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RC

SECTION I - RESEARCH PROTOCOL

1) Title: Nutritional Consequences of Low Dose, Whole Milk Dietary Supplements Given to Lactose-Malabsorbing Children

2) Principal Investigator: Kenneth H. Brown, M.D.

3) Starting Date: 1 September, 1977

4) Completion Date: 1 March, 1978

5) Total Direct Cost: $ 7,895

6) Abstract Summary:

A study is planned to determine whether dietary supplements of whole milk given to lactose malabsorbers will be nutritionally advantageous. Lactose-malabsorbing and normal, control children will receive a vegetable and rice diet either alone or with supplements of lactose-free or lactose-containing milk during these sequential balance periods. Calorie, fat and nitrogen balances will be determined; and breath hydrogen tests will be performed to evaluate dietary carbohydrate absorption.

7) Reviews:

a) Research Involving Human Subjects: _____

b) Research Committee: _____

c) Director: _____

d) BMRC: _____

e) Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective: To determine whether a dietary supplement of whole milk will be nutritionally advantageous or disadvantageous to lactose-malabsorbing children maintained on marginally adequate vegetable diets.

2. Background: Nutritional rehabilitation of children has traditionally been accomplished through the use of milk-based formulas. These formulas can be the vehicle for high calorie and high-quality protein intakes in a variety of clinical situations. They are easy to prepare; are easy to administer - either orally or by tube feeding; and, until recently, have been relatively inexpensive and readily available. However, the use of milk-based formulas as rehabilitation foods has become a controversial issue receiving consideration both in scientific journals and lay publications. (1, 2) The review by Simoons et al. illustrates that the controversy is based on social, economic and political considerations as well as scientifically derived nutritional information. (1)

The nutritional quality of milk must be evaluated with two considerations in mind: milk can not only provide those specific nutrients which it contains, but it may also affect the absorption of other dietary nutrients. Lactose is the milk nutrient most commonly malabsorbed and implicated as responsible for the secondary malabsorption of other nutrients. (3) Although lactose-containing milk-based formulas are useful in the rehabilitation of malnourished children (4, 5), milk can induce a severe, fermentative diarrhea in lactose malabsorbers (6); and whole milk is clearly inferior to low-lactose or lactose-free formulas for the treatment of

children with severe protein-calorie malnutrition (7, 8, 9), many of whom are lactose malabsorbers (10). The effect of milk ingestion on the absorption of non-milk nutrients has not been well studied, but there is one suggestion that lactose ingestion may cause steatorrhea in some adult patients with isolated lactase deficiency (11). Nevertheless, the Protein Advisory Group of the United Nations(12), the Food and Nutrition Board of the United States National Research Council (13), and the Committee of Nutrition of the American Academy of Pediatrics (14) continue to state that "based on present evidence it would be inappropriate to discourage programs for increasing milk supplies and consumption because of a fear of milk intolerance." (15)

The conflicting views may result, in part, from the fact that milk can be used in the diet in one of two ways: either as the single source of an individual's nutrients, or as a supplement to the usual dietary intake. Since the degree of an individual's intolerance relates to the amount of lactose ingested (16, 17, 18), one might also expect that the nutritional consequences of milk ingestion by a lactose malabsorber also relate to the amount of milk consumed. Lactose malabsorption and its secondary complications are generally believed to result from an imbalance between the lactose load and the total effective lactase activity. This imbalance is related to the size of the lactose load and type of lactose-containing food, the time period of ingestion and rate it enters the intestine, the severity of the intestinal lactase deficiency, and probably other unrecognized factors (19). Unabsorbed lactose exerts an osmotic effect in the small intestine and colon, drawing water into the intestine, and hastening transit time. (It is the decreased transit time which is hypothesized to be the mechanism for secondary malabsorption of other nutrients (11, 20).)

One study in which milk was given to children as the only food demonstrated increased stool weight and stool nitrogen and decreased nitrogen retention among lactose malabsorbers. Increased losses of fat and of calcium in the stool were noted only when the stool volume was very large; otherwise they were not significant. (21) Another study using milk as the only food source also showed decreased nitrogen absorption among lactose malabsorbers while on the lactose-containing formula, and no change in fat absorption. (20) Calloway and Chenoweth studied nutrient utilization in lactose absorbers and malabsorbers receiving 1000 g of lactose-varied milk formulas in addition to other non-nitrogen-containing foods and formula. They found that two of four adult lactose malabsorbers given normal-lactose, partially-skimmed milk in four divided doses had significantly larger fecal wet and dry weights, presumably related to their increased fecal calories. Only one subject had significaltly increased fecal nitrogen while on lactose-containing milk, and none had increased fat excretion. (22)

There are no studies testing milk's efficacy as a source of added calories and high quality protein when given as small volume supplements to the usual diet of a lactose-malabsorbing child. There are two important issues to relolve: 1) Do small volumes of milk given with standard vegetable diets induce clinically significant symptoms (i.e. intolerance) in lactose malabsorbing children? and 2) Do the supplements of calories and protein contained in the milk more that offset any potential increases in fecal excretion of calories (as fat and carbohydrate metabolites) and nitrogen induced by lactose ingestion?

