En: Diarrhea and Malnutrition: Interactions, Mechanisms, and Interventions.

16

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Diarrhea and Nutrient Requirements

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INTRODUCTION

The high prevalence rates, particularly among young children in most developing countries, make the influence of diarrhea on nutritional requirements of major concern. The multiple mechanisms whereby diarrhea of infectious origin can affect dietary requirements for calories and protein are listed in Table I. Estimation of the consequences for nutritional requirements is complicated by large quantitative and qualitative variations in the disease burden among different population and age groups. The effects depend on the type of diarrhea as well as on its frequency, severity, and duration. Moreover, available quantitative data are extremely limited. Those available under each of the categories indicated are examined separately in the text that follows.

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Table I. Potential Nutritional Effects of Diarrhea[a]

Effect	Mechanism	Nitrogen	Calories	Vitamins and minerals
1. Anorexia	Unknown	++	++	++
2. Altered diet	Cultural practices	++	+	++
3. Malabsorption	Morphological, functional			Variable
Acute	changes—G. I. Hurry	+	+	Unknown
Chronic	"Tropical jejunitis"	+	+	
4. Losses				
Urine—metabolic	Stress response	+	—	Variable
pathological	Not relevant to diarrhea	—	—	—
Feces—pathological	Protein-losing enteropathy,	+	±	—
	blood			—
Skin	Not relevant to diarrhea	—	—	—
Other	Vomiting	±	±	
5. Internal sequestering	Variable	—	—	Variable
6. Internal synthesis	C-reactive protein,			—
	immunoglobulins, etc.	*	±	
7. Fever	Increased BMR	—	+#	—

[a]These vary with the etiology, duration, and severity of diarrhea and with the age and physiological and nutritional state of the individual and the diet during the acute episode.
+ = Mild effect.
* = Moderate effect.
# = Proportional to fever.
± = Minimal effect.
— = Negative effect

Classification and Definitions

Investigators of diarrheal disease have repeatedly lamented the difficulty, if not the impossibility, of having a universally applicable definition of diarrhea. This is in part because dietary factors (e.g., fiber) will affect the bulk and water content of the stool without necessarily altering intestinal physiology, and also in part because morphology and consistency of stool is only grossly reflective of its water content. In addition, individual sensitivity or stoicism ("observational threshold") conditions the awareness of daily changes in defecation patterns, although the bloody, mucoid stool of dysentery or diarrhea is readily recognized.

For these reasons, either definitions have been arbitrarily set (e.g., four or more liquid or semiliquid stools per day) or the individual is asked to take note of a change in his habitual pattern in the number or nature of the stools. While the former may well underestimate the incidence of diarrheal disease, the latter approach may be too subjective for

the purpose of quantitative scientific study. Methods appropriate for the metabolic ward will often not be feasible in the field. The dilemma is heightened by the fact that infections with known enteric pathogens result in a clinical spectrum of illness from the asymptomatic to severe.

All of these factors affect the perception of illness and the decision of patients to seek help from the available health facilities. Since the duration of symptoms enters into this decision making, the time dimension becomes an important variable as well. Recognizing all of this, it is clear that diarrhea is a clinical concept that encompasses a range from a rapidly fatal disease to a subtle distinction from the normal, or accepted, state.

For the purpose of a standard, minimal definition, we propose that diarrhea be defined as an increase in the frequency by two or more times of the usual daily number of stools that are, in addition, loose, extending over a period of 24 hours or more. The presence of nausea, vomiting, fever, abdominal cramps, dehydration, or bloody-mucoid stools is consistent with, but not necessary for, the diagnosis. In practice, however, the perception of the patient, or the mother (or surrogate) of the infant or child, of changes in the quantity or quality of the stool is the most reliable guide.

The dysenteric diseases are usually separated from the diarrheas. The latter are fluid-losing enteric processes, whether clear or bloody, whereas dysentery is a syndrome recognized by the presence of multiple, small-volume stools consisting largely of blood and mucus, accompanied by cramps and tenesmus. Diarrhea may precede dysentery, or the clinical distinction may be blurred, as in some cases of shigellosis. The two entities are also generally attributable to lesions of the proximal small bowel and colon, respectively.

