Title of Study: Nutritional management of post-shigellosis growth faltering in children with a high-protein diet.

1. Source of Population:
   (a) Ill subjects: Yes
   (b) Non-ill subjects: No
   (c) Minors or persons under guardianship: Yes

2. Does the study involve:
   (a) Physical risks to the subjects: Yes
   (b) Social Risks: No
   (c) Psychological risks to subjects: Yes
   (d) Discomfort to subjects: Yes
   (e) Invasion of privacy: Yes
   (f) Disclosure of information damaging to subject or others: Yes

3. Are subjects clearly informed about:
   (a) Nature and purposes of study: Yes
   (b) Procedures to be followed including alternatives used: Yes
   (c) Physical risks: Yes
   (d) Sensitive questions: Yes
   (e) Benefits to be derived: Yes
   (f) Right to refuse to participate or to withdraw from study: Yes
   (g) Confidential handling of data: No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure: Yes

4. Will signed consent form be required:
   (a) From subjects: Yes
   (b) From parent or guardian (if subjects are minors): Yes

5. Will precautions be taken to protect anonymity of subjects: Yes

6. Check documents being submitted here with Committee:
   - Umbrella proposal - Initially submitted overview (all other requirements will be submitted with individual studies)
   - Abstract Summary (Required)
   - Protocol (Required)
   - Informed consent form for subjects
   - Informed consent form for parent or guardian
   - Procedure for maintaining confidentiality
   - Questionnaire or interview schedule

I agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Principal Investigator

Date: 21/5/87
SECTION I : RESEARCH PROTOCOL

1. Title : Nutritional management of post-shigella growth faltering in children with a high-protein diet.

2. Principal investigator : Dr Iqbal Kabir
   Co-investigators : Drs A. Islam, S.A. Sarker, A. Breind
   Consultant/adviser : Prof. Roger Eeckels
                       Director, ICDDR,B
                       Prof. John Banwell
                       Dr T. Butler
                       Case Western Reserve University
                       Cleveland, USA

3. Starting date : July 1987

4. Completion date : June 1989

5. Total direct cost : US $61190

   Source of fund : To be submitted

6. Scientific programme : This protocol has been approved by the Clinical Sciences Division.

   [Signature]

   Signature of the Acting Associate Director, Clinical Sciences Division

   Date: 13 April 87
7. ABSTRACT SUMMARY

Previous studies in Bangladesh showed an interruption of linear growth in children with shigellosis. Catch-up of growth following loss due to infections in children has been advocated with higher protein diets, but such diets have not been tested following shigellosis or other infections for an effect on linear growth rate or weight gain. Fifty-four children with culture-proven Shigella dysentery in Bangladesh will be randomly assigned to receive either a diet with a standard amount protein (5 percent of calories as protein) or a high protein diet (15 percent of calories as protein) for 21 days in the hospital. The diets will be isocaloric and provide abundant calories at a level of 150 kcal/kg/day. Heights and weights will be recorded before and after feeding the diets and every month after discharge for 6 months. Serum concentrations of prealbumin, as indicators of rates of protein synthesis, will be measured before and after 21 days of feeding. If the high protein diet supports faster growth during convalescence from shigellosis, a follow-up study will be designed to provide protein supplements to home-based diets in order to achieve similar catch-up growth in a feasible manner for developing countries. The duration of the study will be two years.

8. Reviews:

1. Ethical Review Committee: _____________________________
2. Research Review Committee: _____________________________
3. Director, ICDDR,B: _____________________________
SECTION II: RESEARCH PLAN

A. INTRODUCTION

1. Objectives:

   The objective of the study is to evaluate the effectiveness of a short-time dietary intervention with a higher amount of protein in reducing subsequent morbidity and growth faltering in children with shigellosis.

