Page ..

Date 1/1976

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

28

Principal Investigator Barbara Stoll

Trainee Investigator (if any) _____

Application No. 80-016

Supporting Agency (if Non-ICDDR,B) _____

Title of Study Naturally Acquired Immunity to Tetanus Toxin

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

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

Source of Population:
(a) Ill subjects — Yes (No)
(b) Non-ill subjects — (Yes) No
(c) Minors or persons under guardianship — Yes No

Does the study involve:
(a) Physical risks to the subjects — Yes (No)
(b) Social Risks — Yes (No)
(c) Psychological risks to subjects — Yes (No)
(d) Discomfort to subjects — (Yes) No
(e) Invasion of privacy — Yes (No)
(f) Disclosure of information damaging to subject or others — Yes (No)

Does the study involve:
(a) Use of records, (hospital, medical, death, birth or other) — Yes (No)
(b) Use of fetal tissue or abortus — Yes (No)
(c) Use of organs or body fluids — (Yes) No

Are subjects clearly informed about:
(a) Nature and purposes of study — (Yes) No
(b) Procedures to be followed including alternatives used — (Yes) No
(c) Physical risks — (Yes) No
(d) Sensitive questions — (Yes) No
(e) Benefits to be derived — (Yes) No
(f) Right to refuse to participate or to withdraw from study — (Yes) No
(g) Confidential handling of data — (Yes) No
(h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — Yes No NA

5. Will signed consent form be required:
(a) From subjects — (Yes) No
(b) From parent or guardian (if subjects are minors) — Yes No

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

7. Check documents being submitted herewith to Board:
___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies)
✓ Protocol (Required)
✓ Abstract Summary (Required)
✓ Statement given or read to subjects of nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
✓ Informed consent form for subjects
___ Informed consent form for parent or guardian
___ Procedure for maintaining confidentiality
✓ Questionnaire or interview schedule

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Board for review.

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

Barbara Stoll — 1 033747

Principal Investigator — Trainee

80-016
Rec'd 24/3/80

SECTION I - RESEARCH PROTOCOL

(1) Title: Naturally Acquired Immunity to Tetanus Toxin

(2) Principal Investigator: Dr. B. Stoll

Co- Investigator: Dr. Sirajul Haque

(3) Starting Date: May 1980

(4) Completion Date: June 1980

(5) Total Direct Cost:

(6) Scientific Program Head:

This protocol has been approved by the Host Defense Working Group.

*Signature of Scientific Program Head: [signature]

Date: 24 March 1980

*This signature implies that the Scientific Program Head takes responsibility for the planning, execution and budget for this particular protocol.

(7) Abstract Summary: Tetanus, especially neonatal tetanus, remains a serious health problem in Bangladesh. It has been accepted medical dogma that natural immunity to tetanus does not occur. This project will address the issue of naturally acquired tetanus immunity - especially as it relates to neonatal tetanus.

Fifty women, with no history of tetanus toxoid immunization or recent tetanus antitoxin will be studied. Twenty-five will be mothers of infants with neonatal tetanus hospitalized at the Infectious Disease Hospital and 25 will be age and parity matched mothers of infants with diarrheal disease hospitalized at the International Centre for Diarrhoeal Disease Research, Bangladesh. A questionnaire about cord care after delivery will be administered to all women and samples of blood and saliva will be obtained for antitetanus antibody determination. Antibody levels in these two groups will be compared to answer two important questions.

1. Is there naturally acquired immunity to tetanus?

2. Is there a difference in naturally acquired immunity between women whose infants develop neonatal tetanus and those who don't?

A control group of 25 age and parity matched women with a known history of 2 doses of tetanus toxoid will be identified in Matlab and will have blood and saliva obtained for antibody determinations. Antibodies in saliva and blood will be compared to determine if saliva levels are a valid reflection of blood levels.

9. Review:

a. Research Involving Human Subjects: _____

b. Research Review Committee: _____

c. Director: _____

d. BMRC: _____

e. Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective:

The objectives of this study are:

1) To look for evidence of naturally acquired immunity to tetanus in Bangladesh.

