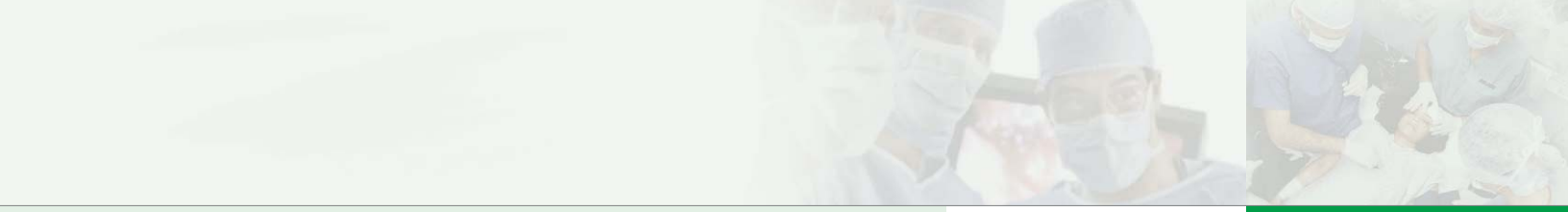

CHAPTER 7

Metabolism in Surgical Patients

Nicholas E. Tawa, Jr., MD, PhD and Josef E. Fischer, MD

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Metabolic Adaptations in Catabolic States and Regulation of Nitrogen Balance
Fundamentals of Artificial Nutrition
Practical Approach to Artificial Nutrition
Controversies in Artificial Nutrition
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OVERVIEW

Artificial Nutrition—Importance and History

Among advances in surgery achieved in the 20th century, nutritional support, along with antibiotics, blood transfusion, critical care monitoring, advances in anesthesia, organ transplantation, and cardiopulmonary bypass, ranks high. During this time, parenteral nutrition has evolved from initial enthusiastic acceptance to more critical review, with demands for efficacy. Dudrick and associates in 1968 first demonstrated that intravenous (IV) nutrition would support normal growth rates in puppies, and parenteral alimentation began to be widely applied in the United States. In the 1960s and 1970s, it was standard practice to feed patients 3000 to 5000 kcal/day (*hyperalimentation*) in an effort to attain an anabolic state. It was not appreciated at that time that such overfeeding practices were potentially dangerous and that with excessive carbohydrate and lipid infusion, the body's ability to metabolize these nutrients was exceeded, thus predisposing patients to iatrogenic immune and hepatic dysfunction.

Today, nutrition is provided in more moderate amounts, and nutritional needs in specific disease states have been explored. Some investigators have also proposed the use of specific nutrient components as drugs (termed *nutritional pharmacology*), an approach that will be validated only when its pathophysiologic mechanisms are better defined. Although modern practice is to make aggressive use of the gut for nutritional support, IV nutrition remains a critical therapy in instances in which enteral support cannot be achieved, either because the gut cannot be used or because caloric requirements cannot be met by the gut alone and must be supplemented parenterally. Studies of body composition in critical illness show, however, that even current approaches to IV nutrition remain unsatisfactory. Thus, in a normal individual, body tissue is compartmentalized as approximately 30% adipose, 30% lean body mass (protein), and 30% extracellular fluid (water). In catabolic illness, extracellular fluid increases to 50% to 60% of total body mass secondary to sodium retention, whereas fat and lean body tissue decrease to approximately 20% each. Although IV nutrition can clearly retard the loss of lean body mass under such conditions, it has proved difficult to induce net accumulation of body protein in a nongrowing adult host without strenuous exercise. Increasing the amount of IV nutrition beyond basal requirements, without exercise, insulin, or other hormonal alterations, in an effort to enhance lean body mass only increases total body water and fat content further, with no beneficial effect on body protein.[1] This is particularly true in patients with sepsis. Furthermore, in patients with malignancy, efforts to nourish the host may increase growth of the tumor.

Clinical Sequelae of Impaired Nutrition

Numerous studies have clearly shown an increased incidence of nosocomial infection, longer hospital stay, and increased mortality in patients with significant unintentional weight loss (>10%) before their acute illness. Even in an individual with initially normal nutritional status, after 7 to 10 days of inanition, the body's ability to heal wounds and to support normal immune function begins

to be impaired. Such deficits include diminished complement and immunoglobulin production, poor cellular immunity, and impairment of various aspects of leukocyte action, including chemotaxis, phagocytosis, and oxidative burst. Other consequences of inadequate nutrition in the postoperative period include poor tissue repair and wound healing and loss of muscle function and strength as a result of progressive muscle wasting, which may contribute to reduced ventilatory performance and prolonged ventilator dependence. Overall, malnutrition will be limiting to all aggressive surgical and medical therapies.

Incidence of Malnutrition in Hospitalized Patients

In the early 1970s, the widespread prevalence of malnutrition in hospitalized medical and surgical patients was recognized and suggested to have a major influence on clinical outcome.[2] Today, it is estimated that as many as 50% of hospitalized patients may be malnourished. In the usual U.S. hospital setting, starvation is generally the result of either anorexia, such as occurs in cancer, sepsis, or liver disease, or poor intake caused by esophageal or gastrointestinal (GI) obstruction. Other conditions, such as scleroderma, motility disorders or pseudo-obstruction, major gastric resection, inflammatory bowel disease, and short-bowel syndrome, may result in inadequate absorption of nutrients. Inadequate nutrition may also be due to excessive loss, as in patients with GI fistulas or protein-losing enteropathies. However, the most common cause of in-hospital malnutrition is poor food served without assistance to frail individuals and timed for the benefit of personnel rather than patients. Patients are also given nothing by mouth for the most trivial reasons (e.g., radiologic studies), and diets are often not advanced rapidly even after minor operations.

