RRC folder copy.

Attachment 1.

Date October 31, 1989

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. Moyenul Islam

Trainee Investigator (if any) /

Application No. 89-011

Supporting Agency (if Non-ICDDR,B)

Title of Study Pathological and microbiological studies on primarily fatal cases of ... respiratory infection

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: N.A. - DECEASED SUBJECTS.
   (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 (FAMILY) 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 — N A Yes No
5. Will signed consent form be required:
   (a) From subjects FAMILY — (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 FAMILY
   ✓ AND 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.

(P.T.O.)

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

Principal Investigator

Trainee

89-011

APPLICATION FOR PROJECT GRANT

1. PRINCIPAL INVESTIGATOR : Dr. M. Moyenul Islam

2. OTHER INVESTIGATORS : Physician to be appointed
Dr. M. Sirajul Islam
Dr. S. Tzipori

3. TITLE OF PROJECT : Pathological and microbiological studies on primarily fatal cases of diarrhoeal illness and acute lower respiratory infection

4. STARTING DATE : December 01, 1989

5. COMPLETION DATE : November 30, 1994

6. TOTAL BUDGET REQUIRED : US$ 129,383 (Annual)

7. FUNDING SOURCE :

8. COORDINATOR : Dr. S. Tzipori S. Tzipori
Laboratory Sciences Division

9. ABSTRACT SUMMARY :

This study proposes to carry out post-mortem examination on fatal cases of diarrhoeal illness and acute lower respiratory infections in patients admitted to Clinical Research Centre of ICDDR,B whenever informed consent can be obtained from family members of the deceased. Comprehensive histopathological, microbiological, serological and toxicological studies will be carried out on samples taken from different levels of gastrointestinal tract, lungs,

liver, kidneys, brain, spleen, lymph nodes and bone marrow. With the development of more sophisticated laboratory techniques, we shall be able to learn more about the aetiology and pathogenesis of diarrhoeal illness, acute lower respiratory infections and their complications. Thus, we shall be able to establish exact causes of death. This knowledge will be useful for providing better medical care to futre patients.

10. AIMS OF PROJECT

a) General aim

The purpose of this study is to identify the cause of death in cases of diarrhoeal illness and acute lower respiratory infections in Bangladesh, by performing post-mortem examination and to carry out comprehensive microbiological studies in cases where autopsies are performed within 6 hours of death. Information gained from this study will help us in understanding the pathophysiology of the complications of diarrhoeal illness, pneumonia and other concomitant diseases. This knowledge will be useful for providing better medical care to patients in future.

b) Specific aims

i) To identify the pathological changes and associated diseases in fatal cases of diarrhoeal illness and acute lower respiratory infections and

to establish the causes of death by post-mortem examination.

ii) To carry out comprehensive microbiological studies at different levels of gastro-intestinal tract and in lungs to make correlations with pathological changes.

iii) To understand the patho-physiology of diarrhoeal illness and lower respiratory infections and their complications by correlating post-mortem pathological and microbiological findings with antemortem clinical and laboratory data.

iv) To provide regular histopathological and histochemical services to other investigators including animal experimentation.

v) To provide regular histopathological and histochemical services to investigators and collaborators from other national institutions.

a) Shishu Hospital

b) Mirzapur Hospital

c) Significance

i) Results of this study will enable our physicians to learn more about the pathogenesis of fatal complications of diarrhoeal illness and pneumonia.

This knowledge will help them to deliver better medical care to other patients in future.

ii) This study will provide accurate data regarding morbidity and causes of death in diarrhoeal illness and pneumonia in developing countries, which has global significance.

iii) This study will also act as a routine surveillance system for diagnostic and therapeutic quality control on patient care at ICDDR,B.

11. ETHICAL IMPLICATIONS

1) This study proposes to carry out post-mortem examinations on fatal cases of diarrhoeal illness and acute lower respiratory infection at the ICDDR,B. The purpose is to learn more precisely than we know now why patients die with diarrhoea and/or pneumonia and whether we should treat critically ill patients in other more optimum ways in order to prevent deaths.

