# DIARRHOEAL DISEASES CONTROL PROGRAMME

Report of the Tenth Meeting of the

STEERING COMMITTEE OF THE
SCIENTIFIC WORKING GROUP ON DRUG DEVELOPMENT
AND MANAGEMENT OF ACUTE DIARRHOEAS

(Geneva, 25-28 March 1983)

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Current status of the Programme</td>
</tr>
<tr>
<td>2. Consideration of the report of the ninth meeting</td>
</tr>
<tr>
<td>3. Review of follow-up action taken by the Secretariat</td>
</tr>
<tr>
<td>4. 1985 budget</td>
</tr>
<tr>
<td>5. Improved ORS formulations (&quot;Super ORS&quot;)</td>
</tr>
<tr>
<td>6. Review of renewal applications, progress reports, and final reports in other areas</td>
</tr>
<tr>
<td>7. Review of new proposals</td>
</tr>
<tr>
<td>8. Clinical research centres (institution strengthening grants)</td>
</tr>
<tr>
<td>9. Overview of proposals submitted to date</td>
</tr>
<tr>
<td>10. Workshop on clinical trials in acute diarrhoea</td>
</tr>
<tr>
<td>11. Reports on and plans for site visits</td>
</tr>
<tr>
<td>12. Collaboration with the pharmaceutical industry</td>
</tr>
<tr>
<td>13. Plans for the study of chronic diarrhoea</td>
</tr>
<tr>
<td>14. Other matters</td>
</tr>
<tr>
<td>15. Plans for the eleventh Steering Committee meeting</td>
</tr>
<tr>
<td>16. List of participants</td>
</tr>
</tbody>
</table>

**ANNEX : Cereal-based electrolyte solutions - research issues**

The tenth meeting of the Steering Committee (SC) of the Scientific Working Group (SWG) on Drug Development of Acute Diarrhoea (DDM) was held in Geneva on 25-28 March 1983.

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1. CURRENT STATUS OF THE PROGRAMME

The Steering Committee (SC) was briefed on the current status of the Programme. In the services component, 95 countries had prepared plans for national CDD programmes, and in 75 of them programmes were in operation. Those 95 countries comprised 72% of all the developing countries and 92% of their total population. In the research component, 294 research projects in 76 countries had been awarded support. Since September 1980, support had been awarded by the SC to a total of 44 research proposals, 72% of which were in developing countries.

The SC was also informed of the recommendations of the Programme's Technical Advisory Group relating to changes in the research management structure. They involved replacement of the Scientific Working Groups and Steering Committees by a single group with responsibility for planning and assessing research applications in each of the 3 globally managed research areas. Each group could also convene ad hoc meetings to review topics of particular importance. The 3 new SWGs would be: Case Management; Immunology, Microbiology and Vaccine Development; and Epidemiology and Disease Prevention.

2. CONSIDERATION OF THE REPORT OF THE NINTH MEETING

The Committee approved, without revision, the report of its meeting held on 4-5 October 1984.

3. REVIEW OF FOLLOW-UP ACTION TAKEN BY THE SECRETARIAT

The Committee considered and endorsed the action that had been taken with respect to the following 2 proposals which had been awarded support on receipt of revised protocols or clarifications:

(a) 84129 - Efficacy of rice powder-based ORS in the management of acute diarrhoea with dehydration in infancy - M.T. El-Mougi, Bab El-Sha'Reya University Hospital, Egypt (US$12 000)

The study will evaluate the efficacy of an ORS formulation containing rice powder as its organic constituent in infants and young children with acute diarrhoea.

(b) 84160 - Development of an improved ORS formulation having antidiarrhoeal properties : A controlled clinical trial of a new formulation and a metabolic balance study - K.N. Jalan, Kokhar! Centre of Gastroenterology, India (US$18 400)

The study will evaluate the efficacy of an improved ORS formulation containing maltodextrin (20 g/l), glycine (4 g/l), and glycy1-glycine (4 g/l) as its organic constituents in infants and young children with acute diarrhoea.

