had arrived at a much higher value, supplying an average of 17 mEq/kg sodium in the first day of rehydration (20) at an overall concentration of 86 mEq sodium per liter fluid volume. How, then, did Talbot and Butler derive their ceiling for sodium administration for infants? Two references are cited in Talbot's syllabus (88): Gamble and associates (183) and McCance and Widdowson (184). Gamble added salt to the milk and water

diet of a normal seven kg child, providing sodium at 12-13 mEq/kg/day for eight days in a concentration probably no greater than 90 mEq/L. While the child retained an excess of 1.1 mEq Na^+/kg/day and gained water over eight days equivalent to 4% of body weight, it apparently remained well. McCance, on the other hand, gave three premature neonates salted milk for 1-2 days, providing sodium at 22 mEq/kg/day in a concentration range of 120-154 mEq/L. The neonates retained 10-14 mEq/kg/day, gained water equivalent to 10% of body weight, became puffy, oliguric, sick and hypertonic. A key difference between the two studies, in addition to the undoubted susceptibility of the prematures, may have been the final concentration of sodium - hence the availability of water for excretion - rather than the absolute amounts given. An important difference between the studies of Gamble and McCance and those of diarrhoeal disease is, of course, the considerable existing deficit of sodium on admission in children with diarrhoea.

Regimens that rehydrate slowly with fluids more like ICF in composition have several consequences, understandable from the general model described in Figure 2: rehydration is not accomplished in the first day; hyponatremia is likely to be produced or persist; and acidosis is prolonged, especially where diarrhoea continues during and beyond the first day. All these consequences have been determined empirically (41, 44, 54, 9[illegible].

So far this review has dealt principally with only the first twenty-four hours of therapy. It is possible that adverse effects of excess sodium loading might be avoided if it occurs for only one day. In fact, the mainstay of the regimen this review recommends is the use of a single intravenous or oral polyelectrolyte solution, both for initial deficit and continuing losses, with the addition of food and low-solute liquids. In practice, and on the average, this has meant providing sodium to (for example): Apache infants 14 mEq/kg/day for 2-3 days (33, 107); Bengali children (average weight 8-9 kg) with cholera, and given tetracycline, 11 mEq/kg/day for 2 days (32); Bengali children (average weight 11 kg) with cholera, on no antibiotic, 20 mEq/kg/day for 4 days (185); urban American infants, 13 mEq/kg/day for 3 days (19).

In all these studies, however, enough water was supplied to reduce the final sodium concentration (total sodium per total water) to approximately 50-90 mEq/L; and while transient puffiness (usually periorbital) was not uncommon, it was of no clinical consequence.

But pediatricians in general are more worried about sodium retention and edema than moderate under-replacement of saline deficits. In the 1940's, a syndrome of "post acidotic state of infantile diarrhea" (186) was described which followed vigorous saline and bicarbonate therapy without potassium. The syndrome included non-pitting edema, tetany, hypocalcemia, hypernatremia, hypokalemia, convulsions and cerebral hemorrhage. These regimens included "normal" saline, or normal saline plus 1/6 molar lactate, or the curious "3:1 regimen" (three parts normal saline to one part 2% sodium bicarbonate) (22, 187, 188). None had potassium. The 3:1 regimen (Na^+ at 177 mEq/L) in one study was associated with a 17% mortality and a high incidence of hypernatremia (187); with a changeover to lactated Ringer's (Na^+ at 128 mEq/L) the mortality fell to 3% and hypernatremia was no longer documented (44, 91). In the regimen recommended by this review, the "post-acidotic" syndrome has not been reported. Marked edema, or pulmonary congestion, may be associated with severe acidosis (157) or with potassium depletion (20); then it reflects a serious problem. Slight puffiness about the eyes in a child otherwise clinically well is commonplace, is not related to electrolyte imbalance (13, 33, 54), and is not a problem. Its presence indicates an excess fluid volume isotonic to ECF amounting to 1-3% of body weight (33). Transient isotonic over-expansion after large doses of NaCl is seen both in adults (189-191) and children (183). The cause of delayed sodium excretion is complex but several explanations may fit: "Post loading, antinatriuresis" describes a brief period of renal tubular reabsorption of sodium in response to a sodium load (192); after chronic salt depletion, salt and water are retained even when a hypotonic salt solution is given (111); and finally, the very handling of children during sampling procedures causes oliguria lasting up to an hour (193).

Talbot and Butler were also concerned that the stress of illness, through various hormonal mechanisms, would increase sodium retention. This is quite true even to the extent that low sodium loads, given slowly, can induce edema and hypernatremia (41, 48, 82). The same may be said of hypernatremia: children with this condition show intense retention of sodium (54, 89). The relief of stress induced by volume depletion, however, is achieved by rapid restoration of extracellular volume and electrolyte deficits, which means using rather more sodium than less. In fact, therapy that just removes clinical shock does little to stop the responses to volume depletion (157).

The concepts developed by Darrow, Talbot and Butler and their colleagues, while not proved correct in all respects, had a profound effect on pediatric fluid therapy because they were

based on meticulous attention to both physiologic and clinical information. A new concept in the treatment of diarrhoea - oral therapy - is similarly based, and is the subject of the final section of this review.