Voluntary informed consent cannot be given by the deceased and will be requested of their family members. This post-mortem study will yield more direct information about fatal complications of diarrhoea and acute lower respiratory infections than any other group of patients.

2) There are no risks for the patients, since they are dead. For the family members, there are potential risks of feeling guilty for allowing physicians to carry out post-mortem examinations. Therefore, family members will be fully explained the nature of the procedure before consent is requested.

3) The family members of the deceased will be consoled before the post-mortem. After the post-mortem examination ICDDR,B will provide transportation expenses for the body to its home in order to minimize the inconvenience caused by the procedure. The relatives 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 patient. 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 patient 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 family members may be benefited by learning about contagious disease, such as tuberculosis in their family or by learning about hereditary diseases which might affect other members of the family at a later time. The benefits to society are great, because the additional knowledge on diarrhoeal diseases and acute lower respiratory infection in Bangladesh may be applied to the care of future patients. These benefits to families and society outweigh the risks, which are non-existent to the deceased and are only of transient, psychological nature to the 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.

12. BACKGROUND, RESEARCH PLAN AND BIBLIOGRAPHY

a) Background

Recent advances in medical knowledge and diagnostic techniques have not reduced the value of post-mortem

examination and a goal-oriented autopsy remains a vital component in the assurance of optimum medical care to the public. Study of a recent autopsy series (1) in a university teaching hospital in USA revealed that a major diagnosis was missed clinically in about 10% of patients. The same study also revealed that systemic bacterial, viral and fungal infections were missed clinically in 24% of patients. In another autopsy series (2), it was found that 13% of major clinical diagnoses were not confirmed at autopsy.

In Bangladesh, except for medico-legal purpose, post-mortem examinations are rarely carried out. A small number of routine hospital autopsies performed at SEATO-Cholera Research Laboratory (4,5,24) and later at ICDDR,B (3) reveal that dehydration, colitis, pneumonia, marasmus, sepsis and hypoglycaemia are the major causes of death in acute diarrhoeal illness. Another striking finding in about a quarter of these patients was segmental necrotizing enterocolitis (3,6). This acute and often fatal complication of infectious diarrhoea, usually occurring in children in developing countries, has been described by various authors as "pig bel: enteritis necroticans" (7,8) and "necrotizing enterocolitis" (9,10). Although various aetiologic agents have been proposed for this disease, including round worms (11), beta toxin of *Clostridium perfringens*

(7) and sweet-potato trypsin inhibitor (8), the pathogenesis of SNE remains unclear. We propose to investigate the role of *C. perfringens* type A and C and possibly other anaerobic bacteria and *Klebsiella* spp. in the pathogenesis of segmental necrotizing enteritis and/or colitis.

It was also noted that acute diarrhoeal illness and pneumonia occurred concurrently (14) and pneumonia was detected in 2/3rd of the fatal cases of acute diarrhoeal illness in Bangladesh (3). Acute lower respiratory infections and acute diarrhoeal illness are the two leading causes of death (respectively accounting for 43% and 33% deaths) in children below 5 years of age in the world (12,13). Comprehensive studies for the identification of infective agents in pneumonia cases were not carried out in the last autopsy series at ICDDR,B. Histological and microbiological examination of lungs will identify the aetiological agents of pneumonia and may help explain the high incidence of concomitant pneumonia in fatal cases of acute diarrhoea (diarrhoea-pneumonia complex).

Although the aetiologic agents in patients with acute diarrhoea can be identified in most cases, there remains a high proportion of cases with debilitating, persistent and recurrent diarrhoea, where no causes are

found. Many of these cases also have malabsorption. Coeliac disease (gluten-sensitive enteropathy of children), tropical sprue (idiopathic tropical malabsorption syndrome), chronic non-specific inflammatory bowel disease as well as various other intestinal and extra-intestinal diseases cause chronic diarrhoea (15,16,17). Many patients with persistent and recurrent diarrhoea come to ICDDR,B. But finally they go to other hospitals with surgical problems or with end-stage systemic complications and we do not normally expect to perform many autopsies on this vast group of patients. Lindenbaum *et al.* (18) in a study at the SEATO-Cholera Research Laboratory described sub-clinical small intestinal disease and sub-normal absorption tests in Bangladeshi population. We intend to investigate these findings again when post-mortem examination is carried out within 6 hours of death. Comprehensive quantitative microbiological studies of entire small intestine may establish the role of bacterial overgrowth and colonization in upper small intestine (and the nature of associated microorganisms) in the aetiology of persistent diarrhoea. Estimation of membrane-bound digestive enzymes and histological appearance of small bowel mucosa will reflect the clinical picture of these cases.

