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METABOLIC EFFECTS OF TOTAL PARENTERAL NUTRITION

P. D. Greig, J. P. Baker, K. N. Jeejeebhoy

Departments of Medicine and Surgery, Toronto General Hospital and University of Toronto, Toronto, Ontario, Canada.

INTRODUCTION

Nutritional support of the sick patient has become increasingly important, particularly in cases of prolonged serious illness. The need for attention to the nutritional requirements of the patients has arisen because improved treatment of sepsis, cardiovascular failure, and fluid and electrolyte abnormalities has allowed patients to survive to a point where nutrition becomes a limiting factor in their further progress. Despite advances in surgical and medical treatment of various disorders of the alimentary tract, the survival of the patient with gastrointestinal disease is often limited by continuing malnutrition as a result of the inability of the patient to eat and/or absorb a normal oral diet. Under such circumstances advances in the field of parenteral nutrition have revolutionized the outcome of these patients.

The objective of nutritional support in the critically ill patient is to restore and maintain adequate nutritional status in the face of illness and inadequate oral nutrition. Central to the understanding of the utilization of parenterally infused nutrients and their effects on body composition is knowledge of the effects of starvation and acute injury on nutritional status.

Effects of Starvation and Trauma on Nutritional Status

The prototypical patient who is the target for parenteral nutrition has an inflamed or injured gastrointestinal tract that prevents the absorption of oral nutrients. In such a patient, starvation results in reduced insulin levels which, in turn, allow the mobilization of free fatty acids from adipose tissue stores to meet the major part of the energy requirements of the patient. However, despite the energy flowing in from adipose tissue stores, protein catabolism continues, resulting in a negative nitrogen balance and wasting

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of both muscle and viscera. As starvation progresses the increasing utilization of fat for energy tends to minimize the breakdown of protein, but the continuing loss of body protein ultimately results in dysfunction of liver, muscle, and the immune system. The loss of 35–40% of lean body mass during such an illness almost invariably results in death. The Irish hunger strikers of 1981 died in this manner after about 60 days of total starvation.

The septic and traumatized patient loses further protein owing to an increased energy requirement and reduced protein synthesis. In addition, levels of catecholamines and corticosteroids in the injured patient rise enormously. These anti-insulin hormones produce the well-known phenomenon of insulin resistance, one consequence of which is reduced utilization of carbohydrate as an energy source.

Gastrointestinal disease with increased loss of intestinal contents through fistula drainage and diarrhea causes additional antianabolic effects. The loss of intestinal contents results in the depletion of electrolytes and trace elements such as zinc, which may then adversely affect nitrogen balance.

Protein Metabolism

The human body is built around a framework of proteins that are not stored to any appreciable extent in an expendable form. The continued loss of body protein during starvation and/or injury is a major cause of morbidity and mortality resulting from malnutrition and/or trauma. Hence, a major goal of nutritional support has been prevention of further protein loss and restoration of total body protein.

The normal adult has a relatively constant cell population; once each cell is replete with protein, further protein retention cannot occur except in two situations. Additional protein retention occurs in the well-nourished adult when cellular hypertrophy is stimulated (e.g. by exercise of muscle) and during the development of obesity due to surfeit feeding.

However, the depleted adult can increase cellular protein in a manner analogous to that of the growing infant. In such a person the ability to retain nitrogen is more evident than in the normal adult. In depleted patients with hypocaloric feeding about 7.5 mg of nitrogen are retained with every kilocalorie of energy intake (18). As caloric intake increases, the ratio of nitrogen retention to caloric intake decreases such that, when caloric intake exceeds energy requirements, only 1.5 mg of nitrogen are retained per kilocalorie. This is associated with an increase in resting energy expenditure. The tissue laid down at the former ratio is largely composed of protein whereas with the latter ratio the excess energy is stored as body fat. Thus in essentially well-nourished human volunteers, positive nitrogen balance is attained only when a large number of calories are given (45–50 kcal per kg body weight) with 15–16 g nitrogen per day.

During starvation, the obligatory nitrogen loss can be reduced by up to 50% by simply giving amino acids without added energy. Blackburn et al (10) hypothesized that under these circumstances, reduced insulin levels promoted fat mobilization and energy from free fatty acids derived from endogenous fat stores aided protein synthesis from the infused amino acids. They suggested that this protein-sparing effect of amino acid infusions might be of benefit to the post-operative patient. However, although the degree of protein-sparing seen with amino acid infusions was greater than that of isocaloric glucose infusions, there was a significant increase in the blood urea nitrogen associated with the inefficient utilization of the amino acids. In clinical studies of patients following elective surgery, the routine use of amino acids did not improve the overall outcome. In view of their cost, amino acids offered no benefit over the traditional glucose support in the average post-operative patient.