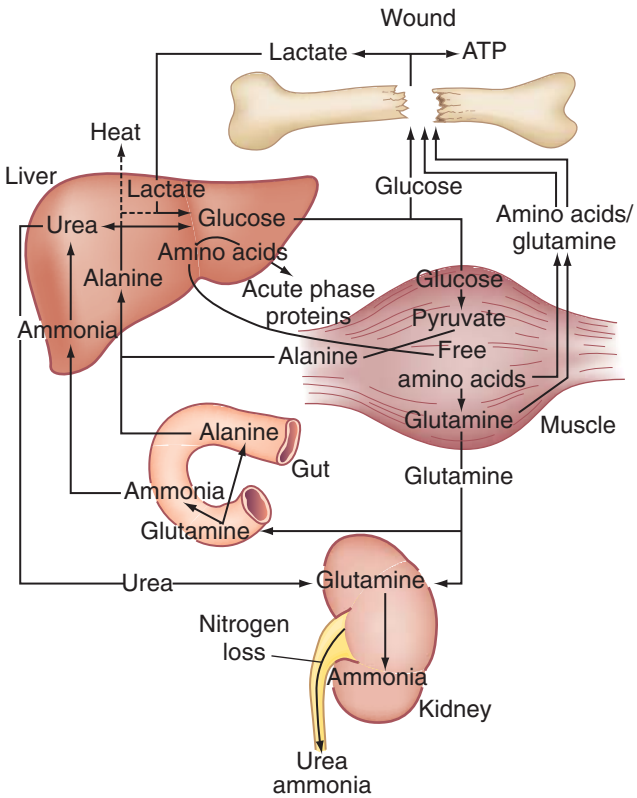


Figure 7-1 Overall scheme of the metabolic response to illness. This scheme includes the metabolic relationship among organs. This relationship has heretofore not been prominently addressed but is now receiving increased attention. One of the articles of faith is that such responses occur as a reaction to injury and are teleologically correct and beneficial. Thus, the wound requires glucose, probably glutamine, and certainly arginine with respect to certain cellular elements. Movement of amino acids from the periphery (muscle) to the liver presumably results in the secretion of acute phase protein, the purpose of which, in turn, is to fight infection. The muscle-gut-liver-alanine-glutamine-glucose cycle is prominently displayed. ATP, adenosine triphosphate. (Adapted from Bessey PQ: Metabolic response to critical illness. In Wilmore DW, Cheung LY, Harken AH, et al [eds]: Scientific American Surgery, Section II, Subsection 11. Healtheon/WebMD, New York, 2000. All rights reserved.)

METABOLIC ADAPTATIONS IN CATABOLIC STATES AND REGULATION OF NITROGEN BALANCE

Amino Acid Metabolism and Transport

Roles of Specific Amino Acids

Amino acids have a core configuration of an amino and a carboxyl group adjacent to a carbon atom, from which a side chain extends, and are thus zwitterions. Amino acids are grouped according to electrical charge and the side chain. The neutral amino acid group includes the following 12 amino acids: glycine and alanine; the hydroxyamino acids serine and threonine; the branched-chain amino acids (BCAAs) valine, leucine, and isoleucine; the aromatic amino acids phenylalanine, tyrosine, and tryptophan; and the sulfur-containing amino acids methionine and cysteine. Aspartate and glutamate are diacidic amino acids, whereas arginine, lysine, and histidine are dibasic. These features largely determine transport across membranes. The essential or indispensable amino acids are those whose carbon skeleton cannot be synthesized by the body; such amino acids include valine, leucine, isoleucine, lysine, methionine, phenylalanine, threonine, and tryptophan. Cysteine and tyrosine may be essential in that they are synthesized from the essential amino acids methionine and phenylalanine, respectively. The remaining 10 amino acids, alanine, arginine, aspartate, asparagine, glutamate, glutamine, glycine, histidine, proline, and serine, are not essential. Though not classically essential, histidine, proline, glutamine, and arginine may become conditionally essential under catabolic conditions, when needs are increased and synthetic rates fall short of increased requirements. This concept of conditionally essential amino acids remains controversial and is discussed later in this chapter. Three major fates of amino acids follow:

1. Protein synthesis
2. Oxidation by the tricarboxylic acid (TCA) cycle, either for production of energy or ultimately leading to

storage as carbohydrate or fat, with the production of urea and carbon dioxide
3. Synthesis of nonessential amino acids and other small molecules such as purines and pyrimidines

The plasma amino acid pool is regulated by exchange of amino acids among skeletal muscle, the liver, and other viscera (kidney and lung). Of the essential amino acids, 7 of the 10 are degraded by the liver, the exceptions being the BCAAs, for which skeletal muscle plays a major role in catabolism. Two amino acids, alanine and glutamine, are carriers for organ exchange of nitrogen, in a complex process discussed later (Fig. 7-1).

Amino Acid Transport

Transport of free amino acids across cell membranes has been studied in only a few types of cells; it is probably universal. Christensen[3] proposed several transport systems:

1. The A-system is an energy- and sodium-dependent system with high affinity for alanine and other neutral amino acids, including the synthetic amino acid α-aminoisobutyric acid. It is concentrative against a gradient and is stimulated by insulin. Insulin stimulates amino acid transport into muscle via the A-system by recruiting specific sodium-dependent amino acid transporters to the plasma membrane (also see later).[4]
2. The L-system is sodium independent and transports the BCAAs (leucine, isoleucine, and valine) and the aromatic amino acids (phenylalanine, tyrosine, and tryptophan), as well as probably methionine and histidine. It operates by exchange for intracellular amino acids and is competitive.
3. Two transport systems are available for the basic amino acids. The carriers for transport of dibasic amino acids and the L-system may be linked in some as yet unknown way.
4. Dicarboxylic amino acids have their own transport system.

Current knowledge about amino acid transport in muscle is summarized in Table 7-1.