Haemolytic-uraemic syndrome (HUS) has been described as a serious complication following *Shigella dysentery* (19,20). Post-mortem percutaneous needle-biopsies of kidneys were studied at Cholera Research Laboratory between 1974 to 1977 in patients of severe *Shigella dysentery* with haemolytic-uraemic syndrome (21). Post-mortem examination of kidney and brain tissue in shigellosis patients who develop HUS will enable us to understand the pathogenesis of this syndrome.

In cases of acute diarrhoea microvascular endothelial damage and focal haemorrhages in the lamina propria of colonic mucosa, morphologically resembling local Shwartzman reaction, have been described (22). These may indicate cytotoxic action of VT or Shiga-like toxin or beta-toxin of *C. perfringens*. When electron-microscope (EM) facilities become available at the Centre, we shall be able to study the occurrence of local Shwartzman reaction in the pathogenesis of acute diarrhoea.

Lately, the possible role of *Campylobacter pylori* in the aetiology of gastritis and peptic ulcer is being widely investigated (23). Histological and microbiological examination of gastric mucosa for *Campylobacter pylori* will help determine its prevalence and role in the aetiology of gastro-duodenal disease and persistent diarrhoea. Thorough post-mortem

examination may also identify diseases common in developed countries, but seldom diagnosed in Bangladesh, e.g. Coeliac disease, Crohn's disease and ulcerative colitis.

Post-mortem examinations are rarely carried out in developing countries for various reasons. Our capability at the ICDDR,B to perform autopsies should prove to be a valuable resource for obtaining more information regarding morbidity, mortality and causes of disease in developing countries.

b) Research plan

1) Patient selection: Any patient, who dies of diarrhoeal illness and/or respiratory infection at the Clinical Research Centre of ICDDR,B will be eligible for entry into this study. Medico-legal implications will always be kept in mind, while carrying out these post-mortem examinations. Cases where foulplay is suspected and there are signs of physical injury or of poisoning, will be excluded from this study and the matter will be brought to the notice of the legal authorities.

2) Informed consent: After the death of a patient, the family will be consoled by the attending physicians and nurses. The physician will ask the family for permission to carry out post-mortem

examination. Reason for the request will be stated and it would be explained that there is need for our physicians to learn the exact cause of death in order to deliver better medical care to other patients in future. Permission for performing autopsies at ICDDR,B has been obtained from the Ministry of Health and Population Control, Government of Bangladesh.

3) Autopsy procedure: The post-mortem examination will be carried out by a trained and certified pathologist. First a subclavian venous blood sample will be drawn and if indicated cerebro-spinal fluid will be collected by lumber puncture. Routinely a thoraco-abdominal incision will be made to dissect abdominal and thoracic organs. Special permission will be obtained to examine the brain, when clinically indicated. Samples from different levels of GI tract, lungs, liver, kidney, spleen, lymph node and bone marrow will be fixed in formol-saline for histopathological examination. Gram-stain for bacteria, Ziehl-Neelsen stain for mycobacteria and periodic-acid-Schiff and silver-staining methods for fungi and protozoa will be carried out in tissue sections, where the clinical and histological features suggest possibility of such infections.