Although both amino acid and glucose infusions have protein-sparing effects in starvation, the main determinant of protein-sparing appears to come from amino acids. In a controlled study of patients undergoing surgical procedures, Greenberg et al (28) assigned subjects to a random protocol consisting of four different regimens—either 5% dextrose alone, amino acids alone (1 g per kg ideal body weight), amino acids with hypocaloric glucose, or amino acids with lipid ($<$ 550 kcal per day). The study suggested that protein-sparing (defined as a reduction in the degree of negative nitrogen balance) resulted from amino acids alone and that the addition of 500–600 nonprotein calories did not influence the outcome. Note that the additional calories given in the study were not sufficient to meet metabolic requirements, and the results cannot be interpreted to mean that additional calories that meet metabolic energy needs may not increase nitrogen retention. The next question was whether it was possible to obtain neutral or positive nitrogen balance without additional energy in depleted patients.

Greenberg & Jeejeebhoy (27) showed that by increasing the amino acid infusion from 0.83 to 1.83 g per kg body weight without added energy, the net nitrogen balance rose from –3.66 g per day to +1.54 g per day. This comparison clearly indicated that high-dose amino acid infusions can effect a positive nitrogen balance even when the results are corrected for the increased blood urea nitrogen. Thus it may be possible to induce a positive or neutral nitrogen balance in depleted and malnourished subjects without the provision of additional calories, provided the amount of protein given is much higher than that required to maintain nitrogen balance with a nonprotein energy intake. The ability to induce a positive nitrogen balance without positive energy balance is contrary to classical teaching but has been confirmed (11) in a comparable patient population.

Other clinical studies with amino acid infusions in starved patients have characterized to a degree this protein-sparing phenomenon. Kaminski et al (37) have quantitated 3-methylhistidine excretion and have shown that amino acid infusions have a predominantly muscle-sparing effect. In addition, Skillman et al (69) have measured an increased albumin synthesis in patients receiving amino acids. Thus it appears that the provision of amino acid substrate both reduces protein catabolism and enhances protein synthesis in the starved patient.

Route of Amino Acid Administration

To determine whether oral amino acids are utilized differently from intravenous ones, keeping all other parameters constant, Patel et al (57) infused casein hydrolysate intravenously and through a nasogastric tube into depleted patients. Nonprotein calories were given intravenously in quantities sufficient to meet metabolic requirements; nitrogen balance and whole blood amino acid profiles were then measured. No difference was noted between the nitrogen balances during the two periods. However, when oral casein was substituted for casein hydrolysate, nitrogen retention was significantly better than with oral or intravenous casein hydrolysate. Comparison of the whole blood aminograms demonstrated a deficiency in sulphur containing and aromatic amino acids with the hydrolysate as compared with whole casein. These findings indicate that the route of administration of protein does not affect its utilization. Similarly, McArdel et al (50) demonstrated similar improvements in nitrogen balance and somatic protein (as measured by 3-methylhistidine excretion) in depleted patients given a 7% amino acid solution with 50% dextrose either intravenously or enterally. They advocated use of the enteral route when possible owing to the ease of handling, and the absence of the elevated glucose and insulin levels that were seen with the intravenous system.

Amino Acid Composition

The amino acid composition is of greater importance than the route of administration, and several authors have set out to determine the ideal amino acid mix. By analyzing the plasma amino acid levels in infants and newborns, Anderson et al (1) determined the amount of infused amino acid that caused an abrupt change in the plasma concentration of that amino acid. (When amino acid infusion exceeds requirements, plasma levels tend to rise abruptly.) Using this technique they have examined a number of mixtures and administration rates and have indicated the combinations likely to provide a balanced input of amino acids. Using a slightly different technique, Winters et al (79) performed a computerized analysis of predicted and observed values of plasma amino acids with different mixtures

and have predicted a "growth" mixture that would result in the optimal amino acid pattern in neonates and infants.

The role of the branched-chain amino acids (BCAAs) in nitrogen balance is of particular interest. Buse et al (14) observed that BCAAs are transaminated to the corresponding alpha-ketoacids and alanine. Therefore, it was suggested that BCAA catabolism may play a role in providing muscle with energy during periods of exercise or limited glucose availability. BCAAs specifically stimulate muscle protein synthesis in vitro (24). Postabsorptively, BCAAs constitute a major part of amino acid uptake by leg muscle (77). In fasting human adults, the provision of BCAAs in the form of leucine resulted in a significant reduction in negative nitrogen balance. (63). Wolfe (80) has demonstrated an equivalent nitrogen-sparing effect of an infusion of the 3 BCAAs alone when compared with a balanced amino-acid infusion. Sherwin (63) and Wolfe (80) showed a 2- to 10-fold increase in the plasma level of the BCAA studied, but the glucose response to the infusion was not consistent between studies. At this time, the role of the BCAAs in protein and energy metabolism is not entirely understood, but they appear to be important in promoting nitrogen retention.

