Attachment 1.

Date 1st July, 198

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. Bardhan & Dr. Sack.

Trainee Investigator (if any) DD

Application No. 80-026

Supporting Agency (if Non-ICDDR,B) _____

Title of Study Non-Shigella Dysentery in Travelers.

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
   (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 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.

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

Rudy Bardhan
Principal Investigator

Trainee

Addendum to Protocol 80-026

After discussion in the combined meeting of Disease Transmission & Pathogenesis and Therapy Working Groups the following change in the protocol is proposed.

In all consenting patients sigmoidoscopy or colonoscopy will be performed, with, if indicated - biopsies. This will be done by Dr. Speelman, he will join the protocol as co-investigator.

During his work at the Department of Gastroenterology of the University Hospital of Amsterdam, Dr. Speelman has performed more than 150 colonoscopies with multiple biopsies and polypectomies without any complication.

Colonoscopy is an important new technique with a remarkable clinical yield in early and more accurate diagnosis. Biopsies can be taken under direct vision. The physical limitations of the forceps restrict the samples to 1 mm superficial pieces of tissue. Thus a limited area of mucosa is all that is obtained. For the purpose of delineating the extent of inflammation in the bowel this is adeguate. In fact mucosal biopsies have been shown to be the most accurate indicator of the extent of involvement of the colon in inflammatory bowel disease.

Many thousands of colonoscopies are performed every year. Wolff did 241 colonoscopies and biopsies without any complication. Teague made a review of 255 cases. Complications are extremely rare, however, they have been described. Performation of the gut is possible. However, these performations have always occurred in the hands of unexperienced operators. From biopsies taken during colonoscopies no complications have been described.

Sigmoidoscopies/colonoscopies can easily be justified on the basis of good medical care. In Europe and U.S.A. this is a standard procedure in patients suffering from colitis of unknown etiology. Many times colonoscopy is needed to reveal the diagnosis. Biopsies can be very helpfull.

Without the possibility for colonoscopy and biopsy not only the gastroenterologist is handicapted, but also the patient. Valuable information that can benefit the patient may be lost without this investigation- procedure.

1) Williams Chr and Teague R.M. Colonoscopy, Gut 14 (990-1003) 1973.

2) Wolff W.I., Colonofiberoscopy - JAMA 217 (1505-1512) 1971.

3) Teague R.M., Salmon P.R., Read A.E., Fibreoptic examination of the colon: a review of 255 cases. Gut 14 139-142, 1973.

4) Wolff W.I. et al. Colonofiberoscopy - a new and valuable diagnostic modality Am. J. Surg. 123 (180-183) 1972.

5) Christic J.P. et al. Indications for fiberoptic colonoscopy Southern Med. of 68 (881-886) 1975..

6) Wage J.D. : The role of colonoscopy in differntial diagnosis of inflammatory bowel disease. Gastrointest. Endosc. 1977, 23, 150.

7) Williams Chr. B. : Colonoscopy in Inflammatory Bowel disease clinics in gastroenterology 1978, 7, 701.

80-026
rec'd 9/7/80

SECTION I - RESEARCH PROTOCOL

(1) Title: NON SHIGELLA DYSENTERY IN TRAVELERS

(2) Principal Investigators: Dr. Bardhan
Dr Sack

(3) Starting Date: July 1980

(4) Completing Date: July 1981

(5) Total Direct Cost: $20,642

(6) Scientific Program Head:

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

Signature of Scientific Program Head: G. Molla
Group Secretary

Date: 7-7-80

(7) Abstract Summary: Non shigella dysentery is a relatively common but poorly understood syndrome in Bangladesh consisting of sub-acute mucoid or watery diarrhea, cramps, little fever and the presence of fecal leukocytes but no definite etiologic agent. This syndrome, locally known as "amasha", has been seen in the

travelers clinic and it is the purpose of this study to characterize the syndrome clinically and epidemiologically and attempt to find a pathogen responsible for it. Bacteriologic and virologic studies will be done in 40 patients with the disease and evidence for a bacterial etiology will be sought from the results of a doxycycline treatment trial. Study of this syndrome in expatriates is more likely to suggest an etiologic agent than a similiar study in Bangladesh patients because of the relatively low prevalence of background pathogens.

