Attachment 1.

2

Date 23.7.91

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. A. N. Alam

Application No. 91-042 (Revised)

Title of Study "The role of prostacycline in the development of Haemolytic-Uremic syndrome in acute shigellosis."

Trainee Investigator (if any) _____

Supporting Agency (if Non-ICDDR,B) _____

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 NA
   (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.

Principal Investigator

Trainee

SECTION II - RESEARCH

A. Introduction:

1. Objective: The objective of this study will be to determine the pathogenesis of HUS in shigellosis - more specifically the role of prostacycline metabolism in the causation of Haemolytic-Uraemic Syndrome (HUS).

2. Background: Shigellosis continues to be a major clinical entity and HUS is an extremely important yet unsolved problem in acute shigellosis. HUS is a clinical syndrome characterized by falling haemotocrit, red cell fragmentation and reticulocytosis, platelet destruction leading to thrombocytopenia, coombs-negative micro-angiopathic haemolytic anaemia, hypofibrinogenaemia, thrombotic occlusion in the microcirculation, the kidney being the main target organ, and acute renal failure; fluctuating neurological signs may also be present. Originally described by Gasser et al[1] in 1955, this syndrome has been reported mainly in infants and young children. HUS is uncommon in adults. However, the occurence together of some of the abnormalities of this disorder has been reported in adults with thrombotic thrombocytopenic purpura, more commonly in women in association with pregnancy or post-partum renal failure, malignant hypertension and systemic diseases, such as, disseminated lupus erythematosus and scleroderma[2-4]. HUS has been described as a complication of infections e.g. typhoid fever, gram-negative bacteraemia, mumps, and infectious mononuclosis.

Microangiopathic haemolytic anaemia as seen in HUS has been found in renal and hepatic allograft rejection. HUS has also been reported in association with the use of drugs such as oral contraceptives, penicillin and phenylbutazone[5-7]. First reported by Rahaman et al in 1975[8], Koster and co-workers[9] reported the occurence of HUS after shigellosis where the association of endotoxaemia, intravascular coagulation, circulating immune-complexes and postmortem finding of fibrin deposition in glomeruli and renal arteries was found in many of their patients. Eight of the nine patients had severe grade of colitis and more than half of these patients died. The complication occurred in about 10% of hospitalized children, less than 2 years old, who showed a leukaemoid reaction (TWBC>50,000 per cumm) and had stool cultures positive for Shigella dysenteriae type I (Shiga bacillus). It occurred most often in the second week of illness when the patients are afebrile and are recovering from an acute episode of diarrhoea. Thrombocytopenia, prolonged thrombin clotting time, hypofibrinogenemia and elevated levels of fibrinogen-fibrin degradation products compatible with disseminated intravascular coagnlation (D.I.C.) were found in their patients with haemolysis. Patients in the haemolytic-uraemic group had significantly lower levels of total protein and complement components C_3 and C_4 which suggested that patients with the most severe haemolysis and renal disease exhibited complement consumption by the classical pathway. Although others have found similar decrease in serum complement - components C_3 & C_4 in HUS[10], selective depression of C_3 & C_4 levels by uraemia alone could not be excluded.

Circulating immune complexes were present too often in uncomplicated shigellosis to relate them to the development of haemolytic anaemia. Screening for 6-GPD was done in their patients with haemolysis and deficiency was detected in a few patients (Koster et al: unpublished observation).

The data generated from their study led to the conclusion that severe colitis in shigellosis is associated with circulating endotoxin, which in turn may produce coagulopathy with renal microangiopathy and haemolytic anaemia. The endotoxin is known to induce vascular endothelial damage[11] and can trigger the coagulation[12] and complement cascades[13] producing disseminated intravascular coagulation. However, others have failed to detect circulating endotoxin in patients with theis syndrome[14]. As the pathogenesis of this syndrome is not clear, various therapeutic approaches have been attempted, including immunosuppression, high-dose corticosteroids, splenectomy, heparin, antiplatelet agents (aspirin, dipyridamole etc), dextran and streptokinase. However, no definite proof of the efficacy of any of these treatments has yet been obtained; although spontaneous unexpected recovery sometimes occurs. Plasma exchange or transfusion of normal plasma has been tried with beneficial effect - they possibly act either by removing a toxic factor from plasma[15] or by supplying a missing component[16] - possibly a physiological inhibitor of platelet aggregation. The nature of this