Specific amino acids have been used therapeutically in patients with chronic renal failure and hepatic failure. In patients with end-stage renal disease, histidine is an essential amino acid, and dietary supplementation with histidine-replete essential amino acids was associated with positive nitrogen balance and increases in albumin and hematocrit (45). BCAAs appear to have a role in optimal nutrition of the cirrhotic. The depressed levels of the BCAAs and the elevated levels of alanine, tyrosine, methionine, and tryptophane seen in cirrhosis can be normalized with a BCAA-enriched diet. Normalizing the plasma amino acid pattern in patients with liver disease may be of importance in the management of hepatic encephalopathy and the patient's overall nutritional status (20).

Energy Metabolism

Studies by Kinney and his colleagues (42) in the early 1970s suggested that increased energy requirements may follow trauma and injury. Energy requirements may increase with trauma and sepsis by as much as 40–60%, and by 100% in burns. It follows that injured-septic patients may require as much as 4000–6000 kcal per day. However, recalculation of the figures based on Kinney's findings suggest a more modest caloric requirement. For example, if the basal metabolic rate of an adult (approximately 25–28 kcal per kg per day) were increased by 60%, as has been observed in severe sepsis, then the caloric requirement would be approximately 40–45 kcal per kg per day which, in a 70 kg adult, would be no more than 2800–3100 kcal per day. Hence in most very sick patients with sepsis and gastrointestinal

disease, one would not expect to exceed this figure. The need in patients with burns is somewhat higher.

Recent determinations of metabolic rates by indirect calorimetry in acutely sick and septic patients have suggested that actual requirements may be even lower. Askanazi et al (5) and Roulet et al (60) showed that the measured metabolic rate was only 13–14% above the expected metabolic rate calculated for these patients by the Harris-Benedict equation. This figure is considerably lower than that suggested by earlier observation. The discrepancy may be explained in part by the fact that, in addition to being stressed, these patients were malnourished and thus had lower initial basal energy requirements.

Is it beneficial to give calories in excess of the requirements in such patients? Giving extra calories may actually be harmful, particularly in the hypermetabolic patient. The evidence for this is provided in the studies of Askanazi et al, who noted two adverse effects when glucose was provided in amounts that significantly exceeded the metabolic rate. First, both urinary norepinephrine execretion and resting energy expenditure rose (5). Second, oxygen consumption and carbon dioxide production increased (7). The provision of excess calories in the form of glucose results in an undesirable respiratory load and an increase in the secretion of antianabolic hormones. In addition, the provision of excess glucose calories is associated with the development of a fatty liver, which may become clinically significant (12, 35, 51) However, all these effects of surfeit feeding were noted when glucose was the only source of nonprotein calories.

Would a mixed calorie source of glucose and lipid be more desirable than glucose only in such patients? Initial studies (46) suggested that lipid had no role in promoting nitrogen retention when given as the only caloric source to acutely ill patients. Subsequently, in a controlled trial of malnourished patients, Jeejeebhoy et al (32) showed that when patients were given a constant infusion of amino acids of 1 g per kg body weight per day together with approximately 60–70 g of glucose to cover minimal glucose requirements, then the additional provision of 40 nonprotein kcal per kg per day either as glucose or as lipid resulted in an equal sparing of nitrogen. Thus lipid calories were found to be equivalent to glucose calories in their effect on protein balance. Although all patients were in positive nitrogen balance throughout the study, the degree of this positive balance was temporarily altered when the patient was switched from glucose to lipid or vice versa. However, after an initial period of two or three days following the change in caloric source, this difference was abolished and the nitrogen balance with the two sources became equivalent again. In addition, it was shown that the equivalent nitrogen balances occurred with extremely different circulating substrate-hormone profiles. The patients receiving all their

calories as glucose had high levels of pyruvate and lactate with relatively lower levels of free fatty acid and virtually no ketones. There was a corresponding marked increase in the circulating insulin levels in these patients. In contrast, those receiving most of their nonprotein calories as lipid had lower lactate and pyruvate levels but significantly higher levels of free fatty acids and ketones. Their insulin levels were correspondingly low. This was interpreted as indicating that the depleted patient could adapt to utilize either glucose or lipid as an energy substrate. Thus it was possible to promote nitrogen retention by two very different patterns of hormone response. The most physiologic substrate-hormone profile has been associated with a 50%–50% mixture of lipid and glucose calories.