(8) Review:

(a) Ethical Review Commmittee: _____

(b) Research Review Committee: _____

(c) Director: _____

(d) BMRC: _____

(e) Controller/Administrator: _____

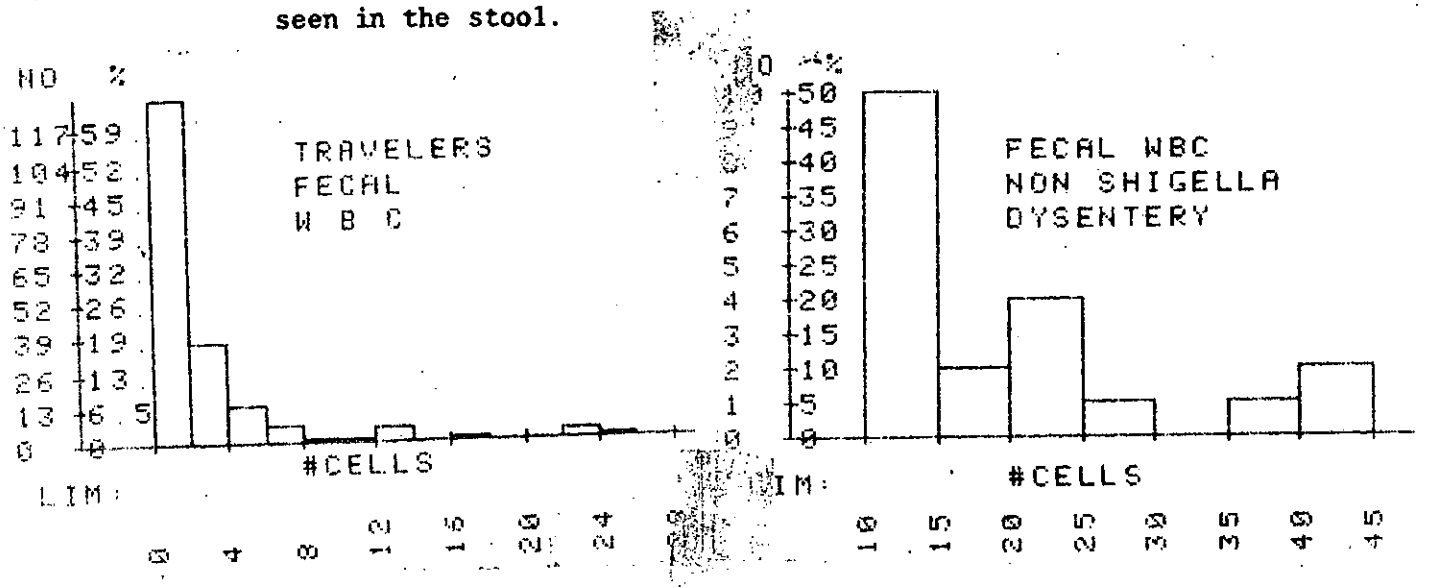
SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective: The objective of this study is to characterize the syndrome of non-shigella dysentery with an attempt to discover its etiology and possible treatment.

2. Background: Travelers diarrhea is a syndrome of acute watery diarrhea and may be caused by a variety of pathogens[1,2,3], the most frequent of which is the enterotoxigenic E. coli. During studies of travelers diarrhea at ICDDRB during the last year other diarrhea/dysentery syndromes were also found to frequently occur. Shigellosis, giardia, and ameba (carrier state only) were found frequently in addition to the ETEC. Additionally however, a syndrome of subacute non-shigella dysentery (NSD) was also noted in many of the patients and appears to be similiar to the "amasha" seen in Bangladeshi patients. The syndrome is characterized by cramps, loose stools with mucus (but rarely blood), no or only low grade fever (<101^{o}F). Acute watery diarrhea, dehydration and higher fever, were not seen in NSD. The illness lasted 1 to 18 days, frequently occurred in family clusters and has had no serious sequelae. The figure illustrates the pattern of fecal leukocyte numbers

in 198 consecutive stool specimens (right) submitted by the patients in the clinic and pattern of fecal leukocytes found in stools of patients with NSD (left). Rarely were rbc's seen in the stool.



Of the 180 patients seen in our clinic approximately 30 have had this syndrome once during the year.

Studies to determine an etiology have not revealed any pathogen. Laboratory studies for Shigellae, Salmonellae, enterotoxigenic E. coli[4,5], invasive E. coli have been negative. Campylobacter studies are now going on but preliminary results suggest that this agent will not explain the majority of the episodes of NSD, although it has been isolated from 8 asymptomatic individuals. Rotavirus, Yersinia[6], and Treponema hyodysenteriae[7] studies have not been done. Parasitologic

examination of stools has revealed no association of parasites with the NSD syndrome, in fact, only in a few episodes has there been any parasite found - usually giardia.

NSD is a "new" syndrome in that it is not documented in the medical literature. It is not however new to ICDDRB. Dr. M.M. Rahaman (personal communication) has found that if patients in Teknaf complain of "amasha", and have wbc's but no rbc's in the stool, the stool culture for shigella is usually negative. (Only a few of these patients have had invasive E. coli). In the Dacca treatment center surveillance also, subacute dysentery with mucus and/or blood is a frequent complain (personal communication, B. Stoll) and stool bacteriology from these patients is usually negative.

