0031-3998/91/2906-0594$03.00/0
PEDIATRIC RESEARCH

Vol. 29, No. 6, 1991
Printed in U.S.A.

Refeeding Enhances Intestinal Repair during an Acute Enteritis in Infant Rabbits Subjected to Protein-Energy Malnutrition

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ABSTRACT. We examined the effects of refeeding during an acute bacterial enteritis on small intestinal repair in infant rabbits subjected to protein-energy malnutrition and in noninfected and infected dietary controls. Malnutrition was induced by litter expansion at 7 d of age. Randomly selected litters from both dietary groups were infected on d 17 with *Yersinia enterocolotica*. Inflammation and intestinal damage were observed in the jejunum and ileum at the "acute stage" of infection in 23-d-old animals from both dietary groups, as evidenced by an inflammatory infiltrate, blunted villi, and reduced disaccharidase activities. In addition, ileal glucose-stimulated Na^+ absorption was depressed. On d 24, a 7-d period of *ad libitum* refeeding of breast milk and rabbit feed was initiated in randomly selected litters of infected-malnourished animals and all dietary controls. Mucosal repair was nearly complete at 31 d of age in infected dietary controls and in the infected-malnourished animals that were refed, as demonstrated by the recovery of segmental mucosal mass and ileal glucose-stimulated Na^+ transport in association with the resolution of inflammation and diarrhea. Only mucosal disaccharidase activities remain depressed. In contrast, in 31-d-old infected-malnourished animals subjected to ongoing nutrient deprivation, severe intestinal damage persisted as evidenced by increased mortality, ongoing intestinal inflammation, mucosal hypoplasia, depressed disaccharidase activities, and reduced glucose-stimulated Na^+ transport. We conclude that a refeeding regimen introduced during an acute bacterial enteritis is well tolerated and promotes recovery of intestinal mass, structure, and function in malnourished infant rabbits and dietary controls. (*Pediatr Res* 29: 594–600, 1991)

Abbreviations

PD, transepithelial potential difference
I_{sc}, short-circuit current
J_{ms}, mucosal to serosal sodium flux
J_{sm}, serosal to mucosal sodium flux
J_{net}, net sodium flux

Recent clinical studies have demonstrated that the duration of an acute diarrheal illness is prolonged in the malnourished infant (1–3). Investigators have also shown that during an acute enteric illness, early nutritional intervention of nourished infants is well tolerated. A rapid return to adequate nutritional intake results in reduced weight loss but does not alter the duration or severity of the diarrheal illness (4–13). Early refeeding also may prevent fatal hypoglycemia, a recently recognized complication of acute diarrheal illness in infants (14). However, the effects of intensive oral nutritional support on the intestinal repair of the acute damage caused by an enteric infection in well-nourished and malnourished infants remains to be determined (15). Also, whether the malnourished infant with enteritis can tolerate early refeeding is unknown (15).

We established a model of protein-energy malnutrition in suckling infant rabbits and used it to demonstrate that nutrient deprivation reduces small intestinal mass, impairs mucosal growth, delays maturation and enhances ileal glucose-stimulated Na^+ transport (16–18). Subsequent research demonstrated that the intestinal injury suffered by the malnourished infant infected with an enteric pathogen is more severe and more prolonged compared to that sustained by infected dietary controls (17). We have also shown that a brief period of refeeding of the noninfected-malnourished infant triggers rapid recovery of small intestinal growth, development, structure, and function (19). The present study was undertaken to assess the role of prompt intensive nutritional intervention in promoting small intestinal recovery from the mucosal damage induced by an acute enteritis in infant rabbits subjected to chronic postnatal protein-energy malnutrition.

MATERIALS AND METHODS

Experimental design. Does and litters of New Zealand White rabbits were quarantined at 4 d postpartum and observed for 3 d to ensure appropriate feeding behavior and good health. All animal experimentation was approved by the University of Calgary Animal Care Committee in accordance with guidelines established by the Canadian Council on Animal Care. Protein-energy malnutrition was induced in the experimental group by combining two litters at 7 d of age to increase litter size to 13 to 16 kits (16). To ensure maternal health and prevent access to solid food, does were alternated at 24-h intervals. Does caged with pups had access to water only. Control litters were derived by combining two litters then reducing litter size to six to eight animals. These does and kits were permitted access to rabbit feed throughout the study. All kits were allowed free access to water for the duration of the study. On d 17, after an 18-h fast, selected litters from both dietary groups were infected by orogastric intubation with *Yersinia enterocolitica* strain MCH 700 S (serotype 0:3), originally isolated from a patient with diarrhea (20). Kits were infected with 10^9 organisms suspended in 1 mL of 10% $NaHCO_3$ solution. Noninfected kits from both dietary groups also underwent the 18-h fast. These manipulations resulted in four groups: noninfected and infected rabbits receiving

Received September 24, 1990; accepted January 24, 1991.
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Supported by the Intestinal Disease Research Unit, the Medical Research Council of Canada, and the Canadian Foundation for Ileitis and Colitis. J.D.B. is the recipient of a Clinical Investigatorship award from the Alberta Heritage Foundation for Medical Research.

the control diet and noninfected and infected nutrient-deprived rabbits (Fig. 1). To define the impact of malnutrition and the enteritis on intestinal structure and function, randomly selected kits from each group were killed on d 23 of life, 6 d postinfection at the height of the illness. On d 24, randomly selected noninfected or infected malnourished litters were reduced in size to six pups to allow increased nutrient intake or nutritional rehabilitation. These kits were allowed to consume breast milk and rabbit feed *ad libitum*. On d 31 or 14 d postinfection, the "convalescent" phase, six groups of animals were studied: noninfected and infected dietary controls; noninfected and infected malnourished animals; and noninfected and infected malnourished groups who had undergone nutritional rehabilitation for 7 d from d 24 to 31 (Fig. 1).

