The effect of dietary lactose on the early recovery from protein-energy malnutrition. I. Clinical and anthropometric indices[1-5]

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ABSTRACT To assess the advisability of using lactose-containing formulas in the rehabilitation of severely malnourished children, indices of clinical recovery, growth and restoration of body proteins and gastrointestinal function were measured longitudinally during the initial 45 days of hospitalization in 20 male, preschool children with kwashiorkor and marasmic-kwashiorkor. All patients received a diet based on cows' milk, but half were allocated to a formula pretreated with β-galactosidase to hydrolyze the lactose, while the others received the untreated, intact milk. The groups were identical with respect to clinical criteria on admission. For the final 37 days of the protocol, the subjects received 4 g of protein and 150 kcal of energy per kg per day. More diarrhea was experienced by the intact lactose group during early hospitalization. Overall, recovery was satisfactory in both cohorts, and there were no differences in rates of growth, body protein repletion, restoration of energy reserves nor intestinal functions. In conclusion, the routine reduction of lactose content from a milk-based diet for severe protein-energy malnutrition offers no advantages. *Am J Clin Nutr* 1984;40:591–600.

KEY WORDS Diarrhea, diet therapy, dietary carbohydrate, growth, lactase, lactose intolerance, milk, protein-energy malnutrition

Introduction

Milk is a source of high quality protein, frequently used for the recuperation of children with protein-energy malnutrition (PEM). Subsidies from the World Food Program, governmental agencies, and some private voluntary organizations have facilitated the distribution of milk for famine relief and for routine programs of inpatient and outpatient treatment of endemic malnutrition. In the extensive 25-yr experience with several hundred children admitted to the Clinical Research Center of the Institute of Nutrition of Central America and Panama (INCAP), milk has been used along with a host of other protein sources as the basis of recovery diets in various forms of PEM. Based on the excellent results obtained (1), cows' milk became the main ingredient in our routine therapeutic diets. However, its suitability for malnourished patients or populations has been questioned, mainly in relation to its carbohydrate, the disaccharide, lactose. Children with severe PEM commonly have a reduced activity of intestinal lactase, the mucosal enzyme responsible for the digestion of lactose (2–5), and it has been

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suggested that feeding this disaccharide can retard nutritional recovery (6, 7). Low-lactose or lactose-free milk can be produced using the processes of in vitro hydrolysis (8) or ultrafiltration (9). These procedures add considerably to the cost of milk, but the increased cost might be justified if the absence of lactose in a milk-based diet were shown to accelerate recovery from PEM.

The theoretical objections to milk-feeding in PEM are generally based on two considerations: *1*) that the carbohydrate, lactose, will be poorly absorbed, with consequently decreased effective utilization of the dietary energy; and *2*) that the osmotic and fermentative effects of nonabsorbed carbohydrate in the intestine will produce or exacerbate diarrhea. In relation to the first issue, it should be considered that the appropriate formulation of the recovery diets requires supplementation of native cows' milk with additional energy sources (dextrins, sucrose, vegetable oil) to provide a food that delivers about 4 g protein and 150 to 200 kcal/kg. Lactose would represent only 11 to 16% of total energy in such diets, and recent studies in rats (10) and human volunteers (10, 11) suggest that a large portion of the energy in carbohydrates escaping digestion and absorption in the small bowel can eventually be absorbed from the colon, most probably in the form of volatile fatty acids (12). The second consideration is not easy to assess, since the criteria used in different studies to describe diarrhea are not uniform and frequently do not allow the determination of worsening of the diarrhea that often accompanies the PEM syndrome.

Thus, given an array of problems with the interpretation of previous reports, and given the newer insights into colonic carbohydrate metabolism, we undertook a systematic randomized trial of formulas based on whole cows' milk versus lactose-hydrolyzed milk during 45 days after beginning treatment of 20 Guatemalan children with severe PEM of the edematous type. This paper describes the clinical results and intestinal functions in terms of stool characteristics. An accompanying paper (13) gives detailed information about the absorption of dietary nutrients.

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Patients and methods

Subjects

The subjects were all male, Guatemalan preschool children of Maya or ladino (Mayan-Caucasian) descent, between the ages of 15 and 36 months, who were referred to INCAP for treatment of kwashiorkor or marasmic-kwashiorkor. Only 20 of 32 children originally admitted completed the experimental protocol. Of the remainder, five died shortly after hospitalization, and seven had persistent vomiting or infections that required intensive and prolonged treatment and drastically diminished spontaneous oral intake. The study protocol was approved by the Committee on Human Research of INCAP and the Committee on the Use of Humans as Experimental Subjects of MIT. Informed written consent was obtained from the patients' parents upon admission to the Clinical Research Center, after the nature and purposes of the study had been explained.

On admission, a clinical history was obtained from the child's mother, with special attention being given to antecedents of diarrheal episodes, prior administration of antibiotics and "home remedies," recent growth pattern, and concurrent infectious illnesses. All children had edema of the lower (and some of the upper) extremities, brittle and easily pluckable hair, decreased subcutaneous fat, and plasma concentrations of total proteins and albumin below 5.1 and 3.5 g/dl, respectively. The clinical severity of their edema was separately assessed by two pediatricians and classified on a scale of 1 to 3.