The occurrence of clusters of cases in families would suggest that the disease is of infectious origin in spite of the failure to isolate known pathogens. A response to antibiotics might be further evidence of a bacterial origin. A few patients have received antibiotics; however, no consistent response has been noted - so this can not be used either for or against a bacterial etiology.

Clinical studies of amasha have been considered for several years at ICDDRB. They have not been initiated however primarily because 1) A clinical defintion of the syndrome is difficult because the "background symptomatology" is relatively high. 2) Etiologic agents, especially parasites, are frequently found in Bangladeshi patients, which again increases the "background pathogen rate". 3) Exact histories detailing symptoms day by day are difficult to obtain.

Study of this syndrome in expatriates should be easier. Histories are available, follow-up (by telephone) is simplified, and background pathogens are minimal. We would therefore like to further define the NSD syndrome, study its epidemiology and hope to identify its etiology, or at least definitively rule out possible etiologic agents.

Possible candidate etiologics include 1) Campylobacter 2) Yersinia 3) Treponema hyodysenteriae, 4) Invasive E. coli, 5) Another unknown invasive bacteria 6) An unknown "colitis" virus.
Of these candidates campylobacter would seem to be the most likely. It is known to be a common enterobacteria in Bangladesh, being found in about 18% of children in a Matlab village and in a similiar percent of patients coming to the Dacca treatment center. Personal communication (Drs Glass, Huq, Stoll).

Eight campylobacter isolates have been cultured from the travelers clinic but none have been isolated from patients with NSD to date. Yersinia enterocolitica would seem less likely since fever and severe abdominal pain and cramps are more common in patients with Yersinia. Treponema hyodysenteriae is an anerobic bacteria which causes dysentery in pigs. It has never been found as a human pathogen - (though it also has never been sought). Invasive E. coli are present in Bangladesh. In studies from Dacca (Gilman) and Teknaf (M.M. Rahaman) E. coli which were positive in the guinea pig eye were found, but only rarely. An "unknown bacteria" or "unknown virus" might also be likely so careful documentation of all fecal bacterial isolates will be necessary. Also documentation of fecal viruses will be necessary using immune electron microscopy.

3. Rationale: We plan to characterize the syndrome of non shigella dysentery (NSD) in a group of expatriates who attend the "travelers clinic" at ICDDRB with hope of defining its etiology and eventual control. Discovery of an agent causing "amasha" in expatriates would likely be important to Bangladeshi people who also appear to suffer from a high incidence of this disease.

B. Specific Aims:

1. Determine the clinical characteristics of NSD
2. Determine the etiologic agent(s) responsible for causing NSD or at least rule out possible pathogens.
3. Determine the prevalence of secondary cases in the families of index cases to look for clustering of cases which would support the hypothesis of an infectious origin.
4. Determine the clinical response of NSD to treatment with doxycycline. (It should be noted that this treatment trial is actually a sub-heading for aim #2 i.e. a response to this antibiotic will help to characterize the etiologic agent. The response to the antibiotic is not critical as a therapeutic measure).

C. Methods of Procedure:

40 adults expatriates of either sex who come to the ICDDRB "travelers clinic" or patients referred by other physicians in Dacca with a syndrome consistent with NSD will be invited to enroll in this study. The clinical criteria for entrance into the study will be

1. Subacute diarrhea or dysentery for less than 5 days.
2. Temperature not exceeding 101^{o}F orally.

3. More than 10 white blood cells per hpf in the stool microscopy.
4. Stool culture negative for Shigellae (this criteria will be fulfilled in retrospect).

Patients less than 18 years or patients who have previously taken antibiotics during the preceeding 7 days or patients allergic to tetracycline will be excluded. The study will be explained to the patient and informed signed consent will be obtained.

After admission into the study, the patient will fill out a questionaire (enclosed) giving details of the episode before the clinic visit. The clinic nurse will also fill out a history (enclosed) outlining the clinical history, and will fill out a form documenting epidemiologic features of the disease (form enclosed). The patients will then have a brief physical exam documenting signs of dehydration, liver or spleen enlargement and abdominal tenderness. A fresh stool sample will be submitted (if the original one is more than 1 hour old), and this will be prepared for further examination immediately (see laboratory exam below). An acute blood sample will be collected.(and subsequently a convalescent, see serology).

To follow the clinical course of the patient, he will be asked to fill out a daily diarrhea diary on which he will record his symptom for 9 days (form enclosed). Also the study nurse will talk to him, either in person or by telephone to inquire as to his symptoms and to remind him to fill out the form every 3 days. The patient will then return to the clinic 10 days after the initial visit to bring his forms, confirm the accuracy of the forms and to submit a convalescent blood sample (see serology below).

