Principal Investigator: Dr. Sultanum Chahum
Trainee Investigator (if any):
Supporting Agency (if Non-ICDDR,B):

Effect of zinc and Copper supplementation on the Dietary Intake and
of Weight-gain in Bangladeshi children Recovering from Severe Malnutrition.

Project status:
- New Study
- Continuation with change
- No change (do not fill out rest of form)

Be the appropriate answer to each of the following (If Not Applicable, write NA).

5. Will signed consent form be required?
   (a) From subjects
      Yes No
   (b) From parent or guardian (if subjects are minors)
      Yes No

6. Will precautions be taken to protect anonymity of subjects?
   Yes No

7. Check documents being submitted herewith to Committee:
   - Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   - Protocol (Required):
   - Abstract Summary (Required)
   - Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   - Informed consent form for subjects
   - Informed consent form for parent or guardian
   - Procedure for maintaining confidentiality

*If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Ctte. for review.

Principal Investigator:

Date: 21 March 1984
EFFECT OF ZINC AND COPPER SUPPLEMENTATION ON THE DIETARY INTAKE AND RATE OF WEIGHT-GAIN IN BANGLADESHI CHILDREN RECOVERING FROM SEVERE MALNUTRITION.

Sultana Khanum

A.N. Alam
Akbar Ali
Medical Officer (CNU)

M. Mujibur Rahman

April 15, 1984

October 14, 1984

US$ 2917

Nutrition Working Group

by M. Rahman

28 / 1984

Seventy five children aged between 6 months to 6 years admitted to the Children's Nutrition Unit (CNU), Dhaka with severe degree of Protein Energy Malnutrition (PEM) will be selected for the study. Zinc and copper supplementation will be given to two study comprising groups 25 in each group. One will receive zinc alone and the second group copper alone in addition to CNU diet and other supplementation. A third control group of 25 children will be offered usual CNU diet and other supplements as given routinely to other patients. The effect of zinc and copper on the dietary intake and rate of weight gain in Bangladeshi children recovering from severe malnutrition will be studied.
SECTION II - RESEARCH PLAN

INTRODUCTION:

1. Objective
   a. To study the effect of zinc and copper supplementation in malnourished children during nutritional rehabilitation on dietary intake.

   b. To study the rate of weight gain in zinc and copper supplemented and nonsupplemented PEM children during recovery.

2. Background:

   Zinc is needed for tissue synthesis both as a component of new tissue and in the forms of zinc metalo-enzymes essential for nucleic acid, protein and hormone (i.e. insulin) synthesis. Studies indicate that the size of body zinc store is extremely limited so that there is a day-to-day requirement for dietary zinc\(^{(1,2)}\). In normal children zinc is required to support growth as well as to replace losses. Hambridge's group has shown that a diet marginal in zinc may be the cause of failure to thrive in North America\(^{(3,4)}\). Zinc and vitamin A are linked through the enzyme retinol alocohol dehydrogenase, essential for the oxidation of retinaldehyde, the vitamin A aldehyde and also through the need for zinc in synthesis of retinol binding protein. The continual formation of the visual pigment is of utmost importance in the prevention of night blindness\(^{(5)}\). Children recovering from PEM may gain weight at over 20 times the normal rate. In this situation where the requirements for new tissue synthesis dominate the total dietary requirements the amount of zinc that has to be utilized by the new tissue may exceed the dietary supply. When this is the case only zinc may both limit the absolute rate of weight gain and determine the composition of new tissue laid down\(^{(6)}\).
Serum zinc and copper level were estimated in 130 severely malnourished children admitted to CNU, Dhaka on admission and during recovery (3–6 weeks) \(^6\). The serum zinc and copper levels were found to be significantly low in all 3 types of PEM (marasmus, kwashiorkor and marasmic-kwashiorkor) compared to 50 age-matched healthy controls. After nutritional rehabilitation the serum level of zinc and copper increased in all 3 types but did not reach the normal level (80–140 µg/dl). However, retinal Binding protein and albumin levels were not estimated due to non-availability of laboratory back up. Golden and Golden \(^7\) found that there was an immediate and definite increase in their rate of weight gain with zinc supplementation in 14 of 16 PEM cases.

Until recently the concept of copper deficiency in man was not widely accepted. Copper deficiency developed in severely malnourished children rehabilitated on milk-based low copper diet was reported by Cordavo Basert and Graham in 1964 \(^8\). In another study they diagnosed copper deficiency in premature and malnourished infants in 1969. Copper deficiency was then observed in untreated malnourished infants by Holtzman et al in 1970 \(^9\). Keppel and Peden in 1972 observed copper deficiency in malnourished infants alimented exclusively on intravenous route \(^10\). Goel, Misra and Seth in 1980 found a reduced plasma copper level in all types of PEM with the mean levels being same in marasmus and marasmic-kwashiorkor \(^11\). Khalil et al in 1974 found significantly lower plasma erythrocyte copper in PEM cases than in normal controls \(^12\). Duran et al reported decreased copper level on admission and during recovery stage of nutritional marasmus \(^13\).