Amino Acid Metabolism in the Liver and Viscera

The liver is the major site in the body for the degradation and synthesis of amino acids and is the most important organ for regulation of plasma amino acid levels. The liver processes and stores ingested nutrients delivered by the portal venous system and releases them in response to neural and hormonal signals. The liver may extract between 75% and 100% of all portal vein nutrients in one pass, with only 25% of ingested protein reaching the general (nonportal) circulation as free amino acids. Most (almost 60%) is converted to urea, a small amount (6%) is used for the synthesis of plasma protein, and 14% becomes liver protein. Although K_m values for hepatic amino acid degradation are high and those for synthesis are low, thus favoring net synthesis, excessive postprandial accumulation of plasma amino acids is prevented, which helps, for example, in avoiding rapid and possibly disruptive increases in amino acid brain neurotransmitter precursors. It is not clear whether the large postprandial urea production from absorbed amino acids is wasteful or is somehow required for hepatic functional integrity. During starvation, the liver metabolizes amino acids released by proteolysis in muscle to form glucose in the process of gluconeogenesis (see later). In parenteral nutrition, nutrients are first supplied to the systemic rather than the portal circulation and thus override the liver. Furthermore, as the normal postprandial production of gut hormones (which may have a role in anabolic signaling) is bypassed by parenteral feeding, overall nutrient disposal is probably less efficient and this phenomenon may contribute to the difficulty in achieving positive nitrogen balance discussed earlier.

The role of the kidney in amino acid homeostasis has not been as well studied as that of muscle or the liver but is probably more important than heretofore supposed. Amino acids in the kidney can have several fates, including the following:

1. Production of urea (with the liver) from ammonia by means of the argininosuccinate cycle
2. Production of ammonia (from glutamine) for urinary acid-base balance
3. Metabolism of other amino acids, such as the BCAAs
4. Participation with the liver in gluconeogenesis from muscle-derived glutamine (see later)

The lung may also have a greater role in the regulation of amino acid levels than has been appreciated, especially when the liver is bypassed or diseased and is thus incapable of modifying portal flow. For example, in sepsis, the lung, in addition to skeletal muscle, can become a major source for glutamine production.

Amino Acid Metabolism in Muscle

Skeletal muscle and cardiac muscle are the major sites in the body for the catabolism of several amino acids, most

Table 7-1 Amino Acid Transporters in Muscle

TRANSPORTER	Na COUPLING	TYPICAL SUBSTRATES	COMMENTS
X-A,G	Yes	Glutamate, aspartate	Insulin insensitive
y^+	No	Lysine, cystine, arginine, ornithine	Insulin insensitive
L	No	Neutral amino acids	Insulin insensitive
A	Yes	Short-chain neutral amino acids	Insulin sensitive, reduced by starvation
ASC	Yes	Alanine, cysteine, serine, threonine	Insulin insensitive
N^m	Yes	Glutamine, histidine, asparagine	Insulin sensitive

notably leucine, isoleucine, and valine, and for the synthesis of others, specifically alanine and glutamine.[5] By contrast, muscle does not degrade the carbon skeletons of other amino acids found in plasma to any significant extent.

Branched-Chain Amino Acid Oxidation

The rate of degradation of BCAAs in muscle is greater than in the liver, and given that muscle accounts for up to 40% of body mass, it is probably the major site for degradation of BCAAs. Unlike most ingested amino acids, the BCAAs are not efficiently extracted from the portal circulation by the liver and pass directly into the systemic circulation to be taken up by peripheral tissues. Although leucine is readily oxidized by muscle, it is also degraded by the kidney, adipose tissue, and brain. The physiologic significance of BCAA metabolism in these tissues is probably distinct from that in skeletal muscle. For example, in adipose tissue, leucine degradation serves an anabolic function by providing precursors for triglyceride synthesis, whereas in muscle, leucine is degraded to acetyl coenzyme A moieties, which are then oxidized in the TCA cycle to provide energy.

In certain catabolic states, including fasting, diabetes, and after traumatic injury, rates of degradation of the BCAAs increase markedly in skeletal and cardiac muscle and in the kidney, whereas the liver and brain show no such effects. This increased oxidation in muscle is regulated by glucocorticoids and other stimuli.[6] Because leucine can serve as an alternative energy source for muscle during fasting, it can also reduce glucose utilization in this tissue. Therefore, during fasting, when leucine levels rise in blood and muscle, its degradation in muscle increases, and gluconeogenic precursor molecules such as pyruvate are preserved.[7]

Production and Release of Alanine

The breakdown of BCAAs in muscle generates amino groups whose accumulation could be toxic. Unlike the liver, muscle lacks the enzymes necessary to dispose of ammonia as urea. Instead, alanine and glutamine are released in much greater amounts than would be expected simply by the net breakdown of muscle proteins. Amino groups generated by the degradation of BCAAs and aspartate contribute to the de novo synthesis of alanine and glutamine in muscle.[5] Alanine production by this tissue seems to play an important role in the maintenance of blood glucose in the fasted state. The liver is very active in extracting alanine from the blood, and in the liver alanine is the most important amino acid used for gluconeogenesis.

Felig in the mid-1970s proposed the existence of a so-called glucose-alanine cycle, in which alanine derived from amino acid metabolism in muscle is carried in the circulation to the liver for conversion to urea and glucose. The glucose synthesized by the liver can then be taken up again by muscle and be converted back to alanine. This flux of alanine between muscle and liver is similar to that of lactate in the Cori (glucose-lactate) cycle, but in addition, alanine helps ferry potentially toxic amino groups to the liver for disposal as urea. Because alanine is derived from preexistent glucose, this cycle does not allow the generation of new carbohydrate from muscle proteins, and overall, as an amino group is ultimately lost, the glucose-alanine cycle is not a true metabolic cycle. However, in fasting, glucose is spared by the oxidation of leucine and prevention of pyruvate degradation in muscle.