Epidemiology: In an attempt to identify other cases and clusters of cases, a family study will be done. When the index patient is identified, he will answer questions regarding symptoms in other members of the family and household servents. Also a member of the family will be designated as "recorder" for the family. The study nurse will visit the family, talk to "recorder", and explain the family study to him/her. A stool specimen for microscopic exam will be requested from all members of the family and servents and these people will be under surveillance for diarrhea symptoms for 9 days after the initial visit. The nurse will talk to the recorder by phone every 3 days to inquire about symptoms. If any persons do develop symptoms

during the surveillance then they will be asked to submit another stool specimen for microscopic exam and culture.

"Secondary or Co-primary cases" will be defined as other members in the family who meet the same criteria as for index cases. "Possible subclinical cases" will be those individual who has >10 wbc/hpf fecal leukocytes in the stool specimen, but are asymptomatic.

The recorder will also answer questions concerning meal preparation, hygiene in the house, water use, and food behavior (see enclosed form). This should help identify specific characteristic risk factors such as drinking unboiled water, eating raw vegetables, eating in restaurants, travel within Bangladesh.

Laboratory Exam:

Bacteriology: The stool specimen from index cases will be plated immediately onto Mac Conkey and SS agar to avoid loss of shigella if present. Stool culture will include a search for Salmonellae, Shigellae, Aeromonas, Vibrio, Enterotoxigenic E. coli and Campylobacter. In addition we will search for Yersinia using cold enrichment for 21 days[7] and T. hyodysenteriae using an anerobe jar with 20% CO_2 and Trypticase soy agar with 5% lysed bovine blood and

spectimomycin[7]. Two E. coli isolates and one isolate of all other colony types on the original Mac Conkey plate will be tested in the Sereny test.

Microscopy and gross examination: The stool will be examined grossly and microscopically to determine the presence of WBC and RBC in the stool wet prep. In addition a Giemsa and Wright stain will be made of a stool smear to keep a permanent record of fecal cellular morphology. Degenerated white cells would likely indicate the inflammation occurring higher in the large intestine). Stools from 10 shigella patients will also be stained with Giemsa and Wright stain to serve as bacillary dysentery controls. In addition the stools will be examined under the dark field microscope to determine the presence of vibrio and spirochettal-like organisms.

Virology: Stools from the admission and follow-up specimens of the cases will be frozen at 60°C to be saved for immune electron microscopy specifically looking for virus particles, which might be responsible for the dysentery.

Serology: A serum sample will be obtained on admission into the study and at the 10 day follow-up for CBC, ESR, Sp. Gr., and serology. The serology would be primarily for IEM and for bacterial agglutination or fluorescent antibody tests

if a pathogen is suspected.

Proctoscopy and Rectal Biopsy:

Selected patients with NSD syndrome will be asked to undergo proctoscopy and rectal biopsy. This could easily be justified on the basis of good medical care since these patients are suffering from colitis of unknown etiology. An experienced proctoscopist may not always be available so patients will be selected on the basis of the availability of an experienced proctoscopists. Rectal biopsies of inflamed or ulcerated mucosa will be preserved in formalin for routine pathology examination.

Doxycycline Treatment Study:

Patients who join the study will be given either doxycycline 100mg daily for 5 days or a similiar placebo in a double blind manner. This will be taken each morning after breakfast. The clinical response will be determined by examining the daily diarrhea diary forms which will be kept by each patient. These forms will record the number of stools each day, the severity of cramps, fever, and other symptoms. A clinical response will be "successful" if the patient is asymptomatic within 48 hours. Since the average natural

history of NSD is a much longer duration of symptoms, and since doxycycline should improve symptoms quickly, if it works at all, this time should be reasonable to determine a response. Also we will judge the clinical response by the severity of symptoms each day as well as the stool white cell count on follow-up days.

(It should be repeated that the reason for doing the antibiotic trial is to help differentiate a bacterial from a non-bacterial cause for NSD. Even if successful in alleviating symptoms, it may be that antibiotics would not be recommended for this apparently self limited disease).

Data Analysis:

This is primarily a descriptive study of the syndrome of non-shigella dysentery hence the main emphasis will be on describing the patients, the nature and duration of symptoms, and the apparent occurrence of secondary or co-primary cases. Secondly we will report our attempt to isolate an agent responsible for NSD. If successful, this would be most important. If not successful, we will at least have ruled out several possible causes. Thirdly we will report the results of the doxycycline treatment

as evidence for or against a bacterial (tetracycline sensitive) origin for the NSD. The two groups will be compared to insure comparability at the start of therapy (age, sex, duration and severity of symptoms, stool wbc, rbc). The two groups will then be compared with regard to duration of symptoms using chi square and T test.

Facilities Required:

1. The office and clinic space is already provided.
2. Lab space is already provided.
3. Hospital resources - nil
4. Animal resources -

   Infant mouse assay - 200 test - 400 mice

   Sereny test - 500 tests - 400 guinea pig eyes (negative G.P. may be used more than once) estimate 100 guinea pigs.
5. Logistic support - The study nurse will have to visit each house for an epidemiologic initial interview - 40 visits x 6 miles each - 240 miles.
6. Major items of equipment - none
7. Specialized equipment - Doxycycline and placebo.