This comparability of lipid and glucose calories in promoting nitrogen balance in depleted patients has been confirmed by many other investigators (8, 19, 25, 48, 81, 82). There are, however, both metabolic and clinical advantages to be gained with the lipid system. Carpentier et al (15) have demonstrated persistent endogenous fat mobilization during total parenteral nutrition using glucose as the only energy substrate. Askanazi et al (6) have found that the respiratory quotient (RQ) in similar patients ranged from 0.96 to 1.04, implying that glucose was utilized for both oxidation and lipogenesis. Thus, during glucose-based total parenteral nutrition (TPN), both mobilization of fat for oxidation and synthesis of fat from glucose occur together. Moreover, in patients receiving a mixture of lipid and glucose for nonprotein calories, the RQ ranged from 0.85 to 0.89, implying a net oxidation of the fat being infused for energy.

The clinical advantages of lipid relate to the effect of TPN on respiration and body composition. Askanazi et al (6) have measured a 20% increase in CO_2 production and a 26% increase in minute ventilation in patients receiving all nonprotein calories as glucose compared with those receiving the lipid-glucose mixture. MacFie et al (48) assessed the change in body composition in depleted patients receiving TPN using either glucose alone, or glucose plus lipid, as the energy source. Although weight gain was similar in both groups, with glucose alone it was limited to fat and water, while with lipid and glucose it was largely nitrogen. Finally, Messing et al (53, 54) and Jeejeebhoy et al (34) have shown that infusion of lipids did not increase liver fat, while infusing glucose did do so.

The question then arises whether the injured and septic patient utilizes fat oxidation as a source of energy production. Carpentier et al showed that patients who were injured and septic continued to mobilize (15) and oxidize (16) fat despite receiving all their nonprotein calories as carbohydrate. Hence, obligatory fat oxidation appears to be prevalent in patients who are injured and septic. Furthermore, Burke et al (13) showed a limit to glucose utilization in patients with burns who were receiving all their calories as

glucose. Only 55% of the energy requirement appeared to be derived from glucose oxidation, implying that the remaining calories were derived from fat oxidation. Hence evidence from two sources suggests that in the injured-septic patient fat oxidation provides a significant part of the energy.

Would giving fat as a source of exogenous calories benefit such hypermetabolic patients? In order to answer this question, Roulet et al (60) randomly divided critically ill patients into two groups. Each group was studied while receiving 5% glucose/water and again while receiving complete parenteral nutrition (amino acids, energy, electrolytes, vitamins, and trace elements). In one group all the nonprotein calories were given as glucose; the other group received half their nonprotein calories as lipid and half as glucose. The order of the infusions of glucose/water or parenteral nutrition was random, and both groups were given comparable amounts of amino acids and total calories (while receiving parenteral nutrition). The results of this study confirmed the observations of Askanazi et al (6) that giving parenteral nutrition with all nonprotein calories as glucose resulted in a significant increase in carbon dioxide production when compared to the mixture of glucose and lipid. The respiratory load created by the need to dispose of carbon dioxide was significantly reduced when a glucose-lipid mixture was given.

In addition, these injured-septic patients continued to have high plasma free fatty acids even when all the calories were given as glucose. Thus fat mobilization continued in these patients even when all exogenous calories were given in the form of glucose. These observations by Roulet et al (60) agreed with those of Carpentier et al (15) and Askanazi et al (6) and were consistent with those of Burke et al (13). Finally, using ^{14}C-leucine, the glucose-lipid mixture was associated with reduced leucine oxidation and increased protein synthesis in relation to catabolism when compared with glucose as the sole source of nonprotein calories. Hence it appears that the significant benefits of lipid in hypermetabolic patients are reduced carbon dioxide production, reduced leucine oxidation,and improved protein economy.

In summary, septic and hypermetabolic patients continue to mobilize and oxidize endogenous fat for energy, even in the presence of the marked increase in glucose and insulin levels associated with amino acid plus glucose infusions. Morever, there is a limit to the utilization of the glucose infused in these patients. This "insulin resistance" likely results from increased circulating anti-insulin factors such as cortisol and norepinephrine since insulin antibodies are unlikely and an intracellular inhibition of insulin effect has not been measured. It may be possible to overcome the "insulin-resistance" with exogenous insulin; however, the other benefits of lipid as a part of the calorie source make it the preferable alternative. The optimal

proportion of lipid to glucose is as yet undetermined, but the provision of 30–50% of calories as lipid has been free of significant side effects and has had the beneficial metabolic effects indicated above.

Essential Fatty Acid (EFA) Deficiency

Certain fatty acids, principally linoleic acid, are essential for the human (30). Linoleic acid, which has 18 carbon atoms and two double bonds, is converted to a longer-chain fatty acid, arachidonic acid, with 20 carbon atoms and four double bonds (tetraene). It appears that, when linoleate is deficient, the same system that elongates the chain of linoleate will use oleate as a substrate and will elongate it to a 20-carbon-atom fatty acid, eicosatrienoic acid, with three double bonds (triene). Since oleate can be synthesized from carbohydrates, there is an alteration in the plasma fatty acid pattern during essential fatty acid deficiency. Linoleic acid and arachidonic acid are both reduced and in their place eicosatrienoic acid appears in the circulation. Holman (30) measured the ratio of eicosatrienoic acid to arachidonic acid as the triene-tetraene ratio and found that elevation of the triene-tetraene ratio was indicative of EFA deficiency.

