

Library 2

Attachment 1.

Date SEPT 20 1984

ETHICAL REVIEW COMMITTEE <sup>ICDDR, B Library</sup> ICDDR, B.  
~~OSCC-1B~~

Principal Investigator Thomas C. Butler Trainee Investigator (if any) DO

Application No. 84-042 Supporting Agency (if Non-ICDDR, B) \_\_\_\_\_

Title of Study Pathological Studies of Project status:  
Fatal Complications of Childhood (X) New Study  
Diarrhoeal Diseases ( ) 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: NA - Deceased  
(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 NA 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 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.

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

Thomas C. Butler  
Principal Investigator

- 2 OCT 1984

84-042  
3/18/84

ICDDR,B LIBRARY  
DHAKA 1212

SECTION I - RESEARCH PROTOCOL

- 1. Title: Pathological Studies of Fatal Complications of Childhood Diarrhoeal Diseases
- 2. Principal Investigator: Dr. Thomas C. Butler
- 3. Co-Investigators: Drs. Rafiqul Islam, Moyenu Islam, and A.K. Azad
- 4. Starting Date: Oct 1984
- 5. Completion Date: Sept 1986
- 6. Total Direct Cost: US\$41,174
- 7. Scientific Program Head:

This protocol has been approved by the Pathogenesis Therapy Working Group

Signature of the Scientific Program Head: Thomas Butler

Date: 30-9-84

8. Abstract Summary:  
Approximately 100 children with diarrhea who die during treatment at the Dhaka Station Hospital will be selected for post-mortem examinations. After informed consent is obtained from family members or when bodies are unclaimed for 48 hours after death, the Pathologist will carry out both gross and microscopic examinations of the abdominal and thoracic organs in order to diagnose the causes of death and associated diseases.

From this study, exact causes of death and associated diseases in Bangladesh can be established and this information will be used by our physicians to render optimal medical care to seriously ill children.

9. Reviews:

a. Research Involving Human Subjects: \_\_\_\_\_

b. Research Review Committee: \_\_\_\_\_

c. Director: \_\_\_\_\_

## SECTION II - RESEARCH PLAN

### A. INTRODUCTION:

#### 1. Objective

During 1982-1984, autopsies were carried out in 100 patients at ICDDR,B under a previous protocol 82-006. The aim of this study is to continue post-mortem studies by establishing accurately the immediate causes of death in patients in Bangladesh with diarrhoeal diseases. By performing post-mortem examinations in selected patients, it will be possible to define diseases in both intestinal and extra-intestinal sites. With this information, we will gain new understanding of how diarrhoeal diseases produce serious complications and we will apply this knowledge to improving clinical management of future patients.

#### 2. Background

Diarrhoeal diseases in Bangladesh are caused by infectious agents that have a widespread distribution in the environment. The most frequently identified causative agents are Vibrio cholerae, enterotoxigenic E. coli, Shigella species, and rotavirus. A newly recognized agent is Campylobacter jejuni. The protozoal agents Entameba histolytica and Giardia lamblia are occasionally found in stools of patients with diarrhoea.

The great majority of diarrhoeal cases are self-limited and improve without specific therapy. Other cases are moderately severe but can still be managed successfully with oral rehydration solutions. Some cases of diarrhoea present with such severe dehydration that intravenous fluid therapy is required to prevent fatal shock. Rare cases, however, will die despite

adequate rehydration and we have at present an incomplete understanding of the pathogenesis of fatal complications of diarrhoeal diseases.

During 1982-1984, 100 fatal cases of invasive diarrhoea were studied by autopsy in a previous protocol 82-006. Children under 5 yr comprised 69% of the patients. The most common diarrhoeal pathogens identified were Shigella species in 29 cases. Entamoeba histolytica in 19 cases, and Campylobacter jejuni in 13 cases. The most frequently identified anatomic diseases were fatty degeneration of the liver in 70 cases, bronchopneumonia in 41 cases. Shigella colitis in 29 cases, and amebic colitis in 19 cases, hemorrhagic necrosis of the intestine in 25 cases. and amebic colitis in 19 cases. The most frequently assigned underlying causes of death were septicemia in 28 cases. Shigella colitis in 13 cases, amebic colitis in 11 cases, hypoglycemia in 9 cases, bronchopneumonia in 7 cases, and necrotizing pneumonia in 6 cases. Multiple causes of death assigned as associated causes were present in 93 patients. Shigella colitis was significantly associated with fatty liver ( $p < 0.05$ ). A new histologic finding in shigellosis was hyperplastic crypts in the submucosa. It was concluded that diarrheal pathogens produce diseases in the intestine that cause death or contribute to death by 1) promoting disease processes in other organs, especially septicemia and fatty liver and 2) combining effects with concomitant diseases in other organs, especially pneumonia.