F. Collaborative Arrangements:

The study will be a collaborative study between ICDDRB (Dr Bardhan) and Johns Hopkins University Division of Geographic Medicine (Dr Sack). The details of this arrangement are outlined in the memorandum of understanding between the two institutions. It is anticipated that Dr Speelman will join this protocol after his arrival, especially regarding the proctoscopic examiantions and biopsy.

Authors will include (but not necessarily be limited to) Drs Bardhan,Sack, Huq, and Mrs France and Boone, and likely Dr Speelman.

PERMISSION FORM - NON SHIGELLA DYSENTERY IN TRAVELERS

The International Center for Diarrheal Disease Research, Bangladesh (ICDDRB) is carrying out a study of a syndrome called non-shigella dysentery (NSD). This is a relatively common diarrheal disease in Bangladesh and occurs in both Bangladeshi people and expatriates. Unfortunately very little is known of the nature of NSD, its spread, its cause or treatment. It does not seem to be a severe disease and in our experience, patients get over it in a few days but sometimes it may last for 2 weeks. This study is designed to describe the natural history of NSD, to define the risk of secondary spread to other family members, to find a cause for it and if possible find a simple means to treat it. We would like you to enter this study if possible. If you do join in the study you can expect the following:

1. We will ask you to fill out a questionaire outlining in more detail your symptoms, and something about your habits this last week.

2. We will ask similiar questions of other members of your family and servants looking for indication that others at your home may also has the illness.

3. We will request another stool specimen every 3 days until you are well (minimum of 9 day follow-up)

4. We will ask you to fill out a diarrhea diary daily during your illness so that we can have an accurate record of your symptoms.

5. We will contact you by phone every 3 days to see how you are, and will also want to know how others in your family are. If anyone else at your home (including servants) develops diarrhea or dysentery during the next 9 days, we expect you to come or notify us the same day. We'll also need a stool specimen from that person.

6. We'll draw some blood today and when you return in 9 or 10 days.(approximately 10ml).

7. We'll give you a medicine for the illness. The medicine may be doxycycline,(a long acting tetracycline)or it may be a placebo (sugar pill). Your response to this medicine will help us determine the cause of NSD. Doxycycline is an established antibiotic which is known to have a very low incidenee of side effects. It should be taken with food to decrease the

SECTION III - BUDGET

A. DETAILED BUDGET

1. PERSONNEL SERVICES

Name		% of effort	Annual Salary	Project Requirement Taka	Dollar
1. Dr Bardhan	Investigator	25%	41,196	10299	
2. Dr Sack	Investigator	10%	38,000		3800
3. Mrs France	Study Nurse	20%	10,000		2000
4. Mrs Boone	Study Nurse	20%	10,000		2000
5. Mrs. S.Choudhury	Secretary	10%	36,456	36456	
6. Daniel Ascension	Admn. Assistant	20%	20,700	4140	
7. Mizanur Rahman	Research Tech	20%	19,982	3996	
8. Shafi Ahmed	Sr.Research Asst.	10%	40,884	4088	
9. Waseque Uddin Ahmed	"	5%	45,312	2265	
10. A.K.M. Kibriya	"	5%	55,980	2799	
11. Animal House Tech		10%	36,000	3600	
				67,643	7800

2. SUPPLIES

Stool cultures 300 at Tk.40	12000
Special cultures 100 at Tk.40	4000
Stool Cups 400	500
Infant mouse assay 200 at Tk.10	2000
Sereny Test - 100 guinea pigs	1500
Misc Clinic path supplies - slides,stains	1000
CBC, ESR, 50 @Tk.40	2000

3. EQUIPMENT - None

4. HOSPITALIZATION - None

chance of stomach upset. Rarely it may cause diarrhea or vaginitis (due to overgrowth of resistant germs) or skin rash.

You do not have to participate in the study. If you choose not to participate we will treat you for your illness with standard medical treatment. If you wish to withdraw from the study after you have entered it, you may do so. This will not affect the medical treatment you receive .

Your medical records will be kept confidential. You may ask questions concerning the study at any time.

