

REVIEW BOARD ON THE USE OF HUMAN SUBJECTS, ICDDR,B.

Principal Investigator DR. T. MORISHITA
DR. R. ISLAM

Trainee Investigator (if any) 2/4

Application No. 80-014

Supporting Agency (if Non-ICDDR,B) Keio University Tokyo

Title of Study Endoscopic Studies
Diarrhoeal Diseases.

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).

Source of Population:

- (a) Ill subjects Yes No
- (b) Non-ill subjects Yes No
- (c) Minors or persons under guardianship Yes No

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

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

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
- (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

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

7. Check documents being submitted herewith to Board:

- 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 Board for review.

Free to obtain approval of the Review Board on the Use of Human Subjects for any changes affecting the rights and welfare of subjects before making such change.

Morishita
Principal Investigator

Trainee

80-014
Rec'd 3/3/80

1. Title : Endoscopic Studies on Diarrhoeal Diseases
2. Principal Investigators: Dr. Tetsuo Morishita
Dr. Rafiful Islam
Dr. Pradip K. Bardhan
Dr. A. M. Molla
3. Starting Date : February 1980
4. Completion Date: March 1980
5. Total Direct cost:
6. Availability of Funds:

7. Abstract Summary:

There is a possibility that a large amount of water may be lost through pathologic desquamation and necrosis of intestinal epithelin, as well as by the hypersecretion of epithelial cells. It is necessary to determine whether pathological changes; such as erosions and ulcers, responsible for fluid loss are present or not in the intestinal mucosa of diarrhoeal diseases including cholera, *E. coli* and *V. parahemolyticus*.

Endoscopic examinations of the upper small intestine of 6 cases of each group will be done in this study.

It is expected that anti-erosive, anti-ulcer agents may lessen the diarrhoea and prevent the colonization and growth of cholera organisms in the intestinal tract, if these changes are adequately diagnosed.

In addition, endoscopy is very useful for differential diagnosis among various diarrhoeal disease, especially for early detection of gastrointestinal cancers.

Direct administration of curative drugs into the intestinal tract and brushing for diagnosis of parasitic diseases are also possible with endoscopy.

This study is essential not only for etiological investigations but also for diagnostic and therapeutic purpose.

8. Review:

A. Introduction

1. Objective :

- a. To determine whether pathological changes responsible for fluid loss are present or not in the small intestine of diarrhoeal diseases including cholera, E. coli and V. parahemolyticus.
- b. To find causes of chronic diarrhoea of unknown aetiology.
- c. To do the confirmative diagnosis of parasitic diseases.
- d. To do the differential diagnosis between infectious diseases and malignant diseases of the gastrointestinal tract which cause diarrhoea.

2. Background :

It had been strongly believed that intestinal mucosa was intact in cholera. ^{1/}

However endoscopic studies reported by Morishita *et al* . ^{2/} revealed mucosal abnormalities such as multiple erosions and minute red spots in the jejunum, which were confirmed with light ^{3/} and electron microscopy. ^{4/} It was postulated that these changes reflected mucosal injury related to infection by V. cholera and might play a role in the fluid loss and facilitate the susceptibility to infection. Further and comparative studies among diarrhoeal diseases are necessary.

The aetiology in 30% of diarrhoeal diseases in Bangladesh are still unknown. It is necessary to make efforts to find causes for diarrhoea.

It is well known that gastrointestinal cancers, ulcerogenic pancreatic tumors such as Zollinger - Ellison syndrome and peptic ulcers are often accompanied with severe diarrhoea. Endoscopic and histological examinations are essential to the patients suffering from diarrhoea especially for early diagnosis of cancer. If cancers and/or fatal ulcers are found, surgical and/or anti-cancer treatment can be started earlier to save the life of the patient.

* Similar informations are lacking in diarrhoeal diseases due to different aetiologies.

3. Rationale:

1. Light and scanning electron microscopic studies in suckling mice with experimental cholera reported by Ohashi et al 5) revealed marked destructive changes in epithelial cells and vascular structure after infection with living cholera vibrios but not after administration of cholera toxin, purified and devoid of somatic antigen.