2. Background:

   Children in developing countries show slower growth rates than children in developed countries, and many are stunted when they reach adulthood. A large part of this growth retardation is caused by malnutrition due to decreased intake of food during infectious diseases. Scrimshaw (1) has attributed the decreased intake/utilization of calories during infection to a combination of anorexia, fever, withdrawal of solid food by parents, impaired intestinal absorption, and nutrient losses in body fluids. The effects of diarrhoeal infections on growth of children in Bangladesh was studied prospectively by Black et al. (2), who concluded that shigellosis had a significant impact on linear growth and diarrhoea due to E. coli had a significant impact on ponderal growth. Diarrhoeal illnesses, respiratory tract infection and skin infection accounted for 90% of all illnesses. Shigella had a longer duration than other type of diarrhoea with 16% episode lasting for more than 20 days (2). Prolonged diarrhoea associated with deep ulceration of colon follows acute shigellosis in a proportion of patients. Besides, the other effects of diarrhoea shigellosis also cause loss of blood and mucus and cause enteric protein loss (3, 4). Study of Kabir et al showed that patients with shigellosis had bulky stool for several days during recovery from acute shigellosis (5). The relationship between diarrhoeal diseases and growth increment in total body length and weight were investigated in Gambian and
Guatemalan children (6,7). In these studies days ill with diarrhoeal diseases were found to be significantly associated with reduced growth in length and weight.

Optimal feeding practices during acute diarrhoea has been controversial and was reviewed recently by Brown and MacLean (8). The theoretical advantages of delayed feeding include the avoidance of increased fluid loss in stool, of acidosis, and of mucosal injury caused by certain foods. The advantages of continued feeding during diarrhoea are to prevent weight loss and protein deficits, to maintain and repair the injured mucosa, and to sustain the benefits of breast feeding. The World Health Organization has opted for continued feeding during diarrhoea, stressing that breast-feeding should continue and weaning diets should be continued as previously except that cow's milk and formula feedings be diluted at least two-fold (8). These recommendations apply mainly to watery diarrhoeas that affect the small intestine. Less attention has been given to shigellosis and other infections that affect the colon (9), and no recommendations are available for intensive feeding during the recovery period.

It should be desirable during and after acute infections of children to try to catch-up lost growth, but no study has been carried out to show whether growth catch-up is possible. Whitehead (10) has made theoretical calculations what the energy and protein requirements should be doubled for catch-up growth. For a 7 kg child the calories required are about 25% higher than for normal growth, or about 150 kcal/kg/day, and the percentage of calories as protein is nearly doubled to more than 11 percent. In Jamaica, Golden (11) estimated the minimum amount of protein to maintain lean body weight in malnourished children was about 3 percent of calories as protein and minimum total caloric intake to maintain lean body weight was 96 kcal/kg/day. The required duration of intensive feeding for growth catch-up should be about three
times longer than the preceding acute disease because of the assumption by Scrimshaw (1) that the anabolic phase of recovery will last three times longer than the catabolic phase of disease.

In addition to growth impairment, infections and malnutrition lead to reductions in serum protein concentration. In Bangladesh, serum protein concentrations in children with severe shigellosis are about half of the normal values (12). In severe malnutrition, depressed serum albumin concentrations are instrumental in lowering plasma oncotic pressure and allowing the edema of kwashiorkor to develop (13). Diets with higher protein content may have a beneficial effect to increase the rate of albumin synthesis, thus raising the serum albumin and protecting children against symptoms of malnutrition. On the other hand, any effort to promote protein synthesis and growth during recovery from shigellosis may be opposed by the acute phase reaction of inflammation. During acute inflammatory reactions, the liver shifts to synthesizing the acute phase reactant proteins, which include the C-reactive protein, and decreases synthesis of other proteins, including albumin and prealbumin (14). Thus, the hypoalbuminemia and impaired growth rates associated with acute infections may be, to some extent, refractory to dietary treatment.