If you agree to participate in the study on non-shigella dysentery please sign your name here:

_____

_____

Date:

		Project Requirement	
		Taka	Dollar
5.	OUTPATIENT CARE - Covered under personnel		
6.	ICDDR,B TRANSPORT - 240 miles @Tk3 per mile	720	
7.	TRAVEL & TRANSPORTATION OF PERSONS - None		
8.	TRAVEL AND TRANSPORT OF THINGS		
	Transport of Supplies & Cultures		1000
9.	RENT/COMMUNICATION/UTILITIES - None		
10.	PRINTING/REPRODUCTION	3000	200
11.	OTHERS - None		
12.	CONSTRUCTION - None		
13.	INDIRECT COSTS 35%	33,027	3150
		127,390	12150
		(US$ 8,492)	

Tk. 15.00 = $1 TOTAL: US$20,642

BUDGET SUMMARY

CATEGORY	TAKA	DOLLARS
1. Personnel	67643	7800
2. Supplies	23000	-
3. Equipment	-	-
4. Hospitalization	-	-
5. Outpatient	-	-
6. Transport - ICDDRB	720	-
7. Travel - Persons	-	-
8. Travel - Things	-	1000
9. Rent Ett.	-	-
10. Printing/Reproduction	3000	200
11. Others	-	-
12. Construction		
13. Indirect Costs	33027	3150
	127,390	12150
	(US$8,492)	

Total: US$20,642

ABSTRACT SUMMARY

1. Adult expatriates with non shigella dysentery (NSD) will be the subjects for this study.

2. The risks from the study are minimal. They consist of possible side effects from the drug doxycycline. This is a known and established antibiotic with a very low incidence of reactions. Nausea, vomiting, diarrhea, vaginitis, & skin rashes occur rarely, Many patients with this syndrome would ordinarily be prescribed this or a similiar drug if not in the study.

3. The patients will be informed about possible reactions to doxycycline.

4. The records will be kept locked in a cabinet of the clinic office. Computer identification will be by code number.

5. Informed consent will be obtained.

6. There will be a medical history taken and epidemiologic information will be obtained. (See enclosed forms).

7. The individual will gain through treatment of his disease. Society will gain if this protocol is successful in defining this syndrome.

REFERENCES

1. Gorbach, S.L., Kean, B.H., Evans, D.G., Evans, D.J., Bessudo, D. Travelers Diarrhea and Toxigenic Escherichia coli. N. Engl J Med 292:933-936, 1975.

2. Merson, M.H., Morris, G.K., Sack, D.A., Wells, J.G., Feeley, J.C., Sack, R.B., Creech, W.B., Kapikian, A.Z., Gangarosa, E.J. Travelers Diarrhea in Mexico: a prosppctive study of physicians and family members attending a congress. N. Engl J Med 294:1299-1305, 1976.

3. Sack, D.A., Kaminsky, D.C., Sack, R.B., Wamola, I.A., Ørskov, R., Ørskov, I., Slack, R.G.B., Arthur, R.R., Kapikian, A.Z. Enterotoxigenic Escherichia coli Diarrhea of Travelers : A Prospective Study of American Peace Corps Volunteers. J. Hopk Med J. 141:63-70, 1977.

4. Blazer, M.J., Berkowitz, I.D., LaForce, F.M., Cravens, J., Reller, B., Wang, W.L. Campylobacter enteritis: Clinical and epidemioligc Features Ann Int Med 91:179-185, 1979.

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NON SHIGELLAE DYSENTERY - PATIENT QUESTIONAIRE FORM 1

This questionaire is designed to accurately record the symptoms you have had which now bring you to the clinic while some questions may seem obvious, it is necessary for us to have an accurate and complete record of your illness.

Office Use only

Study No _____ 1

Patient No _____ 2

Name _____

Age _____ 3

Sex _____ 4

How long have you been in Bangladesh? _____yrs _____mo 5 6

How long ago did you leave your home Country? _____yrs _____mo 7 8

Todays date _____ d,m,y 9 10 11

When did your illness begin _____(date) d,m,y 12 13 14

What was your first symptom? (circle) 15

1. Nausea and/or vomiting
2. Cramps
3. Diarrhea
4. Respiratory symptoms
5. 1 and 2 simultaneously
6. 2 and 3 simultaneously
7. Other _____

_____

When did the diarrhea begin (circle) 16

1. Same day as first symptom (day0)
2. Next day (day 1)
3. Next day (day 2)

#stools the Ist day > (day 0) (give approximate # if exact number not known) _____ 18

next day (day 1) _____ 19

next day (day 2) _____ 20

next day (day 3) _____ 21

next day (day 4) _____ 22

(over)

Office Use Only

Have you changed your plans because of your illness? _____ _____ y=1,n=2
23

Have you stayed in bed? _____ _____
24

Have you taken Lomotil or similiar drug? _____ _____
25

Have you taken any antibiotic? _____ _____
26

If so, name _____

Have you seen mucus in your stool? _____ _____
27

Have you seen blood in your stool? _____ _____
28

Have you had tenismus? _____ _____
29

(Tenismus is a painful spasm in the rectum after a bowel movement).