plasma factor has not been defined. Remuzzi et al[17] observed correction of platelet count and microangiopathic anaemia following plasma exchange and infusion in two of their patients with clinical and histological signs of H.U.S. Prostacycline-like (anti platelet-aggregating) acitivity was undetectable in venous specimens from both patients before plasma exchange but was present in specimens removed an hour after the end of plasma exchange. Remuzzi et al[18] suggested that the disturbed haemostasis observed in HUS patients might be related to the deficiency of a plasma factor which stimulates the activity of vascular prostacycline, the most potent endogenous inhibitor of platelet aggregation. Increased prostacycline-like activity in venous tissues of patients with uraemia and very prologed bleeding time was reported by the same group of workers[19]. Deficiency of endogenous prostacycline could favour the formation of platelet thrombi in the microcirculation and as a logical therapeutic intervention, prostacycline infusion was recently tried with success in three children with the H.U.S.[20].

The primary prostaglandins(PGs) are derived from unsaturated fatty acids, primarily arachidonic acid (a major component of membrane phospholipids of most mammalian tissues) containing 20 atoms of carbon disposed in a cyclopentane ring. They originate from common intermediates, the cyclic endoperoxides. Prostacycline (alternatively called as PGI_2), the most recently discovered member of the PG family, and thromboxane A_2 (another metabolite of arachidonic acid in human platelets or thrombocytes)

maintain a biological balance having opposite actions. The cyclo-oxygenase enzyme system transforms arachidonic acid in the platelets to prostaglandin endoperoxides which in turn lead to the formation of thromboxane A_2 (Tx A_2), a potent inducer of platelet aggregation. In the vessel wall, the enzyme is involved in the production of prostacycline (PGI_2), which has a powerful antiaggregating properties. The opposite effects of these end-products probably maintain a homoeostatic balance in platelet/vessel wall interactions and provide a line of defence against thrombosis[21].

Determination of prostacycline ideally requires biopsy from peripheral veins[18]. This may be difficult to be obtained from children patients in Bangladesh on ethical grounds. Moreover, PGI_2 has a half-life in vivo at 37^{o}c of only 2-3 minutes. Due to such lability, its formation in tissues is estimated by recovery of its stable hydrolysis product, 6-keto-$PGF_{1\alpha}$. Recently, a new method has been described to measure this stable non-enzymatic sole degradation product of PGI_2, in the circulation adpating a radioimmunoassay[22].

B. Specific Aims:

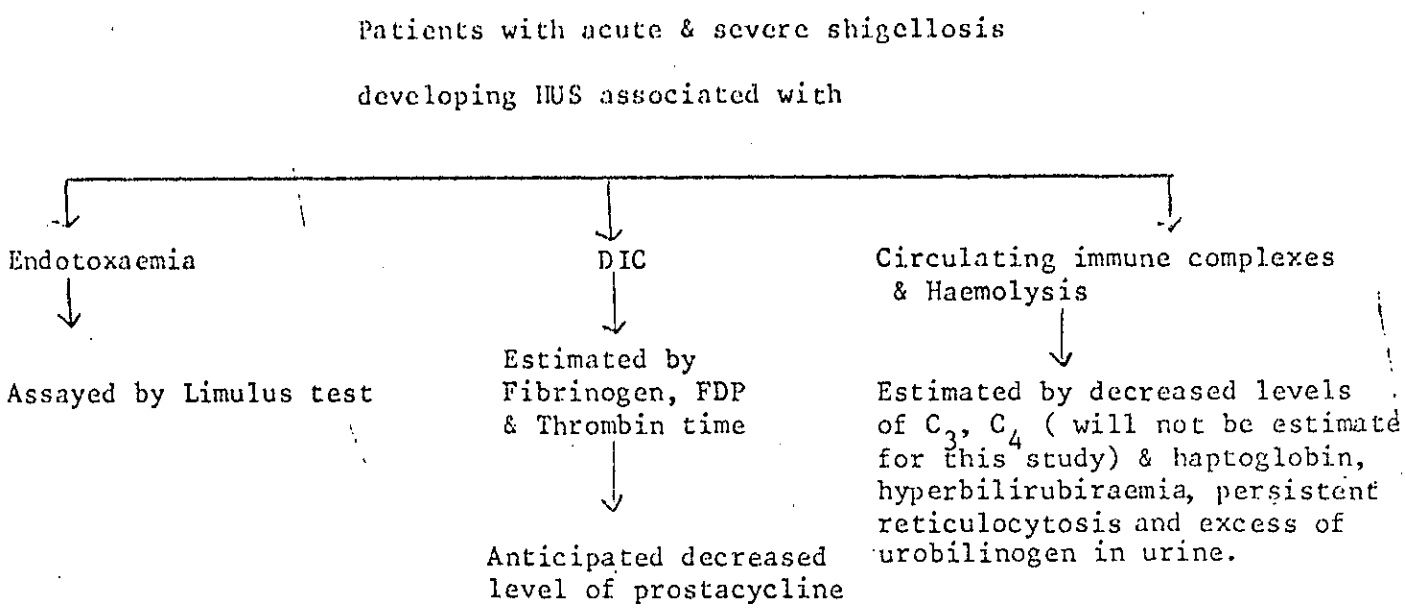
(a) Estimation of 6-keto-$PGF_{1\alpha}$, as a measure for the reduction in activity of prostacycline responsible for subsequent platelet aggregation and HUS.