#### B. SPECIFIC AIMS:

1. By post-mortem examination to determine the immediate causes of death in fatal cases of childhood diarrhoea and to discover the extent of underlying associated diseases, such as chronic tuberculosis and

malnutrition, which may have altered the susceptibility of patients to diarrheal diseases or to fatal complications there of.

2. To make correlations between the pathological findings and both the ante-mortem clinical information and the presence of invasive diarrheal agents, such as Shigella and amebae, so as to suggest to physicians how better to diagnose and treat invasive diarrhoeal diseases at the ICDDR,B.

C. METHODS OF PROCEDURE:

1. Patient selection: Any patient less than 16 yr old who dies at the ICDDR,B Dhaka Station Hospital will be eligible for entry into the study. Patients will be excluded if they died shortly after arrival with a clinical picture of watery diarrhoea and hypovolemic shock.
2. Informed consent: After the death of a patient, the family will be consoled by the physicians and nurses. The physician will ask the family for permission for the ICDDR,B to carry out a post-mortem examination. This procedure will be conducted in a manner that is fully within the laws of Bangladesh and with the permission of the Ministry of Health and Population of the Government of Bangladesh. The manner of the request will be in keeping with Moslem practices to respect the customs and sensitivities of the local people. The reason for the request will be openly state to be the need for our physicians to learn the exact cause of death in order to improve the care for other patients and to prevent contagion in these surroundings. In the absence of family members, when bodies have been unclaimed for 24 hours after death, post-mortem examinations will be carried out by a procedure that is consistant with the laws and practices of the country of Bangladesh.

3. Autopsy. The post-mortem examination will be performed by a fully trained and licenced Pathologist. The body will first be weighed and length measured. A complete autopsy will be done and the brain examined where indicated.

Bacterial cultures will be obtained from blood obtained from the subclavian vein and from an aspiration of lung tissue from any lung area that appears inflamed. Blood smears will be examined for malaria parasites. Stool specimens will be cultured for Shigella, Salmonella, and Campylobacter, and will be examined for E. histolytica and other intestinal parasites.

Tissues will be cut and fixed in buffered 10% formalin. Slides will be stained with hematoxylin-eosin, PAS, and connective tissue stains. Microscopic findings will be correlated with gross pathologic findings to construct the most likely immediate cause of death and underlying contributing causes of death.

Confidentiality of information regarding the identity of the patient and the results of the autopsy will be strictly adhered to by the ICDDR,B personnel. The results of the autopsies, however, will be made available to the patients' family members and, on request, to authorities of the Ministry of Health and Population Control.

D. SIGNIFICANCE AND RATIONALE:

Diarrheal disease is a leading cause of death in children of Bangladesh despite recent improvements in our approaches to rehydration and antibiotic treatment. Our present understanding of the causes of fatal complications in diarrheal disease is incomplete. Post-mortem examinations of fatal

cases will clarify the causes of death and permit our physicians to choose rational therapies for serious patients.

E. FACILITIES REQUIRED

A secured room for post-mortem examination will be utilized. This room will be located in the courtyard beside the hospital ward. Tissues will be processed in the histopathology laboratory.

F. ANALYSIS OF DATA

1. Data sheets containing information on history, physical findings, and laboratory data will be kept for all cases. Autopsy findings will be tabulated by the Pathologist.
2. Autopsy findings will be correlated with clinical and laboratory findings with an emphasis on identified diarrheal pathogen, nutritional status, pneumonia, and history of seizures. Statistical correlations will be examined by Fisher's Exact Test and Student's test.

G. ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

1. This study proposes to carry out post-mortem examinations on deceased children at the ICDDR,B who died with complications of diarrhea. The purpose is to learn more precisely than we know now why children die with diarrhea and whether we should treat critically ill patients in other more optimal manners in order to prevent deaths.

Voluntary informed consent cannot be given by deceased patients but will be requested of their families. The rationale for studying deceased



children is that study of them will more directly yield information about fatal complications than studying any other group of patients.

2. There are no risks for the patients, who have already died. For the family members, there are potential risks involving guilt for allowing physicians to carry out post-mortem examinations. Therefore, families will be fully explained the nature of the procedure before consent is requested.
3. The families of children patients will be consoled before the post-mortem. After the examination the ICDDR,B will provide transportation of the body to the home in order to minimize the inconvenience caused by the procedure. The families will be reassured by the ICDDR,B staff that the family members and our physicians and nurses did everything possible to save the life of the child. The families will be reassured that they made a good decision in permitting the post-mortem examination in the interest of the family and other future patients.
4. Confidentiality of information will be assured by permitting only highly selected personnel to work in the post-mortem room. They will be required not to divulge the identity of patients or results of the examination to anyone outside the participating personnel and family members.
5. Signed informed consent will be obtained from the closest of the relatives attending the child in the hospital. The place will be a quiet room of the hospital. The procedure and reason for the request will be explained and the written form read to the family members. No information will be withheld from family members. Compensation will not be offered.

