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AND
NUTRITION, DIVISION OF FAMILY HEALTH

REPORT OF THE THIRD MEETING OF THE SCIENTIFIC WORKING GROUP ON DRUG DEVELOPMENT AND MANAGEMENT OF ACUTE DIARRHOEAS

(Geneva, 1-3 October 1984)

CONTENTS

1. INTRODUCTION

The third meeting of the Scientific Working Group (SWG) on Drug Development and Management of Acute Diarrhoeas was held in Geneva from 1-3 October 1984. The participants are listed in Annex 1.

The meeting was opened by Dr M.H. Merson, Director, Diarrhoeal Diseases Control (CDD) Programme, who welcomed the participants on behalf of the Director-General and thanked them for their participation in the meeting. He emphasized the important role played by the Programme's SWGs, which undertook scientific reviews of subjects that were of major interest to the Programme and determined the research areas deserving priority. The present meeting would review recent advances in research on feeding during and after diarrhoea, propose recommendations based on available knowledge, and identify future research issues. In view of their equal interest in the topic, the meeting had been jointly sponsored by the Joint Nutrition Support Programme of the Nutrition Unit of the Division of Family Health.

The SWG elected Dr J.R. Hamilton as Chairman, and Professor D. Habte as Vice-Chairman.

2. SCIENTIFIC REVIEW: FEEDING DURING AND AFTER ACUTE DIARRHOEA

The scientific topic discussed in detail by the SWG was "Recent advances in research on feeding during and after acute diarrhoea". The full review, including recommendations for future research, is presented in Annex 2.

3. CURRENT STATUS OF THE PROGRAMME

Dr Merson informed the Group of the current status of the CDD Programme, as summarized in the Interim Programme Report for 1983.[1] As of December 1983, 72 countries had prepared plans for national CDD programmes; in 52 of those countries, programmes were in operation. A total of 231 research projects had been granted support by the Programme, 59% of which were being carried out in developing countries. The Programme was continuing to emphasize the implementation of oral rehydration therapy as a means of reducing diarrhoea mortality, and research aimed at developing a more efficient oral rehydration solution. In the near future it would also be giving more priority in its services and research components to additional strategies that were likely to have a significant impact on diarrhoea mortality and morbidity (e.g., breast-feeding, handwashing, measles immunization, use of safe water and sanitation facilities). The Programme had to date received contributions from 25 governments and agencies.

4. REVIEW OF ACTIVITIES OF THE STEERING COMMITTEE, SEPTEMBER 1982 - SEPTEMBER 1984

Since the first meeting of the SWG in 1980, the execution of the Group's work plan had been the task of its Steering Committee (SC), which had met on 8 occasions. A report on its activities during the past 2 years was presented to the Group; it was emphasized that, in conducting these activities, the SC had been guided by the recommendations made at the first two meetings of the SWG. The major activities undertaken are summarized below:

4.1 Support of research proposals

During the period under review, a total of 82 research proposals were submitted to the SC. Of these, 34 were awarded support. The SC attempted to direct research towards designated high priority areas and also to promote the development of research capability in the developing countries. Of the 34 supported projects, 24 (71%) were being carried out in developing countries either independently or in collaboration with scientists from developed countries. Most projects fell into the following categories: studies of oral rehydration salts (ORS), including improved compositions, comparative efficacy of different formulae, storage and distribution (24%); development and evaluation of drugs, including new drugs and traditional medicines (32%); studies related to nutrition and diarrhoea, including the evaluation of feeding practices (15%); pathogenesis, pathophysiology, and clinical studies (15%). The studies are summarized below.

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[1] Unpublished document WHO/CDD/84.10

4.2 Studies on oral rehydration therapy

4.2.1 Base-substitute for ORS

Laboratory studies supported by the Programme have demonstrated that ORS containing 2.9 grams of trisodium citrate, dihydrate, in place of 2.5 grams of sodium bicarbonate is rendered more stable, making it more appropriate for use in conditions of heat and high humidity. Seven clinical studies supported by the SC, both in infants with acute diarrhoea and in adults and older children with cholera, demonstrated that ORS-citrate was as effective as standard ORS-bicarbonate in correcting acidosis and dehydration. However, preliminary data suggest that diarrhoea output may even be reduced with ORS-citrate, particularly in cholera. A statement summarizing this information was issued by the Programme jointly with UNICEF.[1]

