Attachment 1. 26

Date 15.12.85. 19.12.85

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. B.J. Collins

Trainee Investigator (if any) _____

Application No. 85-092

Supporting Agency (if Non-ICDDR,B) _____

Title of Study Pancreatic exocrine function in acute diarrhoea caused by Vibrio cholerae and Shigella.

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

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

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects (Yes) No
   (c) Minors or persons under guardianship Yes (No)
2. Does the study involve:
   (a) Physical risks to the subjects (Yes) No
   (b) Social Risks Yes (No)
   (c) Psychological risks to subjects Yes (No)
   (d) Discomfort to subjects (Yes) No
   (e) Invasion of privacy Yes (No)
   (f) Disclosure of information damaging to subject or others Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) (Yes) No
   (b) Use of fetal tissue or abortus Yes (No)
   (c) Use of organs or body fluids (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study (Yes) No
   (b) Procedures to be followed including alternatives used (Yes) No
   (c) Physical risks (Yes) No
   (d) Sensitive questions Yes No N.A.
   (e) Benefits to be derived (Yes) No
   (f) Right to refuse to participate or to withdraw from study (Yes) No
   (g) Confidential handling of data (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure (Yes) No
5. Will signed consent form be required:
   (a) From subjects (Yes) No
   (b) From parent or guardian (if subjects are minors) Yes No N.A.
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
   ___ Questionnaire or interview schedule *

* 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 Cttee. for review.

(PTO)

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

Brendan J Collins
Principal Investigator

Trainee

85-042
19/12/85

SECTION I : RESEARCH PROTOCOL

1. TITLE : Pancreatic exocrine function in acute diarrhoea caused by Vibrio cholerae and shigella.

2. PRINCIPAL INVESTIGATORS : Dr. B. J. Collins
Dr. P. K. Bardhan
Dr. A. M. Molla

CO-INVESTIGATORS : Dr. F. Van Loon
Dr. Ayesha Molla

COLLABORATOR : Prof. Klaus Gyr

3. EXPECTED STARTING DATE : 1st January, 1986

4. EXPECTED COMPLETION DATE : 31st December 1986

5. TOTAL DIRECT COST : US $80,767 including 31% overhead

6. SCIENTIFIC PROGRAMME HEAD :

This protocol has been approved by the Pathogenesis and Therapy Working Group.

Signature of the Scientific Programme Head

Date 4/12/85.

7. ABSTRACT SUMMARY:

Epidemiological evidence indicates that recurrent diarrhoeal disease predisposes to malnutrition and the importance of aggresive nutritional rehabilitation of patients with acute diarrhoeal illness has been recognised. Cereal-based oral rehydration therapy has recently proved effective in

(iii) Director's signature & remarks, if any:_____

treating dehydration and this development has made feasible the early administration of nutrients to patients with acute diarrhoea.

Transient nutrient malabsorption has been documented, however, during acute intestinal infection although the mechanisms have not been elucidated. Pancreatic function has not been assessed in patients with acute diarrhoeal disease, yet pancreatic insufficiency has been documented in chronic diarrhoeal disorders. The output of pancreatic bicarbonate and the enzymes, trypsin, chymotrypsin, lipase and amylase will be assessed quantitatively after direct stimulation of the pancreas with secretin-caerulin and after indirect stimulation of the pancreas by a standard liquid test meal in 30 adult patients with acute diarrhoea and in 10 healthy volunteers. The release into the blood circulation of intestinal hormones which influence pancreatic secretion will be monitored during the administration of the test meal. Patients will be selected for study to include 15 acute cholera and 15 acute shigellosis. In addition 10 healthy volunteers will also be studied. Results from this study will establish the secretory status and responsive capacity of the exocrine pancreas and will provide information about the release of pancreas stimulating hormones, secretin, cholecystokinin and vasoactive intestinal polypeptide from small intestinal mucosa in patients with acute bacterial diarrhoea. Information gained from the study will aid our understanding of digestive and absorptive function in acute diarrhoea and will help development of cereal-based oral rehydration therapy and nutritional rehabilitation regimes.

REVIEWS:

(i) Ethical Review Committee: _____

(ii) Research Review Committee: _____

(iii) Director's signature & remarks, if any: _____

SECTION II : RESEARCH PLAN

A. INTRODUCTION

1. Objective:

To determine the secretory status and the responsive capacity of the exocrine pancreas in acute bacterial diarrhoeas.

2. Background:

In recent years considerable attention has been focussed on the relationship between acute diarrhoeal disease and nutritional status in developing countries. From these studies, a number of observations has been made.

a. Children who suffer from frequent episodes of diarrhoeal illness have impaired growth in terms of weight and height gain.[1,2]

b. Weight loss which occurs during an acute diarrhoeal illness is often in excess of the weight gain which occurs in the recovery period.[3]

c. Weight loss in acute diarrhoeal illness is caused by a combination of factors including decreased food intake,[4,5] malabsorption of nutrients,[5,6] and an increased catabolic state especially in febrile patients.[7] The reduction in food intake, which has been observed to be about 42% of normal in one study,[8] reflects both the withholding of food from the patient with diarrhoea as a means of "resting the bowel" and an aversion to food because of symptoms of anorexia, nausea and vomiting.

d. Malnutrition predisposes to more frequent episodes of diarrhoea,[9] to more severe and prolonged episodes of diarrhoea,[9,10] and to an increased mortality from diarrhoeal illness.[9,11] These observations have highlighted the importance of rapid and aggresive nutritional rehabilitation of patients with acute diarrhoeal illness. Oral rehydration therapy is now established as the appropriate method of administering fluid, electrolytes and partly nutrients in these patients.[12] The emphasis of studies of this form of therapy however, has been on its efficacy as a rehydrating solution rather on its nutritional value. The recent introduction of cereal-based oral rehydration solutions has made possible the early administration of fluid rich in nutrients in the form of cereal to patients with acute diarrhoeal disease.[13] Initial results suggest that a rice-based oral rehydration solution is very well tolerated by cholera patients and in fact, less vomiting has been observed during this therapy than occurs with glucose electrolyte solution, so that there is potential for enhanced nutrient intake.[14]

Starch exerts a low osmotic activity and large amounts of cereal can be added to oral rehydration solution without the risk of osmotic fluid loss, thus providing a higher calorie intake than can be achieved with glucose solutions. Rice is the most commonly used cereal in Asian countries and it is composed of polysaccharides (starch), amylopectin, proteins and vitamins. These substrates are enzymatically hydrolysed in the small intestinal lumen and split into monosaccharide molecules, peptides and aminoacids, which are

absorbed and thereby act as carrier molecules for the absorption of sodium and water. The hydrolysis of the high molecular weight rice powder into the constituent low moleclular weight monosaccharides amino acids and peptides is dependent on normal pancreatic exocrine function.