ORAL THERAPY WITH SUGAR-ELECTROLYTE SOLUTIONS

Glucose-electrolyte solutions, taken by mouth for rehydration and maintenance according to carefully designed regimens ("oral therapy" in shorthand), were developed to replace diarrhoeal fluid loss in cholera and reduce the need for intravenous fluids in developing countries where cholera is prevalent. Data obtained from six independent lines of physiologic and clinical research, however, have given oral therapy a broader significance with regard to both medical science and health care delivery.

1. Active Co-transport of Sodium and Organic Substrates in the Intestine: The details of this line of research have been well summarized (194-196). Briefly, several actively transported substances like glucose, galactose, certain amino acids, some disaccharides, and some dipeptides show an absolute or partial dependence on sodium for their absorption, and the rate of sodium absorption is considerably increased in the presence of these substrates. While the kinetics of the sodium-substrate interactions vary by substrate class, a common effect, seen especially in the intact intestine, is the simultaneous enhancement of absorption of water and of other salts, following electro-chemical gradients (197-200). How much of the induced transport is transcellular, or active, and how much across paracellular, or passive, is unknown.

This effect on salt and water absorption was applied successfully to cholera patients when it was shown that the salt-substrate co-transport was substantially intact, and that oral therapy with sodium, potassium, bicarbonate, chloride and glucose in a single solution could maintain normal blood volume and electrolyte concentrations (201-203). The suggested ideal composition of an oral therapy solution was derived in large part from research done on isolated membranes, animal models and human subjects. First, there is considerable evidence that glucose and sodium are absorbed at close to a 1:1 molecular ratio (204-206). Second, maximal water and sodium absorption take place at administered glucose concentrations between 56-140 mM/L (197, 207, 208). At glucose concentrations higher

than 160-200 mM/L, water and salt absorption are reduced, an effect independent of fluid tonicity (208-210). Third, when sodium concentration is considerably below that of the normal jejunal contents, secretion occurs even in the presence of glucose (211). Fourth, bicarbonate - in addition to correcting acidosis - also serves to enhance sodium absorption (212), but the presence of chloride is necessary for the full sodium-glucose effect (199). Fifth, glucose is much better absorbed in the jejunum than in the ileum in man (213). Sixth, rapid flow rates of lumenal contents (over 10 milliliters/minute) reduce absorption substantially (209). Seventh, the loss of sodium on admission in acute, severe diarrhoeal disease averages from 76-109 mEq per liter of fluid loss in infantile diarrhoea (19, 70); and up to 120 mEq per liter of stool (17, 70). Potassium losses may be similarly extensive.

Taking these eight points together, a rational solution for oral therapy should therefore be sufficiently concentrated in sodium to replace losses on a volume for volume basis so that patients do not need to drink excessively, thereby increasing flow rate and delivery of a large load of glucose to the ileum. The glucose concentration should closely match sodium on a molar basis. Potassium and base should be added (empirically this has worked out to be 4-6 mEq/kg/day each). Such a fluid would then contain, per liter, 75-100 mEq of sodium, 20-30 mEq of potassium, 20-30 mEq bicarbonate (with chloride as the other anion) and 75-100 mM of glucose; the osmolarity would be 265-360 mOsm/L. The formula promoted by the World Health Organization contains, in mM per liter, Na^+90, K^+20, HCO^-_3 30, Cl^-80, glucose 111; and 331 mOsm/L.[4] The renal solute load is 220 mOsm/1. Lytren ® (per liter: 30 mEq Na^+, 556 mM glucose, no bicarbonate, milliosmolarity 656), and Pedialyte ® (per liter: 30 mEq Na^+, 278 mM glucose, no bicarbonate, milliosmolarity 387), both in common use, are examples of unphysiologic solutions. They have too little sodium, too much glucose and are too concentrated.

Two other phenomena may be relevant to the discussion. One, described in rabbits, is that sodium given by mouth stimulates natriuresis 5-10 times greater than an equivalent amount given intravenously (215). The effect is seen in normal and in sodium-depleted animals. The second observation, in humans, is that a physiologic dose of ADH, a level attained naturally in volume depletion, abolishes net salt and water absorption in the jejunum; but this effect is reversed when glucose is added to the oral mixture (216). These two studies indicate that oral therapy may be safer than intravenous with respect to sodium loading in children, and that any oral fluid

without glucose (or some other appropriate substrate) will considerably worsen diarrhoea if even a slight depletion of blood volume exists. Diarrhoea itself affects intestinal absorption, as the next section discusses.