4.2.2 Improved ORS formulations - "Super ORS"

It has been postulated that the addition of water-soluble organic nutrients to ORS could substantially improve its absorption efficiency in the small intestine, allowing it to act as an absorption-promoting drug. This has been suggested by two recent studies demonstrating that improved ORS formulations could substantially reduce the stool output and duration of diarrhoea, and the volume of oral fluid required. Thus the SC is supporting clinical trials of several selected, improved ORS formulations containing well-defined organic substrates with the aim of (a) improving hydration (by enhancing reabsorption); (b) reducing stool purging; (c) reducing the duration of diarrhoea; and (d) allowing earlier reintroduction of feeding. These substrates include D-hexoses (e.g., glucose), neutral amino acids (e.g., glycine, l-alanine), and dipeptides (e.g., glycyl-glycine, glycyl-l-alanine), which are absorbed independently of each other. Since trisodium citrate is now the preferred base in ORS, it is being incorporated in these formulations.

The SC is also supporting clinical studies with ORS formulations containing cereals, legumes, or other natural food sources in place of glucose. These include rice-powder and maize-powder-based ORS and a legume ('Mung bean')-based ORS. The studies will evaluate

(a) efficacy, particularly in small infants in whom digestion of these foods may be incomplete; (b) stability of the made-up solutions under hot, humid conditions; and (c) feasibility of their use considering the need for cooking.

4.2.3 Studies on development and evaluation of antisecretory drugs

At the second SWG meeting, in 1982, advances in the development of non-antimicrobial antidiarrhoeal agents, particularly antisecretory/absorption-promoting drugs, were reviewed. It was suggested that an antidiarrhoeal drug that can reduce the magnitude and duration of diarrhoea and obviate the need for intravenous therapy would be an important therapeutic adjunct, provided that such a drug is safe (high therapeutic index), compatible with oral replacement therapy, effective against a broad spectrum of diarrhoeal etiologies, and relatively inexpensive.

The Programme is supporting several basic studies directed at a better understanding of the secretion/absorption mechanism in healthy subjects, in response to secretory stimuli, and the ability of various compounds to alter these processes. These studies are examining the role of calcium and calcium-receptors in enterotoxin-induced intestinal ion transport, the effect of antidiarrhoeal agents on intestinal transport of nutrients such as glucose, amino acids, and dipeptides, the possibility of developing antidiarrhoeal drugs that exploit the secretion/absorption mechanisms of the intestine, and pharmacological intervention in ST-induced intestinal secretion.

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[1] Unpublished document WHO/CDD/SER/84.7

The clinical trials undertaken to date with various drugs shown to have antisecretory properties under experimental conditions - e.g., chlorpromazine, acetylsalicylic acid, berberine, nicotinic acid - have not shown any drug to be of sufficient efficacy and/or of practical usefulness.

4.2.4 Evaluation of other antidiarrhoeal agents including traditional medicines

The SC is supporting studies to evaluate several other antidiarrhoeal agents, which include:

- Cholestyramine: an ion exchange resin that has been shown to reduce the duration and volume of diarrhoea in studies in Finland is being evaluated in a clinical trial in the Philippines.

- Loperamide: an antimotility drug that is claimed to have antisecretory properties is being evaluated in clinical trials in Egypt. The Programme earlier supported a study to determine the efficacy of the drug in infantile diarrhoea at a dose of 0.24 mg/kg/day. The results showed that the drug shortened the duration of diarrhoea, but had no antisecretory effect. A second study is now under way, to evaluate a higher dose of the drug (0.48 mg/kg/day).

- "Bioflorin": a live bacteria named Streptococcus faecium, which is claimed to colonize the small bowel and competitively inhibit pathogenic bacteria, is to undergo a clinical trial in Bangladesh.

- Traditional anti-dysentery medicines: clinical trials are under way in Bangladesh and Madagascar.

4.2.5 Nutrition and diarrhoea

Support was awarded to several studies in this high priority area. They include both (a) metabolic studies to understand nutrient absorption and utilization during diarrhoea of various etiologies, and (b) clinical trials of different feeding regimens during and after acute diarrhoea. The results of some of these studies are described in Annex 2.

4.2.6 Studies of pathophysiology and pathogenesis

The SC is supporting studies aiming at a better understanding of the pathophysiology of viral diarrhoeas and diarrhoea due to Giardia lamblia. These studies should help to develop better case management strategies, particularly with regard to nutrition.

4.3 Activities related to research strengthening in developing countries

4.3.1 Development of designated clinical research centres

Since the second SWG meeting, 3 centres in developing countries (Alexandria/Egypt, Lima/Peru, Rangoon/Burma) have been designated as clinical research centres. These centres have received research strengthening grants to allow them to increase their capacity to undertake clinical trials for the Programme.