In consideration of nutrient requirements during and after an episode of diarrhea or dysentery as defined, it is desirable to separate one etiology from another, for the pathogenesis of illness varies considerably, and with it the nutritional impact in both the short and long term. Determination of etiology, however, requires technology that may not be readily available and, under the best of circumstances, is at present possible in only a portion of the patients, whether in hospital or field studies (see Black *et al.*, chapter 4, this volume). The remainder will be composed of a mixed group of other etiologies as well as unrecognized cases of the identifiable diseases.

From the standpoint of nutritional requirements, however, the specific etiology is less important than is the nature of the resulting pathophysiological lesion. In addition, some cases of diarrhea, particularly in

Table II. Physiological Classification of Diarrheas

Category	Pathophysiology	Site	Example
Electrolyte-losing	Net accumulation of isotonic fluid in gut lumen	Proximal small bowel	*V. cholerae*
Nutrient malabsorption	Villus cell damage or loss	Proximal small bowel	Rotavirus
Inflammatory	Mucosal inflammation and necrosis	Ileum and/or colon	*Shigella* sp.

children, are nonenteric in origin. Diarrhea may be associated with measles, otitis media, malaria, and other common systemic or localized infections, and may contribute to their adverse impact on nutritional status.

A physiological classification will, in fact, reflect the specific etiology and the predominant mechanism(s) involved in pathogenesis. The potential nutritional consequences of illness, and the implications for nutrient requirements, can be considered under three headings: electrolyte-losing, nutrient malabsorption, and inflammatory (exudative) diarrheas (Table II). Chapters 2 and 3 in this volume review the major enteric bacterial and viral pathogens and provide the background data on pathogenesis and pathophysiology for this classification. It is important to remember that any one pathogen can affect more than one pathway.

The hallmark of the electrolyte-losing diarrheas is the excretion of large volumes of isotonic fluids with a resulting problem in body fluid homeostasis. There is no histologically demonstrable damage to the mucosa and no inflammatory exudate in the stool, which contains little or no protein.

In addition to electrolyte losses, agents that damage the proximal small bowel mucosa and reduce the absorptive surface and/or the absorptive function of individual villous epithelial cells may cause a defect in absorption of various nutrients, including nitrogen, carbohydrate, and fat. The data reported in chapter 9 indicate a markedly depressed coefficient of absorption for nitrogen, carbohydrate, and fat in rotavirus infection, presumably by the suggested mechanism, although this is not directly demonstrated.

In addition to causing electrolyte and nutrient losses, agents that damage the distal small bowel and colon, and that induce ulcerative lesions of the epithelial cell lining, promote the exudation and loss from the body of leukocytes, erythrocytes, glycoprotein-rich intestinal mucus, and plasma proteins (see chapter 10). Exudative losses of nutrients will

exacerbate the nutritional consequences of absorptive losses and must be accounted for in calculation of nutrient requirements.

We operationally define chronic diarrhea as the persistence of symptoms for 3 weeks or longer, with or without positive cultures for the original (or another) recognized pathogen. Similarly, the beginning of the recovery or convalescent period corresponds to the earliest return of stools to a normal or near normal pattern, usually with a diminution in subjective (anorexia, apathy, etc.) or objective (fever, cramps, etc.) signs or symptoms.

Diarrheal Disease Morbidity

Diarrhea is rarely a significant health problem during the early months of life for the breast-fed infant because weight loss, if it occurs, is rapidly made up. Once breast milk is no longer an adequate source of food, complementary feeding is inadequate and often contaminated, and growth falters, diarrhea becomes so frequent and nutritionally significant that it has received the name "weanling diarrhea." Some typical morbidity rates are shown in Table III. These amount to about eight attacks of diarrheal disease per child per year.[1]

Since all available evidence suggests a convalescent period several times longer than the acute episode, the effects of diarrhea alone on the growth of children under 2 years of age can be considerable. Field studies demonstrated a strong longitudinal correlation between days ill with diarrhea and depressed weight gain (see chapter 8, this volume).

Table III. Days of Diarrhea Experienced by 45 Cohort Children, Santa María Cauqué[a]

Age (months)	Person-days of observation	Total days with diarrhea	Percent of life experience ill with diarrhea
0-5	8,213	466	5.7
6-11	8,213	788	9.6
12-17	8,213	1,236	15.0
18-23	8,213	1,487	18.1
24-29	7,757[b]	1,184	15.3
30-35	7,605[b]	972	12.8
Total	48,214	6,133	12.7

[a]Source: reference 1.
[b]Attrition due to deaths.