Glutamine Production by Muscle and Interorgan Relationships

Skeletal muscle and cardiac muscle synthesize and release glutamine in similar or even greater amounts than they do alanine. Studies in isolated muscles[5] and more recent experiments in humans have shown that the carbon atoms in glutamine originate primarily from protein-derived amino acids that can enter the TCA cycle and are mainly converted to glutamine, which is then released from muscle. This process is an important initial step in gluconeogenesis from muscle protein. It has been estimated that about 87% of the glutamine released from muscle is derived from de novo synthesis rather than being liberated as a result of proteolysis. The glutamine released by muscle is an important energy source for many cells. For example, glutamine is extensively oxidized by leukocytes and fibroblasts. It is taken up from blood primarily by the kidney, where it serves as a precursor for urinary ammonia, and its carbon skeleton may be used for either gluconeogenesis or energy production, or some of the carbons are released into blood as alanine. In addition, as originally described by Windmueller and Spaeth,[8] the small intestine takes up and metabolizes large amounts of glutamine; in turn, it releases appreciable amounts of alanine. The liver then uses the released alanine for glucose production. This complex multiorgan process appears to play an important role in net gluconeogenesis from the five amino acids originating in proteins and converted to glutamine in muscle.

The level of glutamine within different tissues is determined by the relative activities of glutamine synthase and glutaminase. Transcription of glutamine synthase is strongly activated by corticosteroids in lung and muscle tissue. This leads to enhanced glutamine production and underlies the increased production and release of glutamine from muscle in starvation and disease states such as sepsis or other critical illnesses in which glucocorticoid levels are high.[9] As indicated earlier, the lung also has high capacity for synthesizing glutamine, and this process rises in sepsis. For example, after induction of a sepsis-like state with lipopolysaccharide in experimental animals and in studies measuring lung flux via pulmonary artery catheters in human patients with sepsis, release of glutamine by the lung at least doubles, presumably as a result of increased levels of glutamine synthase. Under these conditions, uptake of glutamine by the small intestine decreases and uptake by the liver increases dramatically. The benefit of these changes is not clear (see Controversies in Artificial Nutrition later).

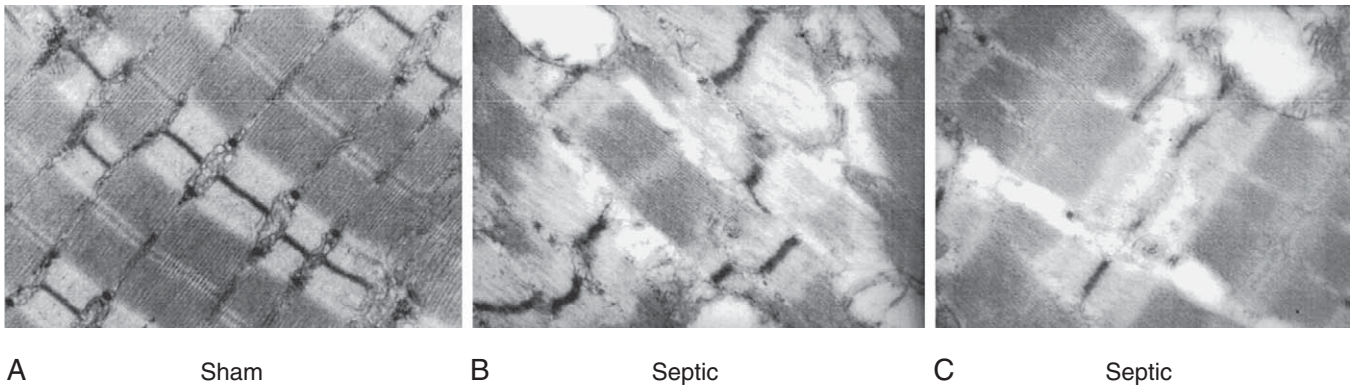


Figure 7-2 Electron micrographs of extensor digitorum longus (EDL) muscles from sham-operated (**A**) and septic (**B** and **C**) rats. Note the loss of registry between adjacent sarcomeres in septic muscles. Z disks were thickened, fragmented, or completely lost in septic muscles (×33,200). (**A** and **B,** From Williams AB, deCourten-Myers GM, Fischer JE, et al: Sepsis stimulates release of myofilaments in skeletal muscle by a calcium-dependent mechanism. FASEB J 13:1435, 1999.)

Regulation of Intracellular Protein Synthesis and Degradation

Physiologic Significance of Protein Turnover

Classic experiments by Schoenheimer in the 1940s with ^{15}N-labeled amino acids demonstrated that cellular proteins are synthesized and degraded continuously. Net mobilization of muscle protein can provide amino acids for metabolism by other tissues, for example, during fasting, whereas net uptake of amino acids by muscle plus incorporation of them into protein is a form of energy storage. However, there is no generic protein store; muscle may serve that purpose, but not perfectly.

A major technical factor limiting the study of protein metabolism in muscle and other tissues has been problems involving measurement of degradative rates. A variety of in vivo methods are available, but all are subject to a number of potential artifacts. Urinary urea or total nitrogen excretion is often regarded as an index of muscle protein breakdown, but these measurements actually represent processes of amino acid catabolism and will be influenced by amino acids released from nonmuscle tissues and from the diet. One useful method for estimating rates of degradation of certain muscle proteins in vivo is measurement of urinary *N*-methylhistidine excretion. This amino acid is formed by a post-translational modification of histidine residues in actin and myosin. When generated by proteolysis, it cannot be reincorporated into protein or significantly metabolized, and therefore its release in urine must reflect breakdown of these contractile proteins. However, actin and myosin also exist in other tissues, and the skin, GI tract, and possibly other organs, besides muscle, may contribute significantly to urinary excretion of *N*-methylhistidine. To analyze rates of protein degradation under controlled conditions, in vitro techniques involving the use of thin rodent muscles offer many advantages. Similar techniques have been applied for measuring rates of protein synthesis and degradation in human muscle biopsy samples. Rates of protein synthesis are determined by measuring rates of incorporation of [^{14}C]-tyrosine or phenylalanine into muscle protein, whereas rates of protein degradation are estimated by measuring the release of tyrosine from muscle.