6. There is no interview.
7. The benefits of this study may accrue to family members by their learning about contagious diseases; such as tuberculosis - in their families or by learning about inherited diseases or cancer, which might affect other members of the family at a later time. The benefits to society are great by increasing knowledge about diarrheal diseases in Bangladesh which may be applied to the care of future children. These benefits to families and society outweigh the risks, which are non-existent to the deceased patients and of transient, psychological nature to family members.
8. This study will require the use of the hospital record and selected organ samples and body fluids obtained during the post-mortem examination. Fetus and abortus samples will not be used.

REFERENCES:

1. Snyder, J.D., Merson, M.H. The magnitude of the global problem of acute diarrhoeal disease: a review of active surveillance data. Bull. W.H.O. 60(4):605, 1982.
2. Nalin, D.R. Mortality from cholera and other diarrhoeal diseases at a cholera hospital. Trop.Geogr.Med. 24:101, 1972.
3. Hirschhorn, N., Lindenbaum, J., Greenough, W.B., and Alam, S.M. Hypoglycemia in children with acute diarrhoea. Lancet 2:128, 1966.
4. Chamblee, R.F., Evans, M.C. New dimensions in cause of death statistics. Am.J.Pub.Hlth.72:1265, 1982.
5. Dammin, G.J. Shigellosis Chapter 4 (3) in Pathology of Tropical and Extraordinary Diseases. An Atlas. Vol 1, Edited by C.H. Binford and D.H. Connor. Armed Forces Institute of Pathology, Washington, D.C. 1976, p.145.
6. Felsen, J. Bacillary dysentery colitic and enteritis. W.B. Saunders Co., Philadelphia 1945. p.222-239.

SECTION III - BUDGET  
A. DETAILED BUDGET

1. Personnel Services: (for 1 year only)

<u>Name</u>	<u>Position</u>	<u>% Effort</u>	<u>Taka</u>	<u>Dollar</u>
Dr. T.C. Butler	Pr. Investigator	20%	-	13,400
Dr. A.K. Azađ	Co. Investigator	20%	20,000	-
Dr. M. Islam	Pathologist Consultant	100%	144,000	-
Mr. A. Rob	Lab. Assistant	100%	33,500	-
Mrs. S. Pashi	Technologist	100%	93,500	-

2. Supplies & Materials: (for 2 years only)

a. Clinical supplies - needles, gloves, syringes, tubes, etc..		-	1,000
b. Lab tests: Cultures : 100 x 6 x Tk.30		18,000	-
Stool ME : 100 x Tk.5		500	-
CBC : 100 x Tk.8		800	-
Biochemistry:Kreatinine: - 100 x Tk.28		2,800	-
SGPT : 100 x Tk.30		3,000	-
Bilirubine: 100 x Tk.31		3,100	-
c. Lab.supplies - media, reagents etc.		-	6,000

3. Equipment & Shipping: (for 2 years only)

Knife sharpener, ---	-	3,200
Autopsy Scale, ---	-	500
Autopsy Saw, ---	-	500
Autopsy knife, ---	-	86
Paediatric weighing scale : ---	3,000	-

4. Patient hospitalization: (for 2 years only)

100 Patients x 2 days x Tk.150	30,000	-
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5. Transportation: (for 2 years only)

100 x Tk.600	60,000	-
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6. Construction costs: (None)

Total :	412,200	24,686
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Total US \$41,174

(Conversion rate US \$1 = Tk.25)

B. BUDGET SUMMARY

	<u>Dollars</u>
1. Personnel Service (1 yr)	25,040
2. Supplies & Materials (2 yr)	8,128
3. Equipment & Shipping (2 yr)	4,406
4. Patient hospitalization (2 yr)	1,200
5. Transportation (2 yr)	2,400
6. Construction cost	-
	<hr/>
Total :	41,174
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International Centre for Diarrhoeal Diseases Research, Bangladesh

CONSENT FORM

(Post-mortem study)

Pathological studies of fatal complications of diarrhoeal diseases

STATEMENT TO BE READ TO THE GUARDIAN WHEN CONSENT IS OBTAINED

Diarrhoeal disease is an important cause of death in Bangladesh despite recent improvements in our diagnosis and therapy. Our present understanding of the causes of fatal complications in diarrhoeal disease is incomplete. You will understand that we can learn more about these complications by investigation of the dead bodies. With this knowledge we will be able to further improve diagnosis and treatment of these diseases. In this way it might be possible that we can save other children/adults in the near future. We therefore ask your permission to carry out a post-mortem investigation on the body of your relative.