(2) Determination of plasma fibrinogen, thrombin time (TT) and fibrinogen-fibrin degradation products (FDP) as evidence of DIC and that of serum

haptoglobin and serum indirect bilirubin as tests for associated haemolysis.

(3) Estimation of presence of shigella endotoxaemia using limulus assay and to find out any relationship between endotoxaemia and level of prostacycline.

A schematic diagram showing the relationship between HUS and associated features like DIC, haemolysis and endotoxaemia is given below:



Methods of Procedure:

Selection of Patients:

Two groups of patients will be studied:

(1) About 100 patients with severe shigellosis (patients passing frank blood in the stool with fever and signs of toxaemia like restlessness requiring hospitalisation) will be screened for the development of anaemia, thrombocytopenia and renal failure. These are the high risk patients who may present with hypoproteinaemia (total protein 5 G/L and albumin fraction $<3.G$), hyponatraemia (plasma sodium <130 mmol) & high leucocytosis (TWBC$>$ 50,000/cumm) and may eventually develop HUS. Extremely few patients without these findings have been known to develop HUS. However, those who improve and do not develop HUS will be excluded from further study. This may allow about 8-10 patients to be finally studied intensively. Patients admitted with frank sings of HUS following history of severe dysentery will also be studied.

(2) Twelve age-matched, uncomplicated but stool-culture positive shigellosis patients will be selected to act as a comparison group. They are unlikely to develop HUS.

All children below 6 months of age and those with severe malnutrition (wt. for ht.$<$ 75% of 50th percentile of [illegible]rd or NCHS standard) and other complications (e.g. pneumonia, unconsciousness, convulsion etc) will be excluded from the study.

Management of patients:

All patients with shigellosis in both groups will be treated by standard therapeutic measures: (i) rehydration with I.V. Dacca solution, (ii) septrin in appropriate doses, sulphamethoxazole 40 mg & Trimethoprim 8 mg/kg body wt/day. (Ampicillin will be avoided as HUS has been described in association with penicillin therapy). (iii) and if they develop HUS, they will be given fresh whole blood transfusion after proper cross-matching.

Procedure after admission:

(a) A flow sheet (attached with the protocol) is designed to record the relevant laboratory data.

(b) Plasma level of 6-keto-$PGF_{1\alpha}$ will be determined by radioimmunoassay using a commercially available RIA kit (New England Nuclear, Boston, USA) following the method described by Salmon[22]. 1 ml. of peripheral blood will be drawn from each patient to obtain 100μl of serum for the assay. The kit as a whole allows one to perform sensitive and reproducible assays without the time and trouble of preparing own components. The mean circulating concentration of 6-keto-$PGF_{1\alpha}$ in healthy subjects ranged from 115-182.5 pg/ml in plasma[22,23].