Routine care was provided by the full-time staff of nursing aides of the Clinical Research Center. Temperature and pulse rates were monitored every 4 h during the first 3 wk, and every 12 h thereafter. Nurses recorded and reported clinical observations at the end of the three daily shifts. Treatment for infections and other complications was started immediately upon detection after admission. The Center was attended full-time by a resident physician who examined each patient daily, and by three experienced pediatricians. Suspected infectious illnesses were confirmed by clinical examination and microbiological cultures, and antibiotic therapy and other supportive measures were instituted as indicated during the course of recovery.

Assignment of dietary regimen

On the day of admission, each child was assigned to either the intact milk (IM) or the lactose-hydrolyzed milk (HM) group by a process of *stratified, binary-choice allocation.* By this process, we attempted to match the groups as closely as possible with respect to age, clinical severity, degree of edema, *estimated* weight for height deficit corrected for edema, serum protein concentrations, and history of diarrhea immediately before admission. Thus, the first child was assigned by

binary choice (a coin toss) to a given treatment. If a subsequently admitted child was closely similarly to the first child in terms of the aforementioned criteria, he would be assigned to receive the opposite dietary treatment. If a child did not substantially resemble any previously admitted patient, he was once again assigned by coin toss to receive one or the other dietary formula. The final goal was to complete 10 children with each of the dietary regimens. Thus, when one treatment quota had been filled, the remaining children were all assigned to the other diet. This "matching" of patients was employed simply to encourage the final equivalency of the treatment groups, and not for pairing the subjects' data in the final analyses of the results.

Diets

Meals were prepared in the metabolic kitchen of the Clinical Research Center. They consisted of a liquid formula providing various amounts of protein and carbohydrate, advanced in a step-wise fashion during the first week of the protocol (Table 1). During the first 2 days in the hospital, the children were fed 0.7 g casein and 70 kcal/kg/day. Thereafter, the protein source was milk from a single lot of recently prepared powdered whole milk (Prolac, Guatemala City). The dry milk contained, per 100 g, 4.7 g residual humidity, 6.2 g ash, 27.4 g protein (15.7% nitrogen), 20.5 g fat, and 41.2 g carbohydrate (calculated by difference). The formulas contained milk, sucrose, soybean oil, and a mineral mixture (14). At full strength, 32% of the carbohydrate calories and 16% of total energy was derived from intact (or hydrolyzed) lactose. Table 1 shows their protein and energy delivery. Additional water was provided ad libitum, and the patients received every day vitamins, minerals, and electrolytes in adequate amounts to satisfy the needs and replenish the stores of malnourished children (14). The total daily ration was divided into five equal servings, fed at 3-h intervals between 8 AM and 8 PM. Thus, from day 8 onward, each meal would deliver 1.2 g lactose per kg of body weight. Dietary intakes were measured by differential weighing of the food containers before and after each feeding.

A commercial, food-grade, β-galactosidase from *Kluyveromyces lactis* (LactAid, SugarLo Company, Pleasantville, NJ) was added to the HM formulas at a dose of 1 drop of LactAid per 2.9 g of milk protein, equivalent to 10 drops per liter of fluid cows' milk, as recommended by the manufacturer for >90% lactose hydrolysis. The liquid formula was thoroughly mixed, divided into individual meal servings, and stored in the refrigerator (4 to 6°C) for use 24 to 96 h later. The hydrolytic effect was previously assessed by comparing lactose hydrolysis after adding the enzyme to the complete HM formula, to reconstituted powdered milk alone, and to reconstituted powdered milk combined with the other ingredients of the formula. After 24 h at 4 to 6°C, 93.7, 89.3, and 95.3% hydrolyses were achieved, respectively.

Anthropometric measurements and growth assessments

The children were weighed each morning, before breakfast, on a triple beam balance (Douglas-Homs Co, Burlingame, CA). On admission and every 7 days, the following indices were measured: length; circumferences of the head, mid-arm, and calf; and subcutaneous skinfold thicknesses in the tricipital, subscapular, and paraumbilical regions (Lange calipers, Cambridge, MD). The edema-free weight on admission was calculated from the extrapolation of the lines corresponding to the initial rate of weight-loss due to diuresis of edema fluid and the initial rate of rapid catch-up growth (Fig 1). Total weight gain in 45 days was calculated from this edema-free weight and the mean weight on days 43 to 47. The daily rate of initial, rapid catch-up weight gain was calculated from the slope of the regression line of data points of body weight from the point of deflection after diuresis to the first change in velocity sited from a graphic plot. This linear segment of daily weight increments ranged from 13 to 41 days (25 ± 7, mean ± SD) in various children. Adequacy of weight for height was calculated in relation to the 50th percentile of the Harvard standards (15).

Intestinal functions

Each stool was evaluated in terms of physical characteristics, pH (litmus indicator paper) and the semiquantitative estimation of the concentration of reducing substances (Clinitest tablets, Ames Laboratories, Elkhart, IN) (16). Complete daily fecal output was collected and weighed on days: 2 to 5; 12 to 14; 22 to 24; 32 to 34; and 42 to 44. The children in group HM were fed the IM formula on days 46 to 50, and their stools examined to investigate changes after eating a lactose-free diet for 45 days.

Feces were classified as abnormal when they were liquid, semiliquid, or contained mucus, visible fat, or blood. Inhospital diarrhea was defined when any two of the following criteria were met in the same day: *1*)

TABLE 1
Composition of recovery diets and schedule of advancement of protein and energy content*

Days of treatment	Protein	Energy	Fat	Lactose	Protein source
	g/kg/day	*kcal/kg/day*	*% kcal*	*g/kg/day*	
0–1	0.7	70	30		Casein
2–3	1	100	30	0.1 or 1.5	
4–5	2	120	40	0.3 or 3.0	Intact cows' milk or with
6–7	3	150	40	0.4 or 4.5	>90% lactose hydrolysis
8+	4	150	40	0.6 or 6.0	

* Five daily meals, each with one-fifth of the amounts described. Supplemented with minerals, vitamins, electrolytes and water.