4.3.2 Workshops on clinical trials in acute diarrhoea

The Programme has initiated a series of workshops for investigators interested in undertaking clinical trials. Two workshops have been conducted so far, one at the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh, and one at the El Chatby Children's Hospital, Alexandria, Egypt; these were attended by 24 investigators from 16 countries.

These workshops were found to be effective in improving the skills of the participants and in generating high quality research proposals.

4.4 Collaboration with the pharmaceutical industry

The Programme continued to seek the active collaboration and cooperation of the pharmaceutical industry. Through the assistance of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), it was possible to secure the participation of representatives from 14 pharmaceutical companies as observers at the second SWG meeting.

Collaboration/cooperation exists at present with:

(a) In the development/testing of drugs:

- Bristol Myers, USA (cholestyramine)
- Gipharmex, Italy (bioflorin)
- Janssen Pharmaceutica, Belgium (loperamide)
- May & Baker, UK (chlorpromazine)

(b) In the development of improved ORS formulations:

- Beecham, UK
- Ciba-Geigy (Servipharm), Switzerland
- Hoechst, Federal Republic of Germany
- Neolab, Switzerland
- Tetrapak, Switzerland

5. BUDGET

The SWG noted the expenditure in 1983 and the funds available to the SC in 1984, as follows:

	Expenditure 1983	Budget 1984
	US$	US$
Consultants	47 465	15 000
Duty Travel	18 755	15 000
Contracts	383 364	500 000
Group Training	24 082	50 000
Fellowships	-	5 000
Miscellaneous	2 406	7 500
Total	476 072	592 500

6. REVIEW OF RESEARCH PRIORITIES

At its first meeting, in 1980, the SWG had developed a list of research topics which it felt should receive priority for funding by the SC. Those priorities had provided important guidance for the SC. One new priority area had subsequently been added - the problem of chronic/persistent diarrhoea following an acute diarrhoeal episode - for which a list of priorities was being prepared. The SWG agreed that the recommendations for research on "feeding during and after acute diarrhoea" (Annex 2) should be incorporated in the revised list of priority research topics for funding by the SC.

ANNEX 1

LIST OF PARTICIPANTS

Members:

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ANNEX 2

RECENT ADVANCES IN RESEARCH ON FEEDING DURING AND AFTER ACUTE DIARRHOEA

Report of the Scientific Working Group on Drug Development and Management of Acute Diarrhoea

1. INTRODUCTION

In view of the high priority accorded by the Scientific Working Group (SWG) at its first meeting in September 1980 to research on the development of optimum diets during and after acute diarrhoea, this topic was selected for detailed review by the SWG at its third meeting in October 1984. To complement this review, the Group first considered relevant aspects of the nutritional requirements of infants and young children, the physiology and pathophysiology of digestion and absorption of food in these age groups, and the cultural factors that influence dietary practices in diarrhoea.

2. FOOD: REQUIREMENTS, DIGESTION, ABSORPTION, AND BELIEFS RELATING TO FEEDING IN INFANCY AND CHILDHOOD

2.1 Nutritional requirements

During the first 4-6 months of life, nutritional needs are wholly and optimally met by breast-feeding. Thereafter, complementary foods must be added to the diet. In developing countries, these weaning foods are usually based on locally available staple cereals, roots and fibres and legumes. They may be low in nutrient density and more difficult to digest, so that the weanling may not be able to satisfy his nutritional requirements, even when he is free from illness. Since increased dietary intake is required during convalescence from diarrhoea, a diet of poor quality can severely impede complete nutritional recovery.

During diarrhoea, the usual nutrient requirements may be modified by increased catabolic processes (especially if diarrhoea is accompanied by fever), by changes in physical activity as a result of the illness, and by increased faecal excretion of endogenous nutrients. Furthermore, a greater proportion of dietary intake may be unavailable for metabolism because of intestinal malabsorption. Finally, transient anorexia, vomiting, and cultural beliefs regarding feeding during illness may prevent optimal dietary intake. Increased feeding during the later stages of acute diarrhoea and following recovery may be an important means of compensating for nutritional needs that are not satisfied during illness.

Infants and young children are more susceptible than older children to the nutritional complications caused by diarrhoea because of their greater nutritional requirements and lower reserves, and because, in the young, diarrhoea tends to be frequent and severe.

2.2 Physiology of intestinal absorption in healthy children

Different foods may be digested and absorbed with varying degrees of efficiency. In general, foods derived from animal sources are more readily digestible than those obtained from plant sources. The assimilation of plant products, however, varies markedly according to the specific food, the extent of cooking, and the type of processing employed (e.g., milling, refining, or fermentation). Specific factors such as phytates, tannins, and fibre that are present in common cereals and legumes may interfere with the digestion and/or absorption of specific nutrients. Finally, interactions among particular foods and nutrients may influence the absorption of individual dietary components.

