

2 or 3.<sup>167</sup> In addition, nutritional modifications are promising (Chapter 3). In the future, gene therapy may be useful to correct for the absence of SMNI and to restore superoxide dismutase type 1 for people with SMA and this defect.

*A pulmonologist who considers the airways but who ignores the respiratory muscles is like a cardiologist who considers the blood vessels but who ignores the heart.*

• Peter Maclem, M.D.

## Nutrition

With Contributions from Irving Haber, M.D., and Jill Gaydos, B.S.

*It is the character of the true philosopher to hope all things not impossible, and believe all things not unreasonable, so is it the character of the physician to hope and believe that the term vis medicatrix naturae (the healing force of nature) does not represent a nonentity; and that there is in the animal body, when in a state of disease, a tendency to return to its healthy state, and that he has means and appliances to assist this curative process.*

• Edward Meryon (1809–1880), the physician who first described, accurately and comprehensively, what came to be known as Duchenne muscular dystrophy<sup>6</sup>

People with neuromuscular diseases (NMDs) have little lean body mass with small protein and mineral reserves and are, therefore, highly susceptible to periods of undernutrition. Malnutrition can exacerbate muscle weakness and decrease lung and immunologic function. Malnutrition and weight loss are independent and significant determinants of morbidity and mortality from respiratory causes.

### Nutritional Requirements

Recommended daily allowances (RDAs) are used to estimate nutrient needs.<sup>168,169</sup> They are designed to provide a margin of safety. Even in the general population, however, RDAs may not be adequate. The elderly often have inadequate gastrointestinal absorption of specific nutrients. Younger patients can also develop malabsorption abnormalities, especially with the presence of gastrointestinal or certain other complicating conditions. In addition, many people eating overly processed foods and few vegetables and fruit may simply not receive enough of many nutrients. It has also been estimated that up to 70% of all children do not receive adequate calcium from their daily diets.

Nutrient requirements of the normal infant and child are determined by taking into consideration rate of growth and physical activity as well as basal energy expenditure. The RDAs for children were estimated using intakes of normally growing infants and the nutrient content of human milk (Table 1). Nitrogen balance studies were used to establish amino acid requirements. The needs for children with NMD or generalized medical conditions can be quite different. The best way to measure adequacy of nutrient intake is to monitor growth.

Fluid needs are determined by the amount of water lost through the skin, lungs, urine,

Table 1. Normal Calorie and Protein Needs: Requirements per Day per Kilogram of Body Weight

Age	Calories (kcal)	Protein (gm/kg Body Weight)
0-5 months	108	2.2
6-12 months	98	1.6
1-3 years	102	1.2
4-6 years	90	1.1
7-10 years	70	1.0
11-14 years (males)	55	1.0
15-18 years (males)	45	0.9
11-14 years (females)	47	1.0
15-18 years (females)	40	0.8
Adults	25-35	0.8
Adults over 60		1.0-1.1

the infant is less than that of an older child, making infants at greater risk for water imbalance. Small children require 100 ml of fluid/kg per day, whereas older children and adults require about 1000 ml of fluid plus 50 ml/kg when they weigh more than 10 kg. Calorie and protein needs per unit of body weight are also greater than those of an adult (see Table 1 and [www.nal.usda.gov/fnic/dga/rda.pdf](http://www.nal.usda.gov/fnic/dga/rda.pdf)) but decline as the rate of growth slows.

Breast milk is usually ideal, but when it is contraindicated, infant formulas provide the appropriate distribution of essential nutrients under normal conditions. As for human milk, it is recommended that infants receive at least 30-50% of total calories from fat. The calories from fat help to spare protein for tissue synthesis. Infant formulas are grouped into standard, soy, protein hydrolysate, and elemental formulas. When non-infant elemental formulas are used for infants, they must be supplemented to ensure that the RDA is achieved for all essential nutrients.