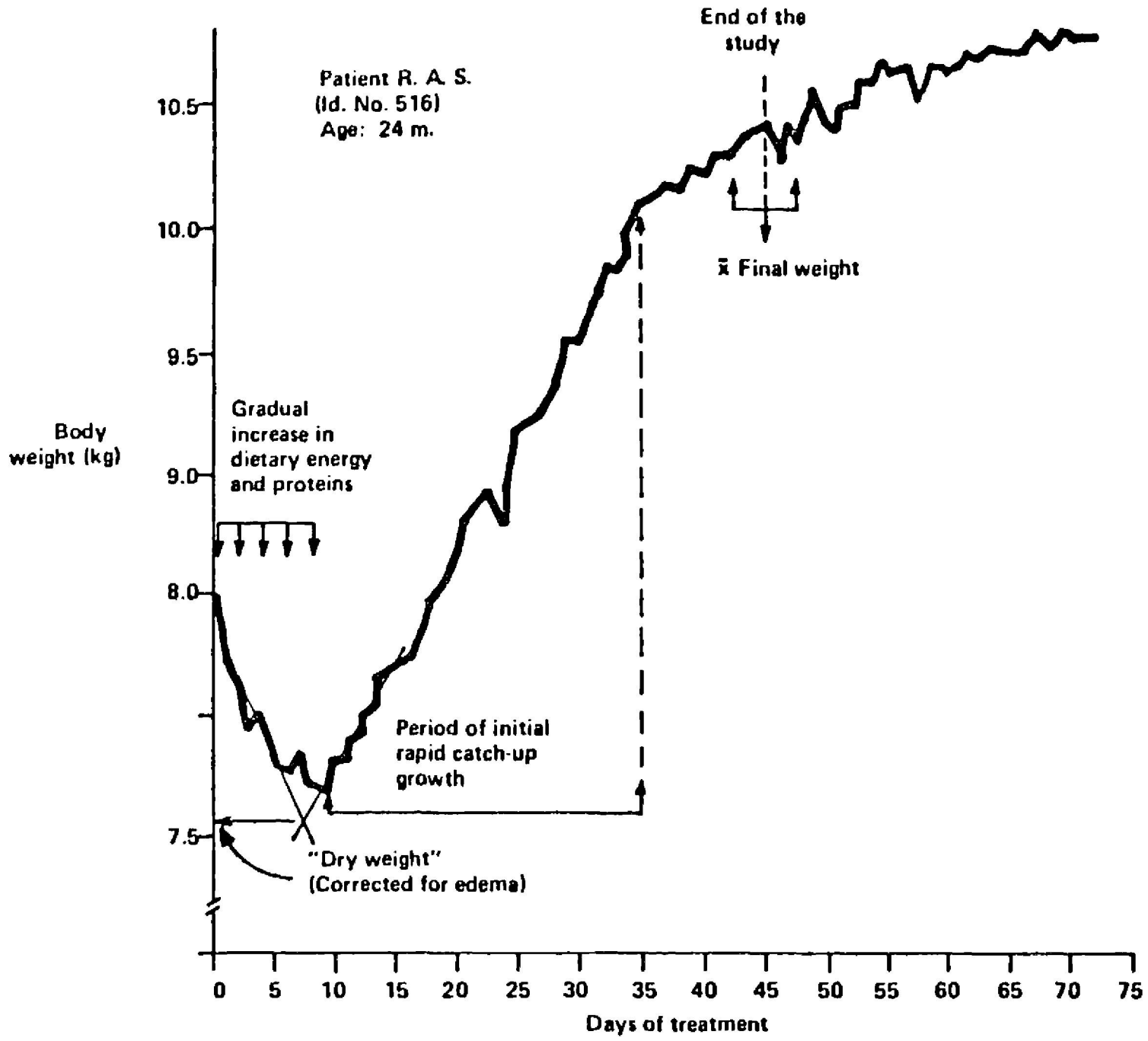

FIG 1. Daily weight chart of a patient treated for edematous protein-energy malnutrition, showing: *1*) the gradual increase in nutrient delivery from 0.7 g protein and 70 kcal to 4 g protein and 150 kcal/kg/day; *2*) the initial weight loss due to loss of edema fluid; *3*) the extrapolations to estimate the patient's weight on admission, corrected for the weight of edema ("dry weight"); *4*) the initial phase of rapid catch-up, which follows a linear function, and the subsequent moderation of weight gain; *5*) the final weight in a 45-day study.

at least half of the stools had abnormal physical characteristics; *2*) more than 150 g of feces excreted in 24 h; *3*) one or more stools had pH below 6.

Other laboratory determinations

A routine battery of tests, which included hematological, biochemical, and bacteriological analyses, was performed on admission, and thereafter as required by each patient's clinical evolution. The concentrations of blood hemoglobin (automated cyanomethemoglobin), plasma proteins (refractometry), and plasma albumin (bromcresol purple) were measured at weekly intervals from blood obtained by fingerprick. Serum iron and iron-binding capacity (pyridyl bisulfite) were measured initially and at the end of the study. Urinary creatinine excretion (automated picrate method) was measured in total urine collected on the same days when feces were collected and weighed. The creatinine-height index (17) was calculated as an indicator of body protein deficit and repletion. The lactose content of the diets was determined by the glucose-oxidase method before and after complete hydrolysis with β-galactosidase.