The procedure in principle will involve transfer of 100μL buffer, 100μL patient's serum, 100μL anti-$PGF_{1\alpha}$ and (^{3}H) $PGF_{1\alpha}$ to glass tubes which are to be mixed and incubated for overnight at 0-4^{o}c. 200μL charcoal-dextran solution will then be added to the tubes and shaken on vortex. The tubes will be left on ice for 5 minutes

and then centrifuged for 5 minutes. 250µL supernatant will be transferred to the vials containing 2 ml cocktail and counted for radioactivity.

(c) Routine finger blood tests e.g. TWBC, DC, HCT, RBC fragmentation, plasma specific gravity, reticulocyte and platelet count will be done on alternate days. The shigellosis patients when they develop HUS usually remain well hydrated. Dehydration or overhydration may change the HCT which will be corrected by the level of corresponding plasma specific gravity using the latter's level as an index for the status of hydration.

(d) Serum electrolytes, protein level (including electrophoresis) urea and creatinine will be done as routine clinical investigations. Serum indirect bilirubin will also be estimated. These tests will require 2 ml of venous blood.

(e) Limulus assay for endotoxaemia will be done in patients at the time of admission and again three to seven days later, as endotoxaemia was detected only before haemolysis and before renal failure is established. 1 ml. of venous blood and commercially available limulus lysate (Sigma) will be required for the test.

(f) Measurement of plasma fibrinogen, thrombin time and fibrinogen-fibrin dedgradation products will be done using commercial test kits (Hoechst-Behring). Haptoglobin (plasma globulin which specifically combine with free haemoglobin and is used up more quickly than they are produced when haemolysis occurs) will be estimated by Single-radial-immunodiffusion (SRID) technique using M-partigen plates (Hoechst-Behring). Total of 2 ml. blood will be required for these estimations.

(g) Urine analysis will be done in all cases. Urine will also be examined for excess of urobilinogen.

(h) Stool for microscopic examination and culture for shigella.

(i) Post mortem bone marrow examination will be done to assess the bone marrow reaction in response to haemolysis.

The above mentioned investigations will be done in all patients at the time of admission. Patients in both the groups will be followed up by routine finger blood tests on alternate days to monitor the sudden fall of haematocrit with leukemoid reaction, reticulocytosis and thrombocytopenia. In patients who eventually may develop HUS, all the investigations, as detailed in the procedure, will be repeated at the height of leucocytosis and subsequently once every week until the complete recovery of the patients. Those who do not develop HUS in the study group will be excluded from further study - but a blood sample will be taken at the time of discharge.

Attempts will be made to bring back the patients for follow-up 4 weeks after complete recovery and the investigations will repeated.

SIGNIFICANCE AND RATIONALE:

Estimation of 6-keto-$PGF_{1\alpha}$ should provide us with valuable information about the activity of prostacycline and its possible role in the formation of platelet thrombi in HUS. This will enable us firstly to understand better the pathogenesis of this serious and fatal complication of acute shigellosis and secondly to provide further grounds for designing therapeutic manouvres like prostacycline infusion in such patients.

E. FACILITIES REQUIRED:

1. Laboratory facilities in the clinical pathology, biochemistry and microbiology department will be utilized. Isotope counter available in the biochemistry department will be used for the radio-immunoassays. The RIA for 6-keto-$PGF_{1\alpha}$ will be done by Mr. M. Rahman in the department of biochemistry under kind supervision of Dr. Brian Seaton.

2. Patients will be admitted in the study ward.

F. DATA ANALYSIS:

It is anticipated that the following data analysis will be performed:

(a) Difference in the level of PGI_2 in these two groups of patients. Students "t" test will be applied to see the difference in PGI_2 activity between the HUS patients and the comparison group. The HUS patients will act as their own control after recovery.

(b) Clinical comparability of the HUS patients and the comparison group.