2. The Effect of Diarrhoea on Intestinal Absorption: Morphologic abnormalities in the intestine accompany acute bacterial and viral diarrhoeas, the severity of which correlate with indices of malabsorption (217). Reversible changes in concentrations of enzymes associated with absorption (Na-K ATPase, disaccharidases) have also been documented (218-221). Persistent disaccharidase deficiency (222, 223) and malabsorption of glucose (224) have been documented in selected hospital cases. Malabsorption in children hospitalized with acute diarrhoea spans a spectrum from clinical intolerance to lactose in about half (72), to sucrose in a third, and to glucose in about 5% (222). Intolerance to glucose can be made manifest by increasing the concentration (225) and rate of administration (226) of the sugar. Sugar malabsorption can lead to an increase in stool loss, continued morphologic damage, bacterial overgrowth, gut ischemia, intolerance to all substrates and a downhill course in a minority of children (159). From such clinical experiences came the general injunction to "rest the bowel" absolutely during the acute phase, with restoration of full diet taking as long as a month (36).

But there were always dissenters from this approach. Chung showed in 1948 that children with acute diarrhoea fed milk and corn syrup (glucose polymers) recovered slightly faster and with better nutritional weight gain than those who fasted, even though the latter group had less total stool output (227). A commercial formula containing casein hydrolysates plus glucose (Pregestimil ®) can replace stool salt and water loss, and provide nutrition (33, 107). Even children with "intractable" diarrhoea, or with malnutrition, gain weight and have less diarrhoea on diets that are predigested but not hypertonic (casein hydrolysates or comminuted protein, amino acids, glucose or glucose polymers, etc.) even to the point of not requiring total parenteral nutrition (223, 228-233). It is probable that these organic substrates facilitate salt and water absorption by the intestine. Since each class of substrate (sugar, dipeptide, amino acid, etc.) appears to interact with separate sodium-carriers in the intestinal membrane, there may be an additive effect when two or more substrate types are used together. Such has been shown in cholera when glucose and glycine are used (234). It also seems possible that one substrate, glucose for example, could reverse the net secretion and attendant clinical symptoms induced by malabsorption of another substrate,

like lactose. Bedine and Bayless have shown this experimentally in men with lactose intolerance (235).

Even so, feeding may increase stool output (34). If fasting caused no harm, feeding might not be worth the extra difficulties in calculating fluid balance. Darrow was particularly concerned that this not happen (19). But, in fact, a third line of inquiry has shown the rapidly deleterious effects of fasting or even semi-starvation.

3. Fasting and Intestinal Function: With as brief a fast as three to five days, glucose, salt, water and amino acid absorption are substantially reduced, as are disaccharidases, with or without changes in histology of the intestine (236-239). The effect is independent of nitrogen or caloric balance, as total intravenous feeding alone causes depletion of intestinal digestive enzymes and gut mass in as little as three days (240, 241). Since not all children with diarrhoea are fasted for three days, it is important to know that fasting and diarrhoea appear to be additive in their effects on disaccharidases (242).

Apart from the intestinal effects, brief fasting has deleterious metabolic effects. For example, three days of no food causes an aldosterone-resistant natriuresis (243) which could lead to hyponatremia. A ten-day hypocaloric diet in man causes a 42% decrease in ventilatory response to hypoxia, and a 25% decrease in BMR (244). This has meaning for marginally nourished children who are particularly susceptible to pneumonia and other infections following bouts of diarrhoea and reduction of intake.

It may still be argued that, although prolonged fasting or reduced intake can be harmful, one should prove the positive effects of feeding during diarrhoea. The fourth line of research points the way.

4. The Induction Effect of Feeding: It is clear from numerous animal and human studies that intraluminal foodstuffs, carbohydrate and protein, increase intestinal digestive enzymes and cell proliferation in a dose-related way, even without prior fasting (237, 245-249). The inductions are somewhat specific: sucrose is a better inducer of sucrase than is glucose, for example. Diarrhoea appears to sensitize this effect. In rats, after a week of mannitol-induced diarrhoea, levels of specific disaccharidases showed increased dependence on corresponding dietary substrates compared to controls without diarrhoea. A mixed carbohydrate diet was most protective against disaccharidase depletion during diarrhoea. The effects were independent

of changes in histology, or number of epithelial cells (242).

The evidence so far presented suggests that both diarrhoea and fasting affect intestinal absorption which, when impaired, can lead to more prolonged diarrhoea, more severe malabsorption, and possible malnutrition. A fifth line of investigation has recently related diarrhoea and malnutrition in whole populations.

5. The Relationship of Diarrhoea to Malnutrition: From Mexico, The Gambia, Uganda, Guatemala, Papua New Guinea, and India (4, 126, 250-254) have come longitudinal studies on cohorts of children which now prove that diarrhoea directly causes malnutrition. First, diarrhoea is the overriding correlate with sequential weight loss in children, with malaria a distant second; episodes of respiratory illness and fever do not correlate with permanent growth retardation (4, 126). Second, the cumulative difference in weight among six-month age-cohorts up to 84 months of age amounted to 11% between children with low, and children with high frequency rates of diarrhoea (4, 250); or the equivalent of about 100 grams body weight per month (251). These values account for a substantial proportion of the weight deficits finally incurred by children in the tropics, which are only partially reversed by generous supplementation with a high protein and calorie diet (4). Third, faltering of growth is acutely related to each episode of diarrhoeal illness (252), in part due to catabolism and malabsorption, but also to anorexia and decreased food intake as well (253). Finally, nutritional deterioration alone increases the likelihood of a subsequent episode of diarrhoea (254). Can appropriate therapy reverse these events? The sixth line of research has begun to define the range of effectiveness of oral therapy, including its effect on nutrition.