Biochemical Pathways for Intracellular Protein Breakdown

Several pathways for intracellular proteolysis have been identified, and each pathway uses a unique complement of proteases, including the acid-dependent proteases (cathepsins) in lysosomes and proteases active at neutral pH and found in the cytosol. This latter group includes the calcium-dependent calpains, the caspases, and the adenosine triphosphate (ATP)-dependent ubiquitin-proteasome pathway. It is now well established that the proteasome is responsible for the majority of protein degradation in mammalian cells, including skeletal muscle.[10] Seminal work by Alfred L. Goldberg and coworkers has yielded considerable evidence that the ubiquitin-proteasome pathway is responsible for the majority of accelerated proteolysis in many different catabolic conditions characterized by muscle wasting.[11,12] However, calpains may have a complementary role, as explored by Williams and colleagues in rats wasting as a result of sepsis. Calcium-dependent release of myofibrils plus disintegration of the Z band, along with increased mRNA levels for calpains 1, 2 and 3, was noted. This finding suggests that in sepsis, calpains might be important in releasing myofibrils from the contractile apparatus, and these then presumably serve as substrate for ubiquitination and degradation by the proteasome (Fig. 7-2).[13]

The importance of the ATP-dependent ubiquitin-proteasome pathway in muscle atrophy is now well established.[11] The majority of the acceleration in proteolysis induced by a variety of catabolic conditions, including

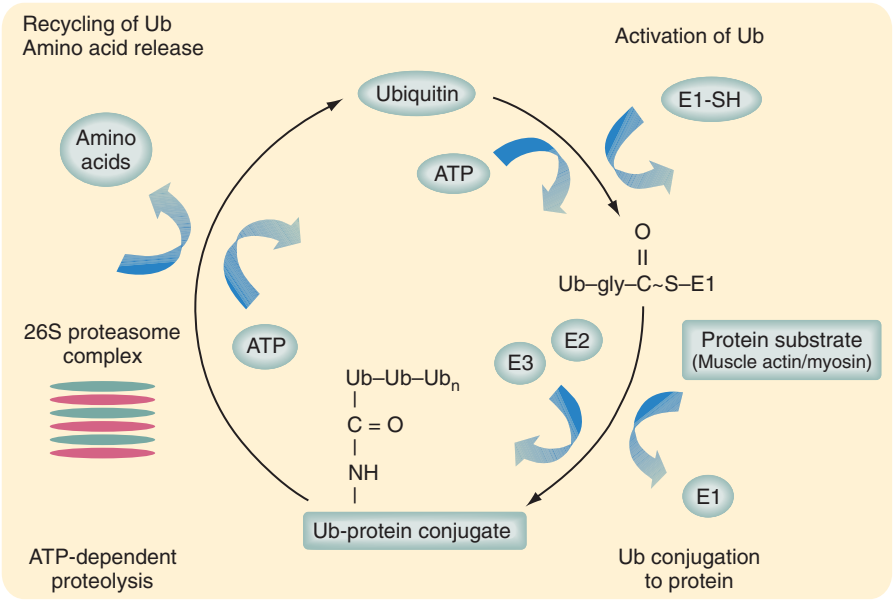


Figure 7-3 The adenosine triphosphate (ATP)-dependent ubiquitin (Ub)-proteasome pathway for protein degradation. In this energy-requiring process, ATP is hydrolyzed (1) during Ub conjugation to protein substrates (2) to allow formation of the proteasome complex and (3) to support the degradative function of the proteasome. *Activation of ubiquitin:* A high energy thiol-ester bond is formed between the C-terminal glycine of the polypeptide Ub and the Ub-activating enzyme E1. *Ub conjugation to protein:* With the participation of E2 and E3 proteins, Ub is transferred to the protein substrate targeted for degradation. Multiple Ub molecules may be attached to each other and to one or more lysine residues on the target protein via isopeptide bonds formed between the carboxyl-terminus of Ub and the ε-amino group of lysine. *ATP-dependent proteolysis:* The proteasome is assembled from proteolytic and regulatory elements and the protein substrate is degraded with the release of short peptides. *Recycling of Ub and amino acid release:* Ub is regenerated by the isopeptidase activity associated with the proteasome and is reused for the degradation of other proteins. Peptides generated by the proteasome are further degraded to amino acids, which in muscle can be released into the circulation for gluconeogenesis or to support protein synthesis in other tissues.

diabetes, acidosis, sepsis, thyroid hormone treatment, and denervation atrophy, can be blocked by proteasome inhibitors.[14] These muscles also show dramatic increases in ubiquitin-protein conjugates, which are intermediates in proteolysis via this pathway, as well as increases in mRNA encoding components of the ubiquitin-proteasome pathway.[11,12] Degradation of proteins via the ubiquitin-proteasome pathway is a multistep process that requires the hydrolysis of ATP, in addition to the 8-kd protein cofactor ubiquitin and the 26S proteasome (Fig. 7-3).[10] The 26S proteasome is a very large (2 Md) complex made up of at least 50 subunits.