Several studies have considered nutrient intake and absorption in acute diarrhoea. Chung showed that the absorption of nitrogen and fat in 4 infants with acute diarrhoea was proportional to the amount of intake.[15] More recently, Molla and Colleagues found not only a reduction in nutrient intake during acute diarrhoea of different aetiologies but also a mild to moderate malabsorption of nitrogen, fat and carbohydrate.[5,6] The mechanisms of the malabsorption were not elucidated in those studies but they highlighted the concern that absorption of the recently introduced rice-based oral rehydration solutions may be limited in acute diarrhoea. Before further development of this important therapy and before we advocate continued intake of food during diarrhoea it is imperative to assess the capacity of pancreatic and intestinal digestive and absorptive function.

The exocrine pancreas secretes up to 6g of protein daily, mainly as enzyme.[16] These enzymes which include amylase, lipase, trypsinogen, chymotrypsinogen, procarboxypeptidase, prophospholipase and proelastase, play an important role in the digestion of carbohydrate, fat and protein. The control of pancreatic enzyme secretion is complex and appears to involve neurological and endocrine pathways.[17] Vagal activity

initiated by the thought smell or taste of food and by gastric distension, releases acetylcholine which stimulates pancreatic enzyme secretion.[18] Secretin, a polypeptide hormone, is released from the duodenum by acid, bile acids and sodium oleate and stimulates pancreatic bicarbonate secretion.[19] The effect of secretin is potentiated by cholecystokinin, gastrin, vasoactive intestinal polypeptide and vagal cholinergic impulses.[19] Cholecystokinin, another polypeptide hormone, is released from the duodenum and jejunum by amino acids, fatty acids and hydrochloric acid.[19] It's most important action is the promotion of pancreatic enzyme output.[19] Bile salts in the duodenum also stimulate the secretion of pancreatic enzymes and this may be important in coordinating fat digestion.[20]

Very little is known regarding pancreatic exocrine function in acute infectious diarrhoea. Greenough in 1965 showed that duodenal fluid aspirated from cholera patients was rich in bicarbonate and amylase.[21] A preliminary study conducted at the ICDDR,B has found normal trypsin concentration in duodenal aspirates from patients with acute diarrhoea.[22] A microscopical study of the pancreas of cholera patients who died in the early stage of the disease suggested the probability that there was increased secretion by the exocrine pancreas in acute cholera.[23]

These observations provide no truly quantitative information about pancreatic function but such information is required before we can clearly understand the pathophysiological background and the scientific basis of the effectiveness of cereal based oral rehydration therapy and implement effective dietary therapy during acute diarrhoea.

Pancreatic exocrine insufficiency has been documented in patients with severe protein calorie malnutrition,[24] and these patients are

prone to more severe and prolonged episodes of acute diarrhoeal illness.[9,10] Abnormal pancreatic responsiveness has been described in patients with untreated coeliac disease, a chronic diarrhoeal disorder, and has been attributed to the diminished release of cholecystokinin and secretin from damaged intestinal mucosa in response to food.[25,26] The effects of the common diarrhoeagenic toxins of bacterial origin upon enterocytes are to induce hyper secretion of fluid and electrolytes by an intracellular effect upon intracellular mesengers (cAMP, cGMP and Ca^{++})[27]. What is not clear, however, is their effect upon the gut endocrine cells in the upper intestinal mucosa. S cells containing secretin and I cells containing cholecystokinin are present in the mucosa of the duodenum and jejunum.[28] A disruption of the functional or morphological integrity of these cells might occur in acute bacterial diarrhoea and lead to reduced release of secretin and cholecystokinin with, accordingly, an impaired pancreatic secretory response.

Vasoactive intestinal polypeptide (VIP) is found throughout the gastro-intestinal tract, in the endocrine cells (D_1 cells) of the mucosa and in the fine submucosal nerve fibres and the myenteric plexus.[29] Biological actions of VIP include stimulation of adenylate cyclase, stimulation of intestinal fluid secretion and inhibition of intestinal absorption as well as stimulation of pancreatic secretion, both exocrine and endocrine.[30] The diarrhoea which accompanies the Verner-Morrison Syndrome is caused by VIP released from pancreatic tumours.[31] VIP has been shown to be released from feline small intestine when exposed to cholera toxin,[32] and it was proposed that the increased secretion in cholera might be secondary to the activation of intramucosal nervous

reflexes in the gut. One report has described higher plasma VIP levels in patients with acute diarrhoea when compared to controls,[33] indicating that VIP may be involved in the diarrhoeal pathophysiology.

These observations highlighted the important and complex interactions between the small intestine and pancreas mediated by various endocrine and neuro-endocrine pathways. Any study of pancreatic function in patients with acute diarrhoeal disease must take account of the full entero-pancreatic axis since a damaged small intestine may be incapable of initiating an appropriate pancreatic secretory response to food.

There are several traditional approaches to the study of exocrine pancreatic function. These include:

1. Intubation tests:
   a. Direct stimulation, e.g. secretin test, secretin-CCK/caerulin test.
   b. Indirect stimulation, e.g. Lundh meal test.
2. Tubeless tests e.g. para-amino benzoic acid (PABA) test.