6. Current Status of Oral Therapy: Oral therapy with glucose and electrolytes has been used in the past. Darrow in the 1940's (19), Harrison in the 1950's (255), and Meneghello in the 1960's (65) recommended the use of oral therapy as a supplement to intravenous fluids, or as a first step to feeding, or for use in the outpatient department. None, however, appreciated the specific role of glucose, or described objective evidence of the usefulness of oral therapy, or developed an optimal formula and method of administration.

Such evidence followed the discovery of the biophysical principles involved. In 1967, under the tutelage of Robert A. Phillips, a group from the Cholera Research Laboratory in Dacca,

Bangladesh reported that actively transported sugars such as glucose and galactose (but not passively transported fructose) in a polyelectrolyte solution could considerably reduce the net volume of stool fluid in cholera (201). Nalin and Cash and co-workers then showed that patients with cholera who received oral therapy required 80% less intravenous fluids for cure (202); that children over two years old and adults, both with cholera, responded similarly to an oral solution of the same composition (256); and that the amino acid glycine, when added to the glucose in the oral therapy mixture could reduce total stool output further (234). The Calcutta group, in the meantime, helped define effective concentrations of sodium and glucose (208, 257) for both adults and children. The use of a single solution for any dehydrating diarrhoea in all age groups seemed to be a startling departure from usual practice. In fact, it simply extended years of experience with a single intravenous solution that yielded the remarkably low mortality rate of under 2% in children under four years of age (31).

Oral therapy had a solid impact on mortality in situations where standard intravenous therapy was scarce. In Bangladesh refugee camps in 1971, the death rate from diarrhoeal diseases soared to 30%. Oral therapy, vigorously administered by family members ("give them as much as they will drink") helped reduce the mortality rate to about 1% (35). Due to the severe shortage of materials and staff, intravenous fluids were reserved to resuscitate those in shock.

In a home treatment programme for Asian Indian children 0-3 years old, case fatality rates fell 3.2 to 1.4 per thousand after oral therapy was introduced (258). The authors used a salt-sucrose solution, about one to two liters per day, with a sodium concentration of about 100 mEq/L.

Administration of oral therapy by lesser trained persons - whether in hospital, clinic, or home - became feasible when it was shown that the majority of dehydrated infants and children would take oral therapy ad libitum up to the level of need as long as they were strong enough to drink or suck, and the fluids were offered freely (33). Children in shock were rehydrated intravenously within a few hours with a lactated Ringer-like solution (plus potassium), then put on oral therapy.

The capacity of children to absorb the fluid, taken either by mouth or delivered by nasogastric tube, is prodigious: reported rates have ranged from 10 to 17 ml/kg/hour in the first one to two days of hospitalization (33, 256-262).

In Costa Rica, of 113 children (3-15 months, mean age 5.5 months) averaging volume depletion equivalent to 5% of body weight (one-third of them were 7-12% dehydrated), only six needed intravenous fluids (261, 262). The rest were totally treated by oral therapy plus additional water. In two reports from India (259, 260), 57 of 59 children (ages 3 months to four years, median age 1 year) were managed solely by glucose-electrolyte fluids given intragastrically despite an acute fluid loss averaging 6-8% of body weight. Half the children had 24-hour stool volumes over 80 grams/kg. Of 99 Apache children (mean age 11 months; 28 were under 3 months of age), one-half were moderately to severely dehydrated, with stool losses averaging 6 ml/kg/hour for the first six hours (33, 107). Only 10 required partial or total intravenous rehydration; only one needed a nasogastric drip because of failure to keep up orally with stool loss. The oral solutions used contained 80-90 mEq of sodium per liter (plus potassium, bicarbonate and glucose)and corrected instances of both hypo and hypernatremia. In Bangladesh 57 children (5-30 months old, mean age 12 months) with rotavirus diarrhoea were treated completely with oral therapy (WHO formula) and compared to 44 treated with intravenous fluids. All did well (263). Twenty-five to 88% of the children in the six clinical studies cited above were febrile on admission. Theoretically this should increase the risk of hypernatremia; but of the 328 children, only three developed elevations of serum sodium, 150-155 mEq/L, none clinically obvious. Mortality in the six reports was nil.

Nichols and Soriano (264) have criticised the concept of a single solution for diarrhoea regardless of etiology, indicating that different types of diarrhoea produce stools with different levels of sodium. Nonetheless, oral therapy has proved equally effective in any dehydrating diarrhoea of children (the limitations to be described below), whether due to cholera (46), where the stool sodium is high (80-120 mEq/L) (214); to reovirus (261, 263) where stool sodium is low (20-25 mEq/L); to shigella and other diarrhoeas (33, 107) where stool sodium is intermediate (40-50 mEq/L).