An analysis of 2136 hospital cases records of PEM cases from CNU showed that inspite of higher energy intake (200 kcal/day) during recovery (2–4 weeks) the rate of growth was not satisfactory. There was no correlation between higher energy intake and rate of weight gain. In these cases zinc or copper or both might have been limiting factors.
3. **Rationale:**

If the study is done successfully the rate of weight gain will be expected to be faster, patients will achieve maximum catch up growth in a shorter rehabilitation time, resulting in rapid hospital bed turn over. This way treatment cost per patient will be reduced. Moreover if discharged with a better nutritional status the long term effect of rehabilitation will be very satisfactory in terms of morbidity and mortality.

**METHODS OF PROCEDURE:**

1) Seventy five malnourished children between 6 months to 6 years of age who are recovering from malnutrition in the Children’s Nutrition Unit will be selected for this study.

2) Children who are on antibiotics and having surgical injury, renal failure, tuberculosis, juvenile diabetes, liver diseases or patients resuscitated with heavy fluid or transfusion will be excluded from the study.

3) Their nutritional status will be determined by weight for height percentage of Harvard Standard and presence or absence of oedema. They will be divided into three groups with age matched controls. One group (controls) will get usual CNU diet and other supplements like rice, meat, vegetables, dal, milk (Table 1), folic acid, riboflavin, ascorbic acid, folfetab and high potency vitamin A capsules both as treatment and prophylaxies. In addition to CNU dietary regime one other group will get zinc alone and the third group will receive only copper supplements. Zinc is variably absorbed, moreover in Bangladeshi children there is considerable loss of zinc in various ways such as, perspiration, chronic diarrhoea etc. so zinc will be given at a dose of 5-10 mg/kg/day as sulphate. Copper supplement 80 mg/kg/day as copper sulphate will be given.
For the zinc and copper group the two elements will be given separately at separate times.

4) In these malnourished children, on admission to CNU, about 3 mls. of venous blood is drawn by jugular venepuncture for routined investigation like blood culture, TCDC, packed cell volume, haemoglobin, plasma protein, blood grouping etc. Three samples of 1 ml of blood will be needed for zinc, copper ceruloplasmin, RBP, prealbumin and serum transferin estimations for the study, that is on admission, and on weekly intervals. This collection will be made from our routine specimen. A further 1 ml blood sample (between 6 weeks to 6 months) after discharge may be needed.

5) Zinc and copper supplementation will be given from the third week after initial resuscitation period when weight gain is steadily increasing.

6) Stool and urine will be collected at intervals like that of blood.

7) Zinc and copper will be estimated from the food mixes used in CNU.


3. Hambidge K.M., Hambidge C., Jacobs M and Baum J.D. Low levels of zinc in hair anorexia, poor growth and hypogeusia in children.


Abstract Summary for Ethical Review Committee:

1) This limited study aims at achieving a rapid weight gain during rehabilitation of malnourished children in Bangladesh by giving zinc and copper supplementation. Rehabilitation of malnourished children is an expensive and long-protracted undertaking. As recovery is delayed due to some limiting factors, many hospital beds are occupied for a long period and many children who need admission from the outpatient department are deprived of inpatient care due to very limited hospital beds. In this study, therefore, zinc and copper will be supplemented to hasten recovery (in the form of sulphates) at a safe and effective recommended dose along with usual treatment schedule offered at CNU to severely malnourished children aged between 6 months - 6 years during nutritional rehabilitation.

2) There are no potential risk involved.

3) The patients will be under consistent observation of physicians and nurses and will get optimum care necessary although there are no potential risk involve.

4) During data analysis only case number will be used.

5) Informed consent in a consent form will be obtained from the authorised legal guardian or the parents of the patient before being included in the study.

6) A brief interview is usually taken before admission to obtain clinical history of the disease.

7) The patient will get free treatment and care during study period and if successful will make early recovery.

8) Hospital record will required.
9) Follow up will be necessary up to 6 months after discharge which will not be a problem because follow-up is usually a part of our normal work.