2. Endoscopic, light and electron microscopic studies in human cholera reported by Morishita et al ²⁾ revealed mucosal changes such as multiple erosions.
3. Epithelial ghost cells are often found in the stool of cholera and other diarrhoeal patients ¹⁾. It is suggested that epithelial cells in the stool may be derived from necrosis and denudation of epithelial cells, and watery stools may be due to pathological changes such as erosions etc.
4. Diarrhoea is seen in 40 - 70% of patients with gastrointestinal cancers, ulcerogenic pancreatic tumors and peptic ulcers.
5. Observation on the mucosa, mucosal biopsy and brushing for cytology from the stomach, duodenum and upper jejunum is possible with the endoscope.
6. Mucosal biopsy and brushing for cytology is easily possible without accidents.
7. Direct administration of therapeutic agents into the gastrointestinal tract is possible with the endoscope.

B. Specific Aims:

1. To give the mucosal pattern of the stomach and small intestine among patients with cholera, E.coli, V. parahemolyticus and other diarrhoea.
2. To do mucosal biopsies, only when clinically indicated.

C. Methods and Procedures:

1. Case selection

Only adult patients will be selected for the study. About 6 cases from each group of cholera, E. coli, V. parahemolyticus and non-specific diarrhoea will be studied.

2. Endoscopic examinations of the gastrointestinal tract will be done in the acute stage and convalescent stage under local anesthesia. The oropharynx is topically anesthetized with 2% Lidocaine hydrochloride (Xylocaine viscous) ^(R) and 3% Lidocaine (Xylocaine spray) ^(R) to suppress the gag reflex. Butylscopolamine bromide (Buscopan ^(R)) is given intramuscularly to lessen the intestinal motility.

Observation and taking pictures of the mucosal surface will be done in the upper jejunum (10 to 20 cm beyond the ligament of Treitz

3. Specifications of the endoscope (Olympus Small Intestinal Fiberscope, type B, Olympus Optical Co. Ltd. Japan) optical system: Forward viewing (deflection of optical axis 8° upward)

Outer diameter : 10 mm

Length : 1,760 m.m.

bending angle of bending section: 150° up, 120° down, 90° right, 90° left.

Biopsy, brushing for cytology and infusion of drugs for therapeutic use are possible.

4. The films are developed in Tokyo.

5. Risks to subjects:

3,000 cases for gastroscopy, 2,000 cases for duodenoscopy and 200 cases for jejunoscopy have already examined by Dr. T. Morishita in Keio University, Tokyo, Japan.

No accidents such as perforation occurred (6).

6. Gulshan clinic which is fully equipped with modern surgical amenities and experts will be kept ready for any accident arising out of the procedures.

7. Regular clinical information of the patients like clinical history, vital signs, intake and output will be recorded as usual.

8. There will be no restriction of antibiotics and rehydration.

9. Detailed haematological investigations will be carried out before the endoscopic examinations.
10. All protective measures will be made ready before any biopsy is taken.

D. Significance:

1. The mechanism of fluid loss through the intestinal mucosa may be understood in a better way.
2. It is expected that anti-erosion, -ulcer agents may lessen the fluid loss and prevent the occurrence of diarrhoea.
3. The differential diagnosis among diarrhoeal diseases, especially for early diagnosis of cancers, is possible.
4. The direct administration of anti-parasite, ulcer agents, antibiotics and other drugs into the stomach and intestine can be possible.

E. Facilities required:

1. Present study ward, physicians and nursing staff can be utilized for patients care and examination.
2. Syringes, needles etc. are available in ICDDR,B.
3. Bacteriological support as well as animal resources for ST, LT study will be required.

F. Collaborative Arrangements:

This will be collaborative study between ICDDR,B and School of Medicine, Keio University, Tokyo, Japan.

References :

- 1/ Gangarosa, E.J., et al : The nature of the gastrointestinal lesion in Asiatic Cholera and its relation to pathogenesis: a biopsy study. Am. J. Trop. Med., 9 : 125, 1960.
- 2/ Morishita, T., et al : Endoscopy of the jejunal mucosa in human cholera. Gastrointestinal Endoscopy, 24:284, 1978.
- 3/ Asakura, H., Morita, A., Morishita, T., et al : Pathological findings from intestinal biopsy specimens in human cholera. Am. J. Dig. Dis., 18:271, 1973.
- 4/ Asakura, H., Tsuchiya, M., Watanabe, Y., et al: Electron microscopic study on the jejunal mucosa in human cholera. Gut, 15: 531, 1974.
- 5/ Ohashi, M., Shimada, T., Fukumi, H. et al: Histopathological studies on experimental cholera in suckling mice: Light and scanning electron microscopic studies. Proceedings of the 7th joint conference, US - Japan cooperative medical science program, cholera panel, Woods Hole, 39, 1971.
- 6/ Morishita, T., et al: Endoscopy of upper G I tract. Prog. Dig. Endosc., 12 : 104, 1978.