2) To look for a difference in naturally acquired antitetanus antibody between women whose infants develop neonatal tetanus and those who do not.

3) To compare serum and saliva antibody to determine if saliva can be a useful sample to monitor antitetanus immunity.

2. Background:

Tetanus, especially neonatal tetanus, remains a serious health problem in Bangladesh. In March 1977 the World Health Organization and the Bangladesh Ministry of Health conducted a survey of morbidity and mortality from several diseases, including tetanus (1). They found that 78 percent of all cases of tetanus in Bangladesh were in children less than one year of age and that 27 percent of all infant deaths were caused by tetanus. They estimated that approximately 75,000 neonates per year in Bangladesh suffer from tetanus and that approximately 70,000 of them die. In Teknaf, Islam et. al. (2) have reported a tetanus related neonatal mortality of 27 per 1000 livebirths.

Clostridium tetani (3,4) is a ubiquitous organism found in soil, animal and human feces, house dust and polluted water especially in tropical and subtropical areas. It is a known inhabitant of human and animal intestines (5,6). The more intense the contact of people with animals and their excreta, the more frequent the presence of C. tetani in their stools (7). People in primarily rural areas of the world, such as Bangladesh, where there is a lifelong intimate association with soil, are in constant contact with C. Tetani.

C. tetani is an obligate anaerobe (8). As a result, wounds and necrotic tissue (such as the umbilical stump) provide ideal conditions for growth. Tetanus is caused by tetanospasmin, a selective neurotoxin, produced by C.tetani. The toxin acts on the motor end plates in skeletal muscle, in the spinal cord, in the brain and in the sympathetic nervous system (9,10,11). Tetanospasmin is one of the most powerful toxins known. It has been estimated that as little as 130 µg of the toxin may kill a man and one-half pound may be enough to destroy the entire population of the world (8). It has been accepted belief that because the toxin is so powerful, the lethal dose is less than the immunizing dose and as a result, natural immunity to tetanus does not occur.

Neonatal tetanus (12,13) occurs following infection of the umbilical cord. Because tetanus antibody readily crosses the placenta neonatal tetanus only develops in infants born to unimmunized women. The cord may be contaminated with C. tetani by unclean objects, such as pieces of bark or old glass, used to cut the cord, or by dirty rags, animal dung or vegetable matter used to cover the umbilical stump. In Teknaf (2), untrained birth attendants perform most deliveries and splits of bamboo and razor blades are the most frequently used tools for cutting the cord. It is striking that despite unsterile cord care practices and the high prevalence of tetanus bacilli in the environment that the death rate from neonatal tetanus is only 27 per 1000 livebirths. With widespread exposure to the organism one would expect a higher attack rate. This led us to hypothesize that there is naturally acquired immunity to tetanus. Moreover, there may be a difference in tetanus immune status between women whose infants develop neonatal tetanus and those who don't, despite similar cord care practices.

Although not widely accepted, there is some evidence in the literature that naturally acquired immunity to tetanus does occur. As long ago as 1924, Ten Broeck and Bauer wrote that "in Peking, one third of the population were carriers of tetanus bacilli, and when tetanus bacilli are present in the stools of men, an appreciable amount of antitoxin can be found in the blood" (6). Moreover, they reported that six pregnant women who had tetanus bacilli in their stools had protective levels of tetanus antitoxin in their blood (14). This report was published before tetanus toxoid immunization was available.

Meira (15) performed a serosurvey of 42 gardeners in Sao Paulo, Brazil. Despite no history of tetanus toxoid or recent A.T.S., 9 (21%) had protective tetanus antitoxin titres (0.01 units or more per ml).Veronesi et. al. (7) carried out a serosurvey among 59 adults in Brazil. They divided subjects into two groups. Subjects in group 1 lived and worked with cattle and their excrta. Subjects in group 2 were urban medical students. None had a history of tetanus immunization. Thirty-four percent of group 1 and 25% of group 2 had protective levels of tetanus antitoxin (0.01 units per ml or greater). This led them to conclude that there is naturally acquired immunity to tetanus. They proposed the following mechanism. C. tetani are natural inhabitants of the human intestines, more common in persons living in rural areas. Occasionally, tetanus spores may germinate in the intestines and produce minute amounts of toxin. Although too small an amount to produce clinical illness, such toxin may sensitize the individual resulting in naturally acquired immunity. Moreover, while disease may not produce immunity, repeated, subclinical amounts of toxin might.