The RDAs and, in particular, requirements for calories and micronutrients differ for adults of different ages and activity levels and in different circumstances. For example, a 25-year-old woman requires 800 micrograms of vitamin A, whereas a man of the same age requires 1000 micrograms. Other RDAs of micronutrients for typical healthy adults include:

- Vitamin D, 5-10 µg
- Vitamin E, 8-10 mg
- Vitamin K, 60-70 µg
- Vitamin C, 60 mg
- Thiamine, 1-1.5 mg
- Riboflavin, 1.2-1.7 mg
- Niacin, 13-19 mg
- Pyridoxine, 2 µg
- Calcium, 800-1200 mg
- Phosphorus, 800-1200 mg
- Magnesium, 280-350 mg
- Iron, 10-15 mg
- Zinc, 12-15 mg
- Iodine, 150 µg
- Selenium, 45-70 µg

## Pathophysiologic Effects of Weight Loss or Gain

As little as 10% weight loss from ideal levels can be associated with high morbidity.<sup>170</sup> Short-term starvation depletes muscle protein and decreases lung connective tissue, protein synthesis, and lung surfactant.<sup>171-173</sup> It also diminishes the body's response to illness or injury.<sup>174</sup> This effect is particularly detrimental for patients with respiratory or ventilatory impairment, who have a high risk of lung injury when intercurrent respiratory infections result in pulmonary infiltrates and scarring because of impaired pulmonary defense mechanisms.

Prolonged food or nutritional deprivation impairs muscle function by reducing available energy substrates. With prolonged fasting, branched-chain amino acids, a component of muscle tissues, become an important energy substrate for diaphragm activity. The rate of the degradation of branched-chain amino acids by the diaphragms of semistarved rats is 10-20 times greater than normal (Fig. 1).<sup>175</sup> In certain NMDs associated with impaired fatty acid oxidation, even a few hours of fasting can result in degradation of muscle protein. Malnutrition impairs immunity and white cell function.<sup>176-179</sup> Bacterial adherence to the lower airways increases in undernourished patients with indwelling tracheostomy tubes.<sup>180</sup> In addition, deficiencies in specific nutrients can have repercussions for respiratory function. Hypophosphatemia, which can be due to malnutrition or rapid glucose loading, can trigger acute respiratory insufficiency or difficulty in weaning from assisted ventilation.<sup>181</sup> Similarly, carbohydrate intake can increase carbon dioxide production and carbon dioxide levels in already hypercapnic patients.

Besides leading to weakening and wasting of skeletal and respiratory muscles, semi-starvation also blunts both the hypoxic<sup>182,183</sup> and hypercapnic<sup>184</sup> drive to breathe. Ventilatory failure and hypercapnic coma can result from starvation alone.

Tilton, Miller, and Khoshoo reported that 54% of 7- to 13-year-old patients with NMD are obese.<sup>185</sup> The most obvious explanation for the obesity is that more calories

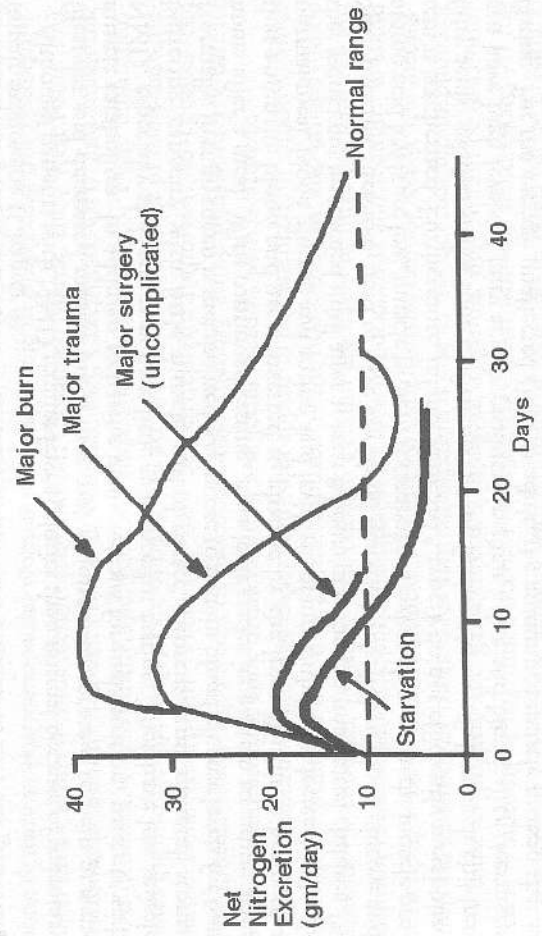


Figure 1. Nitrogen loss associated with undernutrition, major surgery, trauma, and burns.

are taken in than expended; however, this explanation is still debated. As NMD progresses, a loss of lean muscle tissue reduces the resting energy expenditure. Hankard et al. reported reductions of muscle mass by up to 71% in DMD despite obesity.<sup>186</sup> Resting energy expenditure is reduced by 13%, and postabsorptive fat utilization is also reduced in DMD.<sup>186</sup> Furthermore, obesity does not indicate adequate protein stores or adequate vitamin and mineral status. In fact, obesity can mask deficiency states, making the food intake record and biochemical evaluation a vital component of assessment for obese as well as undernourished patients. Obesity can compromise both ventilatory dynamics and central regulation of both spontaneous and assisted ventilation; it also impairs mobility and leads to skin pressure problems.