For older children, diarrheal episodes become less frequent, but for individuals at the higher end of the frequency distribution, diarrhea may still have serious adverse effects on nutritional and health status. Much the same statement can be made for diarrheal disease morbidity in adults. For the individual in borderline nutritional status, and with an inadequate diet, the additional burden of acute diarrhea can be significant.

External Losses

Reduced Food Intake

Anorexia. The effects of diarrhea on nutrient intakes operate through several mechanisms. Anorexia during episodes of acute diarrhea is a leading cause for decreased food intake. Dehydration, electrolyte losses, abdominal distention, acidosis, and vomiting may contribute to anorexia. Anorexia often results in a drastic reduction in food intake or even cessation of breast-feeding for the young infant.

Many authors have shown that, in the lower socioeconomic groups of most developing countries, infectious diseases are responsible for anorexia and marked reduction in food intake during the second year of life when children are commonly being weaned. A strong inverse correlation has also been reported between infectious disease and calorie intake during this period of a child's life (Table IV).[2] Martorell and Yarbrough (chapter 8) found, in a Guatemalan village, an average daily reduction of calorie and protein intake of 20%, equivalent to 175 kcal and 4.8 g protein per day. The effect of diarrhea on food intake was significantly greater than that from other infections.

Hoyle *et al.*[3] studied three groups of matched children in rural Bangladesh (control, acute diarrhea, and acute diarrhea with feeding encouragement). Calorie and protein intake in the control children was 129.9 kcal/kg and 1.9 g protein/kg, respectively. In a group of children with acute diarrhea whose mothers did not receive dietary education, intake of calories and protein was 75.0 kcal/kg and 0.96 g/kg, respectively. In another group with diarrhea whose mothers received dietary education, average intakes were 60.9 kcal/kg and 0.70 g protein/kg per day, respectively. These results suggest that, even with intensive encouragement, increased food intake was not possible, mainly because of child anorexia.

Recently, A. M. Molla *et al.* (chapter 7) studied the intake of protein and metabolizable calories during and after acute diarrhea of various etiologies (Table II). These results confirm that anorexia plays an impor-

Table IV. Calorie Intake by Village Children *during Illness* and Periods *Free* of Symptoms[a]

Child no.	Mean % recommended calories			Mean % recommended calories associated with diarrhea
	Diarrhea[b]	Other Illness[c]	Well[d]	
63	82.6 (5)[e]	60.3 (3)	80.1 (12)	2.5
54	82.4 (12)	—[f]	80.3 (8)	2.1
46	97.5 (2)	103.3 (7)	96.8 (9)	0.7
23	88.3 (4)	85.7 (3)	90.3 (9)	−2.0
35	74.3 (9)	84.5 (6)	78.0 (2)	−3.7
79	102.0 (6)	98.5 (2)	107.6 (8)	−5.6
15	68.5 (2)	72.0 (2)	75.3 (12)	−6.8
80	72.8 (4)	75.0 (8)	82.0 (5)	−9.2
76	83.7 (3)	94.4 (8)	95.7 (9)	−12.0
49	70.0 (3)	64.0 (2)	83.7 (9)	−13.7
24	85.5 (2)	61.8 (5)	101.9 (17)	−16.4
82	65.0 (3)	61.9 (7)	82.2 (5)	−17.2
34	71.2 (11)	69.8 (5)	93.4 (13)	−22.2
91	70.0 (1)	112.0 (1)	99.4 (5)	−29.4
37	69.3 (3)	86.7 (3)	101.1 (11)	−31.8
88	106.6 (5)	—	143.0 (4)	−36.4
69	65.8 (15)	86.8 (14)	122.5 (2)	−56.7

[a]Source: reference 2.
[b]Diarrhea or diarrhea associated with other illnesses.
[c]Respiratory, exanthemic, febrile, skin, eye, ear.
[d]Includes convalescence except 2 weeks following illnesses.
[e]Mean % recommended calories (number of weekly measurements).
[f]No episodes or measurement recorded in period.