An important principle followed in these studies was early feeding with tolerated foods and fluid. In Apache infants, a case in hydrolysate-glucose-medium chain triglyceride formula was started at full strength interspersed with oral therapy, within the first 24 hours (107). Costa Rican children (261, 262) were given half-strength milk within 6-12 hours of admission. Indian children (259, 260) were given dilute cow's milk or breast milk within 12-24 hours. The criteria for when to begin feeding appear to be complete rehydration, and appetite.[5]

A remarkable difference was noted in the weights on discharge of Apache children on oral therapy and fed early, compared to those of the previous year treated with intravenous fluids, fasting and slow return to diet (265). The former group went home at 90-99% of the Harvard median (the average for Apache infants and children generally), the latter at 70-79%. Associated with this was the clinical perception that children rapidly rehydrated with oral therapy were vigorous and hungry soon after. It was hypothesized that oral therapy would help improve or maintain nutrition by restoring appetite quickly and helping mothers (and doctors) see the value of not fasting their children. Given the relationship between diarrhoea and malnutrition, such a finding would be of signal importance.

The hypothesis was borne out in a study done in collaboration with the Government of the Philippines and the World Health Organization (266). An oral-glucose-electrolyte solution (the WHO formula) administered at home to 464 Philippine children with diarrhoea was associated with a greater average weight gain, both during an attack of diarrhoea and over a 7-month period, when compared to a control group. The longer-term effect on weight, relative to a standard, was more pronounced in children who had more than one attack of diarrhoea in the period of observation than in those who had only one attack. The magnitude of the longer-term weight gain was 3-5 percentage points towards the standard weight.

The limitations of oral therapy are partially known. Vomiting has clearly not been limiting in the several hospital or field trials cited above, except when those in shock have not been completely rehydrated intravenously (267), or in the earliest stages of severe cholera (268). Nor have fever or high environmental temperatures affected good outcomes. Peri-orbital edema has been described ranging from 6% to 25% of hospitalized children (33, 260), but was neither associated with hypernatremia or any untoward consequences (therefore, not strictly a "limitation"). About 5% of children in a hospital, and fewer than 1% in a clinic setting have glucose intolerance (33, 27); they are made worse by oral therapy. The condition is easily suspected on clinical grounds (voluminous, watery stools; failure to rehydrate) and confirmed by simple bedside measurements of stool-reducing substances (33). Stool spillage of carbohydrate can be quite high, even with an adequate clinical response, however. In reovirus diarrhoea up to 30% of the administered glucose load appears in the stool (261). Oral therapy also fails in patients with very high rates of stool loss, over 10 ml/kg/hour, perhaps due to fatigue in drinking so much (269). A final possible

limitation is the use of oral therapy in neonates with diarrhoea. There is insufficient experience with this group to support a recommendation at this time.[6]

The study of oral therapy is now at the stage of finding the better strategies of delivery. For instance, sucrose is somewhat less effective than glucose in the oral solutions (262, 263, 270) in the sense that stool volume tends to be larger and duration longer, failure rates slightly higher, and correction of dehydration and biochemical abnormalities slightly slower. But where glucose is too costly or unavailable, sucrose is the appropriate substitute. The addition of magnesium for malnourished children is worthy of study. Another area, just now being explored, is whether the chemicals should be provided prepackaged or in the form of store-bought salt and sugar that the mother measures out herself for domiciliary treatment. Issues of access, safety, cost, and effectiveness in preventing volume depletion and electrolyte imbalance are all important here. Even finding a suitable container for mixing will be a problem in much of the world. More direct comparisons of oral fluids higher or lower in sodium content (e.g., 90 vs 50 mEq/L) are needed. One study (260) attempted this, but gave virtually the same amount of total sodium to both groups. More recently, Nalin has shown in Jamaican children that the solution lower in sodium resulted in persistent (days) hyponatremia in 5 of 24 children, while the one higher in sodium resulted in transient (6 hours), asymptomatic elevations of serum sodium in 3 or 84 (personal communication).

In Western hospitals, the use of oral therapy instead of intravenous fluids can make children more comfortable (33). It would be useful to know how staff time is affected.

It has recently been demonstrated by this author and colleagues that lightly trained and supervised Philippine village women can teach mothers how to prepare and use oral fluids, and to feed their children at home during diarrhoea. The clinical outcomes compared well to those in doctor-based clinics. A gratifying and significant increase in the number of mothers who kept on feeding their children during the illness was seen in the course of a year (manuscript in preparation).

The studies on oral therapy continue the development of knowledge of diarrhoeal disease; their authors are conscious inheritors of the scientific and clinical findings of numerous workers, past and living. The advances in oral therapy also illustrate the felicitous phrase of Rohde and Northrup (2), "taking science where the diarrhoea is."

FOOTNOTES

[1] "Volume repletion" and "volume depletion" are more precise than "rehydration" and "dehydration". Still, the respective words will be used interchangeably to mean electrolyte and water restoration or loss. The word "fluid" also indicates solute and water rather than water alone.

[2] The interquartile range (IQR) is a measure of dispersion about the median and is defined as the third quartile minus the first quartile. On Table 3, along with the medians, are presented the first and third quartile values.