Statistical analyses

Weight gains were calculated by linear regression analysis. Differences between treatment groups were assessed by analysis of variance and by χ^2 and "Student's" t test (18) as appropriate.

Results

Hydrolysis of lactose in diet formula

Analyses of 15 HM aliquots showed that 91 to 100% of lactose was hydrolyzed after treatment with LactAid.

Comparability of treatment groups

Table 2 shows that on admission the groups of children assigned to either dietary

TABLE 2
Selected comparative data on admission and at the end of the study*

	Admission to INCAP		End of the study	
	Intact milk	Hydrolyzed milk	Intact milk	Hydrolyzed milk
Age (mo)	23 ± 6	21 ± 6	24 ± 6	23 ± 6
Ht (cm)	74.6 ± 3.2	75.6 ± 3.5	76.3 ± 3.1	77.4 ± 3.6
Ht for age (mo)	12 ± 2	12 ± 3	13 ± 2	14 ± 3
Wt (kg)	6.87 ± 0.91†	7.13 ± 1.02†	9.14 ± 1.20	9.62 ± 1.34
Wt for ht (%)‡	70 ± 8†	72 ± 7†	89 ± 8	92 ± 8
Lean arm diameter (mm)§	28 ± 3	29 ± 3	32 ± 2	35 ± 3
Calf circumference (cm)	13.7 ± 1.3	13.9 ± 1.5	15.6 ± 1.4	16.1 ± 1.6
Skinfold thickness (mm) ‖	3.4 ± 1.6	3.1 ± 1.1	6.4 ± 2.1	6.0 ± 1.6
Creatinine-ht index¶	0.63 ± 0.16	0.65 ± 0.12	1.07 ± 0.08	1.06 ± 0.10
Severity of edema**	2.0 ± 0.9	2.1 ± 0.9		
Plasma proteins (g/dl)	4.2 ± 0.6	4.4 ± 0.6	7.1 ± 0.3	7.1 ± 0.5
Serum albumin (g/dl)	2.3 ± 0.8	2.2 ± 0.5	5.4 ± 0.4	5.2 ± 0.3
Hb (g/dl)	9.9 ± 0.7	9.5 ± 2.0	10.6 ± 1.4	10.6 ± 0.8
Serum iron (μg/dl)	55 ± 19	58 ± 19	54 ± 33	57 ± 28
Iron binding capacity (μg/dl)	128 ± 42	125 ± 30	347 ± 21	349 ± 44

* Mean ± SD, 10 children in each group.
† Corrected for weight of edema.
‡ Relative to Harvard standards, where 100% = 50th percentile (20).
§ Corrected for skinfold thickness.
‖ Average of 3 sites: tricipital, subscapular, and parumbilical.
¶ Normal ≥0.90 (22).
** 1 = edema below knees; 2 = edema involving thighs; 3 = edema involving arms.

TABLE 3
Intestinal and absorptive function during the first three days of hospitalization

	Intact milk	Lactose-hydrolyzed milk
Children with diarrhea*	8+	4+
Stools		
No of evacuations (stools/day)	4.0 ± 0.9‡	2.8 ± 1.2‡
% with abnormal characteristics	87 ± 20	68 ± 32
Average daily wt (g/day)	243 ± 174	172 ± 108
Children with acid stools (pH ≤5)	5	4
Children with fecal reducing substances:		
only traces	2	4
+ to ++++	7+	4+

* With 2 or 3 of: *1*) acidic pH; *2*) > 150 g feces/day; *3*) >50% liquid stools or any stool with blood or mucus.
† Groups differ, χ^2, $p < 0.05$.
‡ Means differ, "Student's" *t* test, $p < 0.05$.

treatment were similar in age, severity of PEM, anthropometric characteristics, and biochemical indices of malnutrition. Although they had similar histories of recent or current diarrhea, more children in the group fed IM than that fed HM had abnormal stools and diarrhea starting from the day of admission (Table 3).

Clinical evolution

In addition to the anthropometric changes described below, both groups of patients recovered well and in a similar fashion. The clinical signs and symptoms of acute, severe PEM disappeared at about the same rate in both groups. For example, clinical (ie, "visible") edema disappeared within 3 to 15 days of treatment in group IM (10 ± 4, mean ± SD) and within 4 to 18 days (9 ± 5) in group HM. While in the Clinical Research Center, six children from each group had illnesses that did not interfere with the dietary treatment such as upper respiratory infections, otitis media, tonsilitis, diarrhea, and nonspecific fever. These were treated symptomatically, or with the appropriate antibiotics. The length of time during which the six children in each group were ill was 1 to 11 days (5.8 ± 4.2) in group IM and 2 to 15 days (7.8 ± 4.4) in group HM.

The hematological indices of all children improved, although many had not reached normal hemoglobin concentrations by the end of the study (Table 2), not an unusual finding after 45 days of treating children with severe PEM (19).

Growth and anthropometric recovery

The recovery of weight-for-height was parallel with the two dietary treatments, with no differences registered at any interval (Fig 2). Not all children, however, had reached a status of 91% of the standard by the end of the 45-day protocol period (Fig 3), but fully half of both cohorts had attained this landmark of recuperation. Not only were the mean final outcomes with respect to ponderal and linear growth and to recovery of anthropometric indices equivalent in both groups (Table 2, last two columns), but the distribution of the data for each parameter was also closely similar (Fig 4). Of special note is the rate of weight gain during the initial period of catch-up growth: the 8.5 ± 0.9 and 8.7 ± 1.5 g/kg/day of the IM and HM groups, respectively, are not different.