Thus, a combination of the direct biochemical effects of undernutrition and the indirect effects of under- or overnutrition can predispose patients to respiratory tract infections, atelectasis, chronic alveolar hypoventilation, and impaired pulmonary defense mechanisms and lung repair.

### Causes of Malnutrition and Wasting

The underlying mechanisms for muscle wasting include the primary pathologic processes of NMD combined with decreased oral intake, malabsorption, and altered metabolism of nutrients. In addition, many patients are treated with glucocorticoids. Glucocorticoids can further potentiate loss of muscle mass. Rat studies show a significant decrease in diaphragmatic muscle strength even with minimal dosing of methylprednisone over a relatively short period.<sup>187</sup>

Decreased nutrient intake can also be related to eating difficulties resulting from upper limb muscle weakness and contractures,<sup>188,189</sup> cognitive impairments, infections, psychiatric abnormalities (e.g., depression), dysphagia, or loss of appetite, which can be associated with medications, bloating, and shortness of breath. Decreased nutrient intake can also result from vomiting or diarrhea. Indwelling tracheostomy tubes also impair swallowing (Chapter 4).

Although patients with NMD require fewer calories than normal because of sedentary lifestyles and decreased muscle mass, they may require more protein to help prevent muscle catabolism. In addition to having many reasons for malnutrition, patients with NMD, especially children, may have little tolerance for fasting. They have low muscle buffering capacity with little muscle carbohydrate, protein, and mineral stores. Normally, liver glycogen is metabolized to glucose to sustain blood glucose levels for 6–8 hours after a meal. With continued fasting, muscle degrades its protein to amino acids that enter the blood and are converted to glucose by the liver. Within 3 hours of a normal meal, blood glucose and amino acid levels of infants with SMA decrease to levels that would not be reached until after at least 8 hours of fasting in unaffected children.<sup>190</sup> Such patients, therefore, tend to have low blood glucose levels. When blood glucose and amino acid levels are low, muscle protein is catabolized; when they are high, muscle protein is synthesized. Furthermore, infants with SMA type 1 do not efficiently metabolize fatty acids, another major source of energy during fasting. As seen below, such children can have high levels of fatty acid byproducts in their urine and blood after overnight fasting. For the average unaffected child or adult, the amount of muscle protein that is

with NMD who may have less than 10% of normal mass, a much greater proportion is sacrificed. Thus, even the small net loss of protein that occurs during normal overnight fasting may be significant for a child with SMA.

Although vitamin supplements can be critical for children on modified elemental amino acid diets, the fat-soluble vitamins A, D, and K should be administered with caution. Excessive levels of these vitamins stored in the liver and adipose tissues can reach toxic levels.<sup>191</sup>

Because of inadequate bone buffering, serum potassium and phosphate levels quickly decrease to hazardous and potentially lethal levels during respiratory tract infections or episodes of fever and diarrhea or vomiting (Chapter 2).<sup>192</sup> Thus, electrolytes and metabolites are particularly important to monitor and replace during intercurrent illnesses.

### Bone Integrity

Greater than the RDA intake of vitamins, minerals, and protein may also be necessary.<sup>193</sup> Vitamin D functions in the absorption of calcium and phosphorus. Deficiencies of vitamin D, calcium, and magnesium lead to reduced bone mineral content. Even though intake of vitamin D and calcium may be adequate, decreased intestinal absorption of calcium and vitamin D, along with drug interactions and lack of physical activity and weight-bearing, can decrease bone calcium adsorption and greatly increase the risk of fracture with minor trauma. Decreased exposure to sunlight also impairs the conversion of skin 7-dehydrocholesterol into 1,25-dehydroxycholecalciferol (vitamin D).