Before infection, animals were weighed every 3 d; after infection, weight gain, clinical status, and presence of diarrhea were assessed daily. On the day of study, blood was collected for measurement of total protein and kits were killed by an intracardiac injection of pentabarbitol sodium (65 mg/kg).

The small intestine from the ligament of Treitz to the most proximal attachment of the mesoappendix was removed and unstretched segments were measured. A 12-cm segment of ileum ending at the mesoappendix was removed, flushed with cold isotonic saline, and used for studies of Na^+ transport and electrical activity. Two additional 12-cm segments were removed: a proximal segment beginning at the ligament of Treitz and a distal segment just proximal to the segment used for transport studies. These latter segments were flushed and weighed; a 2-cm segment was removed for morphology studies and mucosa was scraped from the remaining 10 cm, weighed, homogenized in 2.5 mM EDTA (100 mg/mL) at pH 7.4 and frozen at −80°C for later estimation of mucosal enzyme activities, protein, and DNA content. Swabs obtained from the jejunum and ileum of both noninfected and infected animals were plated onto Salmonella-Shigella media.

Mucosal morphology. Tissue for light microscopy was fixed in 4% phosphate-buffered formalin, dehydrated, imbedded in paraffin wax, sectioned, and stained with hemotoxylin and eosin. Coded sections were examined by one observer without prior identification of the section. Villus height and crypt death were measured in 10–12 properly oriented crypt-villus units per segment using a calibrated micrometer.

Mucosal enzyme activities. Homogenates were assayed for sucrase and lactase activities by the method of Dahlqvist (21) and Na-K-ATPase activity by the method of Kelly *et al.* (22), and all results were expressed as $U \cdot cm^{-1}$. Protein content was measured by the method of Lowry *et al.* (23) and DNA content by the method of Hinegardner (24) using thymus DNA (Sigma Chemical Co., St. Louis, MO) as a standard.

Ileal transport and electrical activities. For ion transport studies, the mucosa of the distal segment was stripped of its overlying muscle and serosa and four adjacent segments were mounted in short-circuited Ussing chambers, exposing a 0.4-cm^2 surface area to 10 mL of oxygenated Krebs-bicarbonate buffer at 37°C and pH 6.4 ± 0.1 (25). Glucose (10 mM) was added to the serosal side and mannitol (10 mM) to the mucosal side. Ten μCi ^{22}Na (New England Nuclear, Montreal, Quebec, Canada) was added to either the mucosal or serosal side of each tissue segment. The spontaneous transepithelial PD was determined and the tissue clamped at zero voltage by continuously introducing an appropriate I_{sc} with an automatic voltage clamp (DVC 1000; World Precision Instruments, New Haven, CT), except for 15–20 s every 5 min when open PD was measured. Conductance was calculated from PD and I_{sc} according to Ohm's law (26). After a 15-min equilibration period, samples for Na^+ fluxes were obtained from the mucosal and serosal chambers at 5-min intervals for 15 min. Immediately after completion of the basal period, glucose with or without mannitol (final concentration 30 mM glucose and 10 mM mannitol) was added to both sides of the tissue and after 15 min of equilibration, flux measurements were repeated. Tissue pairs were discarded if conductances varied by more than 30%. Steady state unidirectional J_{ms}, J_{sm}, and J_{net} Na^+ fluxes ($\mu Eq \cdot cm^{-1} \cdot h^{-1}$) were calculated in paired tissues in the absence of an electrochemical gradient across the tissue by measuring three consecutive 5-min fluxes and one overall 15-min flux during each of the two periods.

Data are expressed as mean ± SEM and statistical comparisons were made using one-way analysis of variance. Mortality data were analyzed by the χ^2 method.