The secretin-CCK test involves the collection of pancreatic juice with a double-lumen duodenal tube after stimulation of the pancreas by an injection or infusion of secretin ± cholecystokinin.[34-36] This is the 'gold standard' pancreatic function test and its sensitivity and specificity for the detection of pancreatic insufficiency and chronic pancreatitis have been extensively reviewed.[37] If a patient is suspected of having primary pancreatic insufficiency then this is the investigation of choice since the maximal secretory capacity of the exocrine pancreas to exogenous hormonal stimulation is measured. Patients with intestinal disease, however, may have a degree of secondary pancreatic insufficiency

because of defective release of pancreas stimulating hormones, secretin or cholecystokinin, from the intestinal epithelium. The administration of exogenous secretin bypasses the defect and the secretin test may fail to reveal a problem of pancreatic responsiveness to ingested food.

The Lundh test meal, described by Lundh in 1962, involves the collection of duodenal juice and assay of tryptic activity after ingestion of a standard meal designed to stimulate the pancreas in a physiological manner.[38] The traditional meal in this test is 300 ml fluid containing 6% fat (corn oil or soyabean oil) 5% protein (casilan, egg white) 15% carbohydrate (glucose). Several investigators have shown that the Lundh test is a simple and helpful test in the diagnosis of chronic pancreatitis and pancreatic insufficiency.[39-41] Comparison of the Lundh test with the secretin test or secretin-CCK test has been made in a number of studies. Good correlation was found by some investigators,[42-44] one report showed the Lundh test to be less sensitive,[45] and another showed it to be more sensitive[46] than the secretin test.

Most investigators who favour the Lundh test stress that it is simple physiological and inexpensive. A disadvantage in a routine diagnostic setting is its dependance on normal endogenous release of CCK and secretin from intact small bowel mucosa and erroneous diagnosis of primary pancreatic pathology may be made unless this limitation is appreciated. When an entero-pancreatic defect is being hypothesised as in this study, then the Lundh test meal becomes an essential component of a methodical assessment of pancreatic secretory response.

The traditional Lundh test involves the assay of tryptic activity in a collection of duodenal juice but no attempt is made to quantify the enzyme output.[38] By introducing a duodenal marker perfusion system, the volume of duodenal fluid can be calculated and the actual output of trypsin, lipase and amylase from the pancreas can be estimated from the concentrations of these enzymes in duodenal samples. This modification of the Lundh test has been used successfully in a number of physiological studies of pancreatic function and it provides more meaningful data for the quantitative assessment of pancreatic function.[47,48] Experience with this technique has been gained by Klaus Gyr and colleagues,[48] who will be collaborating with this study.

Tubeless pancreatic function tests, such as the PABA test, are useful screening tests for pancreatic function in a clinical setting.[49] They have high specificity but less good sensitivity especially in the detection of mild cases of pancreatic insufficiency, when compared to the secretin test or the Lundh test.[37] There are no quantitative data of pancreatic enzyme output in these tests, as only the pancreas-dependent absorption of a food marker is measured.[37]

3. RATIONALE:

Malnutrition is worsened by recurrent acute diarrhoeal illness and increases the mortality from subsequent intestinal infection. Hence, there is a need for aggressive nutritional rehabilitation of patients with acute diarrhoeal disease. Increased catabolic state, decreased food intake and nutrient malabsorption all contribute to weight loss in patients with acute diarrhoea. The mechanisms of nutrient malabsorption

have not been well defined in diarrhoea. Adequate exocrine pancreatic function is required for the digestion of fats, carbohydrate and protein prior to absorption. There is very limited information about pancreatic function in patients with acute diarrhoeal illness, yet altered release of pancreas stimulating hormones, secretin and CCK from damaged intestinal mucosa may be hypothesised as a complication of enteric infection. It is proposed, therefore, to assess the secretory response of the exocrine pancreas to both exogenous hormonal stimulation and to a modified Lundh test meal in patients with acute cholera and acute shigellosis. These studies will provide better understanding of the pathophysiology of acute diarrhoea and more importantly will provide a firmer scientific basis for the successful implementation of cereal based oral rehydration therapy in the management of dehydration and nutritional rehabilitation in patients with acute diarrhoeal illness.

B. SPECIFIC AIMS

1. To measure quantitatively the exocrine pancreatic response to both physiological (liquid meal) and exogenous hormonal (secretin-caerulin) stimuli in patients with acute diarrhoea, and to compare with that of normal volunteers.
2. To determine the plasma responses of secretin and CCK to a liquid meal and basal plasma VIP levels in patients with acute diarrhoea and to compare results with those from healthy volunteers.

C. PATIENTS AND METHODS

The study population will consist of two groups:

(a) Ten healthy adult Bangladeshi volunteers (all males).

(b) Thirty adult male patients attending the outpatient clinic of ICDDR,B

with a history of acute diarrhoea and having no antibiotic or any other chemotherapeutic treatment outside. Patients will be selected so that 15 have acute cholera, and 15, acute shigellosis. Only those cholera patients who have a history of diarrhoea 24 hours duration and who are observed during the first four hours of hospital attendance to purge at a rate of at least 5 ml/kg/hour will be studied. Shigella patients will be selected if they have a history of diarrhoea of 72 hours duration, since very few shigella patients present within the first 24 hours of illness, and if they have symptoms and stool appearance suggestive of invasive diarrhoea. Any of these patients showing signs of severe toxaemia or passing frank blood and requiring immediate antibiotic therapy will be excluded. Anyone showing signs of systemic complication will be excluded.

Informed consent will be obtained from all patients and volunteers before inclusion of the study.

After admission, a detailed clinical history will be taken and a full physical examination including anthropometric measurements (height, weight, triceps skinfold thickness and mid upper arm circumference) will be performed. Rehydration and maintenance of hydration will be done by intravenous infusion or rice electrolyte oral solution as required. Oral fluids and food will be withheld only during an overnight fast before each of the 2 tests, during which time, I.V. fluids will be given. This experimental design ensures that oral nutrient intake is not totally withheld during the period required to complete the initial assessment and the two pancreatic function tests. An overnight fast is

N.B.: If patients develop complications after admission, they will be excluded from the study and transferred from the study ward to the general ward or intensive care unit for further investigation and management.

the standard recommendation before any test of upper intestinal or pancreatic function and this duration of fast should not compromise our patients' medical condition.