4. 1985 BUDGET

The Committee approved the following budget for 1985:

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount</th>
</tr>
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<tbody>
<tr>
<td>Consultants</td>
<td>15 000</td>
</tr>
<tr>
<td>Duty travel</td>
<td>20 000</td>
</tr>
<tr>
<td>Contracts</td>
<td>630 000</td>
</tr>
<tr>
<td>Meetings</td>
<td>50 000</td>
</tr>
<tr>
<td>Fellowships</td>
<td>5 000</td>
</tr>
<tr>
<td>Misc. supplies</td>
<td>7 000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>727 000</td>
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</table>
5. IMPROVED ORS FORMULATIONS ("SUPER ORS")

5.1 Review of current knowledge and research priorities

The Committee reviewed (i) the status of all proposed and ongoing research studies on improved ORS formulations, (ii) a document on "Improved formulations of Oral Rehydration Salts with antioxidant and nutritional properties: Super ORS", and (iii) a document on cereal-based oral rehydration therapy projects prepared by ICDDR,B, Dhaka.

The SC then reviewed the present state of knowledge on cereal-based oral rehydration solutions and made recommendations for further research in this area (Annex).

5.2 Review of a progress report and new proposals on Super ORS

The Committee reviewed the progress report on one project, which was approved for additional funding, and 12 new proposals for studies of Super ORS:

- 7 were accepted for funding (with or without minor revisions);
- 1 was returned to the principal investigator with a request for revision and resubmission;
- 4 were not approved.

The project for which additional funding was approved is:

83082 - Evaluation of effectiveness of green gram (moong dal) and puffed rice powder as substitutes for glucose in oral rehydration solutions - O. P. Ghai, All India Institute of Medical Sciences, New Delhi, India (US$1200)

The 7 proposals approved for funding are:

(a) 85039 - A randomized controlled trial of a new ORS formulation and standard WHO-glucose electrolyte solution in the treatment of acute diarrhoeal disease in children - M.K. Bhan, All India Institute of Medical Sciences, New Delhi, India (US$15 900)

The study will evaluate the efficacy of an improved ORS formulation containing maltodextrin (20 g/l), glycine (4 g/l), and glycyrrhizin (4 g/l) as its organic constituents in infants and young children with acute diarrhoea.

(b) 85003 - A controlled clinical trial of an improved oral rehydration solution in the rehydration therapy of infants and children with acute diarrhoeal disease - A.O. Grange, University of Lagos, Nigeria (US$22 350)

The study will evaluate the efficacy of an ORS formulation containing maltodextrin (20 g/l) and glycine (8 g/l) as its organic constituents in infants and young children with acute diarrhoea.

(c) - A clinical trial on improved ORS formulations in infantile diarrhoea - A.S. Kassem, El Chatby Children's Hospital, Alexandria, Egypt (US$8 000)

The study will evaluate the efficacy of 2 improved ORS formulations containing (i) maltodextrin (20 g/l) and glycine (8 g/l), and (ii) maltodextrin (20 g/l), glycine (4 g/l), and glycyrrhizin (4 g/l) as the organic constituents in infants and young children with acute diarrhoea.
(d) 85020 - Improved oral rehydration solutions with antidiarrhoeal properties: A controlled clinical trial - Phase II - Dr Khin Maung U, Department of Medical Research, Rangoon, Burma (US$9 000, subject to satisfactory revision of the protocol)

The study will evaluate the efficacy of an ORS formulation containing maltodextrin (20 g/l), glycine (4 g/l), and glycyrl-glycine (4 g/l) as its organic constituents in adults with cholera.

(e) 84197 - Comparison of efficacy of a glucose, glycine, glycyrl-glycine electrolyte solution versus the standard WHO-ORS in diarrhoeic dehydrated children - D. Pizarro, Hospital Nacional de Niños, San José, Costa Rica (US$30 000)

The study will evaluate the efficacy of an ORS formulation containing glucose (12 g/l), glycyrl-glycine (4 g/l), and glycine (4 g/l) as its organic constituents in infants and young children with acute diarrhoea.