Normally, dietary lactose is hydrolyzed by the gut brush border enzyme, lactase, and is absorbed as glucose and galactose. (22) Primary lactase

deficiency, the presumably genetically determined decline of lactase occurs in many populations of children beyond three to five years of age. (3) Secondary lactase deficiency, occurring as a consequence of acute infectious diarrhea (24) protein-calorie malnutrition (5), or other toxic or inflammatory insult to the gut is a transient phenomenon which may occur in any age group and in any population where the primary diseases are found. (25) The small amount of available information concerning lactose absorption in populations of the Indian subcontinent suggests that there may be significant regional differences in prevalence of malabsorption. (26, 27, 28) There is no comprehensive population-study looking at lactose absorption among Bangladeshis, but investigations to determine the prevalence of lactose malabsorption among Bangladeshi villagers are currently in progress in villages surrounding Matlab (see CRL protocol: Lactose Malabsorption in Bangladeshi Villagers as Determined by Breath Hydrogen Testing). Preliminary data suggests that lactose malabsorption may be common among Bangladeshis of all ages.

Rationale: Children with clinically diagnosed lactose malabsorption and normal controls will be admitted to a metabolic ward, so that dietary intake can be controlled while stool and urine output are accurately collected and measured. First, the children will be placed on a rice and vegetable baseline diet with nutrient composition designed to approximate to the usual diet of Bangladeshi villagers. Calorie and protein intakes will be just at or slightly above the per kilogram recommendation of the FAO and WHO of the United Nations. After the baseline balance period, similar balance studies will take place with lactose-free or lactose-containing milk added in limited volumes to the same rice diet at the morning and afternoon meals. The timing of the supplemental milk administration is meant to imitate the usual schedule of relief outpatient

and rehabilitation feeding programs. Both the lactose-free and lactose-containing supplements will be given to all children during sequential study periods. During all balance periods intakes and outputs will be monitored for total calories, nitrogen, and fat so that the nutrient availability from each diet can be assessed. Carbohydrate absorption will also be monitored by means of breath hydrogen tests, and clinical symptoms will be noted during each dietary study period.

SPECIFIC AIMS

1. To determine whether the addition of lactose-containing and lactose-free milk formulas to marginal vegetable diets of lactose-malabsorbing children affects nutrient absorption from the diet.

2. To determine whether such dietary supplements can be delivered successfully in only two daytime doses, as might be logistically feasible for relief or rehabilitation feeding programs.

3. To determine whether such dietary supplements are well tolerated.

4. To determine whether breath hydrogen testing accurately reflects the degree of carbohydrate malabsorption as derived from calorie balance techniques.

METHODS OF PROCEDURE

Selection of Study Subjects Male subjects aged three to seven years will be recruited from the clinic and day-care patient populations of the Children's Nutrition Unit in Dacca. Children with severe malnutrition and children with a recent history of acute of chronic diarrhea or other acute or chronic infectious or metabolic diseases will be excluded from the

tudy. After receiving information about the nature and purpose of the study, onsenting subjects will be admitted to the metabolic study ward for an overn ight stay. On the following morning a lactose tolerance test and breath ydrogen test will be performed (see below). Children with clearly normal or learly abnormal responses will be labeled as lactose-absorbers (L-A) or actose-malabsorbers (L-M), respectively; and will then be considered for mission to the balance studies. All L-A's and L-M's will then be screened r other diseases by means of a hemotocrit and total and differential white ell count, urinalysis and urine culture, stool microscopic exam and culture, ntermediate strength tuberculin skin test, chest X-ray, and serum urea, reatinine, SGOT, alkaline phosphatase, total protein, and protein electro- horesis. Subjects with diseases which might interfere with interpretation f balance studies will be excluded from further investigation; and, when ossible, will be treated for their primary diseases. Children with parasitic nfections and iron deficiency anemia will be treated with the appropriate ndications and included in the study. Four L-A's and eight L-M's will be ad- itted to the study ward for approximately five weeks for metabolic balance tudies. Six children can be accommodated on the ward at one time.