10) One ml of blood on four occasions will be needed during the whole study period.
### SECTION III - BUDGET

#### Personnel Services

<table>
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<th>Name</th>
<th>Position</th>
<th>% Effort</th>
<th>Project Requirement US$</th>
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<tbody>
<tr>
<td>Dr. Sultana Khanum</td>
<td>Principal Investigator</td>
<td>30</td>
<td></td>
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<tr>
<td>Dr. A.N. Alam</td>
<td>Co-Investigator</td>
<td>5</td>
<td>200</td>
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<tr>
<td>Mr. Akbar Ali</td>
<td>&quot;</td>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>Physician from CNU (to be named)</td>
<td>&quot;</td>
<td>10</td>
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</tr>
<tr>
<td>Dr. M.M. Rahaman</td>
<td>Consultant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research Officer (Biochemistry)</td>
<td></td>
<td>10</td>
<td>200</td>
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</table>

#### Supplies & Materials

Routine investigations including blood culture (to be done at the CNU), costing of biochemical assays (attached) 2367

#### 1. Equipments
Nil

#### 2. Patient hospitalization
Nil

#### 3. Outpatient care
Nil

#### 4. ICDDR,B transport
Nil

#### 5. Travel
Nil

#### 6. Transportation of things and patients
Nil

#### 7. Rent, Communication, Utilities
Nil

#### 8. Printing & Publication
Nil

#### 9. Other contractual services
Nil

#### 10. Construction
Nil

Total US$ 2917
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<tr>
<th>Sl No.</th>
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<th>Rate in $</th>
<th>Total Cost $</th>
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<tr>
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<td>2.74</td>
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<tr>
<td>2</td>
<td>Copper</td>
<td>75</td>
<td>2.74</td>
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<td>3</td>
<td>Pre-albumin</td>
<td>75</td>
<td>8.69</td>
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<td>Retinol binding protein</td>
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<tr>
<td>5</td>
<td>Ceruloplasmin</td>
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<td>8.69</td>
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<tr>
<td></td>
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আনুষ্ঠানিক উদ্বাগুয় গবেষণা কেন্দ্র

সমৃদ্ধি পত্র

আনুষ্ঠানিক উদ্বাগুয় গবেষণা কেন্দ্র এবং পি, ওম, ইউ, পুষ্টিহীনতার উল্লেখ চিকিৎসা উন্নয়নের জন্য যৌথভাবে কাজ করে যাচ্ছে। পুষ্টিহীনতার চিকিৎসার বিভিন্ন সমস্যা আছে।

তার মধ্যে একটি হচ্ছে পুষ্টি পুরুষালয়ের সময় ধীরে ওজন বাড়া। দ্রুত ওজন বাড়ানোর জন্য সহযোগী উপাদান হিসাবে চক্ষু ও কপারের ব্যাপারে সমস্ত ধারণা খানা দরকার

কেননা ইহা দুঃখ আরোগ্য ও তাল ব্যাপস্থাপনায় সাহায্য করে।

আমার আগন্তুর শিখে এই গবেষণায় অনুরূপ করতে চাই।

১. আগন্তুর শিখ উল্লেখ চিকিৎসা পাবে।

২. মাত্র ১ সি সি করে মোট ৪ বার রত্ন নেওয়া হবে বৈশ-রাসায়নিক পরীক্ষা

করার জন্য।

৩. প্রয়োজনীয় সুশ্রুত খাবার ও ঐহিত্য সরবরাহ করা হবে।

৪. আগন্তুর শিখ হয় লিঙ্ক (৫-২০ মিন গ্রাম/কেজি/দিন) অথবা ব্যাপার (৫০ মিন গ্রাম/কেজি/দিন) ওয়া সুপ্রস্তু থেকে গ্রহণ করবে।

৫. অন্যান্ত প্রয়োজনীয় পরীক্ষা নিরীক্ষা করা হবে।

৬. আগন্তুর শিখ সম্পূর্ণ সুশস্য হওয়ার পর তুর্কি দেওয়া হবে।

৭. আগন্তুর শিখ সমাপ্তি গবেষণা থেকে শিখে প্রস্তাব করে নিতে পারবেন।

আগন্তুর শিখ একই চিকিৎসা পাবে যদিও আগন্তুর শিখ এই গবেষণায় অংশ

গ্রহণ না করান।

যদি আগন্তুর এই গবেষণায় আগন্তুর শিখে অংশগ্রহণ করতে ইচ্ছা করেন তবে দুঃখ

করে নিজে সুচারু করতে বা বাম হাতের বুড়ো আঁখুলের ছাপ দিন।

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বাম হাতের বুড়ো আঁখুলের ছাপ

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পরিষেকের স্বাক্ষর

তারিখ: -------------------------------------------------

সম্পর্কের মূল স্বাক্ষর

ব্রোগির সাথে সম্পর্ক

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