PRINCIPLES AND PROSPECTS IN THE TREATMENT OF CHOLERA AND RELATED DEHYDRATING DIARRHEAS

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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.

This paper was presented in the 43rd NOBEL SYMPOSIUM which was held on August 6-11, 1978 at the Nordic Education Center, Elfvik Lidingo, Stockholm, Sweden.

ABSTRACT

The recent progress in treatment of watery diarrhea is reviewed in its historical context. The prospects of further improvements in therapy are discussed with reference to the discoveries in the basic sciences which have allowed precise formulation of approaches to cholera. These include further simplification of oral replacement procedures with extension to the care of diarrhea due to most etiologies, the blockade of toxin receptors in the gut, the use of a toxin binding matrix in the gut lumen to prevent toxin reaching gut epithelium and the use of drugs which decrease fluid loss by reducing the level of cyclic AMP in the secretory cells or altering ion secretion mechanisms selective for the gut. Each possible advance will require the same close relationship between basic research in the biological sciences and research at the bedside and in the field in coming years that has borne the bountiful harvest of the past two decades of research in cholera.

INTRODUCTION

A century and a half ago the intravenous treatment of cholera by replacement of water and salts ushered into medicine the technology of intravenous treatment and the basic concept of how diseases associated with major fluid loss could be successfully managed (1,2). Ironically, although the initial insights were correct it took until 1958 for a replacement solution based on accurate measurements of the solutes in cholera stool to be established and subsequently propagated as a correct and totally effective treatment (3). The different solutions used and the tortuous history of inappropriate therapies employed before arriving at a rational treatment can teach us many pertinent lessons about how science can clarify or polemic distract from progress in understanding basic mechanisms of disease and the application of such knowledge for the benefit of the patients (4). At the present time there is little debate over the composition or method of use of intravenous replacement in cholera. The relationship between the composition of stool in cholera and that of some intravenous solutions is seen in table 1.

A happy marriage of knowledge concerning the traffic of small molecules and water across biological membranes and clinical perceptions about watery diarrhea have resulted in an advance in knowledge that now allows the replacement by mouth of losses in cholera and related diseases (5,6,7,8). Less than two decades have passed since this knowledge has been available. Many details remain to be worked out in its adaptation to specific settings in the world. However, even at this time it seems clear that research on cholera, which introduced into medicine the intravascular technologies, will also create the setting in which the use of intravenous fluids may become generally much less needed. This may not only apply to the realm of diarrheal diseases but also to the high technology of hospitals in industrial countries where intravenous hydration is over used and poses significant threats including the spread of resistant hospital-acquired infections. The main therapeutic challenge at present is to teach families to use an appropriate solution for treating diarrhea - ultimately establishing this as a home remedy, or, in current Jargon "demedicalizing" the treatment of diarrhea. To do this, much ingenuity is needed in devising effective and inexpensive ways family members can measure salts and water accurately enough to be within the rather broad limits of biologic safety and efficacy (9,10).

TABLE 1

COMPOSITION OF CHOLERA STOOLS IN ADULTS AND CHILDREN AND OF FLUIDS GENERALLY USED FOR TREATMENT OF CHOLERA

CHOLERA STOOL (average values)	Concentrations (mEq or mM/L)				
	Na+	K+	CL-	HCO_3^-	Glucose
Adult	135	15	100	45	-
Child	105	25	90	30	-
IV SOLUTIONS					
1. DTS (Diarrhea Treatment Solution)	118	13	83	48	50
2. Ringer's Lactate	131	4	111	29	-
3. "5:4:1"	134	13	99	48	-
4. 2 Saline ; 1 Lactate	154	-	103	51	-
5. Normal Saline	154	-	154	-	-
ORAL SOLUTION	90	20	80	30	111
Half-Darrow's Solution with 25% glucose*	61	17.5	52	26	150

* This solution is used widely for treatment of diarrhea in children but has not been tried for cholera because of its low sodium content.

What then is in prospect for the treatment of diarrheal diseases? In the case of cholera and related diseases the one further piece of the puzzle needed is how can the rate of fluid loss be reduced to completely obviate the risk of death and the need of intravenous fluids. With knowledge of the mechanisms of fluid loss from the intestinal tract it is more likely that plausible agents that can limit the overexuberant secretory response in cholera can be found. With such an agent, which must be inexpensive, available and non-toxic, diarrheas caused by adenylate cyclase stimulating toxins like cholera toxin would become simple nuisances manageable by mothers. They would no longer take the fearful toll of life they do now.