tudy Ward Environment and General Ward Procedures Study subjects will be dmitted to the study ward at the Children's Nutrition Unit. General play will e encouraged and exercise periods of at least 15 minutes twice daily will be nforced. A teacher will conduct classes for at least two hours each day. eals, snacks, and supplements will be given according to a fixed routine nder direct supervision. Plates and cups will be washed with drinking water t the completion of each meal and the washings will also be offered for consump- ion. Children will be weighed nude each morning after their morning void and efore breakfast on a scale accurate to ten grams. Urine specimens will be

llected in daily 24-hour blocks for determination of total creatinine, urea,
nitrogen. After passage of stool markers (charcoal), stool will be saved
the deep freeze in seven day pools for subsequent homoginization and
ermination of total fat, nitrogen, and calories. Urine volumes, stool
ghts, and clinical status will be recorded daily. (see Appendix I, 24
r clinical summary form) Stool exams for ova and parasites will be
ained between collection periods to assure that children do not harbor parasites
ing the study.

orption Studies During the first week on the ward, and prior to the
rient utilization studies, the children will be evaluated more critically
carbohydrate absorption status. A xylose excretion test will be per-
med as suggested by Langkowsky et al. (29) and the urinary xylose will be
sured according to the Kerstell simplification (30) of the method of
and Rice. (31)

the next day a lactose tolerance test (LTT) will be repeated according to
ndard procedures. A baseline capillary blood sample will be obtained for
od glucose determination from subjects who have fasted at least eight
r... Then a 2 gm/kg dose of lactose will be given orally as a 10% solution
water. Followup capillary blood specimens for glucose will be obtained at
and 45 minutes after the administration of lactose, and a blood glucose
of less than 25 mg/dl will be considered abnormal. Any symptoms
idative of lactose intolerance occurring within 24 hours of the LTT will
recorded. At the same time as the LTT a breath hydrogen test (BHT)
ll be performed according to the protocol of Solomons et al. (32) An
pired breath sample will be collected either by face-mask and anesthesia
g or directly into a bag and the sample will be stored for no more than

hours in a stoppered plastic syringe before the subsequent determination of drogen concentration on a Quintron gas chromotograph. The samples will be mpared to a commercially prepared standard of 55 parts per million (PPM) drogen in air. Results will be presented on the basis of PPM rise in H ncentration above the baseline sample, and a rise of more than 20 PPM will considered evidence of malabsorption. All children malabsorbing a 2 gm/kg e of lactose will be studied again (by BHT only) using a dose of 1 gm/kg. ldren malabsorbing the 1 gm/kg dose will be studied once again using a m/kg of lactose. All children will also undergo a tolerance test and llowing the ingestion of 2 gm/kg of a glucose-galactose solution, to normal monosaccharide absorption.

d Balance Studies Food and nutrient composition of the various study is listed in tabular form. (see Appendix II) Initially the children l be offered a rice and vegetable diet patterned after the usual nutrient sks of Bangladeshi villagers. (33) Total caloric intake will be determined a per kilogram basis as recommended by the Joint FAO/WHO Expert Committee port on Energy and Protein (34); protein intake will be set above FAO/WHO commendations for reference protein in order to compensate, at least par- ally, for amino acid imbalances and incomplete absorption. After the rst balance period the children will be given a supplement of lactose-free mulated "milk" (casein, glucose, vegetable oil, and minerals) twice daily a dose of 12.5 ml/kg per feeding in addition to the same baseline break- st and mid-day meal given previously. The rest of the baseline diet will main unchanged. Following the second balance period a final diet study riod will substitute a lactose-containing, simulated "milk" (casein, lactose, getable oil, and minerals) for the lactose-free milk. The dosage and timing milk administration will remain the same. The total milk intake of 25 ml/kg/day

ld provide, if totally absorbed, an additional 16 calories and 0.875 gm high quality animal protein per kilogram (Equal to approximately 17% and of suggested daily calorie and protein intakes for this age group). All ldren will receive vitamin and mineral supplements to the diets. Subjects l spend 12 days on each diet: five days for adaptation and seven days for ance study.

rogen balances will be determined by subtracting urinary and fecal nitrogen retion from dietary nitrogen intake. Nitrogen analyses will be performed homogenized semi-micro samples according to the Kjeldahl technique. Diet fecal fat determinations will be performed according to the method of de Kamer et al. (35), and caloric content of diets and stool will be sured by adiabatic bomb colorimetry. Dietary and fecal carbohydrate con- t will be calculated from the colorimetry, nitrogen, and fat data according the formula:

$$\frac{\text{bomb kcal in} \begin{cases} \text{feces} \\ \text{or} \\ \text{diet} \end{cases} - \left(\begin{matrix} \text{fecal} \\ \text{or} \\ \text{food} \end{matrix} \quad N \times 6.25 \times 5.65 + \begin{matrix} \text{fecal} \\ \text{or} \\ \text{food} \end{matrix} \quad \text{fat} \times 9.40 \right)}{4.15}$$

uplicate diet will be prepared for each study subject once during each bal- e period. The mean percentage recovery of nitrogen, fat, and calories from predicted intakes for each study diet (originally computed from food com- sition tables) will be used to determine the actual nutrient intake for the bjects. (The mean percent recovery x individual subjects' calculated intake subjects' actual intake.)