Digestive and absorptive processes are not fully developed at birth but digestive functional development can be stimulated early by feeding. The relative inefficiency of fat assimilation by infants under 3 months of age is largely due to the reduced bile acid pool size secondary to maturational delays in maximal hepatic synthesis and limited ileal reabsorption. Similarly, pancreatic amylase activity does not achieve its full potential levels during the early months of life, which has implications for the digestion of starch. Even in healthy adults, starch (e.g., from wheat, maize, potato) is often incompletely digested in the small intestine and a proportion enters the colon. Colonic bacteria can, to a certain extent, ferment carbohydrate to form short-chain fatty acids (mainly acetates, propionates, and butyrates) which are efficiently absorbed from the colon and provide energy - the so-called colonic salvage mechanism for carbohydrates. This mechanism exists in infants, including neonates, and assumes importance in view of their pancreatic amylase deficiency and limited ability to digest starch. On the other hand, lactase activity, which is maximal at term, begins to decline between 3 to 4 years of age in many ethnic groups.

2.3 Food intake and intestinal absorption during diarrhoea

Most studies have demonstrated that food intake is reduced during enteritis, presumably as a result of the combined effect of anorexia and maternal food-withholding behaviour. In Guatemalan children, it was shown that food intake, on the average, was reduced by 20% during diarrhoeal illness. In a study in Bangladesh, the intake was reduced by about 40% on the average; breast-milk consumption declined by only 12%, but the intake of other foods was reduced by as much as 61%. In dehydrated Indian children already weaned and accustomed to semi-solid and solid foods, an intake of about 80% of the recommended daily calorie allowance was achieved even during the first 24 hours of fluid therapy; in comparison, in dehydrated, breast-fed infants, an average intake of only about 57% of the recommended calorie allowance was achieved from sources other than breast-milk during the first 24 hours of fluid therapy.

Intestinal absorption during enteric infections has been examined in experimental models and in clinical studies. Animal models of enterotoxigenic diarrhoeas indicate few, if any, absorptive abnormalities, but several hydrolytic (disaccharidase) and absorptive (glucose, aminoacids, sodium, chloride) pathways are compromised following experimentally induced viral enteritis. Only limited information is available relating specific infectious etiologies of diarrhoea to gut function in children. Secondary disaccharidase deficiencies and impaired monosaccharide transport may cause transient malabsorption of carbohydrates during some enteric infections. Information on amylase levels during acute diarrhoea is lacking. Unabsorbed carbohydrates add to the intraluminal osmotic load and may increase the severity of diarrhoea in some cases. As indicated earlier, carbohydrates that pass to the large intestine can be metabolized by intracolonic bacteria to form short-chain fatty acids which are absorbed and utilized for energy; when the resultant metabolites (including organic acids) exceed the absorptive capacity of the colon they may contribute to systemic acidosis and osmotic diarrhoea.

Malabsorption of fats and fat-soluble vitamins occurs during and after acute enteric infections. Intraluminal bile acid levels can be insufficient to achieve the critical concentrations required for the formation of mixed micelles. It is likely that increased faecal losses of bile acids (possibly caused by ileal dysfunction) are responsible for steatorrhea following enteric infections.

The role of the colon in the conservation of water, electrolytes, and other nutrients during diarrhoea has not been fully evaluated. Microbial alteration of unabsorbed bile acids and dietary fatty acids can produce metabolites that stimulate colonic secretion, potentially increasing the severity of diarrhoea. On the other hand, limited amounts of short-chain fatty acids produced by the fermentation of carbohydrates by colonic bacteria are absorbed efficiently and enhance the absorption of sodium and chloride.

Malabsorption during enteric infection is partial rather than complete. Studies carried out in Bangladesh, India, Peru, and Thailand using mixed diets composed of common foods and synthetic formula diets have shown that a nutritionally significant proportion of the diet can be absorbed during enteric infections and diarrhoea. On the average, 80-95% of dietary

carbohydrate, 50-70% of fat, and 50-75% of nitrogen are absorbed (depending on the food source of these nutrients, the amount of intake, and the severity of diarrhoea), even during the early phase of illness. Although these figures are somewhat below the normal, they indicate that a significant nutritional advantage is derived from continued feeding during diarrhoea. Furthermore, greater levels of dietary intake are associated with greater net absorption of these nutrients and greater weight gain.