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FLOW SHEET

Case No. : _____

	On Admission	On alternate days	At the height of leucocytosis (>50,000)	1st wk.	2nd wk.	Follow-up
BLOOD TWBC:						
DC						
Hct						
RBC fragmentation						
Reticulocyte ct.						
Platelet ct.						
Electrophoresis of protein						
Indirect Bilirubin						
Serum haptoglobin						
Sodium						
Potassium						
Chloride						
Bicarbonate						
Urea						
Creatinine						
6-keto-PGF$_{1\alpha}$						
Limulus assay						
Plasma fibrinogen						
Thrombin time						
F.D. Products						
Stool : M/E						
Culture						
Urine analysis						

SECTION III - BUDGET

A. Detailed Budget

1. Personnel:

Name	Position	% Effort	Taka	$ Dollar
Dr. A. N. Alam	Investigator	50%		5385
Dr. M. R. Islam	Co-Investigator	20%		2137
Medical Officer	do	50%		1832
Dr. M.M. Rahaman	Consultant	—		—
Research Officer(Biochemistry)		30%		1042
Lab. Technicians:				
Biochemistry		30%	12000	
Cl. Pathology		10%	8000	
Microbiology		5%	4000	
Nurse (Study Ward)		30%	10000	
			Tk.34,000	$ 10,396

2. Supplies and Materials:

A.	Limmulus lysate		800
B.	RIA kits		500
C.	Commercial kits for estimation of plasma fibrinogen, thrombin time, FDP & haptoglobin		1350
D.	Lab. tests (electrolytes, urea, creatinine and electrophoresis of protein for each patient)	4800	
E.	TWBC, DC, HCT, plateles & reticulocyte & bonemarrow exam if available	3000	
F.	Urine analysis	1000	
G.	Stool M/E	800	
F.	Stool culture	3200	
		12,800	13,046

3. Equipment: Nil

4. Hospitalisation cost:

600 patients days

600 x Tk. 150/days 90,000

		Taka	Dollar
5.	Outpatient care: Nil		
6.	TCDDR,B transport:	1600	
7.	Transportation of materials:		200
8.	Rent, Communication, Utilities: Nil		
9.	Printing and Reproduction:		450
10.	Other contractual services: Nil		
11.	Construction: Nil		
	TOTAL =	Tk.104,400	$ 13,696
	($ 1 = Taka 16)=	$ 6,525	
	GRAND TOTAL =	$ 20,221	

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

A clinical investigation is proposed on children to determine the role of prostacycline (PGI_2) for the production of Haemolytic-Uremic Syndrome (HUS) as a complication of acute shigellosis. We like to test the hypothesis that disturbed haemostasis seen in HUS patients might be related to the dificient activity of vascular prostacycline-the most potent inhibitor of platelet aggregation. We would like to study two groups of age-matched children:

(a) 100 children in the study group with severe shigellosis likely to develop HUS. Only those who subsequently develop HUS (may be 10) on screening will be subjected to intensive study.

(b) 12 in the control group with uncomplicated shigellosis not likely to develop HUS. All children below 6 months of age & those with severe malnutrition and other complications (e.g. pneumonia, convulsion, unconsciousness etc) will be excluded from the study.

These patients will be admitted in the study ward and regular clinical evaluation will strictly be done every four hours. 1 ml of blood will be required at the peak of disease to determine the plasma level of 6-keto-$PGF_{1\alpha}$ by radioimmuno assay. Plasma fibrinogen, thrombin time, fibrin-fibrinogen degradation products and haptoglobin will be estimated by using commercial kits. 4ml of blood will be necessary for these and other essential routine investigations e.g. serum electrophoresis, electrolytes, urea & creatinine. 1 ml of blood will be required on admission, again 3-7 days later for limulus assay for endotoxaemia. Routine finger blood tests like TWBC, DC, HCT, RBC

fragmentation, reticulocyte, platelet count will be necessary to follow the course of the disease. Stool M/E and culture for shigella will be done on admission.

The above blood examinations will be done on admission, at the peak of leucocytosis and subsequently once weekly until complete recovery in the first group of patients. These patients will be followed up after 4 weeks and the investigations will be repeated.

This study will provide us valuable information about the activity of prostacycline and its possible role in the formation of platelet thrombi in HUS.

In view of the serious nature of the illness which has a high fatality rate, the pathogenic mechanism involved in the development of haemolytic-uremic syndrome could be established from this study so that future therapeutic measures could be developed to save the life of these otherwise fatal patients.

INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH

Prostacycline - HUS study

CONSENT FORM

The International Centre for Diarrhoeal Disease Research, Bangladesh is carrying out studies to know more about Shigella dysentery. In this study, we aim to know the role of a chemical substance called prostacycline in producing Haemolytic - Uraemic Syndrome, which is a very serious complication seen in Shigella dysentery. We would like your child to join in this study.

If your child participates in this study, the following may be expected:

1. Your child will be given best possible medical care like other patients in this hospital.

2. You will be required to stay in the hospital until complete recovery.

3. During the stay in hospital, we will take 6 ml of venous blood for different laboratory tests on admission. Some of these tests will be repeated 3 - 5 days later and then once weekly until the patient has fully recovered.

4. We will take few drops of blood from the finger of your child on different days for laboratory tests.

5. We will do culture for stool to find out organisms responsible for the dysentery.

6. You will have to return with your child 15 days after discharge, when the above tests will be repeated.

7. If you do not like to include your child in this study, there will be no variation of usual treatment.

8. You will be free to withdraw your child anytime from the study, without any change of the therapy.

If you are willing to participate in this study, please put your signature or thumb impression below.

Signature of Investigator: _____

Signature/Thumb Impression of Guardian: _____

Date: _____

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র

বাংলাদেশ

প্রস্টাসাইক্লিন - এইচ, ইউ, এস, ফাঁড

সম্মতি পত্র

এই গবেষণা কেন্দ্র শিগেলাজনিত রক্তক্ষ আমাশয় রোগ সম্বন্ধে আরো জানার জন্যে গবেষণা চালিয়ে যাচ্ছে। এই গবেষণায় আমরা শিগেলাজনিত রক্তক্ষ আমাশয়ের একটি মারাত্মক জটিলতা এইচ, ইউ, এস'র সাথে প্রস্টাসাইক্লিন নামক একটি রাসায়নিক পদার্থের সম্পর্ক জানার চেষ্টা করছি। আমরা আশা করি আপনার সন্তান এই গবেষণায় অংশগ্রহণ করবে।

এই গবেষণায় অংশগ্রহণ করলে নিম্নলিখিত বিষয়গুলো আশা করতে পারেন ঃ

১) অন্যান্য রোগীর মত আপনার সন্তানও সকল প্রকার চিকিৎসা সুবিধা পাবে।

২) রোগী সম্পূর্ণ সুস্থ্য না হওয়া পর্যন্ত হাসপাতালে থাকতে হবে।

৩) হাসপাতালে থাকাকালীন অবস্থায় বিভিন্ন পরীক্ষার জন্যে রোগীর শিরা হতে ৬ সি, সি, রক্ত নেয়া হবে। এই পরীক্ষা রোগীর ভর্তির সময়, তার ৩-৫ দিন পরে এবং তারপর প্রতি সপ্তাহে একবার করে করা হবে।

৪) বিভিন্ন সময়ে ল্যাবরেটরী পরীক্ষার জন্যে রোগীর আংগুল হতে কয়েক ফোঁটা রক্ত নেয়া হবে।

৫) রক্ত আমাশয়ের সার্বিক কারণ নির্ধারণের জন্যে রোগীর পায়খানা পরীক্ষা করা হবে।

৬) হাসপাতাল থেকে ছুটি দেয়ার ১৫ দিন পর আবার রোগীকে নিয়ে আসতে হবে। তখন উপরোক্ত পরীক্ষাগুলো আর একবার করা হবে।

৭) এই গবেষণায় অংশগ্রহণ না করলেও আপনার সন্তানের সুচিকিৎসার কোন ব্যতিক্রম হবে না।

< অপর পৃষ্ঠা >

৮) আপনি যে কোন সময় ইচ্ছা করলে আপনার সন্তানকে এই গবেষণা থেকে সরিয়ে নিতে পারেন। তাতেও চিকিৎসার কোন তারতম্য হবে না।

আপনি যদি আপনার সন্তানকে এই গবেষণায় অংশগ্রহণ করতে দিতে রাজী থাকেন তবে নিম্নে আপনার দস্তখত বা টিপ সই দিন।

গবেষকের স্বাক্ষর

অভিভাবকের স্বাক্ষর বা টিপসই

তারিখ