Mean % recommended calories for diarrhea = 79.7
Mean % recommended calories for disease-free = 95.9
difference = 16.2%

Thus, 1- to 2-year-old children consume 12,000 calories (50,209 kJ) less per child per year because of diarrhea.

tant role in the reduction of calorie and protein intake during the acute diarrheas. It is important to note that with rotavirus, anorexia persisted for at least 2 weeks after recovery.

Cultural and Therapeutic Practices. Reduction of food intake during diarrhea is also a result of maternal food-withholding behavior and of various cultural practices in different communities of the world. While the withholding practice might be in part a response to the presence of child anorexia during diarrhea, it extends all the way to starvation during the acute stage. Alterations in dietary composition, such as feeding barley water or addition of herbal infusions to the diet, and cultural beliefs against the feeding of milk and solid foods are likely to contribute to decreased food intake during diarrhea.

Absorption

In Acute Diarrhea of Short Duration. Acute diarrhea has been associated with short-term disturbances of the absorption of almost every nutrient studied. This malabsorption is caused by a number of mechanisms operating singly or in combination: mucosal damage; alterations in motility; dilution; changes in chemical structure of molecules through degradation, fermentation, etc.; competition for uptake of nutrients on the part of the causative agent; effect of bacterial catabolites; etc. In evaluating nutrient losses caused by acute diarrhea, increased baseline excretion secondary to preexisting subclinical environmental ("tropical") enteropathy should be taken into consideration.

Mild to moderate diarrheal disease was reported to reduce nutrient intake by approximately 20% in Guatemalan preschool children (chapter 8), while the more severe toxigenic diarrheas studied in similar children in Bangladesh caused decreased intakes of from 30 to 50%. In addition, absorption of ingested protein was decreased by nearly 20% in Indian preschool children with mild to moderate diarrhea (see chapter 14), and by over 30% in diarrhea caused by rotavirus or *Shigella* in Bangladeshi children of this age.

Nitrogen malabsorption during and following episodes of acute diarrhea has been documented by a number of other studies. Losses may be as high as 200 to 400 mg/kg/day (chapter 11) and may decrease rapidly during recovery. Although the coefficient of nitrogen absorption is low during the acute episode, it is possible to increase the absolute amounts absorbed by increasing the quantities provided by the diet. Some pathogens have greater impact than others (see Ayesha Molla *et al.*, chapter 9, Table VI), probably depending on the mechanisms through which they damage mucosal function. *Shigella* infection, which affects the mucosa of the colon, is associated with decreased coefficient of nitrogen absorption, probably by increasing endogenous losses of plasma, leukocytes, erythrocytes, and intestinal epithelial cells. Some of the protein loss may be a consequence of exudative enteropthy. Increased fecal amino acid losses in acute diarrhea have also been documented by Ghadimi and Tejani.[4] The magnitude of fat malabsorption may depend on the etiology of the diarrhea. Rotavirus infection, which damages the epithelium of the proximal intestine, is associated with greater losses than, for example, *Shigella* infection (see Ayesha Molla *et al.*, chapter 9, Table VII).

Mild diarrhea increases fat excretion from 6 to 14% to about 28%, and in severe diarrhea to over 40%. As with nitrogen malabsorption, the speed of recovery is quite variable. Carbohydrate absorption is decreased in diarrhea caused by rotavirus or *Shigella*, but apparently not in that due

to toxigenic *Escherichia coli* or *Vibrio cholerae*. Thus, the effect depends on the invasiveness of the responsible organism.

Invasive infections that cause fever and considerable alterations in systemic metabolism as well as diarrhea produce the greatest metabolic alterations, especially a protein deficit. In adults, the protein losses may reach 0.9 g/kg/day during illness. If there is a loss of serum proteins into the feces as in shigellosis, the protein loss may range from 1.0 to 1.4 g per kg/day.

Considering these consequential losses and the fact that there may be residual defects in nutrient absorption for some weeks after the acute phase of the illness, it should be readily apparent why it takes so long to make up the deficits induced by such infections. It would also seem reasonable that the protein-to-energy ratio would have to increase during repletion. A 30% increase in calories and a 100% increase in protein has been recommended by Whitehead to optimize repletion in young children depleted by infection.[5] Whitehead's estimate of caloric requirements for catch-up growth (approximately 143 kcal/kg) is at the upper range of energy needs specified in the RDA for children in the 6- to 7-kg weight range[6] and found to be required by MacLean and Graham in their treatment of malnourished infants.[7] While Whitehead's estimate of protein requirements (approximately 4 g/kg) is high by present standards (about 2 g/kg), it coincides with the observed intake of recovering children reported by Holt and Fales.[8]

Carbohydrate malabsorption in acute diarrhea has been documented by Lugo-de-Rivera and co-workers.[9] Lifshitz *et al.*[10] have shown that as the severity of diarrhea increases, and as bacterial counts in the upper intestine rise, children develop disaccharide intolerance, the most common being to lactose.