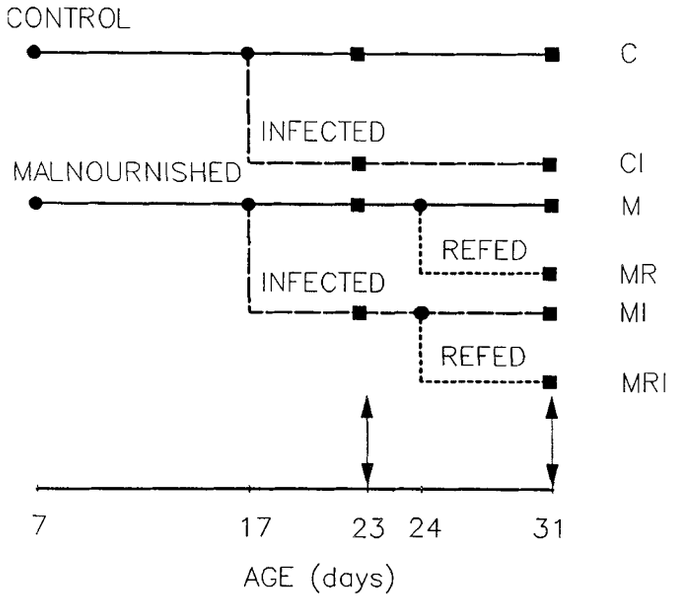

Fig. 1. Flow diagram depicting the ages of dietary manipulation; nfection with *Y. enterocolitica* on d 17; and study (*double arrows* and ■) for each dietary group where applicable. On the *far right* are the ymbols used for each group: control (*C*), control-infected (*CI*), malnourished (*M*), malnourished-refed (*MR*), malnourished-infected (*MI*), nalnourished-refed-infected (*MRI*).

RESULTS

Clinical results. The number of animals studied for each group is shown in Figure 2. Initial mean body weight for the dietary groups did not differ on d 7 when litters were combined (control 136 ± 6 g, malnourished 134 ± 6 g, malnourished-refed 138 ± 4 g). On d 16, the day before the infection of randomly selected litters with *Y. enterocolitica*, the mean body weight of both the malnourished group (206 ± 5 g) and the group of malnourished animals that would later be refed (208 ± 7 g) was significantly less ($p < 0.01$) than that of dietary controls (287 ± 7 g). The weight of the kits to be infected and the noninfected kits within each respective dietary group did not differ. On d 23 and 31, the noninfected and infected malnourished animals weighed significantly less than dietary controls (Fig. 2). However, on d 31 after 7 d of refeeding, both the infected and the noninfected malnourished-refed groups weighed significantly more than the groups subjected to ongoing malnutrition (Fig. 2). The mean body weight of the noninfected-malnourished-refed group, which had recovered to the level of dietary controls, was significantly greater than that of the infected-malnourished-refed group ($p < 0.001$).

Most of the infected rabbits developed a mild diarrheal illness lasting 2–3 d, which began 4–6 d after infection. However, five infected-malnourished animals developed severe persistent diarrhea and subsequent dehydration and died between 5 and 10 d after infection. Mortality was significantly greater ($p < 0.05$) in this group than in the infected dietary control or the infected-malnourished-refed groups. Data on the animals that died are not included in the analyses summarized below. When the intestine was examined at the "acute phase" of the illness on d

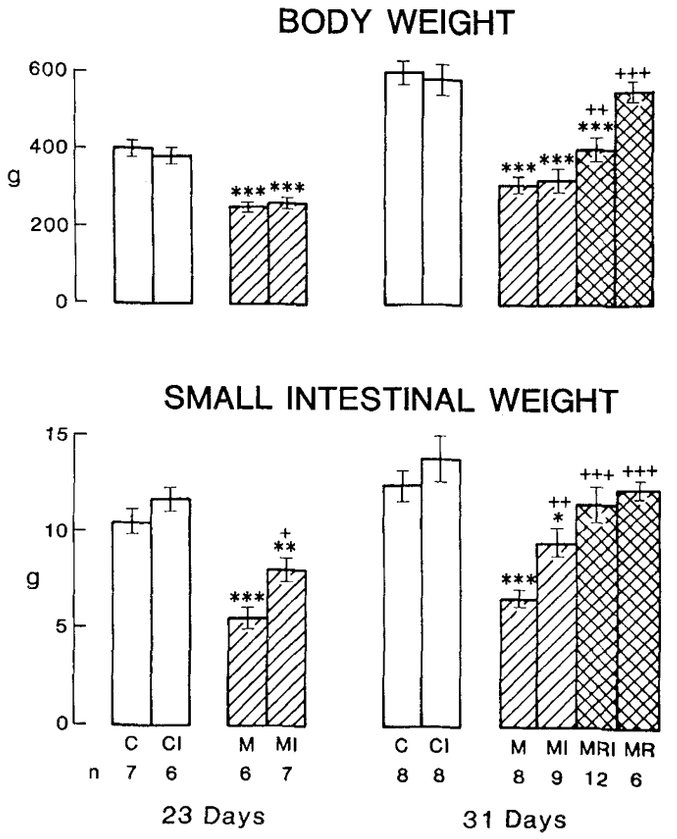

Fig. 2. Mean body and total small intestine wt (g) of noninfected and infected (I) controls (*C*, □), malnourished (*M*, ▨) and malnourished-refed (*MR*, ▩) rabbits at age in days, where *n* is the number of animals (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ comparing CI, M, MI, MRI, or MR to C; +$p < 0.05$, ++$p < 0.01$, +++ $p < 0.001$ comparing MI, MRI, or MR to M).