It is known that tetanus antitoxin crosses the placenta (14). Naturally acquired immunity may explain why, despite similar cord care - i.e., similar exposure to C.tetani, some infants develop neonatal tetanus and some do not.

In the 1978 cholera vaccine pretrial, it was found that individuals who were previously immunized with tetanus toxoid had detectable antitetanus antibody levels in both serum and saliva (16). Serum and saliva antitetanus antibody levels have not been compared in a systematic manner, however.

3. Rationale:

Neonatal tetanus is a signficant cause of neonatal mortality in Bangladesh. Aspects of neonatal tetanus have been research efforts in both Matlab and Teknaf. This study proposes to investigate an important and controversial basic issue - is there naturally acquired immunity to tetanus in Bangladesh? Also, because there is evidence that people who have been immunized with tetanus toxoid have antibody levels detectable

in serum and saliva we propose to compare serum and saliva antibody levels to determine if saliva (an easily obtained specimen) is a useful sample to monitor antitetanus immunity.

B. SPECIFIC AIMS

1. To look for naturally acquired immunity to tetanus toxin by measuring antitetanus antibody levels in 50 women with no prior history of tetanus toxoid immunization.

2. To look for a difference in antibody titres (IgA and IgG specific) to tetanus between women whose infants develop neonatal tetanus and those who do not.

3. To compare serum and saliva antibody levels in the above 2 groups of women and in a third group of women who have received 2 doses of tetanus toxoid.

C. METHODS AND PROCEDURES

This study will be carried out at the International Center for Diarrheal Diseases Research Hospital, at the Infectious Disease Hospital and in Matlab.

Twenty-five infants with known neonatal tetanus will be identified at the Infectious Disease Hospital and will be examined by the principal investigator to confirm the diagnosis. Twenty-five infants between 1 and 4 months of age who have no history of neonatal tetanus and are hospitalized at the ICDDR,B hospital for other reasons will also be identified. They will be examined by the principal investigator to definitely rule out tetanus. Mothers in the 2 groups will be matched for age and parity. Only women with no prior history of tetanus toxoid immunization or no recent history of tetanus antitoxin will be included in the study. A questionnaire about mode of delivery and cord care at and following delivery will be administered to all women. Infants will be matched for the method of cutting the cord and any infant born in hospital will be excluded. Two hundred microliters of blood will be drawn by fingerstick and a smaple of saliva will be obtained at the same time for determination of antitetanus antibody levels. Saliva will be obtained after chewing parafilm to stimulate salivation. Total IgA concentration in the saliva specimen will also be measured to correct for possible differences in dilution of saliva.

In addition, 25 age and parity matched women with known tetanus toxoid immunization (2 doses) will be identified in Matlab and blood and saliva will be obtained for antitetanus antibody determinations.

Antibody levels in the three groups will be compared to answer three questions:

1. Is there naturally acquired immunity to tetanus in Bangladesh?

2. Is there a difference in naturally acquired immunity between women whose infants develop neonatal tetanus and those whose infants do not?

3. Are saliva antibody levels a valid reflection of serum levels?

The ELISA method for determining IgA and IgG antitetanus toxoid antibodies is as follows:
Immunopurified tetanus toxoid (provided by Wellcome Laboratories) is first applied to the ELISA microtiter plate. After 24 hours incubation, the plates are washed and dilutions of the specimens are added to the wells, and the plates are incubated again. After washing, alkaline phosphatase conjugated antihuman IgG or IgA is then added to the wells. After further incubation and washing, substrate is added and color development is measured at 405 nm. A standard human serum is included in each plate as a control. For this study, all the serum samples will be tested at dilutions of 1:10, 1:50, and 1:250 and saliva samples will be tested undiluted and at dilutions of 1:5 and 1:25. End points will be determined on specimen positive at the highest dilution.