Body proteins

The restoration of total plasma proteins and serum albumin was rapid, and followed a parallel, identical trajectory without regard to the assignment of diet (Fig 5). After 3 wk of treatment, mean levels of both had returned to the normal range. The recovery of transferrin levels, another index of visceral protein, was adequate by the end of the study, as indicated by the increase in total iron-binding capacity (Table 2). Lean body mass, as estimated by the creatinine-height index, recovered more slowly, but, by the end of the 45 days, all patients in both cohorts had a urinary creatinine excretion appropriate to their height (Fig 3).

Stool characteristics and diarrhea

Table 3 shows that more children had diarrhea and fecal reducing substances dur-

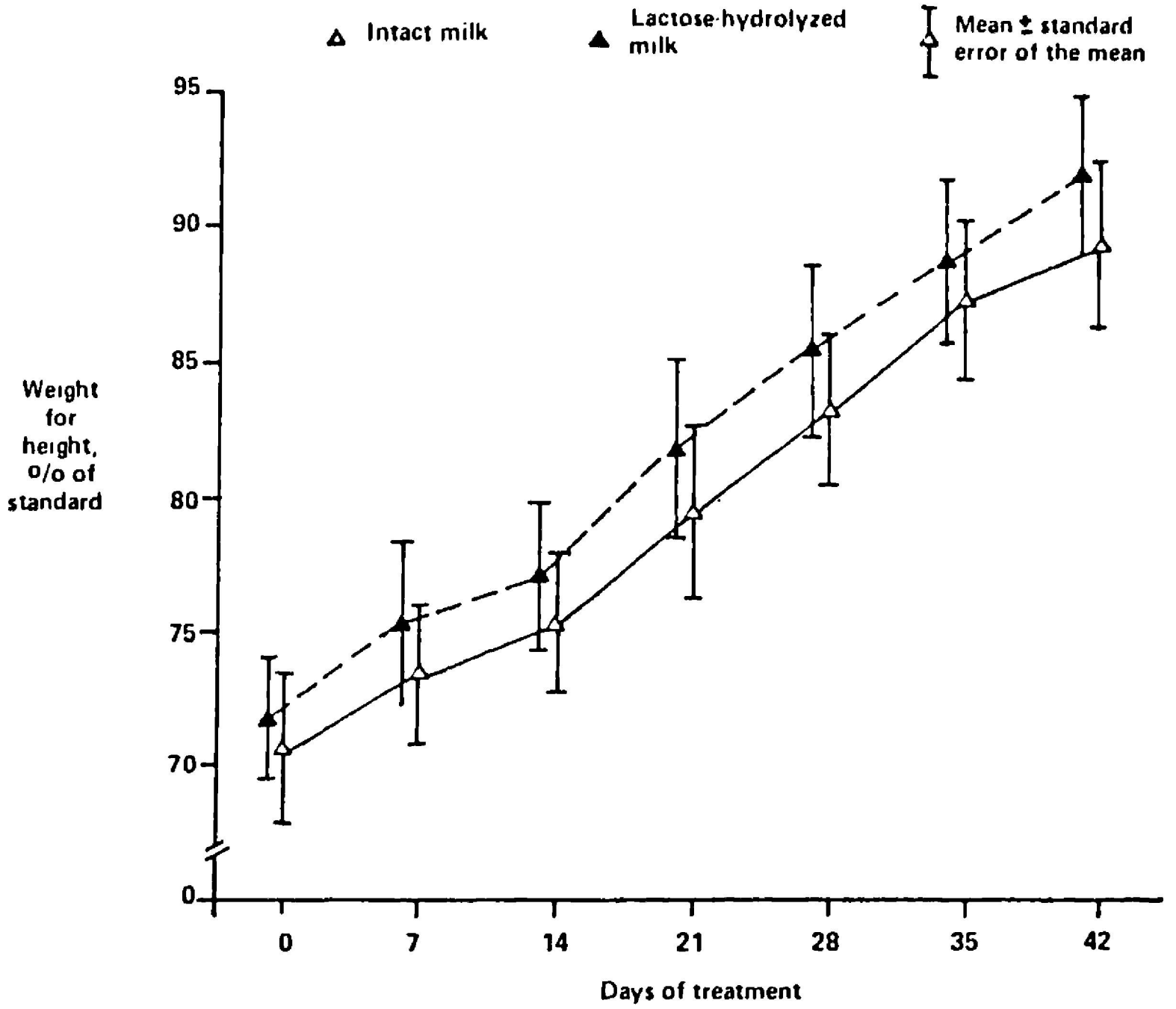

FIG 2. Weight expected for height, as percentage of the reference (median of the Harvard standards), of children treated with intact or lactose-hydrolyzed milk diets. Mean ± SEM of weekly measurements; 10 children in each group.