Giardia lamblia infection is usually asymptomatic in individuals over 2 years of age. In children below that age it may be found in the stools in association with diarrheal episodes (Brunser *et al.*, unpublished data, 1981). Acute episodes and chronic, symptomatic *Giardia* infections are associated with increased fecal fat and nitrogen losses.

Total energy losses, resulting from the combination of all of the preceding causes, may reach nutritionally important levels. Schneider has reported fecal losses of about 150 cals/24 hours, or 5% of the intake of 2800 calories in Guatemalan adults.[11]

In Acute, Prolonged Diarrhea. In a few infants, what started as an episode of acute diarrhea will not respond to dietetic or antibiotic therapy. When the duration of the episode exceeds 3 weeks, the name "prolonged diarrhea" is applied. This condition is characterized by nutritional deterioration, severe diarrhea with food intake, and a tendency to dehydra-

tion. The intestinal mucosa is thin, with moderate to severe damage. There is a decrease in its digestive and transport capacity. Mortality is very high unless patients are carefully treated. Total parenteral nutrition helps to maintain hydration and to restore nutritional status. At the same time, it probably allows the small intestine lesion to heal. Oral feeding is then carried out with small, frequent feedings of an elemental diet. Volume as well as complexity of the diet are increased, depending on the tolerance of the patient. At the same time, parenteral nutrition is reduced. It may take many months before these patients are able to tolerate a normal diet. While prolonged diarrhea is not common, it is disastrous for the individual in whom it develops.

Subclinical, Chronic Environmental Enteropathy. Chronic ingestion of bacteria originating from a contaminated environment results in morphologic and functional changes in the intestinal mucosa. The former are characterized by blunting of the villi and increases in epithelial and lamina propria lymphoid cells. The functional changes are characterized by malabsorption that may result in important losses of nutrients. Provided that the dietary intake is adequate, some of these intestinal losses may be compensated by other processes. Schneider and co-workers[11] showed that, with protein intakes of about 1.5 g/kg per day, Guatemalan villagers with large fecal volumes absorbed less dietary nitrogen than soldiers who lived in a better sanitary environment and whose fecal volumes were smaller (apparent nitrogen absorptions of 77 and 86%, respectively). Nevertheless, nitrogen balance was similar as a result of compensating differences in urinary nitrogen excretion.

Inadequately compensated losses may result in specific nutrient deficiencies. The adaptive mechanism for inadequate dietary energy absorption is primarily a reduction in physical activity, and if this is not sufficient to compensate, weight loss ensues. This is especially true when repeated episodes of clinical diarrhea are accompanied by inadequate dietary intakes, as this may result in cumulative negative balances for one or more nutrients. Unless these losses are compensated by increased intake and absorption, the result will be deranged nutritional status.

Brunser and co-workers (unpublished data) have shown that apparently healthy adult individuals from the medium and low socioeconomic strata have some blunting of villi and crypt elongation, greater basophilia of the cytoplasm of apical cells, and increased numbers of lymphoid cells in the interepithelial cells and the lamina propria. The microvilli of the brush border have somewhat irregular implantation. These morphological changes of the mucosa are known to be associated with subclinical environmental enteropathy wherever it has been studied. It appears with variable degrees of severity in almost every person living

in an unsanitary environment, beginning at a very early age.[12] They also have colonization of the upper intestine by aerobic and anaerobic bacteria.

Metabolic (Urinary) Losses of Nitrogen

Information on urinary losses of nutrients as a direct consequence of diarrheal disease is fragmentary and usually inadequately controlled. As in other systemic infections, it may be assumed that invasive, enteric infections will produce metabolic nitrogen losses, especially when accompanied by fever.[13] Nevertheless, the relationship between urinary nitrogen excretion and dietary nitrogen intake and the tendency to compensate for excessive fecal losses by urinary nitrogen retention make it difficult to interpret data on urinary nitrogen losses during acute diarrheal episodes, such as those presented by Ayesha Molla *et al.* and D. Mahalanabis elsewhere in this volume. The urinary N losses related to fever and other stress conditions in diarrheal disease will be particularly important in children, more so in those under 2 years of age, since diarrheal episodes are often accompanied by a decrease in protein intake because of anorexia and/or maternal behavior in relation to feeding practices.