Prior to the advent of parenteral nutrition, a clinical syndrome of skin rash with appropriate alterations in plasma fatty acid pattern was recognized as indicating EFA deficiency in infants. Adults did not seem to suffer the syndrome because they have sufficient stores of essential fatty acids in their adipose tissue to prevent this deficiency. However, with the advent of parenteral nutrition based on a system of continuous infusion of a fat-free solution, EFA deficiency occurred in adults. EFA deficiency in patients receiving TPN is characterized clinically by a skin rash, reduced plasma levels of linoleate, and an elevated triene-tetraene ratio. These changes were corrected by infusing an intravenous lipid emulsion containing linoleate.

Wene et al (78) recently observed the pattern of EFA deficiency as early as 10 days after starting a fat-free parenteral nutrition, prior to the onset of any clinically observable features. EFA deficiency occurs early in adults receiving TPN because when glucose is infused continuously, high insulin levels block the release of free-fatty acids from adipose tissue stores. Hence plasma fatty acids originate from either exogenously infused lipids or, in the case of fat-free parenteral nutrition, from endogenously synthesized lipids derived from carbohydrates. Since the endogenously synthesized lipids do not include linoleate, the pattern of fatty acids alters rapidly to one seen with EFA deficiency. Hence, during continuous glucose infusion the only way to maintain plasma essential fatty acid levels would be to infuse lipids continuously. Since intravenous lipid can reverse and prevent EFA deficiency, various regimens have been suggested with variable amounts of lipid given either once, twice, or three times a week, but none of these regimens

has been tested rigorously. However, the recent indication that lipid would be advantageous as a calorie source has made superfluous the concept of giving lipids only as a source of essential fatty acid.

Is linoleate the only essential fatty acid in the human, or does linolenate also serve as an essential fatty acid? This fatty acid appears to be necessary for proper myelination of the central nervous system in newborn animals and therefore may have to be provided when parenteral nutrition is used in the newborn. However, the exact need for, and role of, this fatty acid in the human remains to be determined.

Electrolytes

The internal environment of a cell largely consists of a number of cations and anions; the principle cations are potassium and magnesium and the principle anions are phosphate and protein. The repletion of cell contents in the malnourished patient depends on providing not only nitrogen but also the other constituents of the cell, mainly the electrolytes potassium, magnesium, and phosphate. It has been shown that in protein-calorie malnutrition there is also a depletion of total body potassium and total body magnesium. A number of metabolic abnormalities will occur during TPN unless these electrolytes are provided. Rudman et al (61) showed, in a very elegant study, that nitrogen balance only became positive during parenteral nutrition when there was a concomitant administration of potassium and phosphate, highlighting the need for electrolytes during parenteral nutrition.

Sodium

This cation is principally distributed in the extracelluar fluid. Its role during parenteral nutrition, apart from its role in maintaining extracellular and circulating volume, lies in the relationship between sodium retention and the provision of calories. When nonprotein calories were given as carbohydrate, sodium was retained, a phenomenon not seen when calories were given as fat (75). It is not surprising therefore that during glucose-based parenteral nutrition, there was a significant and marked gain of weight, most of which could be accounted for by retention of extracellular water (83). This water (and inferentially sodium) retention plays a major part in the dramatic weight gains seen during glucose-based parenteral nutrition. A possible clinical counterpart to this phenomenon may be so-called "refeeding edema." This dramatic picture of fluid gain may occur in severely malnourished patients who are abruptly started on parenteral nutrition, and may be severe enough to result in congestive heart failure. In addition, the

interstitial accumulation of sodium and water may interfere with gas exchange at the pulmonary alveolar level and contribute to respiratory failure. In comparison, the weight gain with lipid systems is associated with gain in protein and not water (48). These clinical aspects in malnourished patients should be considered. The patient should be renourished cautiously, particularly avoiding an excess of glucose calories and perhaps by the use of significant amounts of lipid.