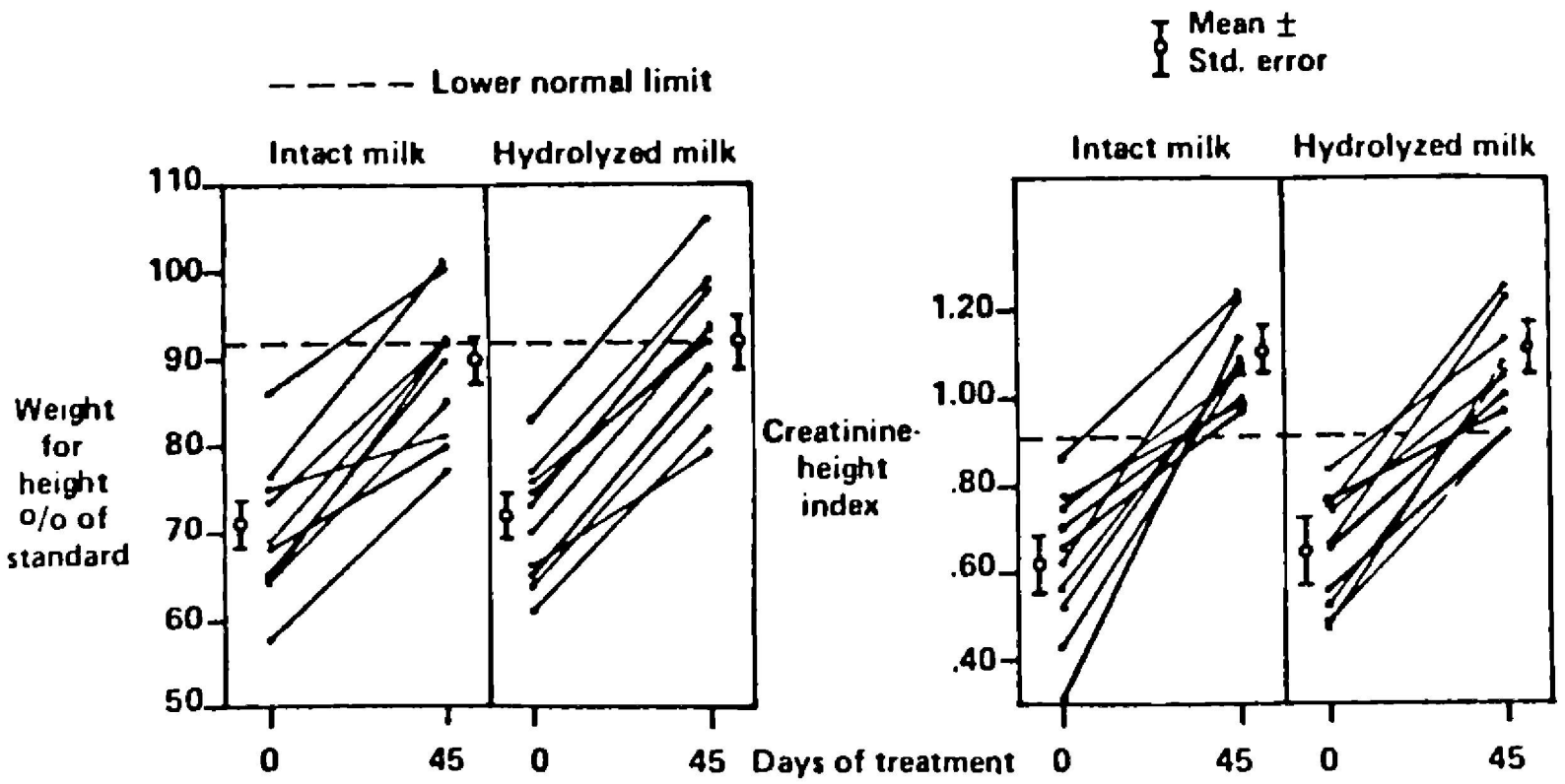

FIG 3. Individual and group (mean ± SEM) changes in two indicators of nutritional recovery after 45 days of treatment with intact or lactose-hydrolyzed milk diets. A minimum of 92% in weight for height and 0.90 in creatinine-height index are considered normal.