the first and fifth day of the adaption period for each study diet a BHT will performed. Breath samples will be collected before and hourly for six hours ter breakfast on those days. Lunch will be postponed until after the com- etion of the BHT.

ood will be obtained before and after each study period so that the total rum protein and albumin can be measured.

ta Collection and Processing Nitrogen, fat, and calorie balance data will collected and summarized for each subject on each study diet (see Balance udies, summary form). The apparent absorption of each nutrient and the nitro- n retention will be calculated. Mean absorption and retention parameters r each patient group (L-A and L-M) on each study diet will be compared by -testing. Other clinical parameters, including weight gain, stool output, and mptoms of intolerance, will also be compared.

arbohydrate-malabsorbing subjects will be ranked according to severity of actose malabsorption as determined by the minimum lactose dose producing a gnificant breath hydrogen rise and also by the calculated amount of carbohy- rate losses in the feces to determine whether there is any correlation between hese two parameters.

IGNIFICANCE

t a time when perhaps as many as half the world's children suffer from some orm of malnutrition it is imperative to critically evaluate various forms of utritional relief and rehabilitation. Although milk has traditionally been n important rehabilitation food, its use has become controversial - primarily ecause it can cause clinically significant diarrhea when given in large doses o lactose-malabsorbing children. The proposed study should help to determine hether two divided doses of milk given in addition to the usual diet of a lac- ose malabsorbing child will be tolerated and nutritionally beneficial. Since ilk supplementation programs of similar design are currently in effect in any parts of the world and since lactose malabsorption is common, it is

portant to have specific nutritional information to determine the value of ch programs.

e study may also provide some data on the usefulness of the breath hydrogen st to detect malabsorption of specific dietary carbohydrate components.

ACILITIES REQUIRED

Office space - 1 office, CRL, for primary investigator, 4 months
- 1 office, CNU, for clinical research assistant, 4 months

Laboratory space - routine samples, CRL biochemistry lab, 3 months intermittent activity
- 2-12' benches, CNU, 5 months
- 1 bomb colorimeter bench, IPH, 1 month

Hospital resources - 3 inpatient beds/day x 30 days, CNU - initial recruiting period
- 6 inpatient beds/day x 90 days, CNU - balance studies

Animal resources - none

Logistical support - 1 vehicle 2 round trips daily CNU-CRL x 120 days = 1440 miles

Major itmes of equipment - 1 freezer, 1 voltage stabilizer

Other specialized items - construction costs, CNU
- special diets
- overhead fees, CNU

OLLABORATIVE ARRANGEMENTS - none

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SECTION III - BUDGET

A. DETAILED BUDGET

PERSONNEL SERVICES

Name	Position	% of Effort	no. of Days	Annual Salary	Project Requirements TAKA	Project Requirements DOLLARS
rown	Primary Investigator	30%	120	$ 16,200		1,618
hatoon	Clinical Research Asst.	100%	150	Tk 14,400	6,000	
hmed	Chemistry Tech.,CNU	100%	150	Tk 12,500	5,208	
1	Chemistry Tech., CNU	100%	150	Tk 8,750	3,645	
losh	Chromatograph Tech.,JHU	100%	45	Tk 12,000	2,077	
ahman	Chromatograph Tech.,JHU	100%	45	Tk 12,000	2,077	
nior Nurse	CNU	100%	120	Tk 31,312	10,438	
nior Ayas	CNU	100%	120	Tk 9,600	3,200	
elen Gomes ary Rosario)						
nior Cook ri Leba'	CNU	50%	120	Tk 5,760	960	
ok's Asst.	CNU	50%	120	Tk 3,720	620	
sher	CNU	100%	120	Tk 2,400	800	
shroom Attendant	CNU	50%	120	Tk 4,800	800	
				Sub Total:	Tk 35,825	$ 1,618

SUPPLIES AND MATERIALS

Items	Unit Cost	Amount Required	Project Requirements TAKA	Project Requirements DOLLARS
ose	$ 19.50/lb.	9 Kg.		386.10
ose	$ 37.22/5 Kg. pkg.	5 Kg.		37.22
in	$ 30.00/10 Kg.	12 Kg.		36.00
table Oil	$ 1.50/Kg.	28 Kg.		42.00
mins (Clostrol)	$ 1.79/Bottle	25 x 240 ml. bottles		44.75
se	$ 9.06/100 gm. bottle	250 Gm.		27.18
osable syringes (needles)		100		15.00
tic syringes, 10 ml.	$ 6.90/20	100		35.00
sware,glass vials for study patients	Tk 1050/mo.		4200	250.00
ratory reagents, CNU & JHU				250.00
cocks		100		54.00
		Sub Total:	Tk 4200	$ 1,177.25