Evidence of intestinal malabsorption during diarrhoea has also been obtained by laboratory tests such as those for d-xylose and lactose tolerance. The relationship between the results of these tests and the ability of patients to benefit nutritionally from common diets is unclear, because the tests are often over-sensitive. Children frequently tolerate a mixed diet despite test results indicating that the absorption of specific dietary constituents is impaired. For the purpose of patient management, it is more appropriate to evaluate the clinical response to the diet (e.g., weight gain) than to consider only isolated laboratory data.

Invasive infections of the gut can cause excessive losses of protein and blood in addition to the absorptive abnormalities outlined above. Significant hypoproteinaemia and iron deficiency anaemia may result from these losses.

2.4 Dietary intervention during acute diarrhoea

A recent study in Peru showed that infants receiving their total caloric requirement from the first day of diarrhoea therapy absorbed more nutrients, retained more nitrogen, gained more weight, and showed improved arm circumference and skinfold thickness - even though they tended to have diarrhoea for a longer period - compared with infants given a restricted feeding regime. Studies in Burma and Egypt showed that infants with acute diarrhoea who were breast-fed without interruption during fluid therapy had fewer diarrhoea stools, smaller stool volume, shorter duration of diarrhoea, and a tendency towards better weight gain on recovery compared with groups in which breast milk was withheld for initial periods of 8 hours and 24 hours during fluid therapy. In Egypt, infants with diarrhoea receiving breast milk or cow milk-based formula from the beginning of fluid therapy had an uneventful clinical recovery with no relapse and no increase in the duration of diarrhoea compared with infants who were fed special low lactose formula, or soya-based, lactose-free formulae; among the 46 of 100 infants in this Egyptian study who showed abnormal lactose tolerance when tested on admission, those who were fed breast milk or cow milk-based formula normalized their lactose tolerance test sooner than those who were on low lactose or lactose-free milk. In American Apache Indian children, a group receiving early feeding with soya formula containing no lactose (from 4 hours after the onset of fluid therapy in dehydrated infants and from the onset of fluid therapy in non-dehydrated infants) had a significant reduction in stool volume, mean intake of oral rehydration salts (ORS), and duration of diarrhoea compared with a group from which food was withheld.

2.5 Intestinal macromolecular uptake in healthy children and during enteric infections

Normally, small but antigenically significant amounts of protein are absorbed by the human intestinal epithelium. Preliminary evidence suggests that macromolecular uptake may be increased during enteric infections. The role of antigen absorbed during diarrhoea in subsequent allergic responses is not known, but there is little evidence to support widespread restriction of diets to exclude cow milk or vegetable proteins during acute diarrhoeal illness. It is perhaps advisable, however, not to introduce such proteins in exclusively breast-fed infants under 6 months of age.

2.6 Intestinal absorption in severely malnourished children

Gastrointestinal alterations frequently accompany severe protein energy malnutrition. Abnormalities include pancreatic exocrine insufficiencies, reduced gastric secretion, mild morphological alterations of the intestinal mucosa, reduced proliferative activity and renewal of mucosal epithelial cells, deficiencies of brush border enzymes, and altered intestinal permeability to macromolecules. The binding properties of enteric bacteria at the

brush border of the intestinal epithelium may also be affected by malnutrition. All of these findings may be a direct response to isolated or generalized macro- or micro-nutrient deficiencies, to specific enteric infections complicating malnutrition, to small intestinal bacterial proliferation in the malnourished host, or to combinations of these factors.

Recognizing these abnormalities, it is not surprising that mild defects in digestion and absorption are common in severely malnourished children. However, the relationships among malnutrition, gastrointestinal abnormalities, and the clinical and metabolic consequences of secondary malabsorption have not been completely elaborated. Unless appropriate nutritional therapy is provided, a downward spiral of malabsorption leading to inadequate nutrient availability and secondary malnutrition causing further malabsorption can be expected. Fortunately, in the absence of profuse diarrhoea, the ingestion of sufficiently large amounts of easily digestible foods permits the uptake of enough nutrients to initiate nutritional recovery. Furthermore, intestinal absorption tends to normalize within a short time after nutritional therapy is instituted. It is not certain, however, how rapidly high energy, hyper-osmolar diets can be safely introduced for severely malnourished children with superimposed diarrhoea. Likewise, information on the absorption and retention of electrolytes and water by malnourished children is lacking. Such information would be helpful for determining the optimal rehydration strategy for severely malnourished children.

The features described above for severe malnutrition are not generally applicable to mild and moderate degrees of malnutrition.