23, all infected animals in both dietary groups demonstrated evidence of a fluid-filled intestine. Subserosal abscesses were present throughout the small intestine and cecum, with the heaviest concentration in the distal ileum. On d 23 in the infected controls, five of six jejunal and all ileal cultures were positive for *Y. enterocolitica*; in the infected-malnourished group, six of seven jejunal and all ileal cultures were positive. On d 31 in infected animals, jejunal cultures from three of eight control, six of nine malnourished, and 10 of 12 malnourished-refed animals and all ileal cultures were positive. No enteric pathogens were cultured and no diarrhea was observed in noninfected animals of any dietary group. Serum total proteins did not differ between dietary groups at either age (data not shown).

Mucosal morphology (Fig. 3). Malnutrition alone significantly decreased crypt-villus lengths in both jejunum and ileum at 23 and 31 d of age compared to dietary controls. Infection of malnourished animals caused a further significant decrease in villus height and an increase in ileal crypt depth on d 23 or 6 d postinfection. This was accompanied by an inflammatory infiltrate and numerous microabscesses that contained an abundance of polymorphonuclear leukocytes. Provision of 7 d of nutritional rehabilitation to 31-d-old infected-malnourished animals stimulated repair of the injured mucosa. Jejunal and ileal villus heights in the infected-malnourished-refed group did not differ from dietary controls and were significantly greater compared to those of the noninfected-malnourished animals. Crypt depths of both segments remained elongated and mild inflammation was observed in only two of 12 jejunal or ileal segments. In contrast to the recovery observed in the 31-d-old infected-malnourished-refed group, significant jejunal and ileal villus blunting and crypt elongation persisted in the 31-d-old infected animals subjected to ongoing malnutrition. This was associated with the ongoing presence of a severe inflammatory infiltrate and microabscesses.

In control diet animals examined 6 d postinfection on d 23, jejunal villus blunting and jejunal and ileal crypt lengthening, as well as a striking inflammatory infiltrate in both segments, were observed. As with the infected-malnourished-refed group, the jejunal and ileal injury had completely recovered and inflammation had resolved in the 31-d-old infected controls. In the noninfected-malnourished group that was refed for 7 d, villus length and crypt depth recovered to levels similar to those of dietary controls at 31 d of age and were significantly longer than those of animals subjected to ongoing malnutrition. No intestinal inflammation was noted in the noninfected animals of the three dietary groups.

Intestinal weight, protein, and DNA content. Total small intestine weight was significantly decreased in the noninfected and infected malnourished groups compared to dietary controls (Fig. 2). In the infected-malnourished group, small intestine weight was greater than in the noninfected-malnourished group, but remained less than that of 23- and 31-d-old dietary controls. In 31-d-old noninfected and infected malnourished animals that had been refed, small intestine weight recovered to that of dietary controls and was significantly elevated compared to the noninfected-malnourished group. Total small intestine weight did not differ between infected and noninfected dietary controls at either time period. The mucosal weight of jejunal and ileal segments paralleled total small intestine weight (data not shown).

Malnutrition alone significantly decreased mucosal protein and DNA content in the ileum compared to dietary controls on d 23 and 31 (Fig. 4). In the infected-malnourished animals, ileal mucosal protein at both ages and ileal mucosal DNA at 23 d were significantly less than dietary controls. Seven d of nutritional rehabilitation provided to 31-d-old infected-malnourished animals initiated a complete recovery of ileal mucosal protein and DNA content to the level of dietary controls.

In infected dietary controls at 23 and 31 d of age, ileal mucosal protein and DNA content remained similar to that of noninfected dietary controls (Fig. 4). The 7-d refeeding period of noninfected-malnourished animals also initiated a complete recovery of ileal mucosal protein and DNA content to the level of dietary controls. Mucosal protein and DNA content in the jejunum did not differ from ileal data for each repetitive dietary group (data not shown).

Mucosal enzyme activities (Fig. 5). Malnutrition by itself caused a significant decline in ileal sucrase at d 31 and Na-K-ATPase activities at both ages compared to noninfected dietary controls. Infection of malnourished animals triggered a further decrease in ileal lactase at 6 d postinfection. Nutritional rehabilitation of the 31-d-old infected-malnourished animals stimulated recovery of Na-K-ATPase activity in the ileum to the level of dietary controls. Lactase activity recovered to the level of the noninfected-malnourished group, but both lactase and sucrase activities remained depressed compared to dietary controls. In contrast, by 14 d postinfection in the group subjected to persistent malnutrition, ileal lactase, sucrase, and Na-K-ATPase activities all remained depressed compared to dietary controls.

In infected animals receiving a normal diet, ileal lactase and sucrase activities were significantly depressed at 6 (d 23) and 14 (d 31) d postinfection compared to noninfected controls. Mucosal Na-K-ATPase activities did not differ between noninfected and infected animals receiving a normal diet. Refeeding of 31-d-old noninfected-malnourished kits stimulated recovery of ileal Na-K-ATPase activity to dietary control levels. In addition, ileal sucrase activity was significantly increased in the noninfected-malnourished-refed group compared to the group subjected to persistent malnutrition.