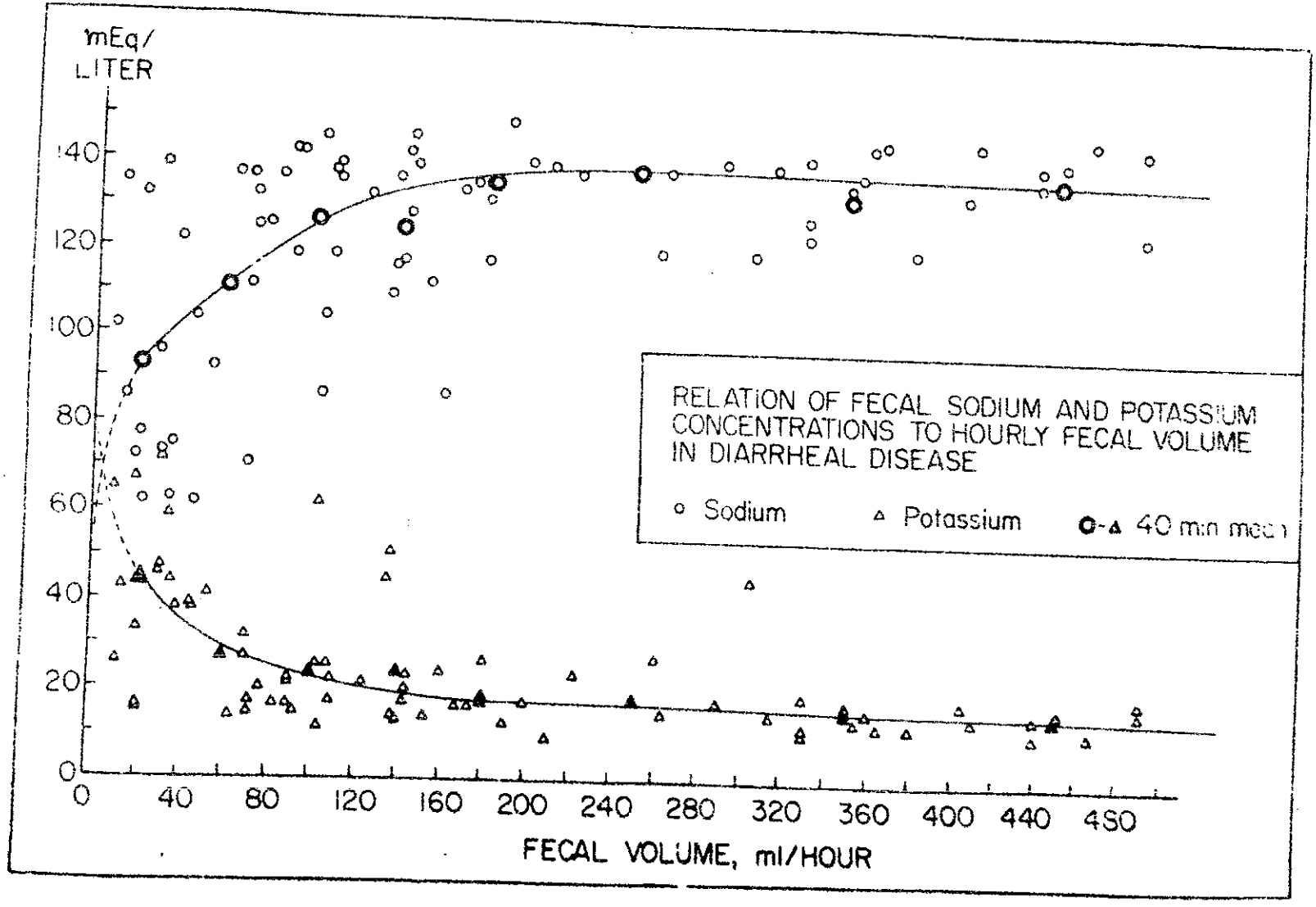
ORAL REPLACEMENT THERAPY

Biological Issues:

There is a wide range of electrolyte composition seen in the stools of diarrhea patients. The data shown in figure 1., indicates that as the rate of fluid loss increases the sodium concentration approaches that of plasma (5). In conditions where the fluid loss is relatively less the concentration of sodium in the fluid is lower and there is a risk of replacing more salt than is lost if an oral solution has too high a sodium concentration. This introduces the risk of hypernatremia and hyperosmolar syndromes that are particularly dangerous in infants and small children (11). At the other extreme, cholera, the loss of sodium is very high relatively speaking and an ideal oral solution should approximate the composition of the losses. There is at present an uneasy compromise between the ideal solution for cholera patients and that for diarrheas of less severity. Since the ability to rehydrate cholera patients by mouth decreases very rapidly as the rate of purging exceeds 100 ml/kg/24 hours, intravenous fluid therapy will often be needed in such cases. Thus if only one solution is to be used as a universal remedy it must represent a safe compromise between the Scylla of hypernatremia and the Charybdis of poor volume replacement and water intoxication. At present the composition is as seen in table 1. The high sodium concentration which is best for cholera, however, is considered excessive for milder diarrheal illnesses.

Which carrier molecule is best for getting sodium across the gut mucosa in diarrhea is an important question. Equally important is the question of which carrier molecule is adequate yet also available at the low cost in areas where

FIGURE 1


mEq/
LITER
140
120
100
80
60
40
20
0
0
40
80
120
160
200
240
280
320
360
400
440
450
FECAL VOLUME, ml/HOUR
RELATION OF FECAL SODIUM AND POTASSIUM CONCENTRATIONS TO HOURLY FECAL VOLUME IN DIARRHEAL DISEASE
Sodium
Potassium
40 min mean

diarrhea is a major problem. At present it is clear that glucose is very good and entirely successful in the role of a generally available substance on which oral electrolyte replacement mixtures can be based. In some areas, however, glucose is expensive and less available than sucrose. Furthermore, the sucrose that is most accessible may be unrefined. Studies have been done by many workers comparing the relative merits of sucrose versus glucose as the carrier for oral replacement solutions. There seems little doubt that glucose is slightly better although no well controlled study has unequivocally demonstrated this. However, all of more than ten studies agree that there is a trend favouring glucose. The question now is whether the difference is great enough to favour the added expense of glucose in a given setting. On balance in areas where glucose is expensive and not available sucrose is a very acceptable substitute (12,16,17). A further question that deserves at least a look is whether some starches such as rice or potato might also be effective. To date there have been no clinical trials bearing on this point.

In the case of crude cane sugar there is an added advantage in its use since there is an appreciable amount of potassium present. When dissolved in water (40 g/L) the potassium concentration ranges from 5 - 15 milliequivalents/liter, table 2. Potassium is also readily available in many fruits and in remote village situations where prepackaged electrolyte mixtures are not available and potassium salts are not in the market knowledge of what may be locally available is important.

Etiologic Variables:

In addition to the questions raised about the composition of replacement solutions and various approaches in their use, there is the question of whether what is true for cholera is also true for other diarrheas. Studies in diarrhea due to toxigenic E.coli seem to affirm that oral therapy given in the same manner as for cholera is highly effective (14). Even more recently evidence is available that in disease due to rotavirus oral electrolyte replacement with either glucose or sucrose is successful (15,16). The question of how important oral rehydration may be in diarrheas due to invasive organisms has not yet been answered.

TABLE 2

COMPOSITION OF LABON - GUR (SALT - BROWN SUGAR) ORAL REPLACEMENT SOLUTION, CRL, DACCA*

	Na^+	K^+	Cl^-	CO_2
Milliequivalent/liter	85 ± 1.7**	7.6 ± 0.4	80 ± 1.9	1.8 ± 0.2

* Analyses of batches prepared by nursing staff of CRL N = 38

** Means ± standard error of mean

From Dr. R. Islam, CRL Dacca

ORAL THERAPY

Operational Issues:

The ultimate simplification of oral fluid replacement is seen in the use of simple table salt and sugar in water as the replacement solution. Many patients with watery diarrhea but not cholera have been treated with such an approach and there is enthusiastic advocacy for it (9,10,18). Recently Dr. Rafiqul Islam in Dacca carried out an investigation on this issue and found that volume replacement is very successful with this simple mixture but there is persistence of acidosis. Furthermore, it is clear that this could become a significant clinical problem at higher rates of purging (19). Once again the issue may not be that salt and sugar solutions are clearly less physiologic than solutions more nearly matching stool composition but that at rates of loss where the problem becomes important biologically intravenous fluids will be needed anyway. Thus one must be very careful about dismissing compromise solutions because they fail to be ideal. The "acid" test is whether advocacy of an available, non-ideal solution might immediately reduce morbidity and mortality while the more complex and academically satisfying solutions may just not be within reach because of cost and distribution problems. In rural Bangladesh it is known that every child will have several episodes of diarrhea each year. This averages out to one episode per year for the entire population of more than eighty million people. The current cost of the prepackaged ideal salts for diarrhea is in the order of ten cents a packet. Assuming a one liter replacement requirement, which is by any criteria a low cost medicine, the $8,000,000 needed is large relative to the entire health budget of the country. It is apparent from this there will have to be compromises made and adaptations prepared to meet differing geocultural and economic situations.

When a scientist or pharmacist prepares a carefully weighed mixture of salts and sugar in the laboratory or clinic the limits of accuracy are small and predictable. When a mother makes a solution in the middle of the night with what measuring devices are available in the home, however, the outcome is less certain. Whether with the ideal mixture or a compromise mixture the chance of preparing a solution with a dangerously high or low concentration exists. In practice this has been seen in table 3. Thus another challenge exists. What is a cheap and foolproof measuring method for the home. Solutions to this problem will have to be adapted to local practices and ideas. It may be more important and effective to provide a good

TABLE 3

ANALYSIS OF SODIUM CONCENTRATIONS OF SAMPLES FROM ORAL REPLACEMENT SOLUTIONS PREPARED BY MOTHERS IN THEIR HOMES IN TEKNAF, BANGLADESH; AFTER BEING INSTRUCTED IN MIXING THE WHO-UNICEF "ORALYTE" PACKETS

Na^+ values mEq/L	Frequency	Percent	
Up to 70	5	9.3	
71-80	10	18.5	
81-100	24	44.4	mean = 95.4
101-120	6	11.1	SD = 26.9
121-140	3	5.6	
141-160	5	9.3	
161-200	1	1.8	
TOTAL	54	100.0	

Data - from Dr. M.M. Rahaman, Cholera Research Laboratory
- Teknaf Study Area, Bangladesh

measuring system that can be generalised to many different cultures and regions than to prepare carefully weighed and packaged salts.

Finally where diarrhea is common there exist many beliefs and practices to cope with the problem. Many of these may be at odds with the proposed treatment of oral rehydration. Thus approaches will have to be devised to introduce this new therapy in as acceptable way as possible. This presupposes that those introducing the method will be very knowledgeable with respect to local beliefs and practices.

Beyond Replacement Therapies:

Since replacement of losses by the intravenous and oral routes has been so successful why should there be any real effort to go further? The answer to this question lies in the fact that many cases of cholera and related diarrhea are severe enough to require intravenous treatment. In many parts of the world where those illnesses are most common there is little or no access to intravenous fluid replacement. Thus discovery of agents which would reduce fluid losses to the point where no one would need intravenous treatment is a very crucial goal. Development of approaches that would accomplish this represents the highest priority in the transfer of the knowledge of basic mechanisms of fluid loss in diarrhea to the arena of treatment.

REDUCTION OF FLUID LOSSES

Receptor Blockade:

A manoeuvre that prevents the inciting agent, the toxin, from binding to a receptor is very appealing. A receptor is known for the cholera toxin and a nontoxic molecule that irreversibly binds to this receptor is available (20). Unfortunately this binding subunit of cholera toxin is expensive to prepare and large amounts would be required, relatively speaking, to saturate all the receptors in the gut mucosa. Basic studies to test the hypothesis that a receptor blockade would indeed prevent fluid loss are needed. If true, then a cheap and effective means must be devised to deliver it in nature. This would be feasible if a strain of V.cholerae or related enteric bacteria were available that could compete with the fully pathogenic organism successfully for the ecologic niche in the upper gut of man and would produce only binding subunit and not active toxin. If

this organism could propagate in the environment and occupy the transmission pathways for the full pathogen it would be even better. To accomplish this goal we will need to know a great deal more about the determinants of pathogenicity of V.cholerae itself and their genetic loci. Genetic engineering will be required to expeditiously arrive at the specifications for the strain desired although with luck useful strains may be found in nature and by mitogenic methods.