After full hydration, blood urea, electrolytes, specific gravity, glucose, haematocrit and total and differential white cell counts will be estimated. Stool will be collected for microscopic, dark-field and microbiological investigation for V. cholerae, E. coli, Salmonellæ, Shigellae and Campylobacters.

Antibiotics will be prescribed as indicated after the pancreatic studies are completed. Patients will be kept in hospital and given full clinical care until diarrhoea stops and they are judged to be ready for discharge.

EXCLUSION FROM THE STUDY

Table 1 summarises the criteria for inclusion into or exclusion from the study.

TABLE 1

CRITERIA FOR SELECTION OF PATIENTS FOR EXOCRINE PANCREATIC FUNCTION TEST

VARIABLES	SELECTED	EXCLUDED
Age (Years)	15 to 40 years	>40 yrs, 15 yrs.
Sex	Male	Female
Diarrhoea	< 24 hrs (cholera) < 72 hrs (shigella)	>24 hrs (cholera) >72 hrs (shigella)
Blood electrolytes and urea (after rehydration)	Normal	Abnormal
Clinical signs		
Coma/convalsions Severe toxaemia suggestive Signs suggestive of septicaemia		Excluded
Anuria	None	≥24 hours

Experimental design:

After an overnight fast, during which time hydration will be maintained by using appropriate intravenous infusions, the subjects will swallow a triple lumen tube. One lumen will be used for continuous perfusion of a non-absorbable marker (PEG 4000, 2 g/l N saline) at a rate of 2 ml/min and will be positioned under fluoroscopic control adjacent to the ampulla of Vater. A second lumen located 30 cm distal to the perfusion site, will be used for continuous aspiration of the duodenal contents. The third lumen, located in the gastric antrum, will be used for gastric aspiration. All studies will be performed with subjects in the half-supine position. After correct placement of the tube, gastric and duodenal aspiration and PEG perfusion will be started simultaneously. The following two tests will be performed in random order in two consecutive days (Figs 1 and 2).

Modified Lundh test

After a basal period of 60 minutes, the subjects will drink a liquid meal (300 ml) within 2-3 minutes. The meal will consist of protein (20 g), fat (15 g) and carbohydrate (80 g). The carbohydrate will be in the form of rice powder, while the protein and fat content will be made up from eggs and butter. Artificial flavouring agents may be added, if necessary.

Gastric aspiration will be discontinued after the basal period but duodenal aspiration and PEG perfusion will continue after meal ingestion for a period of 2 hours, and duodenal aspirates will be collected in 15 minute aliquots.

Blood samples for secretin and CCK radio-immunoassay will be collected at baseline and at 15 min intervals for the next two hours. Each time, 5 ml blood will be collected in ice-chilled tubes containing 150 g EDTA and 5000 KIU a protinin per 5 ml blood. During the basal period, an additional 2.5 ml sample of blood will be collected under similar conditions for VIP radioimmunoassay. All samples will be immediately centrifuged at 4°C and plasma will be stored at -20°C until assayed.

2. Secretin Caerulin test

After a basal period of 60 minutes, synthetic secretin will be infused at a rate of 250 mg/kg body weight/hour for the next 2 hours. Starting from the second hour, synthetic caerulin will be infused at a rate of 40 mg/kg body weight/hour. Perfusors will be used for accurate perfusion (25 ml/hr). No blood samples will be drawn during this study. Duodenal aspirates will be collected in 15 minute aliquots for one hour as a basal collection and for 2 hours after onset of hormone stimulation.

DETERMINATIONS

Duodenal aspirates:

Volume will be measured to 0.1 ml. Bicarbonate will be determined by the back titration method[50] and PEG will be determined turbidimetrically by a modified method of Hyden[51]. Trypsin will be measured by the method of Wiggins[52] and lipase chymotrypsin and amylase will be measured

respectively by the methods of Johnson[53], Imondi[54] and the dyed starch hydrolysis method.[55]

Plasma: The plasma levels of secretin CCK and VIP will be determined by radio-immunoassay.[56-58] The radioimmunoassays will be performed in the laboratory of Prof. K. Gyr, Basel, Switzerland. Plasma samples will be transported from Dhaka to Basel by air in containers packed with dry-ice.

Calculations:

The PEG solution serves as a non-absorbable marker to calculate the duodenal volume for a given period by the following equations.[59]

$$V = (F \times [PEG]\ perf \times 15)/(PEG\ meas).$$

Where V is calculated duodenal volume (ml/15 min)

F is flow rate of PEG solution perfused = 2 ml/min.

[PEG] perf is the concentration of PEG in the perfusate = 2 g/l.

PEG meas is the concentration of PEG in the duodenal juice collected for 15 min.

Using the calculated duodenal volume for a 15 min. period, the measured concentrations of enzymes and bicarbonate in duodenal aspirate can be converted into pancreatic output/15 minutes. The percentage recovery of PEG in the duodenal aspirates can also be readily calculated as a check on the aspiration technique.

Statistical analysis:

In each group of subjects the results of the individual collection periods will be expressed as mean ± SEM, and will be compared by F test

and students t-test. The values of plasma levels of secretin, CCK and VIP will be in pmol/l. The profiles of pancreatic output and plasma hormone responses to the test meal will be obtained by calculating integrated responses and will be compared with multiple t-tests. Difference with a P value of more than 0.05 will be considered to be statistically significant.