To detect a dietary effect on the rate of protein synthesis, the serum prealbumin concentration is more responsive to energy and protein in the diet than is the albumin concentration because prealbumin is a high turnover protein with a half-life of 1.9 days, contrasted to albumin with a high-life of 12-21 days (15). In Egyptian children with kwashiorkor, the serum concentration of prealbumin increased significantly 2-4 weeks after dietary treatment (16). In American premature infants, the serum prealbumin was a more sensitive indicator of nutritional intake than was the serum albumin (15).
3. **Rationale:**

Malnutrition and growth faltering have been observed as a consequence of diarrhoeal illness in developing countries. In addition to other effects of diarrhoea shigellosis also result blood and mucus loss and can cause serum protein loss in the stool. For children with a marginal diet, this loss must be compensated by increase protein intake for optimal growth to occur. It is obvious that the magnitude of protein loss in the stool in shigellosis is much more than in other diarrhoeal stool. High fever, anorexia, abdominal pain and discomfort, food withholding in these children will make the situation more worse. Early intervention with a diet rich in protein may have some positive impact on subsequent morbidity and nutritional status in these children. This study will help us to find out whether a diet of higher amount of protein for a short period will be able to counteract the growth faltering in children with shigellosis.

**SPECIFIC AIMS**

1. To study the effects of a defined diet with higher amount of protein in children with shigellosis; to achieve a rapid catch-up growth.

2. Whether the same diet has an impact in reducing further morbidity in these children?

**METHODS**

**Sample size calculation**

From the Harvard Standard of children between 30 and 50 months of age (12), the mean monthly increment in height is 6.4 mm with a variance of 0.8 mm. To achieve an alpha error of 0.05 for a worthwhile difference between the diets of 3 mm a month in height, the sample size is 2 \( \left(1.96 \times \frac{\text{variance}}{\text{worthwhile difference}}\right)^2 \) = 54 patients.
Patient selection and management

Fifty-four children between 3 and 11 years old who present to the ICDDR,B clinic with dysentery and have a stool culture positive for Shigella species will be selected. Approximately one patient per week will be selected during a one-year period. To be eligible the patients' parents or guardians must consent to remain in the hospital for 21 days, they should live within 3 miles of the hospital for easy follow-up, and they must agree to receive one of the two diets by randomization. Excluded will be patients with third degree malnutrition, i.e. who have body weights less than 60 percent of the Harvard Standard of weight for age (17). Any patient with nutritional edema or other signs of kwashiorkor will be excluded. Patients with complicating illnesses viz. pneumonia, tuberculosis, septicemia, hemolytic-uremic syndrome, or any other associated diseases will be excluded. Children who are breast-fed, have chronic dysentery also be excluded. Clinical cure will be determined by absence of fever, tenesmus, straining during defecation and reduction in stool frequency.

All patients will be given effective antimicrobial treatment for 5 days, chosen on the basis of in vitro sensitivity testing of individual Shigella isolates. During these 5 days of treatment, the standard hospital diet will be provided and, because of anorexia that usually accompanies acute shigellosis, no attempt will be made to push intensive feeding.

Randomization and dietary treatment

At the end of the 5 days of treatment, and after clinical cure patients will be randomly assigned to one of 2 diets using sealed envelopes that contain cards designating diets in an order obtained from a table of random numbers. The diets will be called "standard protein" and "high protein". Both diets will be isocaloric and contain a high caloric content of 150 kcal/kg body weight per
day, which was calculated by Whitehead [5] to support rapid weight gain for
catch-up growth. The standard protein diet will contain 5 percent of total
calories as protein and the high protein diet 15 percent of total calories as
protein. The diets will be comprised of locally obtainable foods that are
proven to be acceptable by the people. The bulk of calories will be obtained
from rice and bread. The protein sources will be eggs, chicken, and dried
skimmed milk. The caloric value and protein content of sample diets will be
tested by bomb calorimetry and nitrogen content will be measured by microkeidja-
method. These assays are currently available at the ICDDR,B Biochemistry
Department. The patients will be treated with these diets in the hospital for
21 days. Nurses will record portions of food uneaten and any meals vomited.

Food will be given ad-libitum at a regular time intervals.