3. EQUIPMENT

Items	Unit Cost	Amount Required	Project Requirements TAKA	DOLLARS
Beds for study ward	Tk 300/bed	6	1,800	
Electrical fittings, study ward			300	
Closet, Shelves - study ward			500	
Fencing for study room			250	
Voltage stabilizer, CMU Lab., 500 Watt		1		25.00
Freezer (23.9 Cu. ft.), CMU Lab./Study rooms		1		390.00
		Sub Total:	Tk 2,850	$ 415.00

PATIENT HOSPITALIZATION

	Project Requirements TAKA	DOLLARS
Usual costs for nursing, diets, laboratory work are shown under personnel and supplies		
Additional laboratory costs, CRL, routine chemistry, pathology, and bacteriology labs. (CBC, U/a, cultures, stool exam, CXR, glucose, serum chemistry, stool fat, colorimetry)	2,500	
CMU overhead (TK200/mo. x 4 mos.)	4,800	
Sub Total:	Tk 7,300	

B. OUTPATIENT CARE - none

C. TRANSPORT

	Project Requirements TAKA	DOLLARS
CRL transport - none		
CMU transport (12 mi/day x 120 days x Tk 1.40/mi)	2,016	
Sub Total:	Tk 2,016	

TRAVEL AND TRANSPORT OF PERSONS

	Project Requirement TAKA	DOLLARS
country transport of study subjects' parents for ward visiting - approx. Tk 6/rd. trip/parent/day x 6 subjects x 100 days	3,600	
Sub Total:	Tk 3,600	

TRANSPORTATION OF THINGS

	Project Requirements TAKA	DOLLARS
oltage stabilizer		6.25
reezer		97.50
gents and glassware (Budgeted at 25% of estimated cost)		125.00
Sub Total:		$ 228.75

RENT, COMMUNICATIONS & UTILITIES

	Project Requirements TAKA	DOLLARS
	100	
Sub Total:	Tk 100	

PRINTING & REPRODUCTION

	Project Requirements TAKA	DOLLARS
nting of forms	200	
eo - data forms, protocols, consents	500	
ox	1000	
lication		300
Sub Total:	Tk 1700	$ 300

OTHER CONTRACTUAL SERVICES

	Project Requirement TAKA	DOLLARS
Local labor - shopping, cooking, maintenance	1000	
Sub Total:	Tk 1000	

CONSTRUCTION, RENOVATION, ALTERATIONS

- All items shown under equipment

MISCELLANEOUS

	Project Requirement TAKA	DOLLARS
Contingency expenses shown at 5% of total direct costs	2930	187
Sub Total:	Tk 2930	$ 187
Total:	Tk 61,521	$ 3,926

B. BUDGET SUMMARY

Category	Taka	Dollars	Total ($)
1. Personnel	45,629	1,618.00	3,929.29
2. Supplies	4,200	1,177.25	1,448.21
3. Equipment	2,850	415.00	598.87
4. Hospitalization	7,300	--	470.96
5. Outpatients	--	--	--
6. Transport	2,016	--	130.06
7. Travel of Persons	3,600	--	232.25
8. Transportation of Things	--	228.75	228.75
9. Rent & Communication	100	--	6.45
10. Printing & Reproduction	1,700	300.00	409.67
11. Contractual Service	1,000	--	64.51
12. Construction	--	--	--
13. Miscellaneous	2,930	187.00	376.03
Total:	Tk 81,321	$ 3,926.00	$ 7,895.05

Conversion Rate $1.00 = Tk 15.5

সম্মতি পত্র

দুধ নমুনাকে এবং ল্যাকটোজ দুষ্টি

কলেরা রিসার্চ লেবরেটরী এবং চিলড্রেন নিউট্রিশন ইউনিটের গবেষনা পর্যবেক্ষক পরীক্ষা করে দেখতে চান যে, যে সব বাচ্চারা ল্যাকটোজ হজম করতে পারেনা সে সব বাচ্চাদের যদি অন্যান্য খাদ্যের সাথে কিছু পরিমান দুধ খেতে দেয়া হয় তবে তা বাচ্চাদের জন্য উপকৃত হয় কিনা।

আমি বুঝতে পেরেছি যে যদি আমি আমার বাচ্চাকে এ পরীক্ষায় অংশ গ্রহন করতে দেই তবে আমাকে নিম্ন বর্ণিত বিষয় সমূহ মেনে নিতে হবে।