Potassium

Potassium is the main intracellular ion. During parenteral nutrition, total body potassium may increase. Body potassium is particularly increased when glucose is the only source of nonprotein calories (49, 67), and MacFie et al have measured a further increase when insulin is added (49) during the administration of parenteral nutrition. On the other hand, when lipid is the major source of calories the increase in body potassium is not as great as with glucose (67). This has been interpreted by some investigators as suggesting that the increase in "body cell mass" as estimated by exchangeable potassium is better with glucose than with lipid (67). Since the objective of these investigators was to increase the "body cell mass" derived from total measurements of total body potassium alone, it is not surprising that this finding was interpreted as indicating the superiority of glucose over lipid as a source of calories. However, further investigation has shown that total body potassium does not reflect total body nitrogen. During the administration of parenteral nutrition with glucose as the main source of calories, the increase in body potassium was not associated with an increase in body nitrogen (52). In addition, MacFie et al (49) have measured an increase in total body potassium without change in nitrogen in patients receiving glucose-based TPN and insulin. This indicates that the rise in body potassium is not a true index of total protein synthesis or total cellular contents, but may reflect an independent increase in potassium due to other processes. Exactly why potassium increases without nitrogen has not been determined, but potassium may be retained with glycogen, or this may reflect a transient intracellular shift of potassium associated with elevated levels of glucose and insulin. From what is known of cell composition it appears that such an increase is not representative of an increase in the cellular mass or cellular contents, since such an increase in cell contents or mass would be expected to be associated with a rise in all cellular constituents. Thus the use of total body potassium as an index of an increase in either the lean body mass or in the total body nitrogen can no longer be considered reliable. This particularly applies to acute changes observed during the administration of parenteral nutrition.

Magnesium

The concentration of magnesium falls when parenteral nutrition is instituted. Using balance studies, Freeman et al (22) have shown that nitrogen balance is not optimal unless magnesium is given concomitantly. It has been suggested that approximately 30 meq should be given per day to optimize nitrogen retention. These findings are not surprising since magnesium is an important intracellular cation and is depleted during protein-caloric malnutrition. As such, the restitution of total cellular contents would be expected to be associated not only with restitution of nitrogen but also of magnesium.

Phosphorus

This major intracellular anion is a constituent of 2–3,diphosphoglycerate (2–3,DPG). Therefore, anabolism of the cell would be expected to be associated with retention of phosphorus together with other intracellular elements such as potassium, magnesium, and protein. During the administration of glucose-based parenteral nutrition, the plasma level of phosphorus rapidly falls as this element is transported into cells under the influence of insulin and glucose. In earlier studies with total parenteral nutrition, Silvas & Paragas (68) showed that the serum phosphorus levels may fall to almost undetectable values; associated with this fall is a clinical syndrome consisting of disorientation, tremors, convulsions and coma, which may be fatal. The hypophosphatemia may be avoided and protein synthesis optimized by the administration of appropriate amounts of phosphorus during parenteral nutrition.

Acid-Base Balance

The administration of some amino acid mixtures is followed by the development of a nonketotic metabolic acidosis with hyperchloremia. When the basic amino acids lysine, histidine, and arginine are administered in their chloride form their metabolism causes an accumulation of hydrogen ions, which together with the chloride results in acidosis and hyperchloremia. However, when these amino acids are administered as acetates the production of hydrogen ion is balanced by concomitant production of bicarbonate from the metabolism of acetate. It has therefore become customary for all amino acid mixtures to be buffered with acetate.

Trace Elements

Trace elements have been recognized as being important in animal nutrition for several years; 15 elements have been identified in this category. In the human the recognition of the value of trace elements has been slow, but with the advent of parenteral nutrition the syndromes of zinc, copper, chromium, and selenium deficiency have been recognized and reported.

Zinc

Zinc is an important element in a number of metallo-enzyme systems. In particular, since it is important for the action of deoxythymidine kinase (58), all cell proliferations require the presence of zinc. It is also important in the maintenance of cellular immunity and delayed hypersensitivity. Finally, zinc is an integral part of insulin as secreted by the pancreas, and its appears that the deficiency of zinc is associated with abnormalities of carbohydrate metabolism.

As far as tissues are concerned, zinc is an integral part of muscle, and under conditions of increased catabolism there is an increased loss of zinc in the urine. During parenteral nutrition in which no zinc was added to the infusate, the plasma zinc levels dropped at a steady rate so that subnormal levels were observed between 2–7 weeks (21, 70). In addition, patients receiving parenteral nutrition without zinc developed a syndrome of redness, scaling, and maculovesicular rash around the nasolabial folds, mouth, and genitalia, together with reddening of the palms and the soles with desquamation (4, 39). Hair loss and a loss of the senses of taste and smell also occurred. The lesions were not unlike those of acrodermatitis enteropathica, which is due to zinc deficiency. The plasma levels of zinc in these patients were grossly decreased, and infusion of zinc reversed the lesions. During this manifestation of zinc deficiency, the skin became infected with staphylococci and fungi, which could not be cleared without giving zinc. In another context, Golden et al (26) noted that children with protein-calorie malnutrition who were anergic could be rendered reactive again simply by the local application of zinc to a site where delayed cutaneous hypersensitivity was being tested. Hence it appears that even in the face of protein-calorie malnutrition zinc deficiency seems to be a paramount cause of the immune deficiencies that are observed.