4) Microbiology: Samples for microbiological studies will be collected if autopsies are performed within 6 hours of death. Mucosal scrapings and contents of GI tract, lungs and other tissue, blood and other body fluids collected during the autopsy will be cultured aerobically and anaerobically to isolate bacterial pathogens which are associated with diarrhoeal illness (*Salmonella*, *Shigella*, diarrhoeagenic *E. coli*, *Aeromonas*, *Plesiomonas*, *Yarsinia*, *Campylobacter*, *Vibrio*, *Clostridia* and *Bacteroides*). Presence of bacteria, which are at present not considered enteropathogenic, e.g. *Klebsiella* sp. will also be recorded. Bacterial isolates will be identified by established techniques. Diarrhoeagenic *E. coli* will be identified according to categories. utilizing bio-assays and DNA-probes, which are in the process of being introduced to the Centre.

5) Bacterial counts: The total number of bacteria present in each segment of the small intestine will be estimated.

6) Microscopy: Specimens will be examined for parasites and smears will be stained with specific stains to detect protozoa (*Giardia*, *Cryptosporidia* and *Amoeba* sp.).

7) Worm burden: The type and number of worms present in the intestines of each individual will be noted and recorded.

8) Electron Microscopy (EM): Representative specimens will be negatively stained and examined under the EM for viral agents. Where appropriate, immune EM will be employed to confirm the presence and identity of viral agents.

9) Virus identification: Identification of group A rotavirus and enteric adenoviruses will be attempted in cases of acute diarrhoea in children below 3 years age.

10) Toxicology: Gut contents will be homogenized and the supernatant extract will be tested for microbial toxins in cell culture by ELISA and in rabbit gut loop.

a) when there is clear evidence of dysentery, test for Shiga toxin will be done;

b) when pseudomembranous colitis is suspected, tests for the presence of toxins produced by *C. difficile* (ELISA and cell culture) and *C. perfringens* types A and B (guinea pig skin test) will be carried out;

c) cases of non-dysenteric bloody diarrhoea will be tested for VT-I and VT-II;

d) clear cases of watery diarrhoea will be tested for cholera toxin, LT and ST;

e) intraperitoneal inoculation in adult mouse and rabbit gut loop will be used in situations where known pathogens are not identified, particularly in cases of persistent diarrhoea;

f) in confirmed cases of shigellosis, the level of Shiga toxin will be measured in sera and the results compared between patients with and without HUS.

11) Estimation of membrane-bound digestive enzymes (MBDE): In cases of persistent diarrhoea, the level of MBDE will be measured in the upper small intestine. It is the best indicator of mucosal damage and maldigestion.

12) Peroxidase-antiperoxidase (PAP) studies: In histological sections showing evidence of bacterial invasion or surface attachment or viral infection where positive isolation was not made, PAP staining methods will be carried out to identify the pathogen. PAP methods can also be

used with convalescent serum from patients to detect foreign antigen in the tissue.

13) Examination of lung tissue: Most of the above techniques can be used to identify pathogenic viruses, bacteria and mycoplasma in lung tissue of ALRI cases associated with diarrhoeal illness.

14) Examination of kidney and brain: In confirmed cases of shigellosis, histological changes in kidney and brain will be compared in patients presenting with and without HUS.

15) Collection of specimens

Intestines:

a) Five equally spaced segments from the small intestine (approximately at 2, 25, 50, 75, 98% levels) will be removed for histology and microbiology. Further 3-4 sections will be taken from the large bowel including caecum.

b) 5 cm long segments of small intestine from each of the above levels will be opened and the mucosa scraped with a sterile wooden tongue depressor. This material will be divided into 2 portions and one-half will be frozen at $-70^{o}C$ for virology and enzymology studies. The second-half will be used for bacterial counts.

c) The contents of another segment of small intestine at 98% level and the caecum/colon (which should be 7-10 cm long and the volume of contents 3-5 ml from each) will be stored separately at -70°C for toxicological studies.

d) Blood will be cultured aerobically and anaerobically and serum stored for toxin measurements at -20°C.

e) Antrum and pyloric portions of gastric mucosa will be taken for histology and some scrapings will be cultured for *Campylobacter pylori* in special selective media and incubated anaerobically.

f) Lung tissue will be taken for histology and another portion will be collected in sterile container with saline. After bacterial culture the latter will be stored at -20°C for mycoplasma and viral isolation.

g) Brain and kidney tissue will be taken for histology only.