Jejunal enzyme activities paralleled those in the ileum for each study group with the exception of lactase activity, which remained significantly depressed ($p < 0.01$) at 31 d of age in both the malnourished-infected and the malnourished-infected-refed

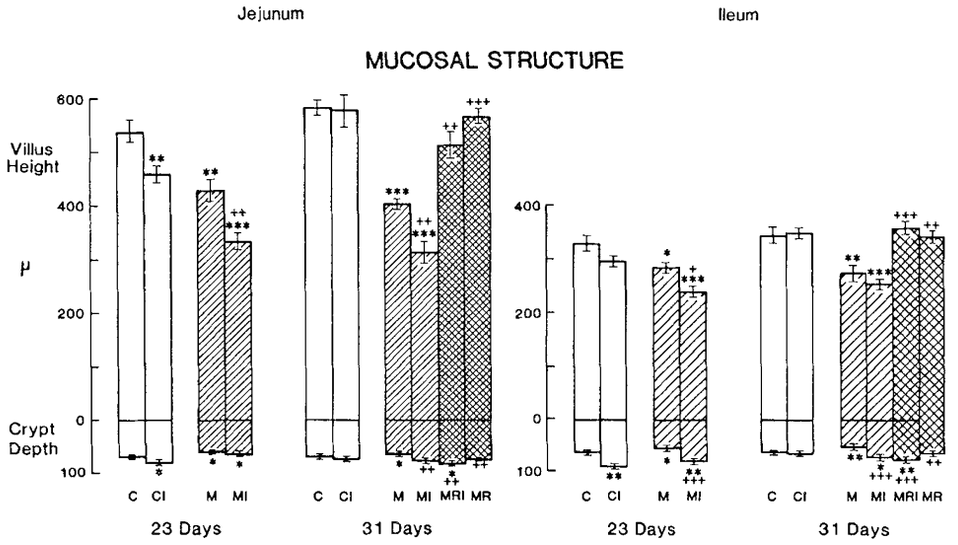

Fig. 3. Jejunal and ileal villus height and crypt depth in μm. Abbreviations and symbols are the same as those used in Figure 2.

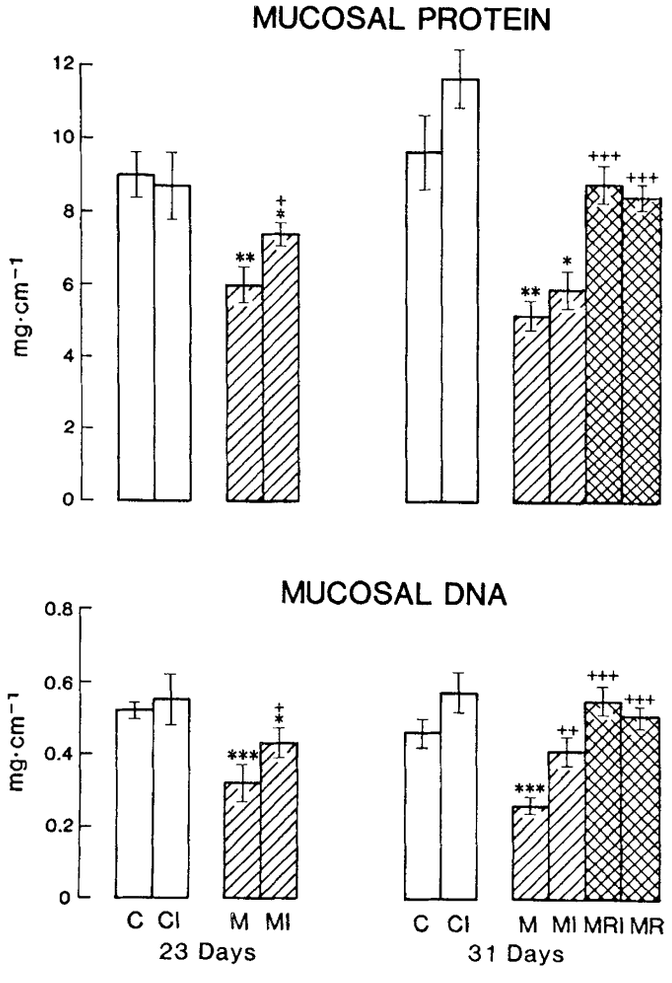

Fig. 4. Ileal segmental mucosal protein and DNA content in mg·m^{-1}. Abbreviations and symbols are the same as those used in Figure 2.

groups compared to the noninfected-malnourished and dietary control groups (data not shown).

Ileal sodium transport and electrical activity. Table 1 summarizes unidirectional and net ileal Na^+ fluxes and electrical activity for each study group measured under basal conditions and after the addition of 30 mM glucose. At both ages in all the noninfected dietary control, malnourished, and malnourished-refed groups, the addition of glucose significantly stimulated J_{ms}, J_{net}, I_{sc}, and PD above basal levels. However, by d 31 in the noninfected-malnourished group, the increase in net Na^+ absorption (ΔJ_{net}) stimulated by the addition of glucose was significantly enhanced compared to the control and the malnourished-refed groups (Fig. 6).