Diarrheal episodes in the course of metabolic studies are not uncommon, but unfortunately the studies are usually terminated or the data discarded unreported. Moreover, studies based on individuals under diverse experimental conditions do not permit generalization. Negative nitrogen balance during diarrhea is generally observed, but much of it is because of decreased food intake and intestinal malabsorption. Available information on urinary losses is summarized in chapter 11.

Data from Schneider's studies presented by Torún (chapter 15) in this volume suggest that adult men with relatively low chronic absorption of nitrogen, total energy, and D-xylose have lower urinary nitrogen losses and similar nitrogen retentions compared with their counterparts who absorbed better.

Loss into Intestinal Lumen

Loss of protein in the intestinal lumen occurs in children suffering from celiac disease, measles, and kwashiorkor, all of which are manifested by severe loss of body mass and malnutrition. The loss of protein is assumed to be due to extensive ulceration of the large bowel and exudation of the serum protein. Recently, Rahaman and Wahed (Chapter 16) devised a methodology to quantify the loss of protein in the feces of

patients suffering from acute diarrheas of various etiologies. Results showed that about two-thirds of the patients studied with enteropathogenic *E. coli* (ETEC), 40% of those with rotavirus, and nearly 100% of patients with *Shigella* lost a substantial amount of protein, as indicated by the marker alpha l-antitrypsin in their feces. Patients with shigellosis on admission were losing between 100 and 500 ml of serum in feces each day. This dropped steadily as the diarrhea subsided and was usually normal by the sixth day.

Internal Losses

To ensure the proper nutritional status of the young child, nutrient intake must be sufficient for maintenance of tissues, growth, and physical activity. Under conditions of stress, such as infection, nutrients are required for physiological responses with obvious or presumed survival value, for example, tissue repair or fever, or for the increased synthesis of cellular and soluble protein components of the immune response and the acute phase protein reactants. When intake is limited, these stress requirements may necessitate sacrifice in terms of tissue maintenance, growth, and physical activity. This diversion can be conceptualized as an internal loss of nutrients, and an increase in nutrient supply is essential to restore positive balances.

Fever. Homeothermy in the human is a well-regulated function. Resting energy expenditures are at a minimum at the normal core temperature but increase sharply with either increases or decreases in temperature. Elevation above normal temperature imposes a 13% increase in basal metabolic rate per °C of temperature in adults. Measurement of the metabolic expenditure at rest of hospitalized patients under the stress of surgical procedures and/or infection shows an increase of 25 to 40% in resting metabolic expenditures. The cost is even greater in infants in whom the relatively large surface area/unit body weight imposes more stringent requirements for metabolic heat production. The actual cost in additional energy consumption to raise body temperature depends upon the balance between heat loss (which is decreased under elevated ambient temperatures or by the insulating effect of subcutaneous fat, and is increased by peripheral vasodilitation, etc.) and demands for heat production from muscle (shivering) to raise body temperature. Body temperature is physiologically regulated by adjustments in both heat production and heat loss under thermostatic control by the hypothalamus. In adults, a period of intense shivering for only 10 to 15 minutes will increase energy consumption threefold, and this level of energy use

extends for at least 50 to 60 minutes in order to pay off the incurred oxygen debt.

Fever appears to be a primitive response, present even in poikilothermic animals, in which behavioral modification, rather than regulated heat production, is used to raise body temperature. The inflammatory stress that incites the fever response causes release of a small polypeptide from monocytes (a monokine, endogenous pyrogen), which acts to reset the hypothalamic thermostatic set point, apparently via regulation of prostaglandin synthesis. Purified endogenous pyrogen also has immunoregulatory effects, as it appears to be biologically identical to leukocyte-activating factor (LAF). There are reports, largely anecdotal, that severely malnourished children do not develop a normal fever response to infection. It is not known how often this is the case, whether endogenous pyrogen is produced in such patients, if the hypothalamus is fully responsive to the monokine, or if inhibitory substances are present.