Unlike typical proteases, the proteasome requires ATP for the degradation of proteins; in particular, ATP hydrolysis is thought to be needed to drive the unfolding and translocation of globular proteins into the proteolytic compartment. The majority of protein substrates are marked for degradation by covalent linkage of a chain of ubiquitin molecules to an internal lysine of the protein substrate. Discovery of the role of ubiquitination in protein breakdown led to awarding of the Nobel Prize in Chemistry to Hershko, Ciechanover, and Rose in 2004. Ubiquitination is now also recognized to underlie many other cell signaling processes not directly related to proteolysis. ATP-dependent proteolysis mediated by ubiquitination requires at least three enzymes, the so-called E1, E2, and E3 enzymes. The E3 ubiquitin-protein ligase can bind only specific protein substrates and ubiquitinates these proteins with the aid of a specific E2 enzyme. However, which E2 and E3 enzymes are involved in the accelerated proteolysis during muscle wasting is still incompletely understood.[12] Very recently, genomic approaches have been used to identify genes regulated during muscle atrophy. These exciting studies have revealed E3 enzymes that appear to be directly involved in accelerated proteolysis in a number of different conditions. For example, mRNA levels for one new E3 enzyme increase severalfold in fasting, diabetes, cancer, and uremia[15] and during immobilization or denervation.[16] The importance of this E3 enzyme in muscle wasting was highlighted by studies showing that when muscles from transgenic knockout mice lacking the functional E3 gene were denervated, they lost half as much mass as muscles from wild-type mice did.[16]

Nutrients and Hormones Regulating Nitrogen Balance

The hormonal milieu of the body provides for either a storage state or a breakdown state. Insulin, the dominant anabolic signal, inhibits lipolysis and increases accrual of nitrogen in muscle, liver, and other tissues. In addition

Table 7-2 Hormones Influencing Energy Use and Nitrogen Balance

HORMONE	MUSCLE PROTEIN DEGRADATION	MUSCLE PROTEIN SYNTHESIS	GLUCOSE UTILIZATION	EFFECT ON GROWTH
Insulin	Decrease	Increase	Increase	Anabolic
Glucocorticoids	Increase	Decrease	Decrease	Catabolic
Cytokines	Increase	Decrease	Decrease	Catabolic
IGF-I	Decrease	Increase	Increase	Anabolic
Growth hormone	No change	Increase	Decrease	Anabolic
Thyroid hormone	Increase	Increase	Increase	Anabolic
Leucine	Decrease	Increase	Decrease	Anabolic
Fasting	Increase	Decrease	Decrease	Catabolic
Long-term fasting	Decrease	Decrease	Decrease	Catabolic
Protein deficiency	Decrease	Decrease	Unknown	Catabolic

IGF, insulin-like growth factor.

to hormonal and nutrient factors, lack of tension or disuse is a major signal activating muscle proteolysis, a phenomenon of considerable relevance clinically. Great advances have been made in understanding the signaling mechanisms mediating the effects of various nutrients and anabolic hormones (Table 7-2). In particular, two protein kinases, Akt and mTOR (the latter inhibited by the immunosuppressive drug rapamycin), appear to be particularly important in regulating mRNA translation and thus protein synthesis in response to various growth factors and nutrients.

It has been known for some time that leucine has regulatory effects on muscle protein balance. Studies from several laboratories have shown that BCAAs stimulate protein synthesis and reduce protein breakdown in isolated skeletal and cardiac muscle. Leucine appears to stimulate protein synthesis and mRNA translation principally via the pathway that involves mTOR, although the inhibitory effects of leucine on protein degradation have been less extensively investigated. However, this action of leucine is not related to its role as a metabolic fuel inasmuch as other carbon sources such as alanine and pyruvate fail to have the same anabolic effects despite being consumed by cells.

Insulin stimulates amino acid transport into muscle (see earlier),[4] increases rates of protein synthesis, and inhibits muscle protein breakdown. Thus, the rise in insulin after meals promotes net protein accumulation in muscle, whereas in the postabsorptive state, when insulin is low, there is net loss of protein and release of amino acids from muscle. Binding of insulin to its receptor on the plasma membrane leads to activation of phosphatidylinositol-3 kinase (PI3K), followed by Akt and S6 kinase, and ultimately initiation of enhanced translation. Insulin can have a limited role in promoting protein synthesis in some catabolic conditions such as after burns. In addition to its effects on protein synthesis, insulin inhibits protein degradation in many tissues.[17] Insulin's direct inhibition of protein breakdown in liver and muscle results largely from inhibition of lysosomal proteolysis. However, the systemic effects of low-insulin states such as fasting or diabetes include muscle wasting as a result of accelerated proteolysis via the ATP-dependent ubiquitin-proteasome pathway, a process that appears to be insensitive to insulin. Under these conditions, glucocorticoids clearly contribute to activation of the ubiquitin-proteasome pathway and are required for muscle wasting. Possibly insulin somehow inhibits this catabolic response to glucocorticoids.

Glucose by itself can inhibit protein degradation in isolated muscle and the liver without affecting overall protein synthesis. This effect of glucose in muscle is not simply due to supplying energy to the tissue because fatty acids or ketone bodies do not reduce proteolysis despite their rapid oxidation. Therefore, elevated plasma levels of insulin and glucose after food intake together promote the accumulation of amino acids in muscle.

Hypophysectomy of young animals prevents growth, including skeletal muscle growth. When hypophysectomized animals are treated with growth hormone, overall body growth is reinitiated and rates of protein synthesis in muscle increase. Growth hormone does not appear to suppress proteolysis directly. Rather, the polypeptide insulin-like growth factors IGF-I and IGF-II, synthesized in part via stimulation by growth hormone, mediate the reduction in proteolysis. IGF-I has well-documented insulin-like effects and enhances protein synthesis by activating the PI3K/Akt/mTOR pathway, which accelerates the initiation of translation. In addition to enhancing protein synthesis, IGF-I and IGF-II inhibit protein breakdown in muscle. For example, the increase in protein degradation in isolated muscle after burn injury can be reversed by IGF-I, but this effect was not seen in muscle from septic animals, where IGF-I increased protein synthesis but had no effect on protein degradation rates.[18] The inhibition of protein breakdown by IGF-I is thought to involve suppression of the lysosomal process, as shown previously for insulin. However, recent evidence suggests that IGF-I, but not growth hormone, can reduce mRNA levels for components of the ubiquitin-proteasome pathway, and this might be an additional mechanism to reduce proteolysis.