[3] Several writers suggested that the sodium concentration of such formulas was to blame (24, 82). This is difficult to accept. Taitz and Byers (133) found children with hypernatremia had been fed improperly diluted cow's milk formula; the formulas, however, averaged a sodium content of only 33 mEq/L with a range of 22-66; Chambers' and Steel's figures (134) were 37 mEq/L, range 26-59. The original commercial sugar-electrolyte formula contained 50 mEq Na/L. One report, however, showed that boiling skimmed milk could elevate the sodium content to as high as 165 mEq/L (85). Except for the latter, the sodium concentrations of suspect formulas reported are really not exceptional, especially when one considers the therapeutic range of sodium used for rehydration (Figure 1).

Several other authors believe hypernatremia may be related to inappropriate caloric and protein loads (133, 134). An excessive caloric load increases evaporative water loss, a situation dramatically worsened under heat stress (132). Decreased intake of a high-solute fluid due to calorie satiation may make matters worse, as ingestion of large volumes of even a high-solute fluid such as cow's milk allows the kidney to generate free water (173). Davies (174) has demonstrated, however, that a child with mild diarrhoea (30 ml/kg/day), receiving a normal amount of twice concentrated cow's milk, need only to concentrate urine to 706 mOsm/L to maintain water balance. The recent decrease in the incidence of hypernatremia may reflect better feeding with low solute milk (136, 137); nonetheless, hypernatremia still occurs, even in children on low-solute milk (137). It is rare in breast-fed children. The simplest reason why breast-fed children are less susceptible to

hypernatremia (75), in spite of the high lactose concentration (7 grams %), in addition to its low protein content, is that breast milk, unlike cow's milk, is taken only in small quantities at each feeding.

[4]In grams per liter: NaCl 3.5, $NaHCO_3$ 2.5, KCl 1.5, glucose 20.

[5]A caveat is in order here. Feeding cow's milk to a population of children with intestinal damage and potassium depletion is likely to cause hypernatremia, and has (260); oral therapy when combined with breast milk appears not to cause hypernatremia, even in reovirus diarrhoea (263).

[6]Pisarro of Costa Rica has just completed a study of 40 neonates, mean dehydration 6.6% of body weight, treated with oral therapy and extra water; 39 required no intravenous fluids (D. NALIN, personal communication).

LEGEND TO FIGURE 1

An analysis was made of 15 studies depicting 20 fluid regimens used in the first day treatment of dehydrating diarrhoea in children. Sodium load (1A), total volume x sodium load (1B), total volume (1C), and "free water" volume (1D) are displayed against mortality. Hyperbolic curves were fitted to the data by computer, with the general equation $Y = b_o + b_1 x^{-1}$ where Y = mortality, b_o = intercept, b_1 = regression coefficient and x = the independent variable. Triangles represent two overlapping points.

LEGEND TO FIGURE 2

The events that follow onset of acute diarrhoea are depicted to show how they may lead to volume depletion that is hypo⁻, iso⁻, or hypernatremic. The top portion gives the general model; the middle shows the predominant events generally leading to hypo⁻ or isonatremia; and the lower portion shows the predominant events generally leading to iso⁻ or hypernatremia. See text for particulars.