CONSENT FORM

Endoscopic Examination in Diarrhoeal Diseases

The International Centre of Diarrhoeal Diseases Research, Bangladesh has undertaken a research programme to examine the changes in the duodenal and upper jejunal mucosa in different diarrhoeal diseases. The findings will help us to make proper diagnosis and treatment, as well as to understand better the mechanism of diarrhoea due to different causes.

A tube having a diameter of about 1 cm. will be passed into your duodenum and jejunum through your mouth under Fluoroscopic guidance. To minimise your discomfort, we will give you a sedative, and we will also apply a local anaesthetic in your throat. When the tube will pass upto the desired place, we will take photographs of the duodenal and jejunal mucosa, and if necessary a small bit of tissue by biopsy.

This procedure has been tried on many patients in other countries without any serious complications, and is now done routinely in the developed countries for diagnostic and therapeutic purposes.

We will take care of you even if you do not join in this programme, or withdraw yourself from this study.

Name

Signature

স্বাস্থ্য পরিচর্যা

উদরাময় রোগে স্বাস্থ্যকলিক পদ্ধতি

আনুষ্ঠানিক উদরাময় গবেষণা কেন্দ্র বর্তমানে বিভিন্ন রোগের উদরাময় রোগে সুদৃঢ়ের মিল্লির পরিচর্যা নিয়ে গবেষণা করছে। ইহার ফলে উচ্চিক রোগ নির্মূ ও চিকিৎসা পদ্ধতি স্থাপন করতে সমর্থ্য হবে।

একটি জন কলম অসুখের সুখ দিয়া প্রবেশ করিয়ে সুদৃঢ়ে পরিচালনা করা হবে। উচ্চিক ও সুপ পরিচালনার জন্য অসুখ একইর সমর্থ্য নিয়ে। অসুখের সাথে অসুখী না হয় সেজন্য অসুখকে প্রথম দিব এই অসুখের গন্ধ অবস্থা করে দেবে। এই কলম সমর্থ্যের লক্ষ্যে অসুখ অসুখের সুদৃঢ়ের কিছু ছবি নেবে। প্রয়োজনীয় মিল্লির সামান্য অংশ দাঁড়োলাদি দ্বারা নেবে।

এই পদ্ধতিতে অন্যান্য দোষে বহু রোগীকে কোন বহু রোগের দুর্গতি চূড়াই পরীক্ষা করা হয়েছে। এবং বর্তমানে উচ্চিক কেন্দ্র দোষে রোগ নির্মূ ও চিকিৎসার জন্য নিয়মিত ভাবে ব্যবহার করা হচ্ছে। একজন অভিজ্ঞ ডাক্তারের সাথে এই পদ্ধতি সম্পূর্ণ নিরাময়। তা সমর্থ্য

স্বাস্থ্যকলম অসুখকলিক কাব্যতা রাখা হবে।

এই গবেষণায় অংশগ্রহণ না করলেও, অসুখী গবেষণা থেকে নিজেকে প্রত্যাহার করে নিলেও অসুখের চিকিৎসা এ যত্নের কোনরূপ প্রতি হবে না।