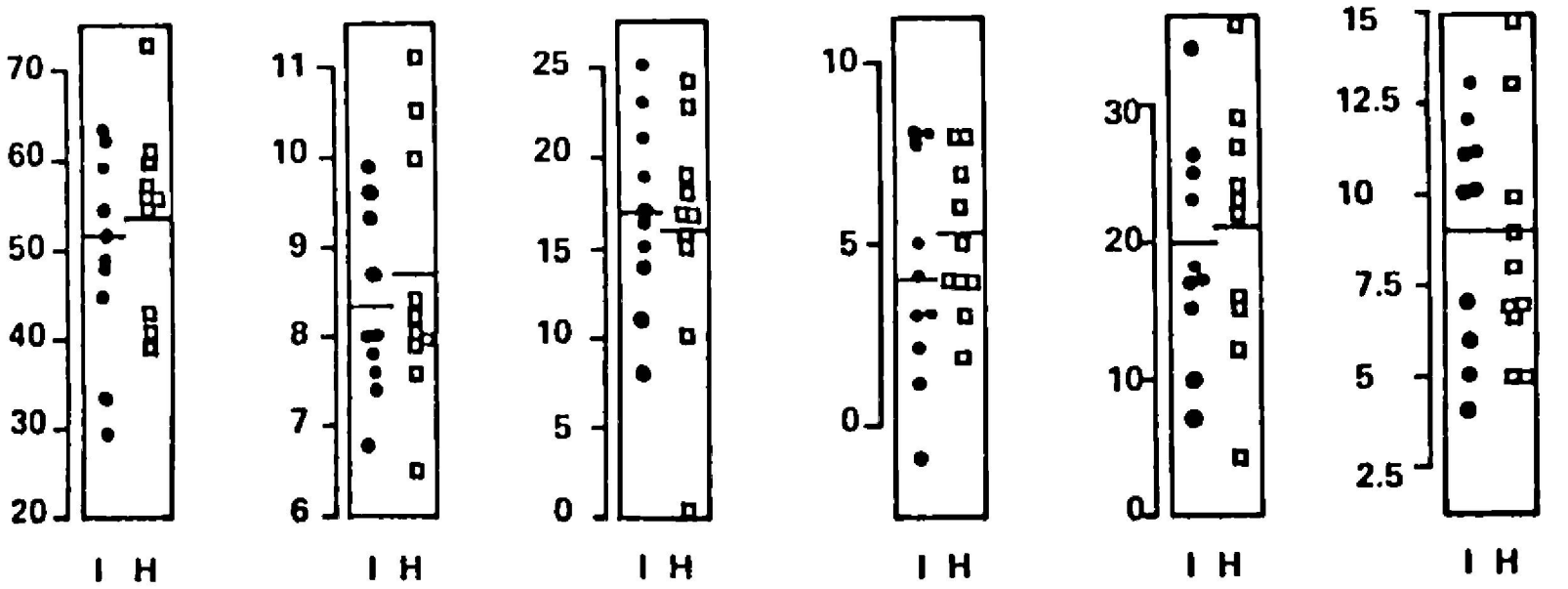

FIG 4. Individual and group (mean) changes in indices of growth after 6 weeks of treatment with intact (*I*) or lactose-hydrolzyed (*H*) milk formulas.

ing the initial 3 days of treatment with IM than with HM. The number of daily stools was also greater in the IM group, although the proportion with abnormal physical characteristics and total fecal weight were similar in both groups. It should be recognized that during this initial postadmission period, no lactose was fed on day 1 and the amount fed on the following 2 days was only 0.3 g/kg/meal, which was one-fourth of the carbohydrate fed from day 8 onward.

Diarrhea disappeared or improved without specific treatment in both groups as nutritional recovery progressed, and no patient required special hydration measures. Stool characteristics and incidence of diarrhea were similar with both treatments at each of the four subsequent metabolic balance periods. Large or abnormal fecal evacuations were not infrequent in two children, but their growth and nutritional recovery were satisfactory. When the children in the HM group were fed intact milk-based formula on days 46 to 50, there were no

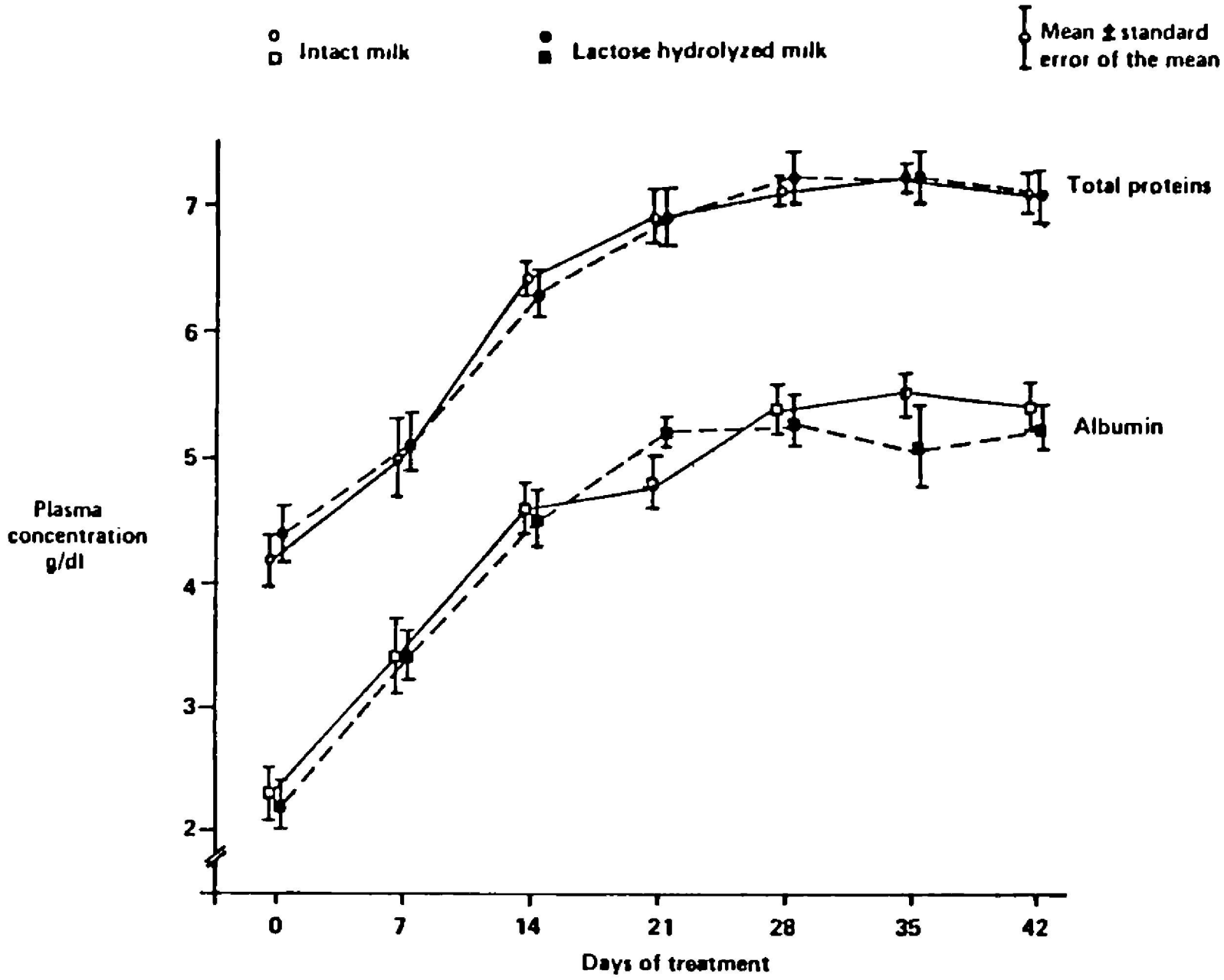

FIG 5. Concentrations of total plasma proteins and serum albumin of children treated with intact or lactose-hydrolyzed milk formulas. Mean ± SEM of weekly measurements; 10 children in each group.