Analysis of data will be straightforward. The first two groups (mothers of infants with neonatal tetanus and mothers of infants without neonatal tetanus) will be compared with respect to age, parity, sex of infant and cord care practice to insure comparability of the two groups. The antitetanus antibodies in the three groups (immunized women and first two groups) will then be compared in both serum and saliva. The differences between the three groups will be compared using chi-square statistics. A graph of the frequency distributionof antibody titres will also be presented. Serum and saliva antibody titres will be compared using chi-square and correlation coefficient analyses.

D. SIGNIFICANCE

This study will attempt to answer several important questions: (1) Is there naturally acquired immunity to tetanus in Bangladesh? (2) Is there a difference in naturally acquired immunity between women whose infants develop neonatal tetanus and those whose infants do not? (3) Are saliva antibody levels a valid reflection of serum levels?

Because it is established medical belief, based primarily on research from developed countries, that there is no naturally acquired immunity to tetanus, an answer to the first 2 questions is very important for Bangladesh and elsewhere.

Saliva is a much easier sample to obtain than blood. If saliva antibody levels are a valied reflection of serum levels, saliva may be used in future serosurveys. This would have important implications for Bangladesh.

E. FACILITIES REQUIRED:

1. No new office space is needed.

2. Personnel

   Field worker to administer questionniare and draw blood - 3 days at ICDDR,B, 3 days at ID Hospital, 5 days in Matlab.

   4 lab technicians for 1 week.

3. No new laboratory space is needed.

4. Hospital support: Routine care will be provided to already hospitalized patients.

5. Logistical support: Vehicles will be needed for trips to the ID Hospital and Matlab.

6. Major items of equipment: No new item is required.

7. Other - none.

F. COLLABORATIVE ARRANGEMENTS

Collaboration with the Infectious Disease Hospital, Dacca has been arranged. See attached letter.

References

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2. Islam, M.S., Rahaman, M.M., Aziz, K.M.S., Munshi, M.H., Rahaman, M., and Patwari, Y.: Birth Care Practice and Neonatal Tetanus in a Rural Area of Bangladesh.
3. Eckmann, L. (ed): Tetanus. Bern, Hans Huber, 1967.
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5. Dubos, R.J., and Hirsch, J.G.: Bacterial and Mycotic Infections of Man 4th ed. Philadelphia, Lippincott, 1965.
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8. Finegold, S.M.: Anaerobic Bacteria in Human Disease. New York, Academic Press, 1977.
9. Brooks, V.B., Curtis, D.R., and Eccles, J.C.: Mode of action of tetanus toxin. Nature (London), 197:120, 1955.
10. Kaeser, H.E., and Saner, A.: Tetanus toxin: A neuromuscular blocking agent. Nature (London) 223: 842, 1969.
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12. Barten, J.C.: Neonatal Tetanus: A review of 134 cases. Trop. Geogr. Med., 21: 383, 1969.
13. Friedlander, F.C.: Tetanus neonatorum. J. Pediat., 39: 448, 1951.
14. Ten Broeck, C. and Bauer, J.H.: The transmission of tetanus antitoxin through the placenta. Proc. Soc. exp. Biol. Med. (N.Y.) 20: 399, 1922/23.
15. Meira, A.R.: O comportamento preventivo e o risco de contrair tétano em um groupo de jardineiros da cidade de Sao Paulo. Congresso Internacional de Higiene. Medicina Preventiva e Medicina Social, VII. Madrid 1971.
16. Sack, D.: personnal communication.

Abstract Summary

Tetanus, especially neonatal tetanus, remains a serious health problem in Bangladesh. It has been accepted medical dogma that natural immunity to tetanus does not occur. This project will address the issue of naturally acquired tetanus immunity - especially as it relates to neonatal tetanus.