(f) A controlled trial comparing the possible advantages of amino acids and maltodextrins present in the new oral rehydration formula in the treatment of acute diarrhoea versus the present WHO oral rehydration formula - H. Romer, Hospital de Niños "J.M. de los Ríos", Caracas, Venezuela (US$22 067)

The study will evaluate the efficacy of an ORS formulation containing maltodextrin (20 g/l), glycine (4 g/l), and glycyrl-glycine (4 g/l) as its organic constituents in infants and small children with acute diarrhoea.

(g) 85027 - Effects of added glycine and glycyrl-glycine to an oral rehydration solution - P. Santos-Ocampo, Department of Pediatrics, University of Philippines, Manila, Philippines (US$14 070)

The study will evaluate the efficacy of an ORS formulation containing glucose (20 g/l), glycyrl-glycine (4 g/l), and glycine (4 g/l) as its organic constituents in infants and small children with acute diarrhoea.

6. REVIEW OF RENEWAL APPLICATIONS, PROGRESS REPORTS, AND FINAL REPORTS IN OTHER AREAS

The Committee reviewed 1 renewal application, 4 progress reports, and 4 final reports. It approved funding for the renewal application:

83063 - Impact of breastfeeding on diarrhoea in infancy - D.A. Mahmood, College of Medicine, Basrah, Iraq (US$500)

7. REVIEW OF NEW PROPOSALS

The Committee reviewed 14 proposals for research in areas other than Super ORS. Of these:

- 6 were accepted for funding (with or without minor revisions);
- 5 were referred back to the principal investigators with a request for revision and resubmission of their proposal;
- 3 were not approved.

The 6 proposals approved for funding are:

(a) 84082 - The study of gentamicin in the treatment of shigellosis - Dr Duan Shu Cheng, First Medical College, Shanghai, China (US$15 800)

The study will evaluate the efficacy and safety of gentamicin in the treatment of shigellosis in children in China, where the drug is routinely used for this purpose.
(b) 84174 - Comparison of safety and efficacy of use of oral and intravenous rehydration solutions - Dr V.I. Pokrovsky, Central Research Institute of Epidemiology, Moscow, USSR (US$20 000)

The study will evaluate the safety and efficacy of oral rehydration therapy in children and adults (including elderly persons) in USSR.

(c) 85016 - Interrelationships between feeding mode, malnutrition and diarrhoea morbidity in infancy among the urban poor in southern Brazil - J.C. Martines, Universidade Federal de Pelotas, Rio Grande do Sul, Brazil (US$30 000)

The objective of the study is to evaluate the relationships among feeding mode, diarrhoea morbidity, and growth rate, with special reference to breastfeeding.

(d) 85026 - Prospective study of low gastric acid secretion as a risk factor for childhood diarrhoea in Lima - R.B. Sack, Johns Hopkins University, Baltimore, USA & C. Lanata, Instituto de Investigacion Nutritional, Lima, Peru (US$35 160)

The study will evaluate the role of a low level of gastric acid secretion as a risk factor for childhood diarrhoea using a newly developed, non-invasive technique for measuring gastric acidity.

(e) 84120 - Bacterial overgrowth in giardiasis and chronic diarrhoea - R.H. Gilman, Johns Hopkins University, Baltimore, USA & R. Leon-Barua, Universidad Peruana Cayetano Heredia, Lima, Peru (US$23 000)

The study aims to evaluate the relationships between Giardia infection, small bowel bacterial colonization, gastric acid secretion, and diarrhoea, with particular reference to persistent diarrhoea.

84039 - Definitions, epidemiology, etiology, impact and pathogenesis of chronic diarrhoea - R.L. Guerrant, University of Virginia Medical Centre, Charlottesville, USA (US$5 000)

The study will examine the daily records of diarrhoeal illness in children (available from earlier prospective studies) to develop a definition and description of persistent and recurrent diarrhoea.