The use of exercise, range-of-motion mobilization, and active assistive exercises can help prevent musculoskeletal contractures (Chapter 6) and may also have a beneficial effect on preserving bone integrity. Osteoporosis has been recognized in nonambulatory boys with DMD, even in weak but still ambulatory boys, and is proximally in the femurs and lumbar spine.<sup>194</sup> Upper limbs can also decalcify when losing function, thus increasing the risk of fracture with minor trauma.<sup>195</sup> Medications used for increasing bone density in postmenopausal women may play a role in preventing this problem.<sup>195</sup> Such medications include alendronate sodium (Fosamax, Merck, Inc., West Point, PA), risenedronate sodium (Actonel, Procter & Gambel, Inc., Cincinnati, OH), and zoledronic acid (Zometa, GlaxoSmithKline, Inc., Research Triangle Park, NC). These bisphosphonates bind to the hydroxyapatite of bone and act as a specific inhibitor of osteoclast-mediated bone resorption. Their use may be particularly important to counter the osteoporosis-inducing effects of glucocorticoid therapy. Bone densitometry can be useful for monitoring bone decalcification and recalcification with treatment.<sup>185</sup>

These medications are now under study and appear to be beneficial for children. Since no evidence indicates that they are metabolized by the body, they are also unlikely to be harmful for children. Products that contain calcium are likely to interfere with the absorption of alendronate. Contraindications include hypocalcemia and inability to stand or sit upright for at least 30 minutes, at least for patients who cannot receive the medications via gastrostomy tubes. This contraindication is due to the fact that bisphosphonates may cause esophageal and gastrointestinal mucosal irritation; they should be discontinued if symptoms of heartburn occur. For postmenopausal women, alendronate, 70 mg once weekly or 10 mg daily, is taken with 8 ounces of water 30 minutes before breakfast.

the same for risperidone sodium. Zoledronic acid can be used by injection on a less frequent treatment schedule.

### Abnormalities in Fatty Acid Oxidation and SMA

There is a curious overlap in the clinical and biochemical features of SMA and mitochondrial myopathies.<sup>62,196</sup> In addition to decreased muscle nutrient stores, metabolic aspects of immobility, systemic illness, and muscle denervation and atrophy, children with SMA also have abnormalities in muscle mitochondrial fatty acid oxidation and carnitine metabolism and impaired insulin regulation, all of which can lead to muscle atrophy and progressive weakening.<sup>190</sup> Any process that increases cytoplasmic free fatty acid levels, such as fasting or defects in fatty acid transport or beta-oxidation, can increase the liver and kidney's production and excretion of possibly toxic dicarboxylic acids. Fasting ketosis reflects normal ketogenesis by the liver's utilization of free fatty acids. However, children with SMA can be catabolic without developing ketosis because of enhanced gluconeogenesis at the expense of muscle mass and a downregulated insulin response.

Dicarboxylic acid levels are elevated in the urine of infants with SMA and in their blood and urine after fasting overnight. The extent of dicarboxylic aciduria is a function of SMA severity. Patients with SMA type 1 tolerate the briefest fasting without ketosis and dicarboxylic aciduria, whereas patients with SMA type 3 express these abnormalities only during prolonged fasting, illness, and periods of physiologic stress. The quantity of fatty acid metabolites generated in SMA type 3 may be considerably lower than in SMA types 1 and 2, reflecting a lower percentage of atrophic muscle fibers. Furthermore, these metabolites may be taken up by liver and metabolized, whereas in the more severe types of SMA the absolute levels of the metabolites are higher or the capacity of the liver is saturated so that the excess is detected in serum and urine.<sup>197</sup> Metabolic analyses, including the appearance of relatively early ketosis, selective renal loss of carnitine,<sup>197</sup> and fatty vacuolization of the liver, suggest that the abnormalities are caused by changes in cellular physiology related to the molecular defects of the SMA-pathogenic survival motor neuron gene or neighboring genes. Abnormal fatty acid metabolism also appears to resolve with age independently of disease severity.<sup>198</sup>

Motor function can improve and developmental milestones be achieved for infants with SMA.<sup>199</sup> However, often before 10 years of age or during periods of physiologic stress, such as intercurrent respiratory tract infections, patients with SMA suddenly lose muscle strength at a high rate.<sup>69</sup> During these episodes loss of strength tends to become progressive and is most severe in infants. Infants with SMA also weaken rapidly when nutrition is compromised by swallowing impairment. It is quite possible that the sudden exacerbations of muscle weakness are due to relative fasting and that the weakening can be abated or averted with proper nutrition.

### Evaluation and Monitoring

#### History and Physical Examination

Appetite and nutrient intake are monitored for deficits. A baseline weight is obtained. Weight should be in the 10th to 25th percentile. Braces/casts, catheter bags and tubing,

has eaten or been fed must be considered during the weighing process. Weight can also be affected by hydration and edema.