2.7 Diarrhoea and malnutrition

2.7.1 Effects of enteric infections and diarrhoea on nutritional status

Longitudinal, community-based studies have shown a strong association between the prevalence of diarrhoea and the degree of growth impairment of children in developing countries. It may be assumed that diarrhoeal disease is an important contributing factor in infantile malnutrition. The association between diarrhoea prevalence and impaired growth appears to occur with all etiologies of infectious diarrhoea that have been examined, but only limited data are at present available. In general, the longer the duration of diarrhoea, the greater the resultant growth faltering is likely to be. It is not clear whether multiple episodes of brief duration cause the same nutritional morbidity as do single, prolonged illnesses.

2.7.2 Effect of nutritional status on the incidence and severity of diarrhoea

Nutritional status does not determine diarrhoeal incidence in communities characterized by elevated rates of diarrhoea, but the duration of symptoms and total volume of faecal losses are greater in undernourished children. It is uncertain whether the latter findings are strictly biological phenomena or whether they are related to socioeconomic and demographic factors that influence both nutritional status and the severity of diarrhoea. Similar findings in malnourished experimental animals suggest, however, that biological factors may be of greater importance. Diarrhoea-associated mortality is relatively high among children with severe marasmus and kwashiorkor.

2.8 Cultural factors influencing the nutritional management of diarrhoea

Culture-specific beliefs concerning the relationships between diarrhoea and the consumption of particular foods pertain both to the causal role of foods in precipitating diarrhoea as well as to the preferred use or avoidance of given foods as therapeutic measures in response to diarrhoea. Cultural factors are also important determinants of the individual's recognition of diarrhoea and malnutrition as diseases that require preventive or therapeutic interventions. These ideas are usually derived from traditional folklore, but they also may be influenced by the current philosophy of the medical community.

A knowledge of local customs is critical for the success of strategies designed to improve the nutritional management of diarrhoea. Health professionals must be aware of existing beliefs in order to present their advice in an effective and acceptable manner. Further interdisciplinary research involving nutritionists, physicians, anthropologists, and other social or behavioural scientists is required to define more clearly the ways in which cultural factors influence feeding behaviour.

3. NUTRITIONAL MANAGEMENT OF DIARRHOEA IN INFANTS AND CHILDREN

There is universal agreement on the need to provide adequate nutritional support to children during and after diarrhoea. This goal can best be achieved by providing easily digestible, nutritionally balanced foods to which the child is accustomed, but there is limited information on the amounts and types of foods that can be safely and effectively offered during different phases of therapy. Trials of different regimens have been initiated and firm recommendations regarding the optimal dietary management of diarrhoea must await their results. Preliminary recommendations are provided here, recognizing that the potential risk of increased diarrhoea with greater dietary intake must be weighed against the advantage of improved nutritional outcome.

Three categories of patients can be defined according to their feeding practices prior to the onset of diarrhoea: (i) exclusively breast-fed infants (i.e., those who are receiving no other source of energy than breast milk); (ii) fully weaned infants who are receiving only liquid foods; and (iii) infants who are receiving both solid and liquid foods (possibly including breast milk and/or animal milks).

Four phases of dietary therapy have been defined: (i) early home therapy (offered immediately following the onset of diarrhoea, before dehydration develops); (ii) rehydration therapy (offered when dehydration is clinically detectable); (iii) maintenance therapy (offered following rehydration therapy, while diarrhoea is still present); and (iv) convalescent therapy (offered when the stools start to improve but are not necessarily of normal consistency). Since most episodes of diarrhoea are mild and not associated with dehydration, convalescent therapy often immediately follows early home therapy, without any need for the intervening phases of rehydration or maintenance therapy.

Little information is available concerning the effect of dietary intake in the home during the early phases of illness, and further studies in this area are required. Likewise (with the exception of breast milk), little attention has been paid to the effect of continued food intake during the rehydration phase. Although it is agreed that the therapeutic priority for the dehydrated child is the replacement of fluid and electrolyte deficits, it is not known whether the consumption of specific foods in addition to ORS will hinder or facilitate rehydration. Early experience with rice-powder ORS suggests that selective feeding during the rehydration phase may, in fact, be advantageous.

Detailed studies of dietary management during the convalescent phase are similarly lacking; yet convalescent therapy may be of great importance in reducing the long-term nutritional impact of diarrhoeal illnesses. Although it is generally agreed that dietary intake should usually be greater than normal during this period - in order to replace nutrients not received during the earlier stages of illness and to compensate for ongoing subclinical malabsorption - the optimal types and amounts of food and rate of nutritional recovery have not been examined. Children with poorer nutritional status prior to the episode, or with greater nutritional complications during the illness, will presumably require more time for complete recovery and/or more intensive dietary interventions during convalescence. Older infants (above 4-6 months of age) who are exclusively breast-fed prior to illness may require the initiation of complementary feeding to achieve potential growth rates during convalescence and thereafter. Many of the traditional diets given to weanlings in developing countries are based on plant products and may not provide adequate amounts of nutrients. Efforts must be devoted to the development of more appropriate diets, taking into account not only nutritional quality but also local availability, cultural acceptability, cost, and ease of hygienic preparation.