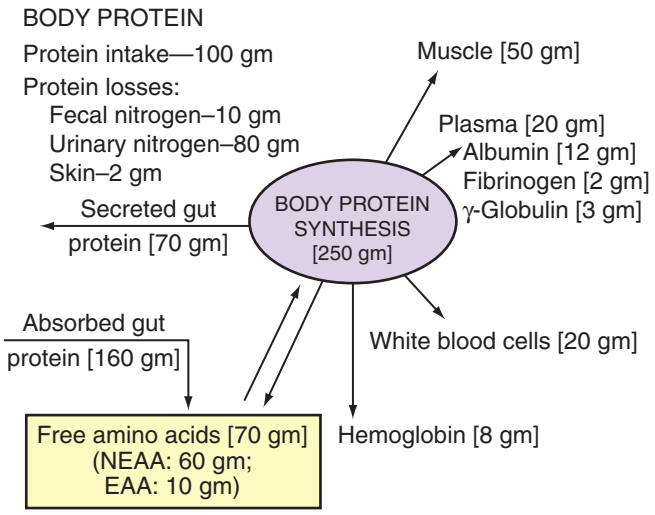


Figure 7-4 **Daily flux of amino acids in the body of a 70-kg man. Total body protein synthesis is 250 g per 24 hours, 50 g of which is muscle; proteolysis contributes approximately the same. Thus, with adequate amounts of energy, nitrogen equilibrium is the result. EAA, essential amino acids; NEAA, nonessential amino acids.** (Data from Munro HN: Parenteral nutrition: Metabolic consequences of bypassing the gut and liver. In Clinical Nutrition Update: Amino Acids. Chicago, American Medical Association, 1977, p 141.)

Glucocorticoids are another class of hormones that influence muscle size. For instance, the overproduction of adrenal steroids in Cushing's syndrome or the high levels used clinically lead to marked muscle weakness and wasting. Glucocorticoids act in several complex ways to retard growth and promote the release of amino acids from muscle, including decreasing DNA and protein synthesis and reducing amino acid uptake by muscle. In the fasted state, glucocorticoids play an important physiologic role in promoting the net breakdown of muscle protein, and this response appears to be important in the regulation of blood glucose. This action of glucocorticoids thus complements the other so-called permissive actions of cortisol in enhancing gluconeogenesis in the liver and kidney.

It is now clear that the accelerated proteolysis caused by glucocorticoids in experimental animals is largely due to activation of the ubiquitin-proteasome pathway in muscle, and in general, pale (glycolytic) muscle fibers appear to be more sensitive to these catabolic effects than dark (oxidative) fibers do. In addition to fasting, glucocorticoids are also important for the increase in proteolysis seen in other physiologic or pathologic states. Thus, the increased ATP-dependent protein breakdown occurring in the muscles of rats with metabolic acidosis, diabetes, or sepsis[19] is dependent on this class of hormone. However, it should be noted that in human studies, no increase in transcripts for components of the proteolytic pathway have been demonstrated, either after short exposure to high-dose prednisolone, which induces proteolysis,[20] or in those with untreated Cushing's disease. Recent experiments to define the effects of glucocorticoids on protein synthesis have shown that these hormones appear to antagonize the stimulatory effects of insulin and leucine on the PI3K/Akt/mTOR pathway described earlier.

Physiologic Adaptations to Food Deprivation

Short-Term Fasting

Complete food deprivation leads to mobilization of body protein to support energy needs. Although the normal turnover of protein is 2.5% to 3% of lean body mass per day (Fig. 7-4), in starvation as much as 300 g of protein per day may be lost initially in humans. Early in fasting, release of amino acids from skeletal muscle increases as a result of a decrease in protein synthesis and a marked rise in protein degradation. These adaptive changes in muscle protein metabolism seem to result from the low level of circulating insulin, although glucocorticoids also play an essential permissive role (see earlier). Early in fasting, under the influence of decreased insulin and elevated glucagon, hepatic glycogenolysis provides a limited store (≤100 g) for maintenance of systemic glucose. However, fat constitutes the bulk of calories available (Table 7-3), and lipolysis and release of free fatty acids occur in response to the low insulin levels. For example, the average adult fat reserve is approximately 10 kg, or 100,000 kcal, 60 times hepatic glycogen stores.

In peripheral tissues during fasting, utilization of free fatty acids and ketone bodies for production of ATP increases, whereas glucose oxidation is inhibited. As discussed earlier, BCAA oxidation in muscle rises, thus sparing glucose. Most importantly, gluconeogenesis in the liver and kidney is activated via muscle-derived glutamine and alanine, lactate, and glycerol released from lipid oxidation, with increased production of urea. This process, in addition to metabolic cycles such as the glucose-alanine or glucose-lactate cycle (see earlier), maintains blood glucose levels for tissues that are highly dependent on glucose for energy, such as the brain, erythrocytes, and the kidney.