১। সে পরীক্ষা ঘরে প্রায় পাঁচ সপ্তাহ অবস্থান করবে।

২। পরীক্ষা চলাকালীন বিভিন্ন সময়ে তার স্বাস্থ্য সম্পর্কিত বিষয় অবগত হওয়ার জন্য প্রায় বিশ (২০) সিসি রক্ত (প্রায় চার চা- চামোচ পরিমান) পরীক্ষা করার জন্য নেয়া হবে।

৩। তাকে প্রতিদিন নির্দিষ্ট পরিমান পুষ্টিকর খাদ্য মেপে খেতে দেয়া হবে।

৪। প্রস্রাব এবং পায়খানা বিশ্লেষনের জন্য সংগ্রহ করা হবে। সে সংগে শ্বাসও পরীক্ষা করা হবে।

৫। বিভিন্ন সময়ে তাকে অন্যান্য খাদ্যের সাথে চিনি জাতীয় খাদ্য ল্যাকটোজও খেতে দেয়া হবে। পুষ্টিহীনতায় আক্রান্ত বাচ্চাদের কেহ কেহ যদি ইহা হজম করতে না পারে তবে তার পেটে বায়ু এবং অসুবিধা হতে পারে, তা ছাড়া পাতলা পায়খানাও হতে পারে।

৬। এই পরীক্ষা চলাকালীন সময়ে বাচ্চার অন্যান্য রোগেরও চিকিৎসা করা হবে।

৭। পরীক্ষার সকল কলাকল গোপন রাখা হবে।

৮। আমি আমার ইচ্ছানুসারে আমার বাচ্চাকে পরীক্ষা থেকে সরিয়ে নিতে পারব, এতে তার নিয়মিত চিকিৎসার যেন ব্যাঘাত হইবেনা।

স্বাক্ষর

স্বাক্ষর ---

সম্পর্ক ---

তারিখ ---

CONSENT FORM

Milk Supplements and Lactose Malabsorption

Medical researchers from the Cholera Research Laboratory and the Children's Nutrition Unit are undertaking studies to determine whether milk is nutritionally beneficial when added to the usual diet of children who cannot absorb the sugar lactose, which milk contains.

I understand that if I enroll my son in the study, I should expect the following:

1. He will remain on the study ward for a period of approximately five weeks.
2. Small amounts of blood totalling approximately 20 ml. (less that 2 dessert spoonfuls) will be drawn on several occasions to determine his state of health and nutritional well-being.
3. He will be given a measured amount of food daily to provide minimally adequate nutrients.
4. His stool and urine will be collected for analytic purposes. Samples of expired air will also be collected periodically.
5. On several occasions he will receive the sugar, lactose, in addition to his daily diet. This sugar may cause gas, cramping, and/or diarrhea in some individuals with malabsorption.
6. Any diseases discovered in my child during the initial evolution or occurring during the study period will be treated according to accepted practice.
7. All results of the study will remain confidential.
8. I may withdraw my child from the study at any time without jeopardizing his future routine clinic care.

Signed _____

Relationship to patient _____

Witnessed by _____

Date _____

Review Board on the Use of Human Volunteers

ABSTRACT SUMMARY

Milk Supplementation and Lactose Malabsorption

1. The study is designed to determine whether milk is an appropriate relief and rehabilitation food for individuals at risk of malnutrition. Since milk is most commonly provided only for children, since children are usually the most nutritionally vulnerable segment of the population, and since children's protein requirements are relatively greater (and they are therefore more likely to benefit from a milk supplementation program), all study subjects will be children. In order to determine whether milk ingestion will benefit lactose malabsorbers, children with documented lactose malabsorption will be selected for study.

2. Some children with lactose malabsorption may develop cramping, gas, and/or diarrhea following the ingestion of lactose. If diarrhea develops it is usually of mild degree. There is also discomfort (but no serious risk) resulting from blood sampling.

3. On most occasions in this study (except during the initial tolerance testing) lactose will be given as milk in low doses and with other foods. Administering lactose in this way should minimize potential side effects. If children develop diarrhea after receiving lactose, appropriate fluid therapy will be provided. If the severity of diarrhea precipitates clinically significant dehydration, the lactose will be discontinued.

4. All subjects will be assigned a study number, and, subsequent clinical and laboratory data will be recorded by study number only. The names of subjects will be kept on file until after the completion of the study, but will be

available only to the primary investigators. Results of the study will be published in professional journals, and specific patient information will be collated by study number only. At the termination of the study, subjects' identifying information be destroyed.

5. Written informed consent will be obtained from the parents or guardians of study subjects. The parents (or guardians) will be informed about the study by a Bengali assistant on the study ward.

6. As part of the study a review of the childrens' general health will take place, thus necessititing a routine medical history interview. The interview will require approximately fifteen minutes.