Copper

Copper is another trace metal with important functions in human metabolism. It is involved in intestinal iron absorption, hemoglobin synthesis, mitochondrial function, collagen metabolism, and is a constituent of oxidase enzymes. Despite the finding (70) that patients receiving total parenteral nutrition without added copper for periods from 1.5–2 weeks had consistently declining levels of plasma copper, clinical manifestations of copper deficiency have been uncommon. Karpel et al (38) described an infant with hypochromic normocytic anemia, neutropenia, and skeletal abnormalities (osteoporosis and metaphyseal irregularity) in association with hypocupremia after 7.5 months on TPN without copper. These abnormalities responded well to the addition of copper. Since then, several cases (9, 17, 76) of adult anemia and neutropenia in association with hypocu-

premia have been described—all responding to copper supplementation. Thus it appears that clinical manifestations of copper deficiency exist but that plasma levels do not accurately reflect body copper stores, which may still contain sufficient copper to fulfill its metabolic role.

Until recently the copper requirements of TPN had not been determined. Shike et al (65) have found daily requirements to be approximately 300 μg in patients without diarrhea and 500 μg in patients with substantial losses of fluids from the gastrointestinal tract. The dose must be decreased in patients with obstructive jaundice, since copper is excreted via the biliary tract.

Chromium

An organically bound form of chromium called "glucose tolerance factor" appears to be required for optimal glucose absorption and utilization. Although chromium supplementation has been reported to improve glucose tolerance in malnourished children (29, 31) and elderly diabetic subjects (44), in these cases the situation has been complicated by many possible micronutrient deficiencies. Direct evidence for the role of chromium deficiency in human disease was presented by Jeejeebhoy et al (33), who described a patient who developed weight loss, peripheral neuropathy, ataxia, and glucose intolerance associated with low chromium levels in blood and hair after 3.5 years on home-TPN. Glucose intolerance and central nervous system abnormalities associated with low serum chromium levels have also been seen in another patient on long-term TPN (23). In both patients, the abnormal glucose metabolism and neurologic symptoms were rapidly corrected with chromium supplementation to the TPN solution.

The time course in these cases suggests that the human body has large stores of chromium. However, when the stores are depleted, the consequent clinical abnormalities of impaired glucose tolerance and central nervous system symptoms occur, paralleled by decreasing blood levels of chromium. Although chromium balance studies have only been performed on a single patient, it appears that 20 μg of chromium daily prevents chromium deficiency.

Selenium

Selenium is important in muscle metabolism and function. It is an essential component of glutathione peroxidase, which helps prevent oxidative damage to cells by peroxides and free radicals. The necessity of dietary selenium has long been known in animals. A dietary selenium deficiency has been shown to produce white-muscle disease in sheep (2) and an exudative diathesis in poultry (72) when these animals are raised on feed grown in selenium-deficient soil. Despite this, evidence for the role of selenium deficiency in human disease has been slow in coming. It is now suggested that

Keshan disease, a congestive cardiomyopathy occurring in certain rural areas of China, is due to selenium deficiency in locally grown foods and may be prevented by selenium supplementation (3, 40, 41). Recently, Johnson et al (36) have described a case of congestive cardiomyopathy with the pathologic features of Keshan disease, associated with reduced erythrocyte and cardiac selenium and glutathione peroxidase levels in a patient on home-TPN unsupplemented by selenium for 4 years. Van Rij et al (74) have also described a patient from New Zealand (a well-known selenium deficient zone) who developed muscular pain and weakness associated with reduced erythrocyte selenium and glutathione peroxidase activity after receiving selenium-deficient TPN for only 30 days. In this instance, addition of selenium to the TPN solution corrected the symptoms as well as plasma selenium levels within 1 week. However, erythrocyte selenium and glutathione peroxidase levels did not change within this time frame.

It would appear, then, that several factors might influence the development of selenium deficiency including geographical location, preceding diet and nutritional state, excessive GI losses, and duration of selenium-deficient TPN. Balance studies (74) in 6 patients with no selenium supplementation in their TPN solution showed a negative balance with a mean of -10 ± 1.7 μg/day. Although further work is necessary, it seems safe to assume that selenium requirements are somewhat greater than 10 μg per day.

Vitamins

The precise vitamin requirements in TPN are still not known. Until recently, the provision of vitamins to such patients has been based on oral dosage schedules, and most institutions have used a multiple vitamin preparation in the hopes that it will provide an adequate vitamin supply without toxicity. However, recent research in parenterally fed patients has helped clarify this area.

An investigation of the requirements for the water-soluble vitamins, thiamine (B_1), riboflavin (B_2), pyridoxine (B_6), niacin, pantothenic acid, and ascorbic acid (C) has demonstrated that regular use of a well-known multivitamin infusion (MVI) maintained adequate blood levels of several vitamins including riboflavin and ascorbic acid (56). Kishi et al (43) studied levels of thiamine and pyridoxine in patients receiving TPN and concluded that 5 mg/day of thiamine-HCl and 3 mg/day of pyridoxine-HCl are sufficient for these vitamins—amounts found in most multivitamin preparations. Additionally, Jeejeebhoy et al (34) have reported vitamin intakes and levels in 6 long-term TPN patients, again demonstrating that adequate levels of water-soluble vitamins can be provided by routine multivitamin preparations.