INHIBITION OF ADENYLATE CYCLASE STIMULATION

It seems unlikely that an approach that would alter the receptor sufficiently that toxin would be released could be done without cell membrane damage. However, the pathway by which toxin stimulates adenylate cyclase might be interfered with or the enzyme itself could be suppressed. Side effects of such an approach should be expected since it is likely that not only would the response to toxin be altered but also the response to the normal hormonal integrative signals of the gut. The consequences of such interference are hard to predict since as yet there is little precise knowledge of which are the important secretory hormones and how they operate normally. Candidates for such an approach would seem to be Phenothiazines (21) and nicotinic acid (22).

Since it has recently been suggested that the cholera toxin is itself an enzyme which catalyzes the ribosylation of ADP (23) this is a potential point of intervention that would permit interference only with the activity of a bacterial product and not a link in the chain of mammalian cell integrative functions. In order to accomplish this an agent would need to be found that would "home" only on the bound toxin's active site after it had been incorporated into the mammalian cell membrane. This seems a challenging proposition.

ACCELERATION OF DEGRADATION OF cyAMP

Another possible approach to reversal of the effects of adenylate cyclase stimulating toxins would be to use agents that would lower CyAMP levels in the face of a sustained stimulus. Agents which accelerate the breakdown of CyAMP are known and should be investigated (20).

INTERVENTIONS IN ION TRANSPORT

In fact the use of the intact carrier (glucose) mediated transport system to increase the transfer of sodium ion and with it water across gut epithelium is an example of an intervention of a compensatory sort which by increasing lumen to blood movement of salt and water balances or reverses the secretory process mediated by raised cyAMP levels. The effect of diuretics such as ethacrynic acid or Furosemide to reduce loss of fluid to the gut lumen is an example of an influence directly on the processes of ion transport (24,25). It seems possible that some agents that affect ion transport in an appropriate direction might be found that would be specific to the intestine by virtue of being specifically bound in these tissues or because they could act from the luminal side and not enter the general circulation. At present I know of no agents of great promise in this category.

RESEARCH PRIORITIES

In these days of targeted research programs and instant relevance I would point out that most of the answers that have led to a completely effective therapy for cholera and subsequently a greatly simplified and inexpensive modification of this treatment were founded on two things. The first was a more complete understanding of the basic mechanisms of the traffic of solutes and water across biological membranes. This required active interest and research among biophysicists, physiologists, and biochemists sustained over many years. The second ingredient was the opportunity for physicians who were acquainted with the biological sciences to be responsible for the care of cholera patients as they were seen in the natural settings of disease. The rapid progress on treatment ushered in by the work of Dr. R.A. Phillips, was complemented by the discovery of cholera toxin by Indian microbiologists (26,27,28). Since the mid 1960's there has been an expanding community of interest comprised of both clinicians and basic scientists. Careful consideration should be given to how the achievements of the past two decades were accomplished before scrapping a well catalyzed reaction mixture for one of the more fashionable current trends in research management.

To solve the problems relating to the discovery of an agent that will safely reduce fluid losses in diarrhea a great deal of fundamental biological research will be needed. Although the

gut was the first endocrine organ given attention only recently has interest returned to it. We as yet have only vaguest outlines of the control mechanisms for secretory and absorptive processes of this very complex organ (29). There is still much to be understood about the cyclic nucleotide systems and how they respond to external stimuli. The process governing the transport of ions, other solutes and water still hold many mysteries. The relationships between the toxic products of bacteria and man are just beginning to unravel. Thus there must remain a very strong support for independent inquiry into the riddles posed by nature if we are to have the necessary setting for further more pragmatic understanding about how to proceed to improve on treating and preventing diarrhea.

I believe the same holds true for understanding how best to apply current knowledge within cultures in which the understanding of illness may be a totally different frame of reference from the rational scientific one to which we adhere. Thus fundamental inquiry into health beliefs and practices in the matrix of specific geocultural settings is essential to any intelligent approach toward application of current knowledge in prevention or treatment.

Equally important as fundamental inquiry into biological and sociological phenomena is to have scientists who are actually in situ where diarrhea is the main problem. Such individuals must be acquainted with and appreciate the contributions and modus operandi of their scientific bretheren who are not bound to the day to day requirements of attending to disease and its complications.

At present there are very few settings in which this sort of "mix" exists. It will take a great effort to preserve such opportunities where they do exist and to create other such situations.

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