The high levels of nutrients required during convalescence may be reached by providing meals of high nutrient density and/or by increasing the number of meals offered per day. Emphasis should be placed on hygienic precautions in the preparation, feeding, and storage of foods. The adequacy of food intake can be assessed by monitoring the child's nutritional status (weight, length) at intervals during convalescence. The health worker should maintain contact at least until the pre-diarrhoea weight is exceeded and, ideally, in previously undernourished children, until nutritional status has returned to within normal limits.

Another issue that must be considered is the importance of anorexia and vomiting during diarrhoeal illness. It is generally recognized that appetite is depressed in some children during the early stages of illness, especially if dehydration and acidosis are present. Divergent findings with regard to the clinical importance of anorexia should be clarified. Possible explanations include the types of food offered (e.g., solids versus liquids, breast milk versus other foods), the microbiological agents involved, and the severity of dehydration and acidosis. In any case, since anorexia and vomiting, when present, are almost universally self-limited and of relatively short duration (i.e., less than 1-2 days), it is generally agreed that foods should be offered repeatedly to the child on an ad libitum basis and that 'force feeding' should be discouraged.

3.1 Dietary management during the maintenance phase of therapy

To date, most clinical studies have evaluated continued feeding during the maintenance phase of therapy. However, only limited data are available, and although attempts have been made to extrapolate from these studies to formulate recommendations for appropriate dietary management during the maintenance phase (and also during early home therapy), further studies are required.

3.2 Management of the breast-feeding child during diarrhoea

Available evidence indicates that breast-feeding should be continued during early home therapy, as well as during the rehydration, maintenance, and convalescent phases of therapy. In the two randomized, controlled studies mentioned in Section 2.4, in which breast-feeding was postponed for either 8 or 24 hours following the initiation of rehydration therapy in hospital settings, it was found that children who continued to breast-feed without interruption consumed less ORS but, nevertheless, required less time to become rehydrated. The same children also tended to have less severe diarrhoea and no increase in clinical complications. Because of the above considerations, and in view of the known importance of sucking for maintaining full lactational capacity, every effort should be made to encourage continued breast-feeding during acute enteritis.

3.3 Management of the fully weaned infant who is receiving only liquid foods (usually milk or milk formulae) at the time of onset of diarrhoea

The appropriate dietary management during diarrhoea of the young infant who is fully weaned is controversial. In developing countries, the major nutrient source for these infants is animal milk (most commonly from cow, goat, or buffalo), either fresh or reconstituted from dried or evaporated, commercially prepared products. Most studies have focused on the use of these milks during the maintenance phase of therapy and little information is available about their effects on diarrhoea or nutritional parameters during other phases of illness.

Although some treatment centres routinely offer whole cow milk-based formula to infants throughout the maintenance phase of therapy, apparently with good results, other centres report more severe diarrhoea and increased rates of complications when these formulae are given early during the maintenance phase. The latter findings may be attributable to malabsorption of lactose or to intolerance of other components of animal milks. The reasons for the inconsistent experience in different treatment centres are not obvious, but genetic differences among patients, differences in the infectious etiologies of diarrhoea, and variations among investigators in the methods of study and definitions of clinical complications are possible explanations. Further studies of this issue are indicated. In

the meantime, there is no strong reason to discontinue the use of milk (feedings) in those places where successful results have been reported in controlled studies. Nevertheless, close follow-up of ambulatory patients is indicated, in order to assure the detection of recurring dehydration or prolonged diarrhoea which might occur in a small proportion of children receiving undiluted animal milks. Appropriate dietary adjustment should be made when these complications are identified.

In areas where it is deemed advisable to reduce the level of milk consumption (either by dilution or by reducing the volume of feed) during early therapy, other nutrient sources should be added to the diet in order to promote optimal nutritional recovery. Little information is at present available on appropriate alternative sources of nutrients that can be prepared hygienically to replace animal milk during diarrhoea therapy. Blends of locally available staple foods (with or without added milk or other animal products) prepared in liquid form may be suitable, but their use has not been evaluated. If such diets prove to be clinically acceptable, operational research will then be required to determine the best ways of teaching mothers and/or community health workers to prepare the diets with the correct proportions of foods under hygienic conditions.