changes in the stool characteristics compared to their last balance period on the hydrolyzed formula.

Discussion

There is no doubt that the combination of nutritional injury and infectious insults reduces the capacity of the intestinal mucosa to digest lactose in severe PEM (1). The use of milk with low lactose content in malnourished populations has led to contradictory and inconclusive results. Zaal (20) reported that lactose-hydrolyzed milk was inferior to whole milk in its effect on growth of school-aged black children in Surinam. The methods of storage and reconstitution of the dried milk used in this study, however, might have altered the quality of the protein in the lactose-hydrolyzed milk via the Maillard reaction. Evaluation of lactose-containing foods in young children with severe PEM syndromes has been conducted in Australia (21, 22), Kenya (23), and Biafra (24). The limitation of these previous attempts to compare lactose-containing and lactose-free diets in the recovery of children with PEM-related to the brief length of observation (21–23), the noncomparability of treatment groups (21, 22), or the noncomparability of nutritional quality of therapeutic diets (24). We addressed these problems by: *1*) instituting a 45-day protocol to permit the quantification of rapid catch-up and overall growth, perhaps the two most sensitive indices of the nutritional adequacy of a recovery regimen; *2*) feeding identical formulas to the two cohorts, except for the addition of a food-grade β-galactosidase to the diet of one (HM) group which effectively hydrolyzed over 90% if the lactose; and *3*) allocating the patients to the alternative dietary

treatments in such a way that the two groups had equivalent characteristics and antecedents of illness at the onset of the feeding trial.

We found a complete overlap of both treatment groups with respect to clinical features, weight gain and other anthropometric improvements, body protein repletion, and overall nutritional recovery. The mean daily weight gain during the initial phase of rapid, catch-up growth was about 13 times greater than the average of healthy children of similar height and age. The difference in stool characteristics observed during the first few days of treatment were not clearly related to the intact milk intake. In any event, the subjects experienced no profuse diarrhea, no impairment of hydration requiring special rehydration measures, and absorption and retention of nutrients was satisfactory (13).

There is no reason to believe that our group of patients did not share the same characteristics of intestinal lactase activity as reported for other series of children with the same type and severity of PEM. The criteria for children as lactose-malabsorbers in other studies has generally been an intestinal mucosal biopsy or a response to a *supra*physiological challenge with lactose in aqueous solution. However, the most reasonable dose and form of lactose with which to assess the absorptive status of malnourished children is probably that which is contained in the amount of milk that provides the protein requirements during recovery; our routine meal delivery of lactose was precisely that amount.

The *gradual* introduction of proteins and energy into the diet of severely malnourished children is an important feature of any well-conceived recovery regimen (14, 25), as the metabolic challenge induced by feeding too much, too soon, may disrupt the labile homeostatic balance of children with PEM (26). In fact, rapid refeeding increases the risk of mortality (27). It is possible that the more conservative approach followed in our dietary therapy reduced the probability of untoward effects of lactose intake in children with a degree of lactase deficiency. If our findings in relation to diarrhea at the beginning of treatment were in fact related to milk intake, they would suggest that the intestine of the recently admitted child with severe PEM might be exquisitely sensitive to lactose. The gradual increase in the delivery of milk protein and therefore of lactose, might result in some form of intestinal adaptation or enzymatic rehabilitation, such that by the time the diet has been appropriately advanced to therapeutic levels, the intestine handles the lactose content of the IM formula as well as the lactose-free carbohydrates of the HM ration.

A prospective follow-up of children convalescing from persistent diarrhea reported from Houston (28, 29), found an inferior immediate growth response in the cohort of patients assigned to receive a lactose-containing formula, as compared to the group fed a soy protein and sucrose regimen. It is difficult to judge whether the extent of the intestinal lesion in that study prevented rapid normalization of lactase activity, or whether the protein source was a factor in the differential response. Such results, however, could suggest that some malnourished patients with intestinal complications might not tolerate lactose during the occurrence or convalescence of the diarrheal disease. In those PEM patients—as in children with severe lactase deficiency and intolerance to lactose following intestinal injury—the reduction of the disaccharide content of milk can be indicated to preserve the use of this highly digestible protein source.

Our data can be interpreted, however, as indicating that lactose hydrolysis or the use of lactose-free diets, are not necessary for the *routine* dietary therapy for preschool children with severe edematous PEM, when sound principles of dietary management and gradual advancement of nutrient density are followed. The additional cost of eliminating the lactose from milk prior to its use for the rehabilitation of malnourished children might have been justified had the clear superiority of our HM regimen been demonstrated. In the absence of such a result, however, we must conclude that available supplies of milk can be used intact to provide the *protein-base* for recovery diets for severely malnourished children, even in the early, postadmission period of recuperation.

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