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FIGURE I

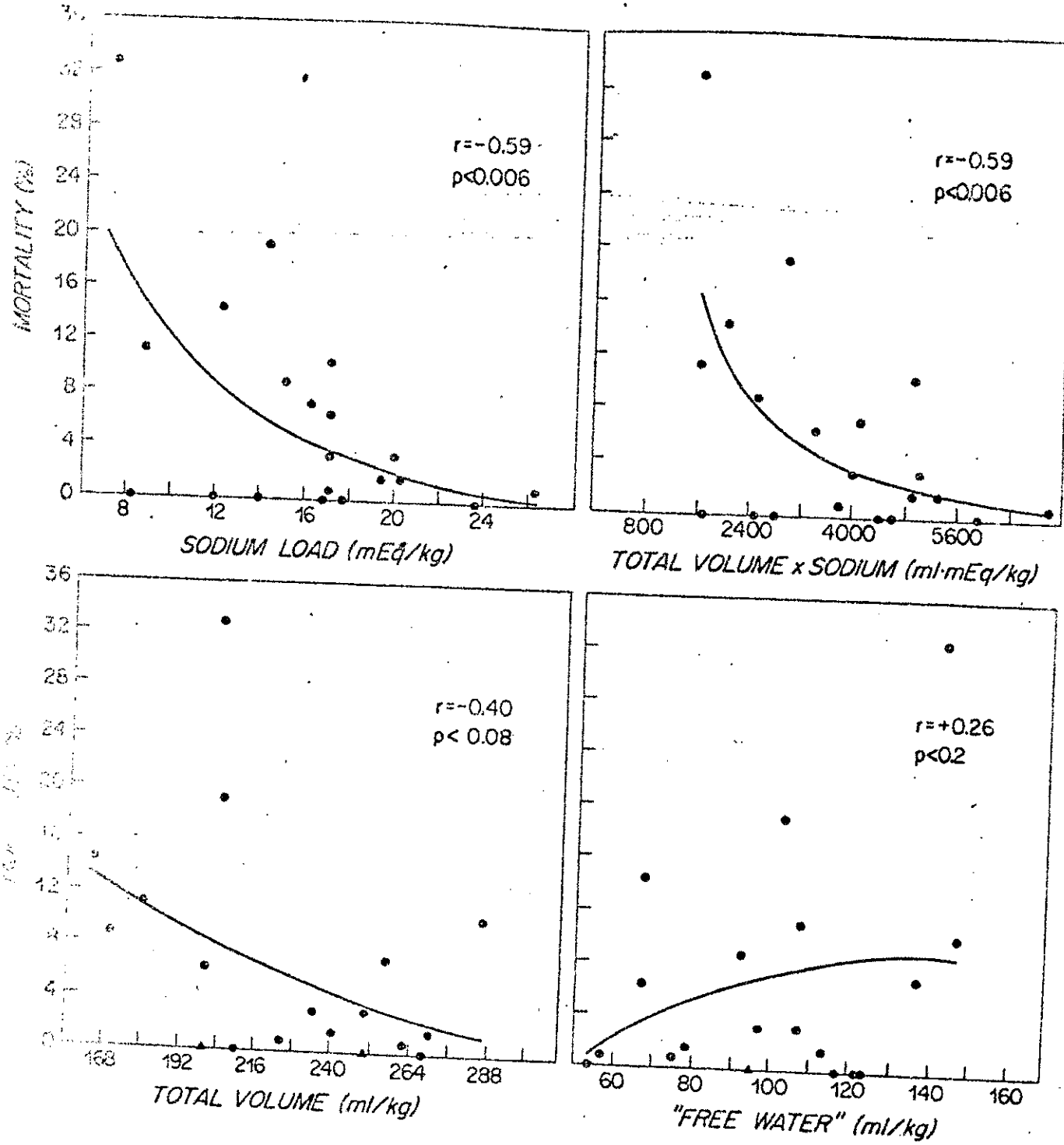
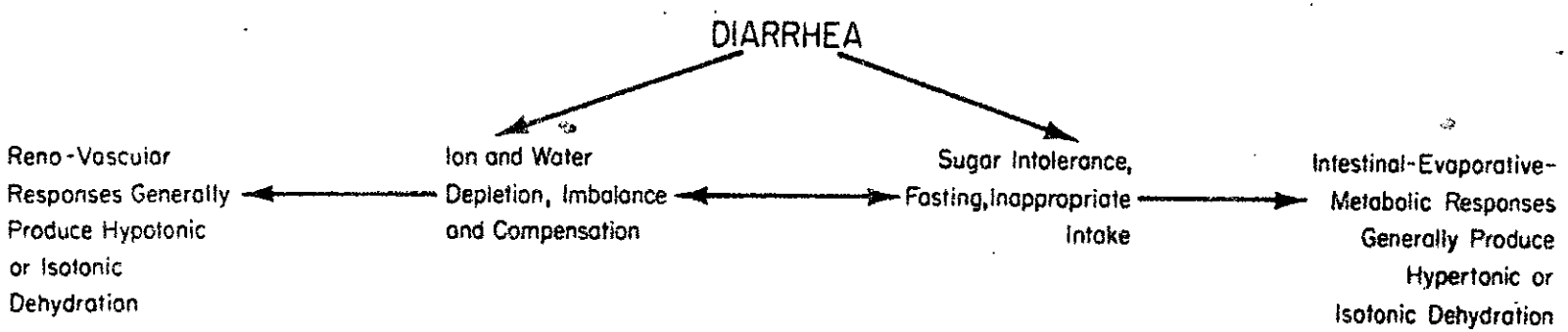

MORTALITY (%)
r=-0.59
p<0.006
SODIUM LOAD (mEq/kg)
r=-0.59
p<0.006
TOTAL VOLUME x SODIUM (ml·mEq/kg)
r=-0.40
p< 0.08
TOTAL VOLUME (ml/kg)
r=+0.26
p<0.2
"FREE WATER" (ml/kg)

FIGURE 2(A)


DIARRHEA
Reno-Vascular Responses Generally Produce Hypotonic or Isotonic Dehydration
Ion and Water Depletion, Imbalance and Compensation
Sugar Intolerance, Fasting, Inappropriate Intake
Intestinal-Evaporative-Metabolic Responses Generally Produce Hypertonic or Isotonic Dehydration