This will be performed by a fully trained and licensed pathologist. The procedure will be conducted in a manner that is fully within the laws of Bangladesh. We have got permission of the Ministry of Health and Population of the Government of Bangladesh to perform such investigations. If you approve, this examination will be performed within 24 hours after death.

A thoraco-abdominal incision will be made. Through this incision, organs will be taken out for inspection and samples retain for microscopic examination. Brain will be examined when indicated. The wound will be stiched and the body will be handed over to you immediately after the procedure. If you wish, the results of the investigations will be made available to you.

For the benefit of human being if you agree to co-operate with us in this study then please put your signature or left thumb impression below.

Signature of the Investigator

Date: \_\_\_\_\_

Signature /Left thumb impression of Guardian

Name of Guardian: \_\_\_\_\_

Signature of the Witness

Date : \_\_\_\_\_

Relationship with Patient: \_\_\_\_\_

Hospital Registration No.: \_\_\_\_\_

Date: \_\_\_\_\_

আনুষ্ঠানিক উদ্বোধন গবেষণা কেন্দ্র,  
বাংলাদেশ

মৃত্যুনা তদনু গবেষণা

সন্মতি পত্র  
=====

বর্তমানে রোগ নিরূপণ ও চিকিৎসা পদ্ধতির যথেষ্ট উন্নতি বিধান সত্ত্বেও বাংলাদেশে পেটের পীড়াজনিত মৃত্যু এখনও প্রধান কারণ। পেটের পীড়াজনিত ভয়ংকর উপসর্গগুলি নিরূপণ করা এখনও জটিল রহস্যে গেছে। আপনি অতি সহজেই বুঝতে পারেন, মৃত রশ্মীর পরীক্ষার আরও পরীক্ষা করলে এসব জটিলতা সমুদ্রে আধারা অনেক কিছু জানতে পারব। এই লক্ষ্যে তবিষয়ে আমাদেরকে একরূপ রোগ নিরূপণে ও চিকিৎসায় যথেষ্ট সহায়ক হবে। অদূর ভবিষ্যতে একরূপ দুরারোগ্য আক্রমণে ছেলে-বুড়ো সবাইকে বাঁচাতে অনেক সাহায্য করবে। অতএব, আমরা আপনার মৃত আত্মীয়ের মৃত্যুনা তদনু দ্বারা পরীক্ষা নিরীক্ষা করার জন্য অনুমতি চাইছি।

অভিজ্ঞ ও অনুমোদিত গ্যাবলজিক্ট দ্বারা এ পরীক্ষা করা হবে। বাংলাদেশ সরকারের আইনের গতির ভিতর এই পরীক্ষা করা হবে। সরকারের স্বাস্থ্য ও জনসংখ্যা নিয়ন্ত্রণ মন্ত্রণালয় থেকে এ ব্যাপারে আমরা প্রয়োজনীয় অনুমতি পেয়েছি। আপনার অনুমতি গেলে রশ্মীর মৃত্যুর ২৪ ঘণ্টা সময়ের মধ্যে এ পরীক্ষা করা হবে।

পেট ও বুকে অস্ত্রোপচারের মাধ্যমে বিভিন্ন অংশ বাহির করিয়া পরীক্ষা করা হবে এবং অণুবীক্ষণ যন্ত্রে পরীক্ষার জন্য এইগুলির অংশ নেওয়া হবে। প্রয়োজনবোধে যগজ পরীক্ষাও করা হবে। অস্ত্রোপচারের পর প্রয়োজনীয় সেনাই করে সাথে সাথেই রশ্মীকে আপনার বিকট হস্তানুর করা হবে। আপনি চাইলে এই পরীক্ষার ফলাফল আপনাকে জানান হবে। আপনি এই মানবতার কাজে সহযোগীতা করতে সক্ষম থাকলে নিম্নে স্বাক্ষর/টিপ সহি দিন।

অতিভাবকের স্বাক্ষর/

টিপ সহি-----

অতিভাবকের নাম-----

মৃত রশ্মীর সহিত সম্পর্ক-----

মৃত রশ্মীর রেজিঃ নং-----

তারিখ-----

গবেষকের স্বাক্ষর

স্বাক্ষীর স্বাক্ষর

তারিখ-----

তারিখ-----