In malnourished animals 6 d after infection, the response to glucose was blunted. On d 23, the addition of glucose failed to stimulate J_{ms}, J_{net}, I_{sc}, and PD (Table 1) and ΔJ_{net} was significantly depressed (Fig. 6). Seven d of nutritional rehabilitation provided to 31-d-old infected-malnourished animals initiated complete recovery of glucose absorption as evidenced by significant increases in J_{ms}, J_{net}, I_{sc}, PD, and ΔJ_{net}. In contrast, in 31-d-old infected animals subjected to continued malnutrition, depression of glucose-stimulated Na^+ transport persisted. Glucose still did not stimulate J_{ms}, J_{net}, I_{sc}, PD, or ΔJ_{net} in these malnourished animals that were 14 d postinfection.

In infected dietary controls 6 d after infection, the response to glucose was blunted in a similar manner to that observed in the infected-malnourished group. By d 31 in the infected dietary controls, glucose once again stimulated a significant increase in sodium absorption, as evidenced by increases in J_{ms}, J_{net}, I_{sc}, PD, and ΔJ_{net}. This response was similar to that observed in the infected-malnourished-refed group.

DISCUSSION

In the developing infant, the intestine is immature and nutrient reserves are marginal. Thus, infants are especially susceptible to enteric damage caused by an acute infectious enteritis. One of the major concerns about providing nutritional rehabilitation to the malnourished infant during an acute diarrheal illness is that the severe intestinal damage caused by the enteritis and malnutrition will retard the digestion and absorption of the supplemental nutrients, especially carbohydrates (27). The maldigestion and malabsorption of sugars may cause an osmotic diarrhea that can further dehydrate the infant, impair nutrient absorption, and diminish the infant's chance for recovery. The purpose of our study was to determine how the injured intestine of the malnourished infant responds to the provision of supplemental nutrition introduced during the height of an acute enteric infection.

Kits were examined at 23 d of age to determine the extent of intestinal injury due to either malnutrition, acute enteritis, or both. The decreased nutrient intake caused by litter expansion induced profound protein-energy malnutrition. By d 23, the

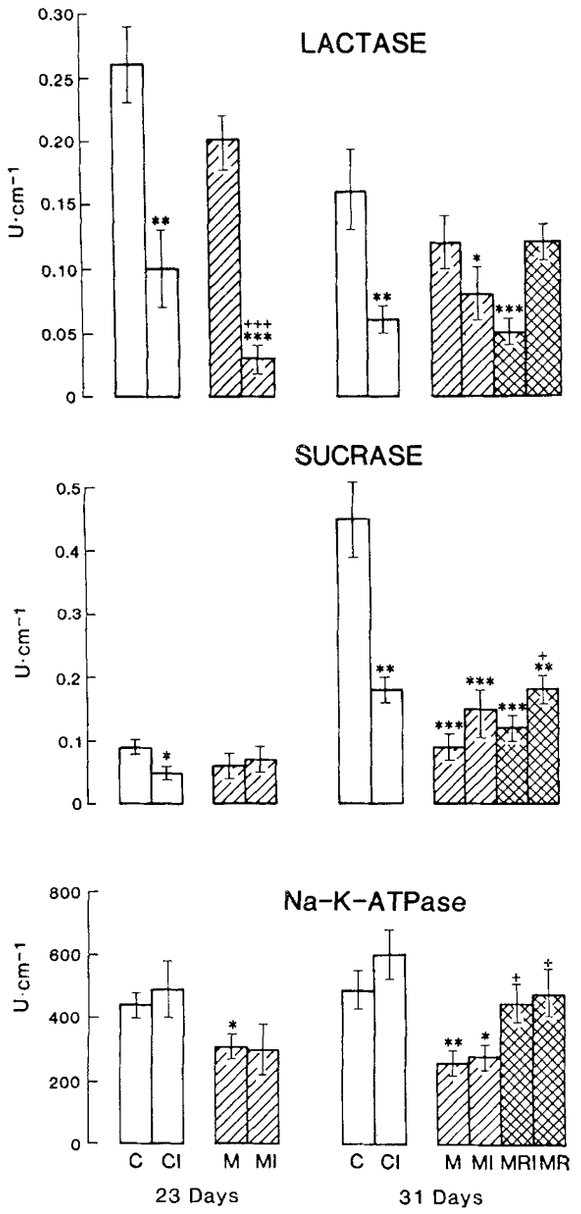

Fig. 5. Ileal mucosal lactase, sucrase, and Na-K-ATPase activities in $U \cdot cm^{-1}$. Abbreviations and symbols are the same as those used in Figure 2.

average weight of the malnourished animals was only 62% of dietary controls, corresponding to a state of moderate malnutrition (28). Although the noninfected-malnourished kits remained clinically well and enteric pathogen free, alterations in intestinal structure and function were noted. Mucosal Na-K-ATPase activity was decreased and mucosal mass was diminished, as evidenced by reduced total small intestinal weight, villus height, crypt depth, protein, and DNA content. Infants rabbits from both the malnourished and dietary control groups that were infected with *Y. enterocolitica* developed a diarrheal illness 4–5 d postinfection associated with positive intestinal cultures. On d 23 at the height of illness, infection caused severe intestinal damage in both dietary groups, as evidenced by alterations in mucosal structure, depressed mucosal disaccharidase activities, and the presence of an inflammatory infiltrate. In addition, glucose-stimulated Na^+ transport in the ileum was severely depressed.