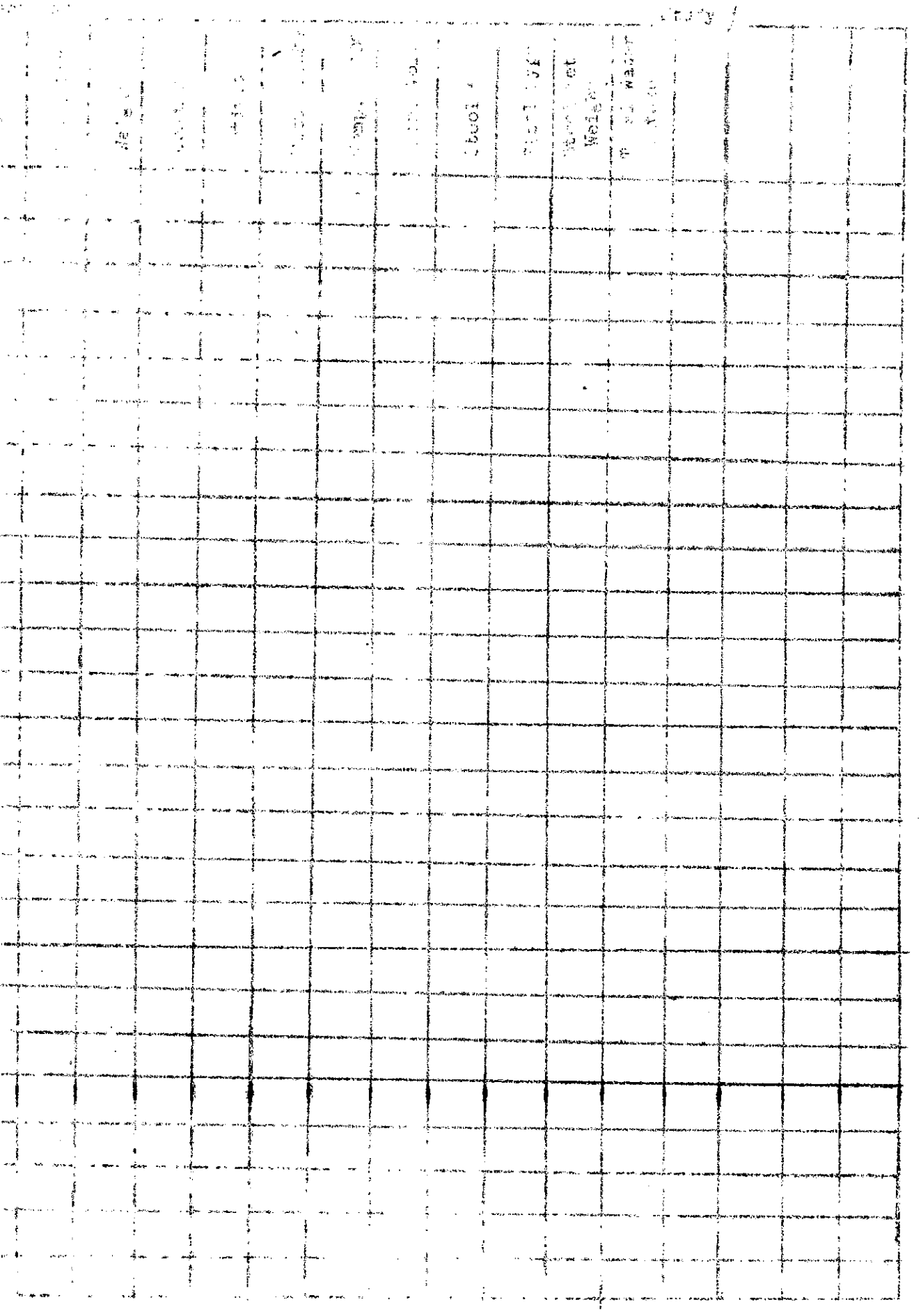
7. Individual subjects will benefit from the complete medical evaluation and subsequent therapy provided for any diseases diagnosed. Parents will also receive information regarding the precise amount of milk allowable in the child's diet. Finally, the children will have the temporary advantage of schooling while on the study ward.

Society will benefit from the study through the information generated regarding milk therapy for lactose-malabsorbing children. Since milk is currently being offered in many clinical centers it is crucial to evaluate the consequences of this form of therapy.

Since the risks to the individual are minimal, the potential benefits of the study both to the individual subject as well as to society in general outweigh any potential risks.