The patient's height is important for understanding the effects of nutrition on growth and for comparison with predicted normal values. When height is difficult to assess because of kyphoscoliosis or other musculoskeletal abnormalities, knee height measurements from under the foot to the top of the femoral condyle have been proposed to estimate height using published formulas of questionable validity.<sup>200,201</sup> Alternate techniques for assessing body size have been suggested, such as arm span and single arm length.<sup>202</sup>

The appearance of the hair, eyes, skin, and teeth is noted. Changes in skin or hair color and texture and tongue or gingival lesions can signal specific nutritional deficiencies. Swallowing ability, taste, and smell are evaluated. Bowel routines are reviewed. Mouth dryness can indicate dehydration or suboptimal vitamin C or zinc levels.<sup>203</sup> Dehydration due to compromised fluid intake can be exacerbated by excessive fluid losses such as from vomiting and drooling. In one study, salivary losses of an 8-year-old girl were 320 ml per day, or 25% of the girl's maintenance fluid requirement.<sup>185</sup> Urine specific gravity is assessed to determine hydration status. A 24- to 72-hour food and fluid intake diary can be helpful.

Caloric requirements vary significantly for normal and NMD children alike. However, caloric and nutrient ingestion is quantitated and almost invariably compared with average quantities for age, sex, and height when matched with the general population. Caloric and nutrient assessments are expressed as a percentage of the RDA over a 3-day period.<sup>204</sup>

A number of indices have been developed to assess nutritional status and quantitate body fat and lean mass:<sup>205:</sup>

- Determination of skin-fold thickness
- Midarm circumference
- Bioelectric resistive impedance
- Creatine-height index
- Body mass index (BMI), which is weight divided by height squared
- Total body conductivity
- Biophotonic absorptiometry
- Underwater weighing
- Isotopic dilution
- Gamma camera
- X-ray computed tomography
- Echography
- Neutron activation
- Weight for zero muscle mass (ZMM), which is described below
- Estimation of body composition by magnetic resonance imaging

The parameters analyzed, patient acceptance, cost, precision, technical difficulties, and various studies using 12 of these methods have been previously summarized.<sup>206</sup>

Tape and caliper anthropometry is the most commonly available and cost-effective method; the results are accurate to  $\pm 3\%$ . Suprailiac and subscapular skin folds are often easier to obtain and can be more reliable than the triceps fold measurement because of the often present contractures of the upper arm. If obtainable, midarm muscle circumference (midarm circumference minus  $3.14 \times$  triceps skinfold) can be used as a muscle mass indicator. Standards for anthropometric measurements are available.<sup>201</sup> The 50th percentile for fat stores is considered ideal for children with NMD.<sup>185</sup> Weight, height, and anthropometric measurements are complementary.

Clinical anthropometry is complicated for patients with NMD by the fact that the

processes. Therefore, generally accepted anthropometric equations for determining body fat mass<sup>207,208</sup> are not reliable for patients with NMD.<sup>209,210</sup>

A recent study demonstrated that ZMM more effectively takes into account muscle fat composition and more successfully indicates overweight status (excessive body fat composition) than BMI for patients with DMD and ALS.<sup>211</sup> To calculate ZMM, one must provide a creatine-free diet for 6 days and then measure total urinary creatinine excretion for the next 3 days. This measurement permits the estimation of total lean muscle mass. It can be subtracted from the patient's body weight, and the weight at zero muscle mass is divided by the theoretical body weight for zero muscle mass to determine presence of any excessive body fat. Of a total of 7 patients with ALS and 34 patients with DMD, BMI was normal (20–25 kg/m<sup>2</sup>) for all 7 patients with ALS and for 29 patients with DMD, whereas 5 patients with ALS and 30 patients with DMD were classified as overweight by ZMM.

In summary, assessment for pediatric patients with NMD is complicated by altered growth dynamics and metabolism as well as by atrophied muscle mass, diminished nutrient buffer, and limb contractures and weakness. Children require more frequent assessment by physical examination, assessment of caloric and nutrient intake, anthropometric measurements, and biochemical analyses because of deficiency in the muscle mass "buffers." Concomitant abnormalities of fatty acid metabolism and insulin regulation can also complicate the clinical picture for patients with SMA and certain other pediatric conditions.