Information regarding the identity of the patient and results of autopsy will be treated as strictly

confidential. However, results of the autopsy will be made available to the family members and on request to the Ministry of Health of Government of Bangladesh.

FACILITIES REQUIRED

The present morgue, coldroom and laboratory spaces will be utilized.

ANALYSIS OF DATA

1. Data sheets containing information on history, clinical findings and antemortem laboratory data will be prepared.

2. Post-mortem histopathological and microbiological findings will be tabulated.

c) Bibliography

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13. PUBLICATIONS OF PRINCIPAL INVESTIGATOR

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14. FLOW CHARTS

After recording gross autopsy findings, samples of following tissue will be fixed in formol-saline and paraffin sections will be stained by the following methods and findings recorded:

I. Haematoxylin and Eosin stain:

	Sites of block	Findings
a)	Small intestine at 2% level	:
b)	Small intestine at 25% level	:
c)	Small intestine at 50% level	:
d)	Small intestine at 75% level	:
e)	Small intestine at 98% level	:
f)	Caecum	:
g)	Body of stomach	:
h)	Antrum of stomach	:
i)	3 or more additional blocks from colon (from pathological sites)	:
j)	Right lung (pathological sites) 2 or more blocks	:
k)	Left lung (pathological sites) 2 or more blocks	:
l)	Liver	:
m)	Spleen	:
n)	Pancreas	:
o)	Right kidney	:
p)	Left kidney	:
q)	Right adrenal	:
r)	Left adrenal	:

s) Mesenteric lymph node and enlarged/suspicious lymph nodes from other sites :

t) Bone marrow from lumbar vertebral body/other pathological site :

u) Brain and meninges :

II. Where the clinical history and/or histological features recorded above are suggestive, the following histochemical staining procedures on relevant blocks will be carried out and findings will be recorded:

		Findings
A.	Tissue-gram stain	
	Block a)	:
	b)	:
	c)	:
	d)	:
B.	Ziehl-Neelsen stain	
	Block a)	:
	b)	:
	c)	:
	d)	:
C.	Periodic acid-Schiff stain	
	Block a)	:
	b)	:
	c)	:
	d)	:

D. Silver stain (Warthin-Starry)
(for fungi, protozoa and
Campylobacter)

Block a) :

b) :

c) :

d) :

III. Peroxidase-antiperoxidase immunohistochemical method will be carried out in sections showing evidence of infection, but culture was negative or could not be done.