By 14 d postinfection, the 31-d-old infected dietary controls that were fed *ad libitum* throughout the illness exhibited nearly complete intestinal recovery from the injury. Crypt-villus length, mucosal protein, and DNA content returned to the levels of noninfected dietary controls, inflammation resolved, and there was recovery of glucose-stimulated Na^+ absorption. Only mucosal disaccharidase activities remained depressed. The delayed recovery of disaccharidase activity is a well-recognized phenomenon observed after acute enteric infections in infancy (29, 30). Clinically, despite the sustained depression of disaccharidase activities, body and intestinal growth were not retarded and kits were able to tolerate breast milk and rabbit feed without evidence of persistent diarrhea.

By 31 d of age, average body weight of the noninfected-malnourished group had fallen to 51% of control values. This is indicative of severe malnutrition, defined as a body weight less than 60% of expected weight for age without edema (28). Intestinal mucosal mass remained depressed and mucosal function was further reduced in response to continued nutrient deprivation as evidenced by depressed segmental sucrase and Na-K-ATPase activities. The 31-d-old nutrient-deprived infants that were 14 d postinfection with *Y. enterocolitica* demonstrated severe damage throughout the small intestine that was associated with persistent inflammation, structural damage, and reduced function. Mucosal disaccharidase activities and glucose-stimulated Na^+ absorption remained depressed. The continued depression of glucose-stimulated Na^+ transport would likely impede intestinal, glucose, Na^+, and fluid absorption. This profound impairment of transport capacity probably contributed to the severe diarrhea and dehydration seen in the infected animals that died between 5 and 10 d postinfection. The apparent preservation of small intestine weight, mucosal protein, and DNA content despite a decrease in villus height is probably a reflection of the extensive inflammatory infiltrate. The preservation of mucosal Na-K-ATPase activity in the infected compared to the noninfected group also likely represents the presence of Na-K-ATPase activity in inflammatory cells infiltrating the mucosa rather than a preservation of activity in epithelial cells, as has been previously demonstrated in older *Y. enterocolitca*-infected rabbits (31). In summary, the infected-malnourished animals exhibited an increase in mortality and minimal evidence of intestinal recovery by 14 d postinfection.

In contrast, nutritional supplementation initiated during the acute diarrheal illness resulted in decreased mortality and rapid intestinal repair in previously malnourished infant rabbits. When infected-malnourished animals were provided with 7 d of nutritional rehabilitation that was initiated during the acute phase of the illness, no animals died, the diarrheal illness was not prolonged, and recovery was nearly complete. Although body weight did not recover to the level of dietary controls, small intestine weight did, which suggests that repair of the intestinal injury must occur before systemic repletion can take place. Nutritional rehabilitation was associated with recovery of crypt-villus structure and mucosal mass as well as resolution of the inflammatory infiltrate. In addition, mucosal Na-K-ATPase activity was increased compared to the malnourished group and there was a return of glucose-stimulated Na^+ transport to the level seen in the noninfected control and malnourished-refed groups. As with the infected dietary control and the infected-malnourished groups, only repair of segmental disaccharidase activities lagged behind the recovery of other parameters of intestinal function compared to the noninfected control groups. The lack of recovery observed in the infected animals subjected to ongoing malnutrition compared to the restoration of intestinal growth and function seen in the infected group that received supplemental nutrition cannot be attributed to differences observed during the acute stage of infection, because the degree of injury in the two groups did not differ when studied at 23 d of age. Although intestinal cultures for *Y. enterocolotica* remained positive in a similar number of infected kits from all dietary groups at 31 d, we can not rule out the possibility of more persistent infection as op-

Table 1. *Sodium fluxes and electrical activities in short-circuited ileal epithelium**