Have you had abdominal cramps? _____ _____
30

How severe (circle) _____
31

1. very severe, makes me double up
2. moderate - bothersome but can carry on
3. noticeable but not really painful
4. none

Have you had fever more than 101°F _____ _____
32

Have you had fever between 99-101 _____ _____
33

Have you had chilly feeling? _____ _____
34

Have you had shaking chills? _____ _____
35

Have you had ache-all-over-feeling? _____ _____
36

How would you describe your stool? (circle) _____
37

1. like water, 2, very runny, 3. loose 4. formed
5. hard, 6. bloody, 7. other _____

Are you allergic to tetracycline _____ _____
38

Have you signed the consent form

NURSES REPORT OF DIARRHEAL ILLNESS FORM 2

NON SHIGELLA DYSENTERY

Study No _____ 1

Patient No _____ 2

Patients Name _____

Questionaire Checked _____ 3 y=1 n=2 Date ___ ___ ___ 4 5 6 d,m,y

Does patient fit criteria for study? y=1 n=2

History less than 5 days _____ 7

Fever less than 101°F _____ 8

Stool WBC >10 _____ 9

Surgical abdomen not suspected _____ 10

No Lomotil taken _____ 11

No antibiotic taken _____ 12

No allergy to tetracycline _____ 13

No pregrant _____ 14

Drug given (number) _____ 15

Telephone number residence _____

Office _____

"Recorder" for family study _____

Address of patient _____

_____

_____

Follow-up dates#1 _____ (3 days from todays date)

#2 _____ (6 days from todays date)

#3 _____ (10-days from todays date)

(over)

FOLLOW-UP VISITS

#1 date_____

diary checked_____ (16)

1 = satisfactory
2 = deficiencies corrected
3 = diary not reliable
4 = no diary

How does the patient feel now re diarrheal disease?_____ (17)

1. well 2. nearly well 3. same 4. worse

Follow-up stool specimen obtained_____ (18) 1=y 2=n

Number of specimen ND_____ (19)

Date of specimen relation to original visit_____ (20) days

Did patient come or call_____ (21) 1=come, 2=called, 3=neither

#2 date_____

diary checked_____ (22)

1 = satisfactory
2 = deficiencies corrected
3 = diary not reliable
4 = no diary

How does the patient feel now re diarrheal disease?_____ (23)

1. well 2. nearly well 3. same 4. worse

Follow-up stool specimen obtained_____ (24) 1=y 2=n

Number of specimen ND_____ (25)

Date of specimen relation to original visit_____ (26) days

Did patient come or call_____ (27) 1=come, 2=called, 3=neither

#3 date_____

diary checked_____ (28)

1 = satisfactory
2 = deficiencies corrected
3 = diary not reliable
4 = no diary

How does the patient feel now re diarrheal disease?_____ (29)

1. well 2. nearly well 3. same 4. worse

Follow-up stool specimen obtained_____ (30) 1=y 2=n

Number of specimen ND_____ (31)

Date of specimen relation to original visit_____ (32) days

Did patient come or call_____ (33) 1=come, 2=called, 3=neither

DAILY DIARRHEA DIARY - NON SHIGELLAE DYSENTERY FORM 3

Since you have agreed to be included in this study of non-shigella dysentery, we need to obtain an accurate and complete record of your illness. Since its very important that yuu fill out the record each day, may be you could keep it in the bathroom.

Study No _____ (1)

Name _____ Patient No TC _____ (2)

Date										
Day	0	1	2	3	4	5	6	7	8	9
# stools										
description of stools*										
severity of cramps**										
#vomiting episodes***										
Feverish feeling yes/no										
If, yes, highest temp.										
Changed plans due to illness; yes/no										
Took medicine										
Stool specimen (please ✓ on days when collected)										

*1 - like water 4 - formed 7 - other
2 - very runny 5 - hard 0 - none
3 - loose 6 - bloody

**0-no cramps
1-noticeable cramps
2-moderately severe cramps, but can carry on
3-severe cramps which make you double up

***if none put "0"

fever _____ 1=y, 2=n

STOOL MICROSCOPIC REPORT - NON SHIGELLA DYSENTERY

FORM 4

Study Number _____ 1

Specimen Number

TC _____ 2

Appearance 1=watery 2=very loose, with color
3=soft 4=formed 5=hard
6=bloody 7=other 0=none _____ 3