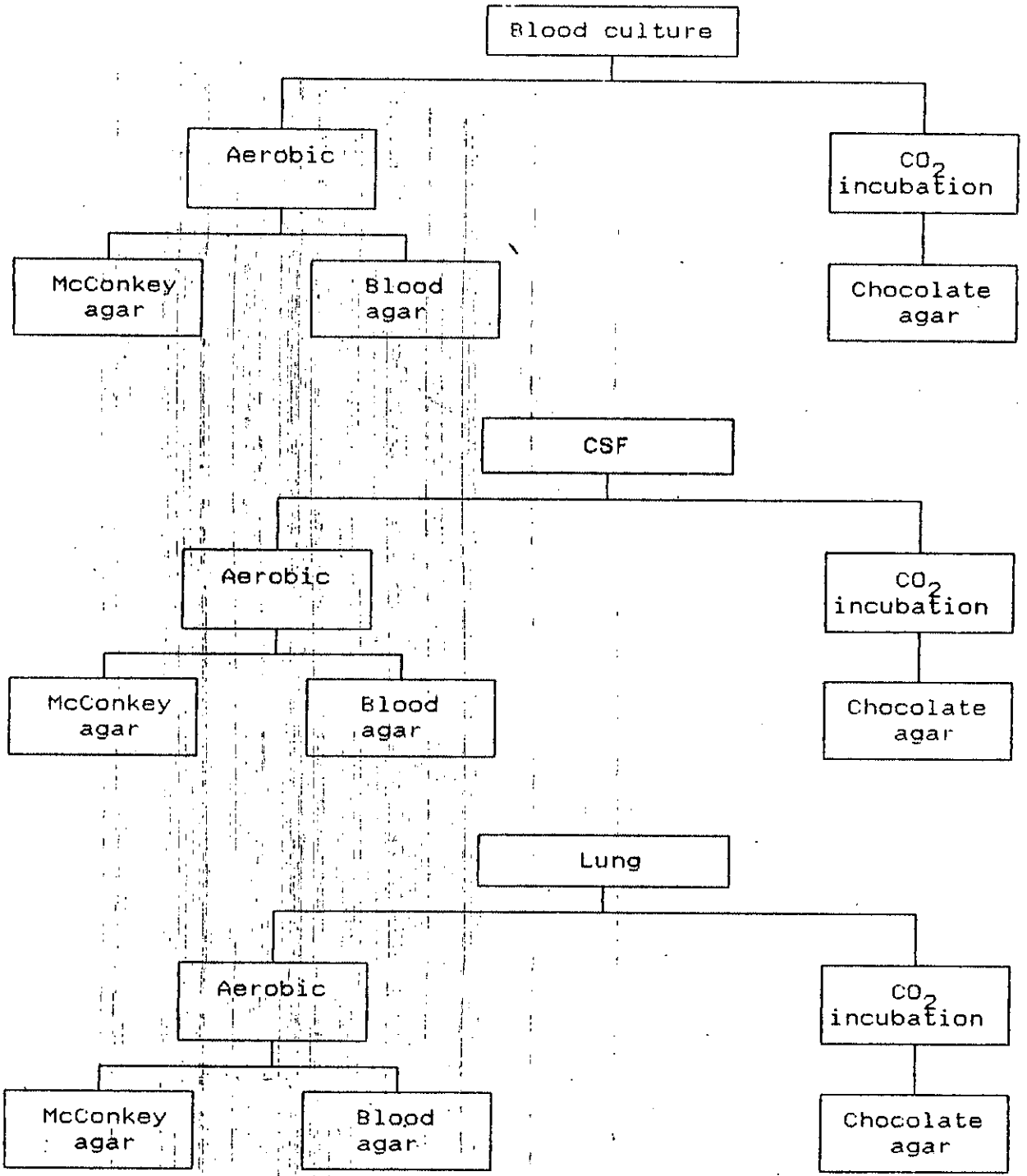
Block a) :

b) :

c) :