		J_{ms}	J_{sm}	J_{net}	I_{sc}	PD	G
23 d							
C	Basal	13.4 ± 0.5	14.0 ± 0.4	−0.6 ± 0.6	3.3 ± 0.2	−2.8 ± 0.2	32 ± 1
	Glucose	15.4 ± 0.6†	13.1 ± 0.6	+2.3 ± 0.7†	4.8 ± 0.2‡	−3.7 ± 0.2‡	34 ± 2
CI	Basal	11.3 ± 0.6	10.9 ± 0.3	+0.4 ± 0.4	3.7 ± 0.3	−2.6 ± 0.4	27 ± 2
	Glucose	13.0 ± 0.9	11.4 ± 0.9	+1.6 ± 0.7	3.9 ± 0.3	−2.6 ± 0.3	31 ± 2
M	Basal	17.3 ± 0.8	17.1 ± 0.8	+0.2 ± 0.7	3.3 ± 0.2	−2.3 ± 0.2	46 ± 3
	Glucose	22.1 ± 0.9‡	17.0 ± 0.8	+5.0 ± 0.5§	5.7 ± 0.4§	−3.7 ± 0.3‡	51 ± 3
MI	Basal	14.5 ± 0.8	15.2 ± 1.0	−0.7 ± 0.4	2.8 ± 0.3	−2.3 ± 0.2	33 ± 2
	Glucose	16.3 ± 0.8	16.2 ± 0.7	+0.1 ± 0.8	3.4 ± 0.3	−2.6 ± 0.3	36 ± 3
31 d							
C	Basal	12.8 ± 0.8	13.9 ± 0.8	−0.1 ± 0.3	3.6 ± 0.2	−2.8 ± 0.2	27 ± 1
	Glucose	18.1 ± 0.7§	14.9 ± 0.7	+3.2 ± 0.8‡	5.5 ± 0.3§	−3.6 ± 0.2†	31 ± 2
CI	Basal	11.5 ± 0.7	12.0 ± 0.8	−0.5 ± 0.5	3.1 ± 0.2	−2.4 ± 0.4	30 ± 2
	Glucose	14.5 ± 0.9†	11.8 ± 0.8	+2.7 ± 0.6‡	4.6 ± 0.2§	−3.5 ± 0.3†	31 ± 2
M	Basal	14.4 ± 0.8	15.2 ± 0.7	−0.8 ± 0.2	3.4 ± 0.2	−3.4 ± 0.2	41 ± 2
	Glucose	20.6 ± 0.9§	16.3 ± 0.6	+4.3 ± 0.8§	5.8 ± 0.4§	−4.5 ± 0.3‡	46 ± 2
MI	Basal	17.8 ± 0.5	18.1 ± 0.5	−0.3 ± 0.6	3.6 ± 0.3	−2.8 ± 0.3	38 ± 3
	Glucose	19.9 ± 0.9	19.8 ± 0.7	+0.1 ± 0.8	3.7 ± 0.3	−3.3 ± 0.2	44 ± 3
MR	Basal	15.0 ± 0.7	15.2 ± 0.8	−0.2 ± 0.6	3.3 ± 0.3	−2.8 ± 0.3	37 ± 2
	Glucose	19.2 ± 0.8‡	16.3 ± 0.8	+2.9 ± 0.5‡	5.1 ± 0.3‡	−3.8 ± 0.3†	42 ± 3
MRI	Basal	11.8 ± 0.4	12.1 ± 0.4	−0.3 ± 0.3	3.8 ± 0.2	−3.2 ± 0.2	33 ± 1
	Glucose	15.2 ± 0.8§	11.8 ± 0.6	+3.4 ± 0.5§	4.6 ± 0.2‡	−4.0 ± 0.2‡	34 ± 2

* Values are mean ± SEM for noninfected and infected (I) dietary controls (C), malnourished (M), and malnourished-refed (MR) groups. J_{ms}, J_{sm}, J_{net}, and I_{sc} are in $\mu Eq \cdot cm^{-2} \cdot h^{-1}$; PD is in mV; and G (tissue conductance) is in $mS \cdot cm^{-2}$.

† $p < 0.05$, basal period *vs* glucose-stimulated period.

‡ $p < 0.01$, basal period *vs* glucose-stimulated period.

§ $p < 0.001$, basal period *vs* glucose-stimulated period.

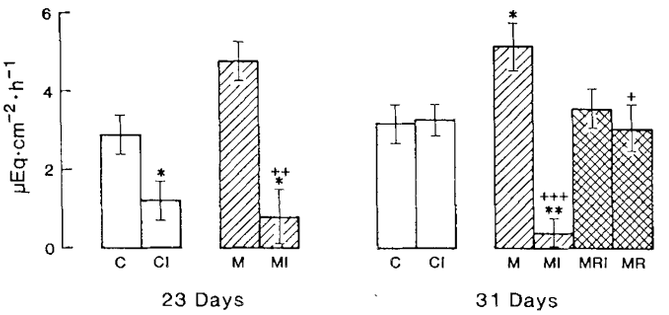

Fig. 6. Increment of ileal Na^+ absorption above basal levels after the addition of 30 mM glucose (ΔJ_{net}) in $\mu Eq \cdot cm^{-2} \cdot h^{-1}$. Abbreviations and symbols are the same as those used in Figure 2.

posed to persistent colonization in the infected-malnourished group.

Several factors may be responsible for the decreased mortality and enhanced intestinal repair observed in infected-malnourished animals that received nutrient supplementation compared to infected animals subjected to ongoing malnutrition. Extra energy provided in the form of increased quantities of breast milk and rabbit feed presumably plays an important role in the intestinal recovery associated with the refeeding process, as shown in slightly older noninfected rabbits that were refed with feed alone (19). The presence of growth factors such as epidermal growth factor and the immune components, including maternal Ig and lymphoid cells, all known to be present in breast milk, also may have contributed to intestinal recovery from the bacterial enteritis. To what extent each of these components contributed to the restoration process after an acute enteric infection remains to be determined.

In summary, our study demonstrates that early nutritional rehabilitation of the malnourished infant rabbit subjected to an acute enteritis is well tolerated, improves overall nutritional status, and enhances intestinal repair. Our work provides experimental evidence in support of the establishment of clinical trials designed to provide early refeeding for malnourished infants suffering from acute enteric infections.

Acknowledgments. The authors thank P. Brockway, D. Philpott, and K. van der Lee for expert technical assistance, as well as C. Brooks and G. Hardy for care devoted to the preparation of the manuscript.

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