**Study diet**

(150 kcal/kg/day with 15% protein)

<table>
<thead>
<tr>
<th>Time</th>
<th>Meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>07 a.m.</td>
<td>Bread + milk + suzi</td>
</tr>
<tr>
<td>10 a.m.</td>
<td>Milk + suzi</td>
</tr>
<tr>
<td>12 noon</td>
<td>Rice + chicken</td>
</tr>
<tr>
<td>03 p.m.</td>
<td>Milk</td>
</tr>
<tr>
<td>06 p.m.</td>
<td>Rice + chicken</td>
</tr>
<tr>
<td>09 p.m.</td>
<td>Milk</td>
</tr>
</tbody>
</table>

**Control diet**

(150 kcal/kg/day with 5% protein)

<table>
<thead>
<tr>
<th>Time</th>
<th>Meal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bread + milk</td>
</tr>
<tr>
<td></td>
<td>Milk + suzi</td>
</tr>
<tr>
<td></td>
<td>Rice + chicken</td>
</tr>
<tr>
<td></td>
<td>Milk</td>
</tr>
</tbody>
</table>

Adjustment will be made on concentration of different nutrients to make it
isocaloric.

**Research measurements**

Before the start of the test diets, patients will be weighed to the nearest
gram and height measured to the nearest mm on a stand-up scale. Blood will be
obtained for serum albumin and prealbumin, as measures of the rate of protein
synthesis. The serum prealbumin measurements will be done by radial
immunodiffusion assay. At the end of the 21 days of dietary treatment, the weight and height measurements and serum protein levels will be repeated. Serum total protein, albumin and prealbumin will be done at 3 months and 6 months.

**Home follow-up measurements**

To test the possible beneficial effects of the high protein diet on subsequent growth and health, monthly home visits will be made for every 15 days. A portable scale will be used for weight and height. Recurrences of diarrhoea or occurrences of other diseases will be recorded during the follow-up visits.

**Morbidity data**

Questions will be asked about whether the child developed diarrhoea, character of stool (watery, dysentery, bloody), running nose with or without purulent discharge and without respiratory distress (will be graded as URTI), fever, cough with respiratory distress (will be graded as LRTI), skin infection, scabies, impetigo etc. However, all these patient will be given proper health education in respect to personal hygiene. They shall be asked to report to the hospital for any illness or will be transferred to the hospital if detected during follow-up visit for better management and diagnosis. For diarrhoeal illness if patient cannot be taken to hospital a stool specimen will be brought to hospital laboratory for diagnosis. For validation of field data on weight and height every 4th patient will be brought back to hospital every month for accurate measurement of weight or height.

**Data analysis**

Monthly increments of heights and weights of the patients will be calculated and compared to the Harvard Standard (12). The means of the increments of height and weight during each month and the means of serum protein concentrations will be compared between the two dietary groups by Student’s t
test. Rates of recurrence of diarrhoeal disease and other infections will be compared using Fisher's Exact Tests and Chi-square tests.

COLLABORATIVE ARRANGEMENTS

This study will be carried out in collaboration with Case Western Reserve University. Dr. John Banwell in the Division of Gastroenterology and Nutrition, Dr. Thomas Butler in the Division of Geographic Medicine, and Dr. Harold Houser in the Department of Epidemiology and Biostatistics will participate.
REFERENCES


ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

1. Fifty-four children aged 2-5 years with bacteriological proven shigellosis will be given a diet containing higher amount of protein or regular amount of protein for 21 days. Both the study patient and control patients will be followed up for 6 months at their home. The impact of supplementing higher amount of protein on their nutritional state and further morbidity will be evaluated.

2. Patients with severe malnutrition and other complicating illnesses will be excluded.

3. There is no potential risk involved in the study, every precaution will be taken to safeguard the interest of the patient.

4. All the records will be kept strictly confidential and will remain with the investigators.

5. Informed consent (signed or thumb impression) will be obtained from the guardians or parents. There is no procedure in this study which may unmask the privacy of the subject.

6. Interview will be taken only to the history of illness and is needed only for clinical management of the disease.

7. The patient will benefit from the treatment of diarrhoeal illness. General benefit to the community include to set a policy, whether short-term nutritional therapy with a diet with higher amount of protein is effective in reducing further morbidity and growth faltering in children with shigellosis.