Fifty women, with no history of tetanus toxoid immunization or recent tetanus antitoxin will be studied. Twenty-five will be mothers of infants with neonatal tetanus hospitalized at the Infectious Disease Hospital and 25 will be age and parity matched mothers of infants with diarrheal disease hospitalized at the International Centre for Diarrhoeal Disease Research, Bangladesh. A questionnaire about cord care after delivery will be administered to all women and samples of blood and saliva will be obtained for antitetanus antibody determination. Antibody levels in these two groups will be compared to answer two important questions.

1. Is there naturally acquired immunity to tetanus?

2. Is there a difference in naturally acquired immunity between women whose infants develop neonatal tetanus and those who do not.

A control group of 25 age and parity matched women with a known history of 2 doses of tetanus toxoid will be identified in Matlab and will have blood and saliva obtained for antibody determinations. Antibodies in saliva and blood will be compared to determine if saliva levels are a valid reflection of blood levels.

1. Subject population: see above description.

2. The only ptential physical risk is discomfort from fingerstick blood drawing (one time). Moreover, this study is attempting to find a more acceptable procedure (saliva) for antibody determination.

3. Fingerstick blood drawing will be done as carefully as possible, under the supervision of the principal investigator.

4. Patients will be identified only by number and all records will be kept by the principal investigator to safeguard confidentiality.

5. The study procedure will be explained to all subjects and a written consent form will be obtained (see attached form).

6. An approximately 5 minute interview will be conducted in the ID and ICDDR,B Hospitals.

7. The direct benefit to be gained by the subject is that all babies will be examined by the principal investigator, a pediatrician and neonatologist. The scientific question of whether or not naturally acquired immunity to tetanus occurs is important and has never been addressed in Bangladesh. Moreover, if saliva antibody levels prove to be a valid reflection of serum levels, saliva (an easily obtained specimen) may replace blood in future studies of antitetanus antibody levels.

8. Only one blood specimen (200 microliters) and one saliva specimen will be required.

Consent Form-- Naturally Acquired Immunity to Tetanus Toxin

We are conducting a study to find out if people in Bangladesh develop immunity-- resistance to tetanus without having a vaccination against the disease. We are also trying to determine if such resistance in mothers has any effect on which babies develop neonatal tetanus.

To answer these questions we must draw one fingerstick blood sample from mothers whose babies develop neonatal tetanus, one from mothers whose babies do not, and one from women who have received tetanus vaccine. We will compare the tests in blood and saliva and will need one sample of salive from each women. We will administer a short questionnaire to the mothers about how their baby's umbilical cord was cut and how it was cared for after birth. Babies of mothers involved will be carefully examined by a study doctor, a potential benefit to you.

All records will be kept by the principal investigator and will be totally confidential.

If you do not want to participate in this study you may refuse or you may withdraw from the study at any time. You will receive the same kind of care regardless of your decision to participate in the study or not.

_____

Subject

_____

Investigator

সম্মতি পত্র

স্বাভাবিকভাবে ধনুষ্টঙ্কার রোগ প্রতিরোধ ক্ষমতা অর্জন

ধনুষ্টঙ্কার রোগ প্রতিরোধক গ্রহণ না করে বাংলাদেশের লোকেরা প্রতিরোধ ক্ষমতা অর্জন করতে পারে কি না সে সম্পর্কে আমরা একটি অনুসন্ধান চালাচ্ছি। আমরা আরও চেষ্টা করছি যে, এরূপ প্রতিরোধ ক্ষমতা যদি মা অর্জন করে তাহলে তার শিশুর উপর এর কোন ক্রিয়া করে কি না।

এ কাজের জন্য আমরা ধনুষ্টঙ্কারে আক্রান্ত আদ্যন্ত শিশুর মায়ের আঙ্গুলের অগ্রভাগ হতে অল্প রক্ত ও মুখের লালা নেব। ঐ রক্ত ও লালার তুলনামূলক পরীক্ষার জন্য আমরা অনুরূপভাবে যে শিশুর মায়ের ধনুষ্টঙ্কার নেই তার ও যে ধনুষ্টঙ্কার প্রতিরোধক নিয়েছে তার ও মুখের লালা ও আঙ্গুলের রক্ত নেব। আমরা একটি সংক্ষিপ্ত প্রশ্নমালার মাধ্যমে জানতে চেষ্টা করব যে, তাদের শিশুদের নাড়ী কিভাবে কাটা হয়েছিল ও জন্মের পর কিভাবে পরিচর্যা করেছিল। সংশ্লিষ্ট মায়েদের সতর্কতার সাথে ডাক্তার দিয়ে পরীক্ষা করা হবে।