Vitamin B_{12} and folic acid are not provided in many multivitamin preparations. However, vitamin B_{12} has long been used parenterally in patients

with pernicious anemia where the daily maintenance dose has already been determined—approximately 3–5 μg per day. Folate deficiency is relatively common in hospitalized patients and, although much larger doses have traditionally been given, Lowry et al (47) have demonstrated the adequacy of as little as 0.69 mg per day of folic acid.

The fat-soluble vitamins are also supplied in many multivitamin preparations. Although the problem of vitamin A toxicity and hypercalcemia has been reported, it is rare. Lowry et al (47) studied vitamin A levels in 40 patients given TPN in hospital and concluded that normal serum vitamin A levels can be maintained using 1500–2000 IU/day. In our home parenteral nutrition patients, withdrawal of vitamin A entirely has not caused low serum levels in 11 patients after 6 months, probably because of substantial body stores. Thus it appears that the margin of error for vitamin A administration is wide but that about 2000 IU/day may be sufficient.

Although vitamin E is supplied by the polyunsaturated fatty acids contained in lipid, Jeejeebhoy et al (34) have shown reduced serum vitamin E levels in long-term TPN patients even with daily lipid infusions. More recently, Thurlow et al (73) have described 10 patients who developed low serum vitamin E levels, in vitro platelet hyperactivity, and in vitro red blood cell hemolysis during TPN. These abnormalities were corrected in 7 patients with 50 mg d,l α-tocopherol given daily. It appears, then, that at least 50 mg of vitamin E must be supplied daily.

Vitamin K is normally derived from diet and produced by gut bacteria. In a patient receiving TPN the latter source may itself suffice. However, if changes occur in the gut flora (e.g. with antibiotics) this supply may no longer be adequate. In this case weekly supplementation with 10 mg of Synkavite (sodium menadiol diphosphate) seems sufficient.

Investigation of calcium and bone metabolism in patients receiving long-term TPN (64) revealed that with average daily intakes of vitamin D_2 amounting to 250 IU (along with 400 mg calcium and 500–700 mg phosphate), the plasma 25–OH cholecalciferol levels were normal. However, a syndrome of continued calcium loss from the skeleton with a histological picture of increased bone osteoid and reduced calcification of the new osteoid was noted (66). These changes occurred despite the normal levels of 25-OH vitamin D. However, these patients were also found to have low levels of 1,25-dihydroxy vitamin D, perhaps as a result of suppressed secretion of parathormone caused by calcium infusion in the TPN solution. It was tempting to speculate that the changes were due to a deficiency of 1,25-dihydroxy vitamin D. This speculation was not substantiated when trial withdrawal of vitamin D from the infusion caused clinical remission of bone pain and fractures, reduction in the increased bone osteoid, and increase in the area of calcifying new osteoid despite continuing low levels of 1,25-dihydroxy vitamin D. Hence this syndrome is clearly aggravated by

giving vitamin D. At present, the needs for this vitamin in TPN have not been established, but the use of vitamin D in short-term TPN is not recommended.

Although the genetic syndrome of biotin-responsive carboxylase deficiency has been known for some time (59, 71), acquired biotin deficiency had until recently been shown to occur only in association with raw egg ingestion (62), the whites of which contain a protein capable of binding biotin intraluminally and preventing its absorption. Despite low plasma biotin levels in 6 long-term home-TPN patients, Jeejeebhoy et al (34) found no pathology. However, Mock et al (55) have recently documented a child who, after 3 months on TPN, developed a clinical syndrome consisting of an exfoliative rash and organic aciduria associated with reduced plasma, whole blood, and urinary biotin concentrations. Resolution of the clinical and biochemical features occurred after biotin supplementation of the TPN. Although still possibly due to a genetic deficiency, the evidence appears strong that this was indeed an acquired defect resulting from previous nutritional deficiency and long-term antibiotic therapy. Despite this, the need for routine biotin supplementation in TPN is still not resolved.

In summary, most vitamins are easily and safely provided to the patient on TPN. However, some controversies still exist. It is our present practice to supply a multivitamin preparation containing all vitamins except A, D, E, and biotin on six out of seven days per week. On the seventh day, vitamins A and D are added in the doses of 1000 IU and 100 IU, respectively. Vitamin E is supplied by the lipid used in the TPN regimen (50% of nonprotein calories), but on the basis of recent information will probably have to be increased. The issue of biotin has not been decided upon as yet.

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