8. CLINICAL RESEARCH CENTRES (INSTITUTION STRENGTHENING GRANTS)

The Committee reviewed the present status of the clinical research centres. It recommended that commissioned research in priority areas be promoted in the centres and that further efforts be made to identify new centres for possible designation.

The Committee then reviewed progress reports and renewal applications for institution strengthening grants from 2 centres and approved funding for both:

83112 - Clinical Trials - Khin Maung U, Department of Medical Research, Rangoon, Burma (US$25 000)

83085 - Clinical Trials - E. Salazar-Lindo, Universidad Peruana Cayetano Heredia, Lima, Peru (US$25 000)

9. OVERVIEW OF PROPOSALS SUBMITTED TO DATE

The Committee reviewed a computerized listing of proposals submitted to and funded by the 3 global and 6 regional SWGs. It noted that an increasing majority of the proposals received and supported by the SC were from institutes in developing countries.
10. WORKSHOPS ON CLINICAL TRIALS IN ACUTE DIARRHOEA

The Committee reviewed plans for holding workshops on clinical trials in French and Spanish in 1986. It felt that El Chatby Children's Hospital in Alexandria, Egypt, might be a possible site for the French-speaking workshop. The Committee also considered that an additional workshop in English would help to stimulate more high-quality research proposals.

11. REPORTS ON AND PLANS FOR SITE VISITS

Reports on site visits made and plans for future visits were discussed. It was agreed that visits be made to investigators in Chile, India, Indonesia, Turkey, and USSR.

12. COLLABORATION WITH THE PHARMACEUTICAL INDUSTRY

The Committee reviewed ongoing collaborative activities with specific pharmaceutical companies:

Beaufour

The SC considered the possibility of conducting a clinical trial of the antidiarrhoal effect of an improved clay, "Smectite", which is classed as an absorbent. It recommended that the matter be reconsidered at a subsequent meeting when more information was available from the ongoing studies supported by the Company.

Ciba-Geigy

Formal statements by the Company on the withdrawal of clioquinol from the market and the promotion of ORT were noted with satisfaction.

Janssen

The Committee reviewed a report on the second (high dose) loperamide trial in Egypt and expressed the opinion that loperamide should not be used in children below 5 years of age with acute diarrhoea.

13. PLANS FOR THE STUDY OF CHRONIC DIARRHOEA

The Committee reviewed and approved the document "Persistent diarrhoea in children - Research priorities" (document CDD/DDM/85.1).

14. OTHER MATTERS

The Committee recommended that high priority be given to the development of guidelines and protocol outlines for research in 2 areas: the impact of early home therapy of diarrhoea in preventing dehydration and the risks and benefits of adding food flavours and colouring to ORS. It further requested the Secretariat to identify centres/investigators to conduct such research.

The SC also requested the Secretariat to provide a summary of available information on flavoured/coloured formulations and on their acceptability and risks in the treatment of diarrhoea.

15. PLANS FOR THE ELEVENTH STEERING COMMITTEE MEETING

It was agreed to convene the eleventh meeting of the SC in Geneva from 7 to 10 October 1985.
16. LIST OF PARTICIPANTS

Members:

Dr J.-F. Desjeux, INSERM U83, Paris, France

Professor D. Habte, University of Addis Ababa, Ethiopia

Dr J.R. Hamilton, Hospital for Sick Children, Toronto, Ontario, Canada

Professor D.R. Laurence, Department of Medicine, University College, London, United Kingdom (Chairman)

*Dr Majid Molla, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh

Professor R.B. Sack, Division of Geographic Medicine, Francis Scott Key Medical Center, Baltimore, MD, USA

Secretariat:
Dr J.F. Dunne, Pharmaceuticals

Dr D. Mahalanabis, Diarrhoeal Diseases Control Programme (Secretary)

Dr M.H. Merson, Diarrhoeal Diseases Control Programme

Dr A. Pradilla, Nutrition.