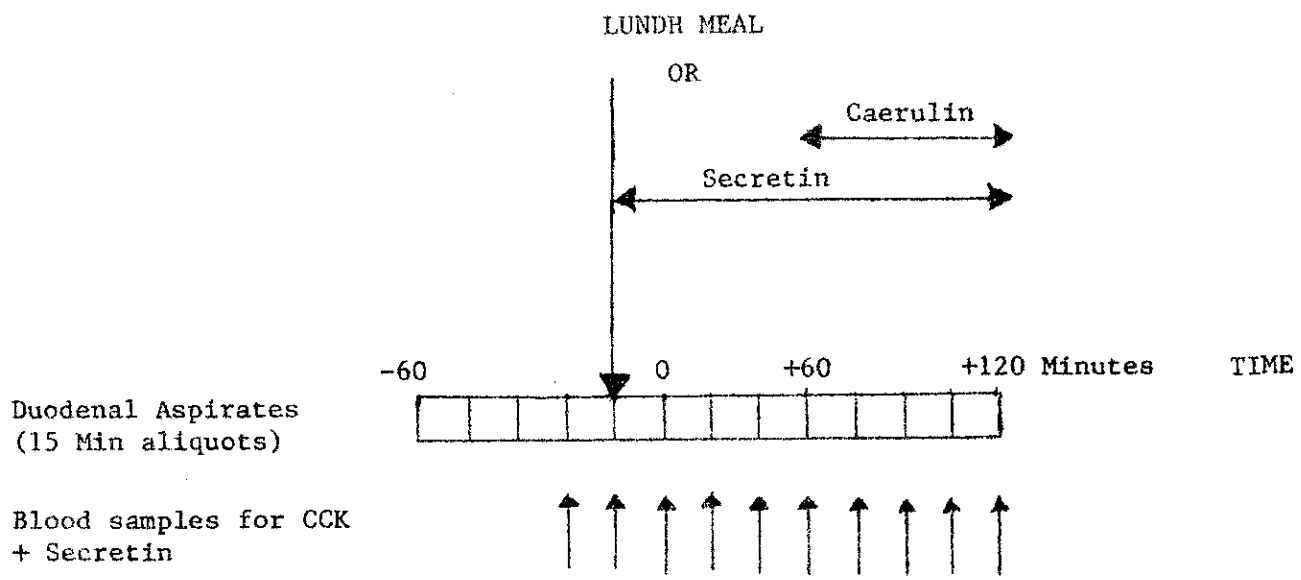
D. SIGNIFICANCE

There are serious nutritional consequences of recurrent enteric infections, and the importance of aggressive nutritional rehabilitation has recently been recognised. Studies have shown that transient nutrient malabsorption is a common occurrence in most enteric infections but the mechanisms for the malabsorption have not been defined. Pancreatic function may be impaired in chronic diarrhoeal illness such as coeliac disease but has not been formally assessed in patients with acute infective diarrhoea. The proposed study will provide information about exocrine pancreatic function during acute diarrhoea which may aid our understanding of the pathophysiological mechanisms of nutrient malabsorption in these patients. Data from the study may also provide a scientific rationale for the observed effectiveness of cereal-based oral rehydration solutions and may facilitate the further development of oral rehydration therapy and nutritional rehabilitation programmes.

Fig. I : Sequence of investigations after admission

Day 1	Overnight fast	Day 2	Overnight fast	Day 3
Admission	12 M.N. - 8 A.M.	Lundh test or Secretin test	12 M.N.-8A.M.	Secretin test or Lundh test
Rehydration with I.V. fluids or oral fluids	I.V. fluids only	Then, oral fluids & food as required.	I.V. fluids only	Then, oral fluids, food & antibiotics

Fig. 2 : Sequence of duodenal aspirate collection + blood sampling during pancreatic tests.



E. Facilities required

1. Office space - the present study room will be used. No extra space is necessary.
2. Laboratory space - Existing ICDDR,B laboratory facilities will be utilised.
3. Hospital resources - Existing facilities in the study ward will be utilised.
4. Animal resources -
5. Logistic support - Data processing and computer support from the Data Management Branch of ICDDR,B will be necessary.
6. Transport - Not required.
7. Major items of equipment - Not required.
8. Others - Nil.

F. Collaborative arrangements:

Collaboration with Professor Klaus Gyr, Prof. of Gastroenterology, University Hospital, Basel, Switzerland.

Collaboration with Dr. B. J. Collins of Department of Gastroenterology, Queen's University of Belfast will continue during running of this protocol.

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ABSTRACT SUMMARY

1. The association of malnutrition and nutrient malabsorption with acute diarrhoeal disease has been recently established. Detailed assessment of digestive and absorptive capacity in these patients has not been performed and, in particular, pancreatic exocrine function has not been evaluated. This study will, therefore, provide new insight into digestive function during acute diarrhoeal illness and results may influence the approach to nutritional rehabilitation in these patients.
2. Insertion of a triple lumen duodenal tube, per nasally is associated with some discomfort to the patient. The technique has been extensively employed in many research studies of gastrointestinal physiology and is currently being performed in research studies in this centre. Complications of intubation of the small intestine in healthy subjects are virtually nonexistent.[60] Patients with watery diarrhoea have minimal mucosal inflammation in the duodenal region and so no additional risk is anticipated in these patients. There are no other social or legal risks. There are no non-invasive means of assessing quantitatively the pancreatic response to a test meal or to exogenous hormone stimulation. Infusion of secretin and caerulin intravenously is a well established diagnostic technique used in the assessment of pancreatic function and it carries minimal risk.
3. Only patient identification numbers will be used during analysis of results.
4. Signed consent will be obtained from the patients and volunteers.

5. Interview will be taken in the hospital to obtain clinical history.

6. If pancreatic function is found to be persistently low in any individual, then appropriate therapeutic measures will be taken for that patient. The results of this study may help to modify future approaches to oral rehydration and nutritional rehabilitation of diarrhoeal patients.