### Laboratory Evaluation

Undernutrition reduces liver protein synthesis. Serum levels of albumin and iron transport protein (transferrin) reflect protein availability to the liver for protein synthesis. Both protein and transferrin have half-lives just under 2 weeks. Therefore, their serum levels reflect long-term but not short-term changes in protein status. Prealbumin and retinol-binding protein are more useful for assessing short-term nutritional interventions because of their shorter half-lives of 2 days and 12 hours, respectively.<sup>212</sup> Measures of the urinary nitrogen level, a measurement of nitrogen metabolism, are usually accomplished by a 24-hour urine collection.<sup>213</sup> Other tests that assess nutritional status include total iron-binding capacity, cholesterol, and serum vitamin levels, especially of vitamins A, C, and E. Vitamin levels are especially important because patients with NMD have a high incidence of vitamin deficiencies. In addition, because of the minimal muscle protein reserves, it may be beneficial to monitor blood amino acid levels. Glucose, potassium, and phosphorus levels need to be monitored closely during acute illnesses.

### Nutritional Interventions

The goals of nutritional management of patients with NMD are to limit wasting, lean body mass depletion, and loss of muscle strength; to enhance well-being; and to preserve energy reserves to help resist respiratory complications. Possible additional benefits are also discussed.

### Spinal Muscular Atrophy and Other Neonatal Neuromuscular Diseases

Caloric needs for infants with NMD are 80–100 cal/kg; older children with NMD also

prevent dehydration, urinary system calculi, and constipation. It is especially important to prevent constipation, which can cause fever, urinary retention, and difficulty in breathing for infants and older children with NMD. Fluid intake is often insufficient because of decreased thirst, difficulty to obtain or swallow fluids, or communication impairment.

Three general dietary goals have been identified: (1) increase in dietary complex carbohydrates, (2) about 2 grams of protein per kg per day, and (3) a feeding schedule that limits overnight fasting to 4 hours for a young infant and 8 hours for older children. A minimum of 5% of calories need to come from essential fatty acids. Infants are awakened for feeding at 4-hour intervals or placed on continuous drip or 4-hour interval boluses via gastrostomy tubes. Some children grow nicely with as little as 50–60 calories/kg and 1.2 gm of protein per day.

In addition to avoiding hypoglycemia and muscle protein catabolism by avoiding prolonged fasting, infants with SMA have also been anecdotally reported to benefit from taking elemental or semielemental formulas such as Tolerex and Pediatric Vivonex (Novartis, Inc., Minneapolis, MN), which provide high quantities of amino acids and small-chained polypeptides.<sup>197</sup> These formulas are easier to digest and may allow better utilization of nutrients and spare muscle protein while avoiding hypoglycemia. A late evening supplement of complex carbohydrates such as uncooked corn starch (1 gm/kg) can sustain blood glucose levels and reduce the effects of overnight fasting.<sup>199</sup> In addition, considering that denervation itself can cause a decrease in muscle carnitine concentrations and the abnormalities in fatty acid metabolism associated with infantile SMA, supplemental riboflavin, coenzyme Q10,<sup>116</sup> and L-carnitine have been suggested along with 200–300 mg/kg of glutamine and 250 mg/kg of arginine.<sup>197</sup> The elemental formulas, glutamine, and arginine provide extra essential amino acids to shift the ketoacid/amino acid equilibrium in favor of muscle protein retention and synthesis. The glutamine may simultaneously remove ketoacids from degradative pathways. Glutamine supplementation is well established for patients with inborn errors of amino acid and organic acid metabolism, for burn patients, and for postsurgical care.

Both Tolerex and Pediatric Vivonex have essential fatty acids, but the former has only 1 gm of fat per 300 calorie packet as opposed to 5 gm per 200 calorie packet for the latter. Tolerex also has twice as many complex carbohydrates per pack as Pediatric Vivonex. For children, both Tolerex and Pediatric Vivonex are low in calcium, iron, iodine, potassium, vitamin C, B complex, fat-soluble vitamins, and folic acid. Supplements are necessary.

Recent evidence gleaned from animal models indicates that such children may also benefit from receiving more than the RDA of folic acid and vitamin B12. Folic acid should be provided daily, 65 micrograms for children from 0 to 6 months of age, 80 micrograms from 7 to 12 months of age, 150 micrograms from 1 to 3 years of age, 200 micrograms from 4 to 8 years of age, 300 micrograms from 9 to 13 years of age, and 400 micrograms for older people. At the same ages vitamin B12 is provided at 0.5, 1.5, 2, and 2.5 micrograms, respectively; 3 micrograms should be provided from 9 to 13 years of age and subsequently.

In addition to corn starch and mineral and vitamin supplements, the low fatty content of these elemental formulas is often compensated by adding several grams of primrose or safflower oil with water or white grape juice. It is necessary to make these formulas