8. The study will require rectal swab for bacteriological culture on admission and venous blood samples for prealbumin.
## PERSONNEL SALARY

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>% of effort</th>
<th>Annual salary</th>
<th>Project requirement (US Dollar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. I. Kabir</td>
<td>Pr. investigator</td>
<td>50</td>
<td>5760</td>
<td>2x2880 = 5760</td>
</tr>
<tr>
<td>Dr. S. A. Sarker</td>
<td>Co-investigator</td>
<td>20</td>
<td>4920</td>
<td>2x984 = 1968</td>
</tr>
<tr>
<td>Dr. A. Islam</td>
<td>Co-investigator</td>
<td>10</td>
<td>5760</td>
<td>2x576 = 1152</td>
</tr>
<tr>
<td>Medical Officer (to be named)</td>
<td></td>
<td>20</td>
<td>4200</td>
<td>2x840 = 1680</td>
</tr>
<tr>
<td>Field workers (to be recruited)/GS 3</td>
<td></td>
<td>100</td>
<td>1440</td>
<td>3x2x1440 = 8640</td>
</tr>
</tbody>
</table>

Sub-total: 19200

## SUPPLIES AND MATERIALS

- Dry skimmed milk, chicken, egg: 900
- Office supplies: 300

Sub-total: 1200

## CAPITAL EXPENDITURE

- Weighing machine, scale, caliber: 1000

## OTHER COST

- Rent, communication & utilities: 50
- Printing and publication: 500
- Service charges: 50

Sub-total: 600

## INTERNATIONAL TRAVEL

For attending conference/seminar: 2000

## INTERDEPARTMENTAL SERVICES

- Computer (for data analysis): 2000
- ICDDR,B transport (Dhaka): 54 x 6 x 10 = 3240-mile x Tk.12 = 1296
- Xerox and mimeography: 200
- Laboratory investigation (Pre-albumin, fat, protein, CHO analysis of diet): 500
- Patient hospitalization (Tk.500/day x 21 x 54 pts): 18900
- Medical illustration: 50

Sub-total: 22946
### B. SUMMARY BUDGET

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Local salaries</td>
<td>19200</td>
</tr>
<tr>
<td>2. Supplies &amp; materials</td>
<td>1200</td>
</tr>
<tr>
<td>3. International travel</td>
<td>2000</td>
</tr>
<tr>
<td>3. Other costs</td>
<td>600</td>
</tr>
<tr>
<td>4. Interdepartmental services</td>
<td>22946</td>
</tr>
<tr>
<td><strong>Total direct cost</strong></td>
<td><strong>45946</strong></td>
</tr>
<tr>
<td>Plus 31% overhead</td>
<td>14244</td>
</tr>
<tr>
<td><strong>Capital expenditure</strong></td>
<td><strong>60190</strong></td>
</tr>
<tr>
<td></td>
<td><strong>61190</strong></td>
</tr>
</tbody>
</table>
Follow-up MORBIDITY form

POST-SHIGELLA FEEDING STUDY

Patient identification: ___/___/___

Name: ___________________________ Sex: _______ Age: _______

Date of interview: ___/___/___/___/___/___/___ Week of follow-up: ______

Date of previous interview: ___/___/___/___/___/___/___

Address: ___________________________________________

Previous 15 days symptoms:

- Diarrhoea

  Stool character:
  Watery
  Mucoid
  Bloody

  Vomiting

  Loss of appetite

  Fever

  Cough

  Skin rash

  Nasal discharge

  Purulent cough

  Hurried respiration

  Discharge of pus from ear

  Skin infection

16
<table>
<thead>
<tr>
<th>Item</th>
<th>Notes</th>
<th>Items</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding history</td>
<td>_/ _/</td>
<td>SKFT (cm)</td>
<td>_/ _/ _/</td>
</tr>
<tr>
<td>Formula milk</td>
<td>_/ _/</td>
<td>Wt (kg)</td>
<td>_/ _/ _/ _/ _/</td>
</tr>
<tr>
<td>Animal milk</td>
<td>_/ _/</td>
<td>MAC (cm)</td>
<td>_/ _/ _/ _/ _/</td>
</tr>
<tr>
<td>Rice</td>
<td>_/ _/</td>
<td>Length (cm)</td>
<td>_/ _/ _/ _/ _/</td>
</tr>
<tr>
<td>Rice suzi</td>
<td>_/ _/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapati</td>
<td>_/ _/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat/fish</td>
<td>_/ _/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td>_/ _/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others (specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CONSENT FORM