7. The use of hospital records and body fluids will be required.

SECTION III : BUDGET

DETAILED BUDGET

PANCREATIC EXOCRINE FUNCTION IN ACUTE BACTERIAL DIARRHOEA

1. Personnel services

Name	Position	% of effort	Project requirement (In US Dollars)
1. Dr. B.J. Collins	Principal Invest.	50%	$ 5,000
2. Dr. P.K. Bardhan	-do-	50%	2,280
3. Dr. A.M. Molla	Co-Investigator	20%	12,600
4. Dr. V. Van Loon	Co-Investigator	20%	7,200
5. Dr. Ayesha Molla	Co-Investigator	20%	8,400
		SUB-TOTAL:	$35,480

2. SUPPLIES AND MATERIALS:

Office supplies, paper, syringes, needles, vials for blood and intestinal fluid samples. Test meal constituents.	$ 500
Caerulin and secretin for I.V. infusion.	$ 1500
SUB-TOTAL:	$2,000

3. LABORATORY TESTS

Blood test	Cost/test	No. tests	Total costs	
Haematocrit	$1.03	30	$ 20.6	
Total count	1.03	30	20.6	
Differential count	1.03	30	20.6	
Specific gravity	0.46	30	9.2	
Urea and electrolytes	4.11	30	82.2	
Glucose	1.58	30	47.4	
			$200.6	$200.6
Stool test				
Dark field exam. for vibrios	$1.32	30	$ 26.4	
Culture for shigella/ salmonella/E. coli/vibrio	8.11	30	162.2	
Isolation of campylo-bacter	5.28	30	158.4	
			$347.0	$347.0
			C.F.	$547.6

B.F. $ 547.6

Intestinal fluid:	Cost/test	No. test	Total cost	
P.E.G. (costed to include supply of P.E.G.)	$4.90	960	$2940	
Trypsin	1.7	960	1632	
Amylase	3.8	960	3648	
Lipase.	2.8	960	2688	
Chymotrypsin	2.8	960	2688	
Bicarbonate		960	2100	
			$15696	$15696
Gastrointestinal hormones: Secretin] Radioimmunoassay in Cholecystokinin] Basel, Switzerland) V.I.P.]			$1,000	$ 1000
SUB-TOTAL:				$17243.6

4. Equipment

Triple lumen intestinal tubes.] Suction pump.]			$1,000	$1,000
SUB-TOTAL:				$1,000

5. Patient hospitalization

a. Patients	5 days/patients	150 pts/days	$2586	
b. Volunteers	2 days/volunteer	20 vol/days	345	
			$2931	
SUB-TOTAL:				$ 2931

6. Travel and transportation of patients	$ 200	$ 200
7. Transportation of hormone samples to Basel	300	300
8. Rent, communication and utilities	100	100
9. Printing and reproduction	500	500
10. Other contractual services:		
a. Secretarial assistance	300	
b. Data analysis	600	900
11. Payment of volunteers (Tk.2000/volunteer)	1000	1000
		3000
SUB-TOTAL:		$ 3000

BUDGET SUMMARY

		Project requirement
1.	Personnel services	US $35,480
2.	Supplies and materials	2,000
3.	Laboratory costs	17,243
4.	Equipment	1,000
5.	Patient hospitalization	2,931
6.	Travel and transportation of patients	200
7.	Transportation of hormone samples to Basel	300
8.	Rent, communication and utilities	100
9.	Printing and reproduction	500
10.	Other contractual services	900
11.	Pay ent to volunteers (Tk.2000/volunteer)	1,000
	Total:	US $61,654
	Plus 31% Overhead	$19,113
	Grand total:	US $80,767

CONSENT FORM FOR PATIENTS

(Statement read and clearly explained to the subject when consent is obtained).

ICDDR,B is carrying out research to assess the digestion of food during acute diarrhoea. This research may help us to provide better treatment to the patients and to understand better the disease process. We would like you to join in the study for the well being of mankind.

If you decide to participate in the study, you can expect the following:

1. You will be given all necessary care.
2. It will be necessary for you to stay at least 3 days in hospital.
3. From midnight, on the first and second day of admission, you will have nothing to eat by mouth until the completion of the test on the next morning.
4. A thin rubber tube will be passed through the nose and into the stomach and upper bowel, under fluoroscopic guidance. This is a safe procedure and has been performed on many patients during research studies at this centre. When the tube is in position one of two tests will be performed on each of 2 successive mornings.
5. In one test, you will be given a special test meal to drink, and some saline fluid containing a harmless chemical, PEG, will be passed down the tube, into the bowel. Samples of fluid from the bowel will be withdrawn through the tube. This will not cause any harm. Some blood samples will be taken from your arm before and after you are given the test meal.

When the test is complete - usually about 4-5 hours after introduction of the tube, the tube will be removed and food and drink will be given.

6. In the other test, two substances, secretin and cholecystokinin which help food digestion, will be infused intravenously into your arm vein. A harmless chemical PEG will be passed down the tube into your bowel, as before, and samples of fluid will be withdrawn through the tube. When the test is complete - usually 4-5 hours after introduction of the tube - the tube will be removed and food and drink will be given.

7. You will be treated to the best of our ability even if you do not join in this study or withdraw from the study at any time.

If you are willing voluntarily to join in this study, then please sign your name or give left thumb impression on this consent form.

Signature of investigator

Date_____

Signature or left thumb impression of the patient

Date_____

CONSENT FORM FOR HEALTHY VOLUNTEERS

(Statement read and clearly explained to the subject when consent is obtained)

ICDDR,B is carrying out research to assess the digestion of food during acute diarrhoea. This research may help us to provide better treatment to the patients and to understand better the disease process. To complete our research we need some information about digestion of food in healthy volunteers. We would like you to join us in the study for the well being of mankind.

If you decide to participate in the study, you can expect the following:

1. You will be asked to come to hospital at 8:30 a.m. after an overnight fast on 2 successive mornings. Thus you can have no food or drink on the morning of each test.

2. A thin rubber tube will be passed through the nose and into the stomach and upper bowel under X-Ray guidance on each morning. This is a safe procedure and has been performed on many patients during research studies at this centre. On each morning one of two tests will be performed.