Endogenous Energy Sources in Infection. During systemic infections, the pattern of energy utilization is altered. The pool size of glucose increases and glucose oxidation and turnover are augmented. Fasting levels of insulin, glucagon, growth hormone, and corticosteroids are elevated, and the normal response of hormone levels to glucose infusion is distorted, resulting in a diabetic type of glucose disappearance curve. The major source of energy is via *de novo* hepatic gluconeogenesis. This occurs largely at the expense of protein stores via deamination of amino acids, principally alanine. The source of amino acids appears to be the contractile proteins of muscle. Catabolism of muscle has been demonstrated by measurement of 3-methyl-histidine metabolism, which is a marker for muscle protein. The rate of conversion of alanine to glucose, assessed with ^{14}C-alanine, is increased beyond the rate of glucose utilization, accounting for the fasting hyperglycemia. The alteration in normal regulatory feedback mechanisms is also observed here, for the increase in gluconeogenesis in the septic patient is not suppressed by glucose infusion as it is in the fasting normal subject.

These metabolic alterations have not been documented in the common diarrheal diseases but would certainly be expected to be present in diarrheas associated with fever. Catabolic events are reflected in the weight loss that occurs during diarrhea, correcting for dehydration. However, weight loss is certainly in part caused by decreased food intake, estimated to be 160 kcal/day in a field study of Guatemalan children.

Since carbohydrate storage pools are limited, and the induced "pseudodiabetic state" and insulin resistance preclude effective use of energy stored as fat, under conditions of preexisting malnutrition or hepatic

damage gluconeogenesis may not be adequate to meet demands, either because of reduced supplies of gluconeogenic precursor amino acids or abnormalities in hepatic function *per se*. Under these conditions hypoglycemia may occur, and hypoglycemic convulsions can occur during acute diarrhea, especially in infants and children.

Turnover of Leukocytes. Granulocytes are present in three pools: in blood, in tissue, and in the bone marrow. Each of these pools may have several subcompartments, as, for example, the circulating and marginated (endothelium adherent) compartments in the blood. There are approximately 10^{10} granulocytes/kg body weight. Over 90% are present in the marrow, 6 to 8% are in the blood, equally divided between circulating and marginated compartments, and a few percent are transiently present in tissues. Production and maturation occurs in the marrow, the cells are released to the blood pool, which has a half-life of about 7 hours, and these cells transiently pass through tissues where they die or exit from the body via mucous membrane surfaces.

Daily turnover can be estimated from the blood pool size and the half-life, and approximates 10^9 cells/kg body weight/day. Under normal circumstances, and estimating the protein content to be 50 mg/10^9 cells, daily protein synthesis in production of granulocytes is 50 mg/kg body weight. If the energy cost of protein synthesis is estimated at 5 kcal/gram, then the energy requirement for normal granulocyte turnover calculates to be 0.25 kcal/kg body weight/day. Demands for increased granulocyte production during various disease states may accelerate up to about 10-fold, representing a maximum energy cost of 2.5 kcal/kg body weight/day. During acute infection, preformed cells are released from the marrow storage compartment, but the biosynthetic costs do not change if one assumes that the storage compartment must eventually be repleted.

Turnover of Plasma Proteins. Increased consumption and turnover of a number of plasma proteins occur during acute infection. These include the complement proteins, immunoglobulins, and the largely liver-derived acute phase proteins (APPs) such as C-reactive protein, serum amyloid A protein, alpha-1-acidglycoprotein and alpha-1-antitrypsin. For some of the APPs, serum levels increase from barely detectable levels to the mg/dl range, a dramatic increase in specific biosynthetic activity, estimated to be equivalent to a turnover of 350 to 700 grams of protein during the course of systemic infections in adults. This figure should be compared to the total turnover of some 300 to 400 grams of protein per day in normal adults.

At the same time, however, priorities for protein synthesis in the liver are altered and production of albumin decreases. The rapid drop in

serum albumin levels during sepsis reflects both the decreased production and increased breakdown of this protein. To the extent that the decreased anabolism of albumin compensates for the increased production of APPs, there may be little or no additional nutrient requirements involved. However, net nitrogen balance is severely affected by the other metabolic changes occurring, particularly the catabolism of muscle protein, deamination, and increased excretion of nitrogen (10 to 15 grams/day in septic adults).