Fermented milk products (in which a proportion of lactose is hydrolysed during the fermentation process, producing acid milks which are resistant to contamination with bacterial enteropathogens) have been used successfully in some areas to manage patients with diarrhoea. Further controlled clinical trials of these products are required.

3.4 Management of children who are consuming solid foods prior to the onset of diarrhoea

Usually these children are older than those discussed previously, but they may also be consuming breast milk or animal milk in addition to solid foods prior to the onset of diarrhoea. The considerations regarding the continuation of breast-feeding or the consumption of other milks are the same for these children as for those described previously. In general, these children should be easier to manage because of the wider range of previously consumed foods from which appropriate foods can be selected for use during diarrhoea.

Little specific information is available regarding individual staple foods that may be more or less digestible during diarrhoea. However, studies in healthy children indicate that the digestibility of different staples varies considerably and it is possible that these differences may be even more pronounced during diarrhoea. More studies are required to evaluate the digestibility of common foods during diarrhoea. It should nevertheless be noted that excellent clinical results have been reported in limited numbers of children who have consumed mixed diets based on rice, banana, milk, and bread, or on wheat noodles and milk. Thus, there is some basis for expecting common foods to be well tolerated during the maintenance and early convalescence phases.

Several theoretical considerations are pertinent to the formulation of appropriate mixed diets for children during diarrhoea. First, the diets must include an adequate balance of nutrients of sufficient density to assure a reasonable assimilation of nutrients from a relatively small amount consumed. Second, more easily digestible foods should be offered initially; milled cereals, for example, are probably preferable to whole-grain cereals with high fibre content, though specific studies are lacking. Finally, diets should be iso-osmotic to avoid further increases in diarrhoea. Foods such as fruit juices or soft drinks that have a high sugar content must be avoided or diluted with water. While intestinal function is compromised by infection-induced injury, it is preferable to offer smaller and more frequent feedings than may be customary in healthy children. This type of feeding is less likely to exceed the absorptive capacity of the intestine.

Intestinal dysfunction may be severe in children with marasmus and kwashiorkor, and extraintestinal infectious and non-infectious complications are common; these cases therefore require special attention. The treatment of severe protein energy malnutrition is the subject of a WHO publication[1].

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1 The treatment and management of severe protein-energy malnutrition. WHO (1981).

4. RECOMMENDATIONS FOR RESEARCH

From the above review it is evident that a considerable amount of further research is required in the following areas:

4.1 Studies on anorexia/food intake during enteric infections

- the causes of anorexia associated with specific enteric infections or specific pathogens;
- the relationship between anorexia and the types of food offered (e.g., solids versus liquids, breast milk versus other milks);
- the impact of food intake when offered in a standard manner during various phases of diarrhoeal illness, e.g., early home therapy, rehydration, maintenance, and convalescence.

4.2 Studies on nutrient digestion and absorption during and after diarrhoea

- the relationship between the etiology of diarrhoea and intestinal malabsorption;
- the absorption of vitamins and minerals during and after diarrhoea;
- the digestion and absorption of animal milk and fermented milk products during enteric infections;
- the processes of digestion and absorption in malnourished children with diarrhoea;
- the importance of pancreatic function, hepatic function, and bile salt metabolism in the digestion and absorption of food in diarrhoea;
- the role of the colon in the conservation of nutrients during diarrhoea;
- the impact of enteric infection on the absorption of macromolecules and their immunological significance, function, and allergic responses;
- the digestibility of various common food items (e.g., cereals, legumes, fats and oils, vegetables) and the effects of consumption of these foods during all phases of diarrhoea.

4.3 Studies on dietary interventions during and after diarrhoea

- the effects of dietary interventions during various phases of diarrhoeal illness on the nutritional status of the child and the severity of diarrhoea;
- the effect of continued breast-feeding and/or consumption of other foods during the rehydration phase of therapy on the speed of rehydration, aggravation/amelioration of diarrhoea, and the risk of fluid/electrolyte imbalance;
- the digestibility and nutritional quality of commonly available foods as evaluated through dietary interventions during and after diarrhoea. The effects of continued breast-feeding, and use of animal milk and fermented milk products should also be evaluated in the same manner;
- the efficacy of ORS formulations based on common food sources of carbohydrate and protein (e.g., cereals, legumes, potatoes);

- the effect of nutritional status on intestinal immunological function and susceptibility to and recovery from enteric infections;

- the appropriate formulation and use of ORS in severely malnourished children;

- the sociocultural determinants of usual feeding practices and changes in such practices in response to diarrhoea;

- operational aspects such as the training of health workers and mothers in methods of preparing diets from locally available foods for feeding during diarrhoea and following recovery.

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