3. In one test you will be given a special test meal to drink and some saline fluid containing a harmless chemical PEG will be passed down the tube and into the bowel. Samples of fluid form the bowel will be withdrawn through the tube. This will not cause any harm. Some blood samples will be taken from your arm before and after you are given the test meal.

   When the test is complete, usually about 4-5 hours after introduction of the tube - the tube will be removed and you will be free to go home.

4. In the other test, two substances, secretin and cholecystokinin which help food digestion, will be infused intravenously into your arm vein. A harmless chemical, PEG will be passed down the tube into your bowel, as before, and samples of fluid will be withdrawn through the tube. This test also takes 4-5 hours usually to complete,

and when it is over, the tube will be removed and you will be free to go home.

If you are willing voluntarily to join in this study, then please sign your name or your left thumb impression in this consent form.

_____	_____
Signature of Investigator	Signature or left thump impression of volunteer
Date_____	Date _____

রুগীর সম্মতি পত্র

(সম্মতি নেয়ার সময় বিবৃতি রুগীকে পড়ে শোনানো হয়েছে এবং পরিষ্কার করে বুঝিয়ে দেয়া হয়েছে।)

উদরাময়ে পরিপাক পরিমাপ করার জন্য আন্তর্জাতিক উদরাময় গবেষনা কেন্দ্র গবেষনা করছে। এই গবেষনা রুগীদের ভালো চিকিৎসা দেয়ার ও রোগের ধারাবাহিক প্রক্রিয়া বোঝায় আমাদের সাহায্য করবে। আমরা এই মানবজাতীর কল্যানার্থে আপনি আমাদের গবেষনায় যোগদান করুন।

যদি আপনি গবেষনায় অংশগ্রহণ করার সিদ্ধান্ত নিয়ে থাকেন তাহলে আপনি নিম্নলিখিত বিষয়গুলো আশা করতে পারেন :—

① আপনাকে সব প্রয়োজনীয় চিকিৎসা প্রদান করা হবে।
② আপনাকে কমপক্ষে তিন দিন হাসপাতালে থাকতে হবে।
③ ভর্তির প্রথম ও দ্বিতীয় দিনের মাঝ রাত থেকে পরের দিন সকাল পর্যন্ত পরীক্ষা শেষ না হওয়া পর্যন্ত কিছু খেতে পারবেন না।
④ ফ্লুরোস্কোপের সাহায্য নিয়ে একটি সরু রাবারের নল নাকের মধ্য দিয়ে পাকস্থলীতে ও অন্ত্রের উপরের অংশে প্রবেশ করানো হবে। এটা একটা নিরাপদ প্রক্রিয়া এবং এটা এই কেন্দ্রে গবেষনার জন্য বহু রুগীর উপর প্রয়োগ করা হয়েছে। নলটি যথাস্থানে থাকার সময় প্রতিদিন একটি করে দুটি পরীক্ষা পর পর দুদিন সকালে সম্পাদন করা হবে।

(৪) একটি পরীক্ষায় আপনাকে একটি নির্দিষ্ট খাবার দেয়া হবে এবং ক্ষতিকারক নয় এমন রাসায়নিক পদার্থ, সিলিকা সহ কিছু পরিমান লবনাক্ত তরল পদার্থ নলের মধ্য দিয়ে অন্ত্রে প্রবেশ করানো হবে। নলের মধ্য দিয়ে তরল পদার্থের নমুনা বের করে আনা হবে। এতে আপনার কোন ক্ষতি হবে না। পরীক্ষাগুলোর খাবার দেয়ার আগে ও পরে আপনার হাত থেকে কিছু রক্তের নমুনা নেয়া হবে। নল প্রবেশ করানোর ৪-৫ ঘন্টা পর পরীক্ষা শেষ হয়ে যাবে এবং তখন নলটা সরিয়ে নেয়া হবে এবং খাবার ও পানীয় দেয়া হবে।

(৫) অন্য পরীক্ষায় দু'টি পদার্থ যেমন সিফেক্টিন ও কোলিসিস্টো-কাইনিন, যেগুলো খাদ্য পরিপাকে সাহায্য করে আপনার শিরার মধ্য দিয়ে প্রবেশ করানো হবে। ক্ষতিকারক নয় এমন রাসায়নিক দ্রব্য সিলিকা নলের মধ্য দিয়ে আগের মতো অন্ত্রে প্রবেশ করানো হবে এবং তরল পদার্থের নমুনা নলের মধ্য দিয়ে বাইরে আনা হবে। ৪-৫ ঘন্টা পর পরীক্ষা শেষ হলে নলটি সরানো হবে এবং খাবার ও পানীয় দেয়া হবে।

(৬) আপনি যদি আমাদের গবেষনায় যোগদান না করেন তবুও গবেষনা থেকে নিজেকে প্রত্যাহার করে নিলেও আমরা সাধ্যমতো আপনার চিকিৎসা করবো।

আপনি যদি স্বেচ্ছায় এই গবেষনায় যোগদান করতে চান তাহলে দয়া করে সম্মতি পত্রে আপনার নাম স্বাক্ষর করুন অথবা বাম বৃদ্ধাঙ্গুলের ছাপ দিন।

গবেষকের স্বাক্ষর

তারিখ

রুগীর স্বাক্ষর কিংবা বাম বৃদ্ধাঙ্গুলের ছাপ

(৪) একটি পরীক্ষায় আপনাকে একটি নির্দিষ্ট খাবার দেয়া হবে এবং ক্ষতিকারক নয় এমন সামান্য রাসায়নিক পদার্থ, পিচ্ছিল সরু পিচ্ছ পরিমান লবনাক্ত তরল পদার্থ নলের মধ্য দিয়ে অন্ত্রে প্রবেশ করানো হবে। নলের মধ্য দিয়ে তরল পদার্থের নমুনা বের করে আনা হবে। এতে আপনার কোন ক্ষতি হবে না। পরীক্ষাগুলোর খাবার দেয়ার আগে ও পরে আপনার হাত থেকে কিছু রক্তের নমুনা নেয়া হবে। নল প্রবেশ করানোর ৪-৫ ঘন্টা পর পরীক্ষা শেষ হয়ে যাবে এবং তখন নলটা সরিয়ে নেয়া হবে এবং খাবার ও পানীয় দেয়া হবে।