8. The study will require the use of subjects' blood, urine, feces, and expired air as well as routine hospital records.

APPENDIX 1



Milk Supplementation and Lactose Malabsorption

APPENDIX II - STUDY DIET

(All items listed per kilogram of subjects' body weight)

Meal	Food	Amount (Grams)	CHO (Grams)	FAT (Grams)	PROTEIN (Grams)	Total Calories
Morning	Rice (as pudding)	5.0	3.94	0.035	0.33	18
	Sugar	1.5	1.5	--	--	6
	Spices	--	--	--	--	--
Midday	Rice	5.0	3.95	0.035	0.33	18
	Potato (curry)	5.0	1.11	0.006	0.10	5
	Pumpkin (fried)	5.0	0.38	--	0.05	1.5
	Vegetable Oil	0.75	--	0.750	--	6.7
	Onion	1.0	0.09	0.002	0.01	0.5
	Spices	--	--	--	--	--
Evening	Rice	5.0	3.94	0.035	0.33	18
	Potato (curry)	5.0	1.11	0.006	0.10	5
	Pumpkin (fried)	5.0	0.39	0.015	0.05	1.5
	Vegetable Oil	0.75	--	0.750	--	6.8
	Onion	1.0	0.09	0.002	0.01	0.5
	Spices	--	--	--	--	--
	Banana	9.0	2.00	0.018	0.10	7.6
Total Nutrients			18.20	1.67	1.41	95.1
Total Calories			73	16	6	

Note: Food values presented on basis of uncooked edible portion as listed in food composition tables of the U.S. Dept. of Agriculture.

Milk Supplementation and Lactose Malabsorption

APPENDIX II - STUDY DIETS (Continued)

Simulated "Milk" Formulas

(all food and nutrients listed per 100 ml formulae)

Food	Amount (gram)	CHO (grams)	FAT (grams)	PROTEIN (grams)	Total Calories
Casien Powder	4.07	--	--	3.5	14
Vegetable Oil	3.50	--	3.50	--	31.5
Lactose or Glucose	5.00	5.00	--	--	20
Total Nutrients		5.00	3.50	3.50	65.5
% Total Calories		30	48	21	

LACTOSE TOLERANCE TEST

Name: _____ Date: _____ Dose: _____

	Tests					Symptoms		
	Blood glucose level	Blood galactose level	Breath H_2 i)	Breath H_2 ii)	Gas	Distension	Cramps	Laxative
20 min.								
45 min.								
1 hr.								
1½ hr.								
2 hr.								
2½ hr.								
3 hr.								
4 hr.								
5 hr.								

Symptom code: none, mild, moderate, severe

Nitrogen Balance Studies

Patient Name _____ Study # _____

Date										
Hospital Day										
Weight										
Urine Volume										
Urine Creatinine Conc. (mg %)										
Total Urine Creatinine(mg)										
Urine Urea Conc. (mg %)										
Total Urine Urea										
Urine Nitrogen Conc.(gm %)										
Total Urine Nitrogen(gm)										
Daily Stool Wgt.										
Stool Nitrogen Conc.(gm %)										
Total Stool Nitrogen(gm)										
Daily Milk Volume (Weighed)										
Milk Nitrogen Conc. (gm %										
Total Milk Nitrogen										
Estimated Cutaneous Nitrogen Losses(gm)										
Total Nitrogen Intake (gm)										
Total Nitrogen Output (gm)										
Nitrogen Balance										

LACTOSE ABSORPTION STUDIES - HISTORY FORM

me _____ Study No. _____

ge _____ Sex _____ Date of Study _____

urrently breast feeding ☐ Yes ☐ No

ge of introduction of supplementary feedings: _____ months

ge at complete weaning: _____ months

eason for weaning: _____

_____

s milk consumed in current diet ☐ Yes ☐ No

f yes: amount per day _____ ml, in _____ feedings

number of days per week _____

any untoward effects following milk consumption? (Describe) _____

_____

_____

f no: age when milk was discontinued _____

reason for discontinuing _____

any untoward effects following milk consumption in past?(Describe) _____

_____

_____

by other milk products in usual diet (curds, cheese): ☐ Yes ☐ No

f yes: usual amount of consumption _____

any untoward effects following consumption? _____

_____

oose motions: ☐ currently ☐ in past week

☐ in past month ☐ in past 3 months

☐ other

umber of bowel movements per day: _____

escription of stool currently: ☐ formed ☐ soft ☐ loose ☐ watery

☐ mucous ☐ blood and mucous

List all medicines taken in past week _____

_____

edicines taken in past month _____

_____

BALANCE STUDIES

Date of Hosp. Adm :

Date	Weight gm.	Age Mo. Hgt. cm.	Diet Type	Cal/kg	Prot. gm/kg	Days of collection	Wgt. gain gm/d gm/kg/d.	Nitrogen mg/day Diet	Feces	% Abs.	Urine	Milk	% Ret.	Urine mg/day Urea	Creat. mg/day	Stool gm/day Wet wgt.	Dry wgt.	Fat gm/day Diet	Stool	% Abs.	Calories Diet	Stool	% Abs.	Serum Prot/ Alb.	Comments