1. Only adult patients will be selected for this study. About 6 cases from each group of *V. cholerae*, *E. coli*, and *V. parahaemolyticus*, and non-specific diarrhoea will be studied. There will be no special population group.
2. The potential physical risks are gastro-intestinal haemorrhage and perforation. G.I. haemorrhage occurs only when biopsies are taken, but it is very little in quantity, and stops within 2-3 minutes. Perforation is an very unlikely event in the hands of an expert. Dr. Morishita has done more than 5,000 endoscopic examinations without any major haemorrhage or perforation. There is also a risk of sore-throat, but it is very minor in nature and clears within 48 hours. There are no psychological, social, legal or other risks involved. There is no other alternate method suitable for this study.
3. Bleeding disorders will be screened out by detailed blood tests. This will minimise the risk of gastro-intestinal haemorrhage. A topical anaesthetic, a tranquilliser, and Buscopan (it lessens intestinal motility) will be given to the informed patient to make him relaxed and co-operative. It will facilitate the smooth passage of the endoscope, thus lessening the risk of perforation. Still, a fully equipped clinic will be on standby for any accident.
4. There will be no personal identification of the patient.
5. Informed consent will be obtained from the patients.
 - (a) Does not apply
 - (b) No information will be withheld from the patient.
 - (c) A statement that precautionary measures will be available is included in the consent form.
6. Except asking clinical history, there will be no other interview.
7. Though diarrhoea is a very common disease, we still do not know all the causes, particularly that of the chronic diarrhoeas. Moreover, there is still a lot of controversy over the mucosal changes associated with diarrhoea. This study is essential not only for etiological investigations and better understanding of pathophysiology of diarrhoeal diseases, but also for diagnostic and therapeutic purposes.
8. The study requires a small bit (0.5 mgm) of small intestinal mucosa by biopsy and intestinal juice by brushing, only when clinically indicated. Blood will be taken only for patient care and screening for bleeding disorders.

SECTION - III BUDGET

A. DETAILED BUDGET

PERSONNEL SERVICES

<u>Name</u>	<u>Position</u>	<u>% Effort</u>	<u>Project requirement</u>	
			<u>Taka</u>	<u>Dollar</u>
Dr. Tetsuo Morishita			No cost to ICDDR, B.	
Dr. R. Islam	Chief Physician	5%	2,500.00	-
Dr. P. K. Bardhan	Physician	15%	3,000.00	-
Dr. A. M. Molla	Scientist	5%	3,000.00	-
A Microbiology Technician		5%	500.00	-
A Biochemistry Technician		5%	500.00	-
A Clinical Pathology Technician		5%	500.00	-
A Veterinarian		5%	750.00	-
			<hr/>	
			10,750.00	-
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SUPPLIES AND MATERIALS

Office supplies		500.00	-	
Printing/Publication		1,000.00	-	
Inj. Buscopan & Xylocaine Spray	Provided by Dr. Morishita			
Miscellaneous		500.00	-	
			<hr/>	
			2,000.00	-
			<hr/>	

EQUIPMENT

Nil

PATIENT HOSPITALISATION Tr. 150 X 3 X 24

10,800.00 -

OUTPATIENT CARE

Nil

ICDDR, B TRANSPORT

Nil

TRAVEL & TRANSPORTATION OF PERSONS

Nil

TRANSPORTATION OF SUPPLIES

Nil

RENT, COMMUNICATION, & UTILITIES

N11

PRINTING AND REPRODUCTION

N11

OTHER CONTRACTUAL SERVICES

N11

CONSTRUCTION, RENOVATION, AND ALTERATIONS

N11

LABORATORY TESTS :

<u>Item</u>	<u>Unit Cost</u>	
Blood Count	24 X Tk. 4.20	100.80
Platelet Count	24 X Tk. 1.20	28.80
Bleeding Time & Clotting Time	24 X Tk. 1.75	42.00
Blood Electrolytes	24 X Tk. 3.00	72.00
Stool C/S	24 X Tk. 15.50	372.00
ST, LT	24 X Tk. 3.00	72.00
Stool M/E	24 X Tk. 2.00	48.00
Mice	24 X 2 X Tk. 3.00	144.00
		<hr/>
		879.60
		<hr/>

BUDGET SUMMARY

<u>C A T E G O R Y</u>	<u>TAKA</u>	<u>DOLLAR</u>
1. Personnel Services	10,750.00	-
2. Supplies & Materials	2,000.00	-
3. Equipment	-	-
4. Patient Hospitalisation	10,800.00	-
5. Laboratory Tests	879.60	-
6. Outpatient	-	-
7. Travel & Transportation of Persons	-	-
8. Transportation of Supplies	-	-
9. ICDDR,B Transport	-	-
10. Rent, etc.	-	-
11. Printing & Reproduction	-	-
12. Other Contractual Services	-	-
13. Construction & Renovation	-	-
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Total -	24,429.60	-