(৫) অন্য পরীক্ষায় দুটি পদার্থ যেমন সিসক্রোফিন ও ফোলিসিস্টো-কাইনিন, যেগুলো খাদ্য পরিপাকে সাহায্য করে আপনার শিরার মধ্য দিয়ে প্রবেশ করানো হবে। ক্ষতিকারক নয় এমন সামান্য রাসায়নিক দ্রব্য পিচ্ছিল নলের মধ্য দিয়ে আগের মতো অন্ত্রে প্রবেশ করানো হবে এবং তরল পদার্থের নমুনা নলের মধ্য দিয়ে বাইরে আনা হবে। ৪-৫ ঘন্টা পর পরীক্ষা শেষ হলে নলটি সরানো হবে এবং খাবার ও পানীয় দেয়া হবে।

(৭) আপনি যদি আমাদের গবেষনায় যোগদান না করেন কিংবা গবেষনা থেকে নিজেকে প্রত্যাহার করে নিলেও আমরা সাধ্যমতো আপনার চিকিৎসা করবো।

আপনি যদি স্বেচ্ছায় এই গবেষনায় যোগদান করতে চান তাহলে দয়া করে সম্মতিপত্রে আপনার নাম স্বাক্ষর করুন অথবা বাম বৃদ্ধাঙ্গুলের ছাপ দিন।

গবেষকের স্বাক্ষর

তারিখ

রুগীর স্বাক্ষর কিংবা বাম বৃদ্ধাঙ্গুলের ছাপ

সুস্থ স্বেচ্ছাসেবীদের জন্য সম্মতি পত্র

(সম্মতি নেয়ার সময় বিবৃতি পত্রে লেখানো হয়েছে ও পরিষ্কারভাবে বুঝিয়ে বলা হয়েছে।)

উদরাময়ে পরিপাক পরিমাপ করার জন্য আন্তর্জাতিক উদরাময় কেন্দ্র গবেষনা করছে। এই গবেষনা রুগীকে ভালো চিকিৎসা দেয়ার ও রোগের ধারাবাহিক প্রক্রিয়া বোঝার জন্য আমাদের সাহায্য করবে। এই গবেষনা সম্পূর্ন করার জন্য সুস্থ স্বেচ্ছাসেবীর খাদ্য পরিপাক সম্বন্ধে আমাদের কিছু তথ্য জানার প্রয়োজন। আমরা চাই মানবজাতীর কল্যানার্থে আপনি আমাদের গবেষনায় যোগদান করুন।

আপনি যদি আমাদের গবেষনায় অংশ গ্রহনের সিদ্ধান্ত নিয়ে থাকেন তাহলে নিম্নলিখিত বিষয়গুলো আশা করতে পারেন।

① রাতে কিছু না খেয়ে পর পর দু'দিন সকাল ৮:৩০ এর সময় আপনাকে হাসপাতালে আসতে বলা হবে। সুতরাং প্রত্যেক পরীক্ষার দিন সকালে আপনি কিছু খেতে কিংবা পান করতে পারবেন না।

② নাক-রে'র সাহায্যে একটি সরু রবারের নল আপনার নাকের মধ্য দিয়ে পাকস্থলীতে এবং এর অন্ত্রের উপরের অংশে প্রতিদিন সকালে প্রবেশ করানো হবে। এটা একটা নিরাপদ প্রক্রিয়া এবং গবেষনার জন্য এই কেন্দ্রে এই প্রক্রিয়া অনেক রুগীর উপর প্রয়োগ করা হয়েছে। প্রতিদিন সকালে একটি করে পরীক্ষা করা হবে।

(৩) এই পরীক্ষায় আপনাকে একটি নির্দিষ্ট খাবার দেয়া হবে এবং ক্ষতিকারক নয় এমন একটি রাসায়নিক দ্রব্য পিলইক্ষি সহ লম্বনাক্ত প্লাস্টিক নলের মধ্য দিয়ে অন্ত্রের মধ্যে প্রবেশ করানো হবে। তরল পদার্থের নমুনা নলের মধ্য দিয়ে অন্ত্র থেকে বাইরে নিয়ে আসা হবে। এতে কোন ক্ষতি হবে না। পরীক্ষাশুরুর খাবার দেয়ার আগে ও পরে আপনার হাত থেকে কিছু রক্তের নমুনা নেয়া হবে। ৪-৫ ঘন্টা পর পরীক্ষা শেষ হলে ~~নল~~ নলটা সরিয়ে নেয়া হবে এবং আপনি বাড়ী যেতে পারবেন।

(৪) অন্য একটা পরীক্ষায় সিসক্রেটিন ও কোলেসিস্টোকাইনিন নামে দুটি পদার্থ যা লিভারকে সাহায্য করে, আপনার শিরার মধ্যে প্রবেশ করানো হবে। ক্ষতিকারক নয় এমন একটি পদার্থ সিলইক্ষি নলের মধ্য দিয়ে আপনার অন্ত্রে প্রবেশ করানো হবে এবং আগের মতো নলের মধ্যে দিয়ে তরল পদার্থের নমুনা বাইরে নিয়ে আসা হবে। এই পরীক্ষা শেষ হতে ৪-৫ ঘন্টা সময় লাগে এবং এটা শেষ হলে নলটি সরিয়ে নেয়া হবে এবং আপনি নির্বিঘ্নে বাড়ী যেতে পারবেন।

আপনি যদি স্বেচ্ছায় এ গবেষণায় যোগদান করতে চান তাহলে এই সম্মতি পত্রে আপনার নাম সহি করুন কিংবা বুড়ো আঙুলের ছাপ দিন।

গবেষকের স্বাক্ষর

তারিখ

স্বেচ্ছাসেবকের স্বাক্ষর/বুড়ো আঙুলের ছাপ.

তারিখ