Post-shigellosis feeding study

Your child is suffering from blood dysentery. The present knowledge from different studies suggests that due to profuse loss of blood, mucus, and high fever children can develop malnutrition and growth faltering. To counteract this problem we are investigating whether a diet with higher amount of protein supplementation is helpful to improve the nutritional status and further morbidity in these children. If you agree to participate into the study, your child will have to stay at hospital for additional 21 days after treatment with appropriate antibiotic. Your child will receive either a regular hospital diet or study diet which contain higher amount of protein. Your child will be discharged after 21 days, and 5 ml of blood will be taken from your child on admission and on discharge to see the change in protein status in your child. Your child will be visited by field worker every month and body weight, height, and mid-arm circumference will be measured. You will be also asked about any history of illnesses on each visit and proper treatment will be provided.

If you agree to participate and agree to comply with follow-up please sign here. You may withdraw your child anytime and proper care will not be altered by that.

----------------------------------------
Signature of investigator
----------------------------------------
Signature/Thumb impression of guardian

Date: ________________________________
অদ্যমতি পুনরায়
শিগেলা- সবচেয়ে- আকারের- পর্যায়
(Preliminary Shigella feeding Study)

আলমত যে, মন্ত্রি-আমাকের হেডারে। এখানে কিভাবে
শিগেলা হেডার থেকে মে, প্রশ্ন- রক্ষণ, প্রশ্ন, এবং ঘটনার
জন্য শিগেলা- পুষ্টিগত এবং বুদ্ধি, বিশ্লেষণ হত
প্রস্তুত করবে। এই অনুচ্ছেদ- অর্থনৈতিক অ্যানাল্যাসে একজন যান্ত্রিক
অধ্যায অনুসারে একজন প্রমাণ যার অর্থনৈতিক কাজ প্রয়োজন
নয়, যে আগ্রহ পুনরায় প্রশ্নগল্লীতে প্রীত হয়ে আমাকে
যেও আলমার বিশ্ববিদ্যালয় প্রয়োজনীয় অনুষ্ঠান তুলনা দ্বারা প্রতিষ্ঠানের গুরুত্ব
আলমারে আরো ২২ দিন আমাকের হেডার হবে।
আলমারে আলমার নামে আলমার বিশ্ববিদ্যালয়ের
নামে আলাদা অন্যতম আমার একজন অনিবার্য আমার প্রাক্কালে
২২ দিন পর আলাদার বিভাগের তথ্যালয় থেকে প্রাছি-প্রদর্শন
বিষয়। আলাদার- প্রথম অর্থ- আলাদা অর্থনৈতিক অ্যানাল্যাস
জন্য অন্যতম অপর এবং প্রীত হয় আলাদা তার অর্থ- বেলুকে সাথে ছিন্ন-প্রাঙ্গণ রুদ্ধ হবে। মূলনৈতিক অর্থনৈতিক আলাদার
প্রথমে আলাদার শিগেলা- পর্যায়ের উন্নত এবং অত্যন্ত আলাদার
নিয়ে আলাদা। অন্যদিকে আলাদার বিশ্ববিদ্যালয় অন্যতম অন্যতম
আলাদাকে প্রতিষ্ঠা করা হবে এবং প্রয়োজনীয় অর্থনৈতিক
তথ্য হবে।

আলাদার নামে অল্পের অংশের রাজি আলাদা তবে
নিজের শাহর- দিন। আলাদা যে শেষ অনুমান আলাদার শিক্ষাদে
অল্পের কথা নিশ্চিত হবেন তাতে তার
অর্থনৈতিক- প্রাচীন রাজি- না।

নাম/প্রাচীন

অভিজ্ঞতার যান্ত্রিক/দৃষ্টিক-
প্রাচীন।