* Unable to attend
CEREAL-BASED ELECTROLYTE SOLUTIONS — RESEARCH ISSUES

Cereal contains starches and proteins that are broken down by the digestive processes in the gastrointestinal tract to release monosaccharides (primarily glucose), amino acids, and short chain peptides, all of which are organic solutes that enhance the absorption of sodium and water. Thus, cereals can convert the standard ORS solution into a “Super ORS” in the same way as defined additives such as glycine, glycy1-glycine, and maltodextrin. Cereals differ, however, in that they provide more calories and can be given in larger quantities with little or no osmotic penalty, because of their polymeric nature. Nonetheless, cereal-based ORS solutions should be thought of as rehydration solutions only, and not as a food or source of calories, since to regard them as the latter may: (a) discourage resumption of early feeding, including breastfeeding, immediately following rehydration, and (b) result in the consumption of excess salt during the maintenance phase of therapy and during convalescence, especially in areas where cereals are a prominent component of the normal diet in infancy.

It is considered unlikely that the majority of treatment centres (e.g., hospitals, clinics) would use cereal-based ORS solutions instead of “Super ORS” containing defined additives (soon to be developed) for the treatment of dehydration, as the latter will probably be less bulky, easier to prepare, and have a longer shelf-life. Cost will probably not be a factor because the defined additives are likely to be inexpensive. It is, however, possible that some manufacturers could provide available precooked cereal powders for use in preparing packets of cereal-based ORS.

It is clear that cereal-based salt solutions are most suited for use in the home. The required ingredients (i.e., rice and salt) are readily and cheaply available, and have only to be prepared properly by the knowledgeable mother. Such salt solutions used early in the course of diarrhoea might prevent dehydration and hence the need for further medical attention. They differ from ORS in that they do not contain potassium or citrate (or bicarbonate).

The Steering Committee is of the opinion that studies on cereal-based ORS and cereal-based salt solutions should proceed in settings where they can be compared, as appropriate, with standard ORS, “Super ORS” made from defined additives, and other household-available solutions, and where outcomes can be readily quantified.

The following studies are recommended:

1. Rice-based electrolyte solutions are the only cereal-based solutions that have been properly evaluated, and for which the details of preparation have been worked out. Their further evaluation should include:

(a) A hospital-based study of the efficacy of rice-based ORS in infants aged 3 months and younger, in whom the digestion of rice starch may not be complete.

(b) Additional hospital-based studies to compare rice-based ORS (with citrate) with glycine-ORS (or another “Super ORS” if any is found to be superior to glycine-ORS).

(c) Field studies of rice-salt solutions prepared by mothers to determine feasibility, acceptability, and efficacy in preventing dehydration and in decreasing the adverse nutritional consequences of diarrhoea at home.
2. Other cereals need to be evaluated, in a similar manner to rice, as possible substrates in cereal-based ORS and cereal-based salt solutions, since in many parts of the world rice is not available. They include wheat, potatoes, bananas, sorghum, maize, and perhaps others of regional importance. The sequence of such studies should be (a) preparing the solutions to determine their physical state and palatability; (b) if the mixtures are acceptable, conducting controlled trials of cereal-ORS solutions in hospitalized adults and children to determine (i) their efficacy as rehydration solutions, (ii) their effect on stool volume, and (iii) their acceptability; and (c) if they are found to have an efficacy similar to that of rice, undertaking field studies to determine their feasibility, acceptability, and efficacy as cereal-salt solutions in early home treatment.

The following additional points are noted:

- It is important in all studies of "Super ORS" (including cereal-based ORS) solutions and cereal-salt solutions that early feeding (beginning at the end of the initial rehydration period of 4-6 hours) be routinely implemented.

- Some of the above-mentioned studies could be undertaken by the designated clinical centres.

- It would be desirable to obtain cost estimates from baby food manufacturers for a packaged, pre-cooked cereal-based ORS solution.