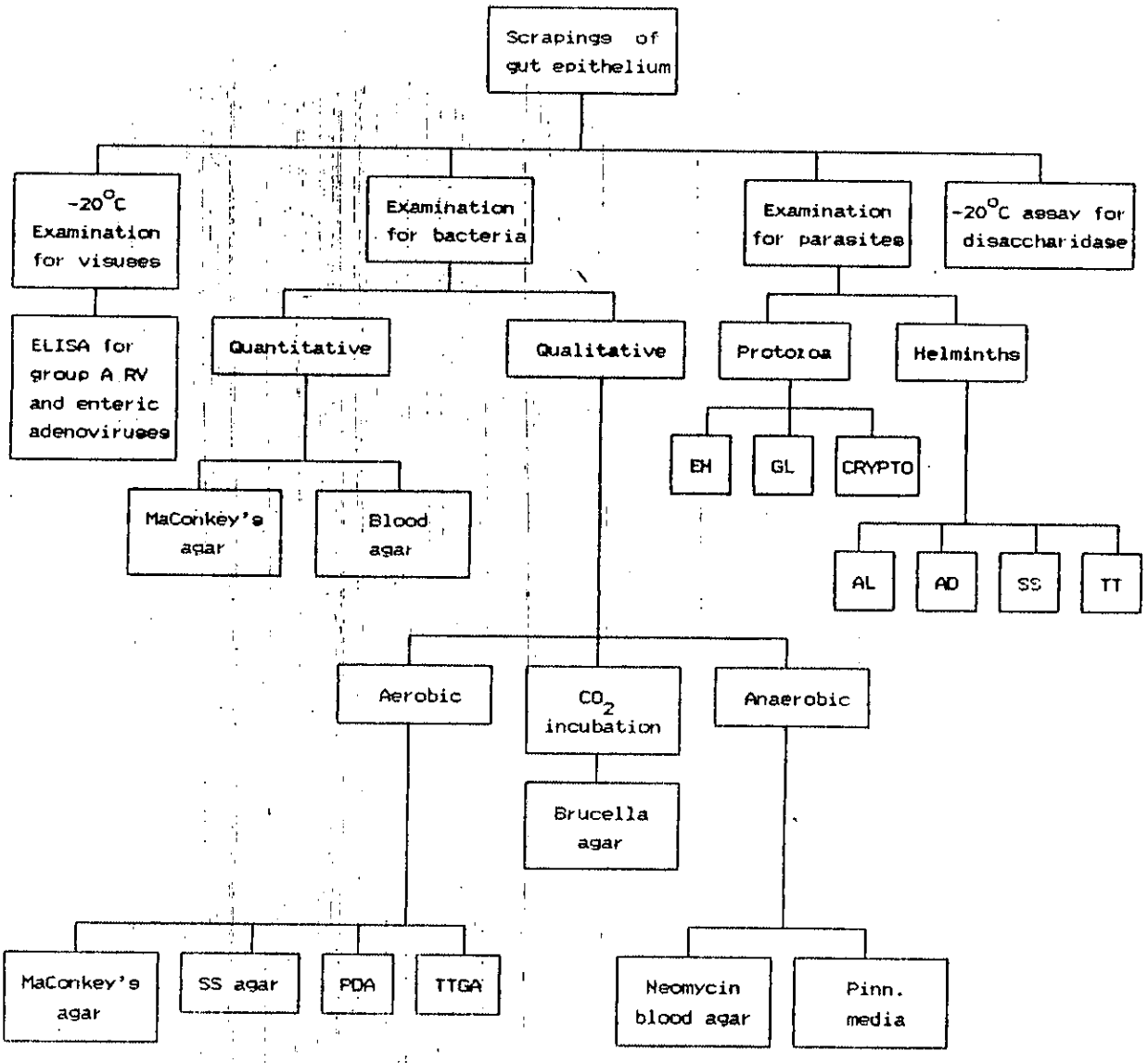
d) :

Flow charts for bacteriological examinations of various post-mortem samples



NOTE: Culture for *M. tuberculosis* will not be done

Flow chart for microbiological analysis of gut scrapings



SS = *Shigella-Salmonella* agar
PDA = *Plesiomonas differential* agar
TTGA = Monsur's agar
EH = *Entamoeba histolytica*
GL = *Giardia lamblia*
AL = *Ascaris lumbricoides*
AD = *Ancylostoma duodenale*
SS = *Strongiloides stercolaris*
TT = *Trichuris trichuria*
CRYPTO = *Cryptosporidia*

14. ITEMIZED SPECIFIC TASKS FOR EACH LISTED INVESTIGATOR

a) Dr. M. Moyenul Islam

To perform autopsy and histological interpretation.

b) Dr. S. Tzipori and Dr. M. Sirajul Islam

To carry out microbiological investigations and indentification.

16. BUDGET

1. Personnel cost (for one year)

Dr. M. Moyenul Islam, P4	70%	US$ 45.640.00
Dr. K. A. Chowdhury, NOC	100%	18,252.00
Dr. M. S. Islam, NOB	30%	3.360.00
Medical Officer, NOA	100%	8,615.00
Research Officer, GS5	100%	8,196.00
Research Officer, GS5	100%	4.800.00
Laboratory Attendant, GS2	100%	3,720.00
		92,583.00

2. Supplies and Materials

Glassware	3,000	
Hospital supplies	1,500	
Stationary	300	
Chemicals, media, etc.	12,400	
Lab supplies	1,000	
Janitorial supplies	300	
Non-stock supplies	4,000	
Freight, etc.	7,500	30,000.00

3. Other costs

Utilities	1,000	
Printing & publications	1,000	
Service charges	600	2.600.00

4. Inter-departmental services

Xerox and mimeograph	600	
Medical illustration	1,000	
Maintenance	600	
Bacteriology test	2,000	4,200.00

US$129.383.00

CONSENT FORM

(Post-mortem study)

Pathological and microbiological studies of Fatal cases of diarrhoeal illness and acute lower respiratory infections

STATEMENT TO BE READ TO THE RELATIVE/GUARDIAN WHEN CONSENT IS OBTAINED

Diarrhoeal disease and pneumonia are important causes of death in Bangladesh despite recent improvements in our diagnosis and therapy. Our present understanding of the causes of fatal complications in these diseases 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.