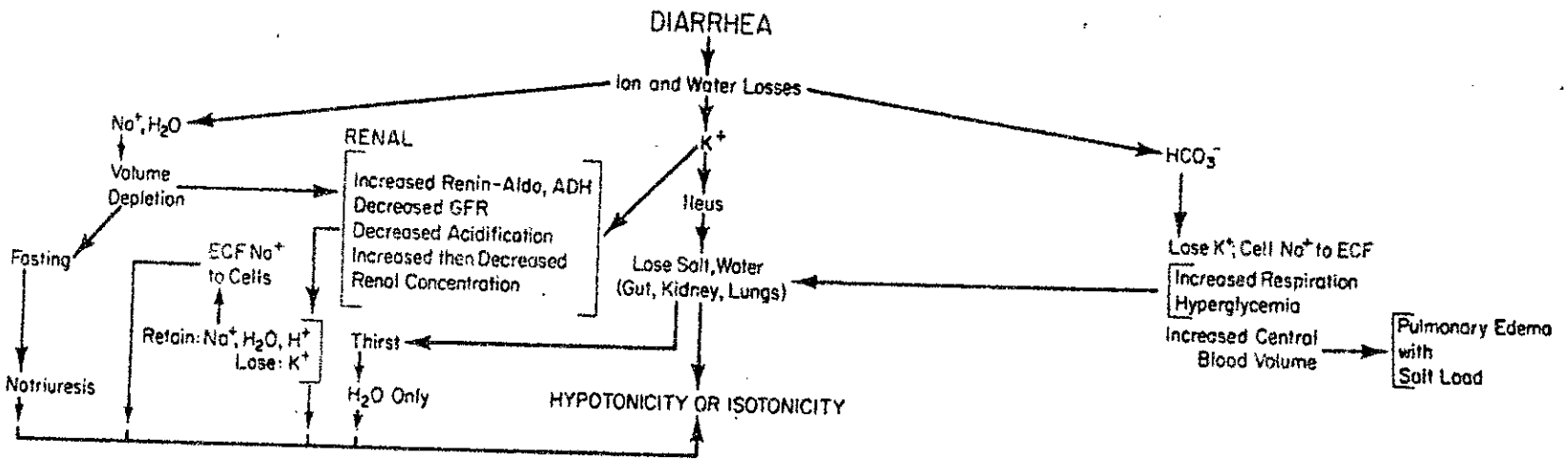
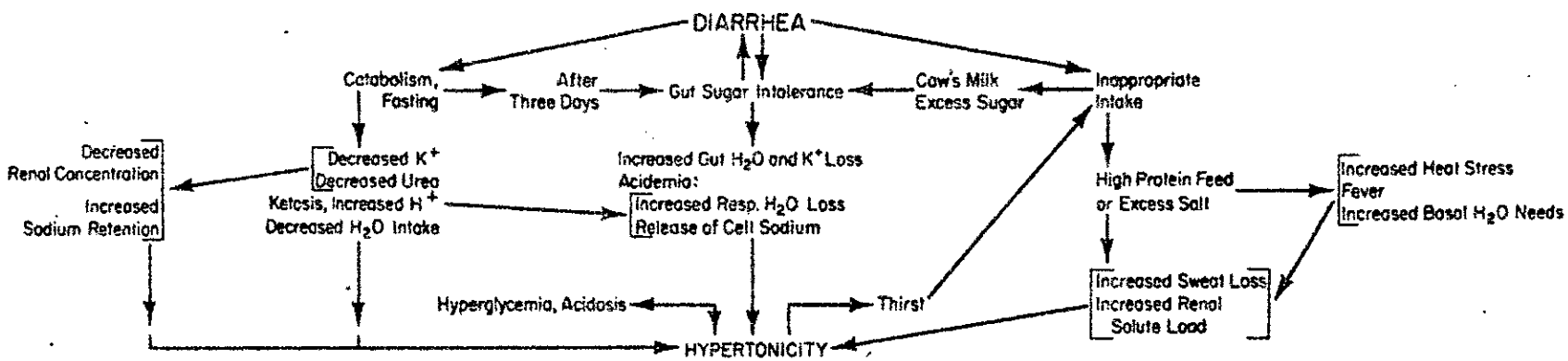

DIARRHEA
Ion and Water Losses
Na^+, H_2O
Volume Depletion
Fasting
Natriuresis
RENAL
Increased Renin-Aldo, ADH
Decreased GFR
Decreased Acidification
Increased then Decreased Renal Concentration
ECF Na^+ to Cells
Retain: Na^+, H_2O, H^+
Lose: K^+
Thirst
H_2O Only
K^+
Ileus
Lose Salt, Water (Gut, Kidney, Lungs)
HYPOTONICITY OR ISOTONICITY
HCO_3^-
Lose K^+; Cell Na^+ to ECF
Increased Respiration
Hyperglycemia
Increased Central Blood Volume
Pulmonary Edema with Salt Load

FIGURE 2(b)


DIARRHEA
Catabolism, Fasting
After Three Days
Gut Sugar Intolerance
Cow's Milk Excess Sugar
Inappropriate Intake
Decreased Renal Concentration
Increased Sodium Retention
Decreased K+
Decreased Urea
Ketosis, Increased H+
Decreased H2O Intake
Increased Gut H2O and K+ Loss
Acidemia:
Increased Resp. H2O Loss
Release of Cell Sodium
High Protein Feed or Excess Salt
Increased Heat Stress
Fever
Increased Basal H2O Needs
Increased Sweat Loss
Increased Renal Solute Load
Hyperglycemia, Acidosis
Thirst
HYPERTONICITY

ICDDR,B (CRL) publications can be obtained from Publications Unit International Centre for Diarrhoeal Disease Research, Bangladesh, G.P.O. Box 128, Dacca - 2, Bangladesh.

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CRL Annual Report 1977.

CRL Annual Report 1978.

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