সমস্ত রেকর্ডপত্র গোপনীয়তার সাথে রাখা হবে। আপনি যদি এ কাজে অংশগ্রহণ করতে না চান যে কোন সময় তা প্রত্যাখ্যান করতে পারেন। এ কাজে অংশগ্রহণ না করলেও আপনি অনুরূপ পরিচর্যা লাভ করবেন।

নাম :-
স্বাক্ষর বা টিপসই;
তারিখ :

Section III - Budget

A. Detailed Budget

1. Personnel Services :

Name	Position	% time used	Salary Taka	Salary Dollar
Dr. Barbara Stoll	Scientist	40%x2 mo.	-	1200
Dr. Sirajul Huq	Scientist		-	-
Dr. David Sack	Scientist		-	-
1 field worker		100%x3 wks.	1800	-
4 laboratory technicians		100%x1 wk.	1200	-
	Subtotal		3000	1200

2. Supplies and materials

Item	Unit cost	Taka	Dollar
Antibody Determination	15x150	2250	-
Stationary, Forms, etc.		500	-
Miscellaneous		250	-
	Subtotal	3000	-

3. Equipment: None

4. Patient Hospitalization: None

5. Outpatient care: None

6. ICDDR,B Transport:

3 trips to ID Hospital:	35 taka
5 trips to Matlab:	1950 taka
Sub-Total:	1985 taka

7. Travel and Transportation of persons: None

8. Transportation of things: None

9. Rent, Communications, utilities: None

10. Printing and publications:

Forms, xerox	Taka 500	$ -
Publication	-	200
Subtotal :	Tk. 500	$ 200

11. Other contractual services: None

12. Construction, renovation, alteration: None

B. Budget Summary

Category	Taka	Dollar
1. Personnel	3000	1200
2. Supplies	3000	-
3. Equipment	-	-
4. Hospitalization	-	-
5. Outpatient care	-	-
6. ICDDR,B Transport	1985	-
7. Travel, persons	-	-
8. Transport, things	-	-
9. Rent/communications	-	-
10. Printing/Reprod.	500	200
11. Contractual services	-	-
12. Construction	-	-
Subtotal:	8485	1400
30% overhead:	2545	420
Grand total	11030	1820

= $ 2555

Questionnaire-- Naturally Acquired Immunity to Tetanus Toxin

Name: Number:

Age:

No. of Pregnancies:

No. of Livebirths:

No. of Stillbirths:

No. of Neonatal Deaths:

Causes:

No. of Living Children:

Present Pregnancy:

Length: Full Term _____ Pre Term_____

Labor: Normal _____ Abnormal_____

Delivery: Normal _____ Abnormal_____

Delivery performed by: Dai_____ Relative_____ Trained Midwife____
Doctor____ Other_____

Object used to cut the cord: Razor blade____ Bamboo split____
Glass____ Other____

Cord: Tied____ Not tied_____

Care given to cord after birth: Nothing_____ Ash____
Cow Dung____ Antibacterial ointment____
Other____

Sex of Infant: Male____ Female_____

ফোন : ৩০২৪২৯

গণপ্রজাতন্ত্রী বাংলাদেশ সরকার

সিনিয়র কনসালটেনটের দপ্তর

সংক্রামক ব্যাধি হাসপাতাল, ঢাকা

স্মারক নং—সবহা/-

তারিখ March 17, 1980

Dr. Barbara J. Stoll
ICDDR,B
Dacca

Dear Dr. Stoll:

Thank you for asking me to collaborate in study, "Naturally Acquired Immunity to Tetanus".

I am happy to be associated with the study and agree to collaboration between the I.D. Hospital, Mohakali and the ICDDR,B.

Sincerely yours,

17/3/80.

KMHS Sirajul Haque