pH (measured) _____ 4

gross blood 1 = yes 2== no _____ 5

gross mucus 1 = yes 2 = no _____ 6

guaiac (indicate positivity on a 0 to 4 scale) _____ 7

Fecal pus cells (mean of range) _____ 8

Fecal rbc (mean of range) _____ 9

Fecal macrophages(mean of range) _____ 10

Neutral fat (indicate positivity on a 0 to 4 scale) _____ 11

Parasite Exam

ameba cysts 1 = yes 2 = no _____ 12

ameba trops 1 = c rbc 2 = without rbc 3 = neg _____ 13

giardia cysts 1 = yes 2 = no _____ 14

giardia trophs 1 = yes 2 = no _____ 15

trichomonas 1 = yes 2 = no _____ 16

hookworm 1 = yes 2 = no _____ 17

Ascaris 1 = yes 2 = no _____ 18

Strongyloides 1 = yes 2 = no _____ 19

Pinworm 1 = yes 2 = no _____ 20

Other worm 1 = yes 2 = no _____ 21

Dark field exam 1 = spirochetes seen
2 = Vibrio seen 0 = neg _____ 22

Hematology

Hct _____ 23

WBC _____ 24

ESR _____ 25

PMN _____ 26

Band _____ 27

Lymph _____ 28

EOS _____ 29

STOOL BACTERIOLOGY REPORT - NON SHIGELLA DYSENTERY FORM 5

Study No _____ (1)

Specimen No _____ (2 3)

1 = y 2 = n

Salmonell	(4)	Aeromonas	(11)
Shig flex	(5)	V. cholerae	(12)
Shig Sonnie	(6)	NAG	(13)
Shig boydii	(7)	Campylobacter	(14)
Shig dys I	(8)	T. hydrodysenteriae	(15)
Shig dys > II	(9)	ETEC 1=LT/ST	(16)
Yersinia	(10)	2=LT, 3=ST, 4=N	(17)
		Invasive E. coli	(18)

Sensitivity Pattern

Isolate ND _____ (19 20 21) (_____ (22) # from above)

Tet (23)	Chlor (26)	Gent (29)
Amp (24)	Sulfa (27)	Septra (30)
Strep (25)	Neo (28)	

Isolate ND _____ (31 32 33)

Tet (34)	Chlor (37)	Gent (40)
Amp (35)	Sulfa (38)	Septra (41)
Strep (36)	Neo (39)	

Serotyping of ETEC 0 _____ (42) K _____ (43) H _____ (44)

Serotyping of Invasive E. coli 0 _____ (45) K _____ (46) H _____ (47)

FAMILY SURVEILLANCE SHEET

NSD FORM 6

Person	Date:										
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											

Record any symptoms in family members or servents during the 9 days after initial visit. If 1,2,3,4, present, then get stool specimen

1 = diarrhea (≥3/day)
2 = vomiting
3 = abdominal cramps
4 = fever >101
5 = fever 99-101
6 = ache all over
7 = cough, cold
8 = sore throat
9 = other
0 = healthy

Chinese		
Intercon		
Other Western		
Private Club		
Canteen at Work		
Friends meal		
Cocktail party		
Small tea stall		
Other small vendor		

FAMILY FORM - NON SHIGELLA DYSENTERY FORM 7

Study No _____

Name of Index Patient _____ Patient No _____

Date of Ist visit of Patient

Names of other family members and house staff

	Name	Age	Sex	Position
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Indicate, by number, which of the above have had a diarrheal illness "X" days before the patients visit.

3 days _____(list #numbers of persons)
4-7 days _____(illness)
8-14 days _____

(For each person listed, fill out patient questionaire for patient number put index number ___ F #)

What best describes your routine at home regarding water_____

1. always boil for at least 15 min
2. always boil but not sure how long
3. usually boil
4. don't boil
5. don't know
6. other

What best describes your routine for drinking water at a restaurant _____

1. never drink
2. only if the waiter says its boiled
3. only at a restaurant I am familiar with
4. only at a private club
5. occasionally drink
6. usually drink
7. other

What do you do regarding raw vegetables _____

1. never take
2. only from my garden
3. take after they have been soaked in chemical
4. take after they have been washed
5. take, but don't know washing procedure
6. other

ADDENDUM TO PROTOCOL

After further discussion with Drs Molla, Islam, Butler, Asma, we would like to make the following minor changes in the protocol.

1. Fever greater than 101 will not disqualify a patient from the study, so that we do not eliminate one end of the disease spectrum of NSD. However, patients with fever >101 must be seen by Dr Bardhan and many of these febrile patients will be treated initially for shigellosis rather than being included in the treatment trial.

2. We will obtain 3 stool specimens for shigella cultures, though the other bacteriology will only be with the first.

3. Proctoscopy will be done on all consenting subjects; however, rectal biopsy will not be done.

4. Dr. Tom Butler will be advising Dr. Bardhan during the initial stage of the study.

D. SIGNIFICANCE

This study is a diagnostic evaluation of an important illness that resembles Shigella infection clinically. Discovering the causes of non-shigella dysentery in travelers should directly lead to rational suggestions for antibiotic treatment or other approaches. The treatment trial with doxycycline will enable physicians to know whether this drug or other antibiotics will be useful in the empirical treatment of non-shigella dysentery. Because travelers are developing this illness in Bangladesh, the results of this study will also be applicable to patients in local clinics.