Nutritional Repletion in Adults

Nutrients lost due to diarrheal disease must be repleted during or after the diarrheal episode. The amounts of nutrients to be repleted will depend on the nature, intensity, and duration of the diarrhea. Thus, diarrhea caused by rotavirus, *Giardia lamblia*, or other agents of malabsorptive diarrhea may produce larger nitrogen and vitamin losses than secretory diarrheas do (e.g., cholera, enterotoxigenic *E. coli*). Similarly, chronic diarrheas may produce a depletion of some nutrients that would not be significant if confined to acute episodes. An example is the development of vitamin B_{12} deficiency in tropical sprue.

The extent of possible repletion of nutrients during the acute diarrheal episode will be dealt with in chapter 17 of this volume. During convalescence from diarrhea, allowances should be made for additional amounts of the nutrients that were lost, or that were not ingested because of anorexia or dietary restrictions. It is difficult to specify the precise amounts of additional nutrients or food required, not only because of the great variation in the disease itself but also because of possible adaptive changes. These may include changes in the efficiency of utilization of some nutrients (e.g., greater N retentions after protein depletion) and other complex, not well-understood regulatory mechanisms (e.g., interactions of energy intake, energy expenditure, and weight changes). However, it seems sound to recommend a period of higher energy intake, proportional to the loss of weight, after correcting dehydration, and of more dietary protein, proportional to the duration of anorexia and diarrhea. The need will generally be greater in malabsorptive than in inflammatory or secretory diarrheas. Repletion of vitamins and minerals will depend mainly on the duration of the disease and on the intestinal segment involved (e.g., duodenojejunitis or colitis).

In summary, individuals should be provided with diets with more essential nutrients after a diarrheal disease so that rapid repletion is assured. This can be of critical importance if the patient has had a mar-

ginal or inadequate dietary intake and nutritional status before the diarrheal episode.

Significance of Repletion for Catch-Up Growth

In children, diarrhea causes both a depletion of lean body mass and a cumulative deficit due to growth failure. While this is true of all infections, the effects of diarrheal infections tend to be greater because absorption is affected as well as intake and metabolic losses. Certainly dietary intake following diarrhea must be significantly higher if rapid repletion is to occur than for individuals who have not been so depleted.

In adults, catch-up growth is not a concern, but repletion is also important and will not occur satisfactorily unless food intake is greater than required for maintenance. The largest effect is on protein needs, but increased dietary calories, vitamins, and minerals are all required for optimum recovery.

Practical Implications

Table I lists the various kinds of nutrient loss in diarrhea. Individually, some are small, but the cumulative effect is nutrient depletion, weight loss, growth impairment, and sometimes precipitation of clinical nutritional disease. The nitrogen retentions observed during the recovery period from diarrheal and other infectious episodes usually exceed the measured losses. The most likely explanation is that this is due to the considerable nitrogen that is diverted to internal protein synthesis associated with the body's response to infection.

Nevertheless, the effect on *average* requirements of the total population is small and probably negligible in most populations, even those that are underprivileged. This is a misleading way to approach consequences for requirements, however, because they are important primarily during the recovery period and especially so for young children. It is then that the diet may limit repletion and, in children, catch-up growth. Field data indicate that if children do not catch up within a reasonable period, they become stunted. In addition, if the diet is not adequate for prompt repletion and catch-up, the effects of diarrheal and other infections during the weaning period, i.e., in children 6 months to 2 years of age, tend to be additive and lead to the precipitation of clinically evident nutritional disease.

Safe allowances for protein are designed to allow for the needs of nearly all of the population and are now calculated to be 25% above the estimated mean requirement. There is a similar need to specify the additional amount of protein and energy that would be required for the catch-up needs of nearly all children following an episode of diarrheal or other infections. Whether or not the distribution of catch-up is skewed, if an allowance is made for five, seven, or nine times the mean daily growth calculated from annual weight increments, then the diet during the catch-up period must provide 48, 72, and 96 more protein and 8, 12, and 16% more calories, based on the 1981 FAO/WHO/UNU Expert Consultation on Protein-Energy Requirements. In terms of food consumption, children will eat much less than usual during acute episodes of diarrhea and should have available more food than usual during the recovery period when appetite and need are increased.

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