An abdominal incision will be made. Through this incision, parts of different organs will be taken out for inspection and microscopic examination. The wound will be stitched 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 cooperate with us in this study then please put your signature or left thumb impression below.

_____
Signature of Investigator

Date _____

_____
Signature of Witness

Date _____

_____
Signature/Left thumb impression of Relative/Guardian

_____
Name of Guardian

Relationship with patient _____

Hospital Registration No. _____

MISC/CONSENT.FRM

بسم الله الرحمن الرحيم

Major General M R Choudhury
MBBS (Cal), D. Bact (Lond), FCPS, MRC Path (Lond), FAS
Commandant,
ARMED FORCES INSTITUTE OF PATHOLOGY AND TRANSFUSION, DHAKA CANTONMENT, BANGLADESH
Telephone : 604230

A.F.I.P&T

25 September 1989

C/5

Dr. Saul Tzipori
Associate Director
Laboratory Sciences Division
ICDDR,B, Mohakhali, Dhaka

Dear Dr. Tzipori,

Thank you for your letter dated 16 Aug'89. I have gone through the protocol entitled "Pathological and Microbiological Studies on Primarily Fatal Cases of Diarrhoeal Illness and Acute Lower Respiratory Infection". By and large this is a well written protocol which envisages to probe into an area of research which is important. I however have certain comments/observations for your consideration.

1. In my opinion the prescribed format of ICDDR,B for preparation of protocols should have been followed. 'Abstract Summary' an essential part of such write-ups is conspicuous by its absence.

2. A flow chart depicting the procedures which are to be adopted in this investigation, may be incorporated in the protocol.

3. The investigators should indicate specifically the types of viruses which are to be isolated and studied.

4. Specific indications should also be laid down for toxicological studies.

5. Post-mortem investigations from medico-legal points of view should have been included.

In the light of the above, I feel that this protocol may be modified.

With warm regards.

Yours sincerely

(M R CHOUDHURY)

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Phone : 313048
319401
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বাংলাদেশ শিশু স্বাস্থ্য ইনষ্টিটিউট

ঢাকা শিশু হাসপাতাল, শের-ই-বাংলা নগর
ঢাকা-১২০৭, বাংলাদেশ।

Bangladesh Institute of Child Health

Dhaka Shishu Hospital, Sher-e-Bangla Nagar
Dhaka—1207, Bangladesh.

Dated, the 28th November'89

To,
Dr. Saul Tzipori
Associate Director
Laboratory Sciences Division

Dear Dr. Tzipori,

Thank you for asking to review the protocol. This project may hopefully contribute to increase the knowledge on diarrhoeal mortality specially in the cases where the causative organism is not known. The work may also lead to the recognition of some entero-pathogens which are not yet identified as the causative organism of diarrhoea. Further, it might help to understand the exact pathogenasis of different organisms. However, I am afraid that the established ELISA methods will fail to detect all the entero-toxins such as the new cholera toxin. Because the in vitro tests for NCT is yet to be developed and the production of NCT by the organisms other than Vibro has not yet excluded. The use of rabbit ileal loop model, as proposed in the project proposal, is unlikely to give any response to the supernatant of the homogenised gut as the toxin (s) released is supposed to irreversibely bind to the receptor site of the gut and the excess toxin(if any) will be too little to give any diarrhoeagenic response. The attempt can be made with concentrated (20 - 30 times) supernatent of the homogenate.

Otherwise I suggest that the proposal should be supported.

Sorry for the delay in responding. We are trying to get Govt. permission for autopsy.

With best regards.

Yours sincerely.

(Prof. M.S. Akbar)