In the liver, the accelerated proteolysis induced by fasting occurs largely in lysosomes. However, in muscle tissue, activation of the ATP-ubiquitin–dependent proteolytic pathway is primarily responsible for the increased protein degradation in fasting. In rodents deprived of food for 48 hours, levels of total ubiquitin mRNA in muscle and the mRNA for several proteasome subunits increase coordinately threefold to sixfold.[11,12] Muscles from fasted animals also contain higher amounts of proteins conjugated to ubiquitin than do muscles of fed controls. This finding suggests an increased rate of ubiquitin conjugation in muscle during fasting, and it correlates with activation of the ATP-ubiquitin–dependent pathway in isolated muscles. Further detailed analysis of the transcriptional adaptations occurring in muscles of mice fasted for 48 hours has recently been performed with cDNA microarrays by Jagoe and coworkers.[21] This technique allows simultaneous measurement of changes in mRNA levels for several thousand genes (the so-called transcriptosome) and has revealed a number of important new alterations in gene expression that had not been noted before. One markedly induced gene, subsequently proven to be the new ubiquitin ligase, or E3, is atrogin-

Table 7-3 Normal Stores of Available Energy and Rates of Use in a Man Weighing 65 kg

	TOTAL BODY CONTENT (g)	AVAILABLE STORE			DAILY UTILIZATION* (g)	EXHAUSTION TIME (DAYS)
		g	mJ	kcal		
Carbohydrate	500	150	2.5	600	All used in first 24 hr	<1
Protein	11,000	2400	40	9,600	60	About 40†
Fat	9,000	6500	235	58,500	150	About 40†

*Assuming energy expenditure of about 6.7 mJ (1600 kcal)/day.

†Experience in voluntary starvation suggests that the limit of resting starvation in young men in excellent physical condition may be as much as 60 to 70 days (Maize Prison, Northern Ireland).

From Passmore R, Robson JS: A Companion to Medical Studies, vol 3. Oxford, Blackwell Scientific, 1974.

1[15,16] and was discussed earlier. Other features in fasting include reduced transcripts for many of the enzymes involved in later stages of glycolysis and coordinated changes in mRNA encoding translation initiation factors that might favor the translation of a subset of stress-related proteins.

Long-Term Fasting and Dietary Protein Deficiency

In prolonged fasting, gluconeogenesis from body proteins and loss of muscle mass are gradually reduced. The most important factor reducing glucose needs during fasting is a decrease in the brain's requirement for glucose, with ketone bodies being used instead for a large part of ATP production by the brain. As the use of alternative fuels to glucose increases, muscle proteolysis falls below levels seen early in starvation, and eventually proteolysis is lower than in the fed state. In humans, 1 week of fasting is necessary for this adaptation, as indicated by a diminished forearm arteriovenous difference in amino acids and by decreased urinary *N*-methylhistidine excretion. Both the lysosomal and nonlysosomal ATP-dependent pathways are suppressed in muscle of rats fasted for prolonged periods, and very similar reductions in muscle proteolysis occur in animals fed a protein-deficient diet.[22] It remains likely that these nutritional states share common signals and mechanisms for reducing proteolysis, for example, through reduced thyroid status, although additional mechanisms may also be important for these adaptations.

Physiology of Inflammation and Sepsis

Changes in Energy Metabolism and Protein Turnover

Sepsis is the major cause of surgical mortality. The metabolic tragedy of sepsis is that the suppression of proteolysis seen in prolonged starvation does not occur and breakdown of protein continues. In fact, lean tissue loss can approximate 900 g/day in patients with severe sepsis, traumatic injuries, closed head injury, or major burns, and generalized muscle wasting ensues. In humans and animals with sepsis, there is clear evidence of increased proteolysis and net release of amino acids from muscle, and furthermore, most of the increased proteolysis results from activation of the ubiquitin-proteasome pathway. Pale glycolytic muscles (*fast twitch*) appear to be far more sensitive to sepsis than dark oxidative ones are. For example, ubiquitin mRNA increases severalfold in pale extensor digitorum longus muscle from septic rats, where ATP-dependent proteolysis also rises, but it does not change in dark soleus muscles (gravitational or *slow twitch*), in which ATP-dependent proteolytic activity is unchanged.[23] The mRNA for many other components of the ubiquitin-proteasome pathway increases in muscle in experimental models of sepsis[19,24] and in septic patients. Sepsis increases rates of ubiquitination of muscle proteins,[12] and inhibitors of the proteasome dramatically reduce total and myofibrillar proteolysis in muscle from septic animals.[14] Although they contribute little to overall proteolysis, other pathways, in addition to the ubiquitin-proteasome pathway, may also have a role in the muscle wasting in sepsis. For example, increased mRNA levels for cathepsin B and calpain have been found in muscle during sepsis, and the calpains also appear to play a role (see earlier).

Sepsis leads to reduced protein synthesis, especially in fast-twitch muscles, as a result of reduced rates of initiation of translation. Furthermore, the response to stimuli that normally promote increased protein synthesis, such as BCAAs or insulin, is diminished. In contrast, hepatic protein synthesis, largely of acute phase reactant proteins found in plasma, is increased in the septic state, but hepatic synthesis of structural components is not.

As discussed earlier, insulin normally inhibits gluconeogenesis. However, in sepsis and other inflammatory states, gluconeogenesis continues despite the administration of either fat or carbohydrate, and peripheral insulin resistance with impaired skeletal muscle uptake of glucose occurs. For these reasons, hyperglycemia in response to IV feeding during sepsis is common, particularly in patients predisposed to diabetes. This insulin resistance or stress-induced hyperglycemia is caused by multiple factors, including elevated counter-regulatory hormones (catecholamines, glucagon, and glucocorticoids) and cytokines (primarily tumor necrosis factor [TNF]; also see later) (Fig. 7-5). Numerous strategies have been proposed to counter hyperglycemia while providing IV nutrition to patients with sepsis or severe inflammation, such as that resulting from burn injury. One approach is lipid supplementation. However, whether lipid metabolism continues normally in sepsis is controversial. Perhaps in moderate sepsis fat continues to be used, whereas in severe sepsis fat is used inefficiently. To truly understand why these metabolic profiles are altered will require a better understanding of the effect of the various mediators released during severe inflammation and sepsis on the pancreatic beta cell and peripheral tissues.

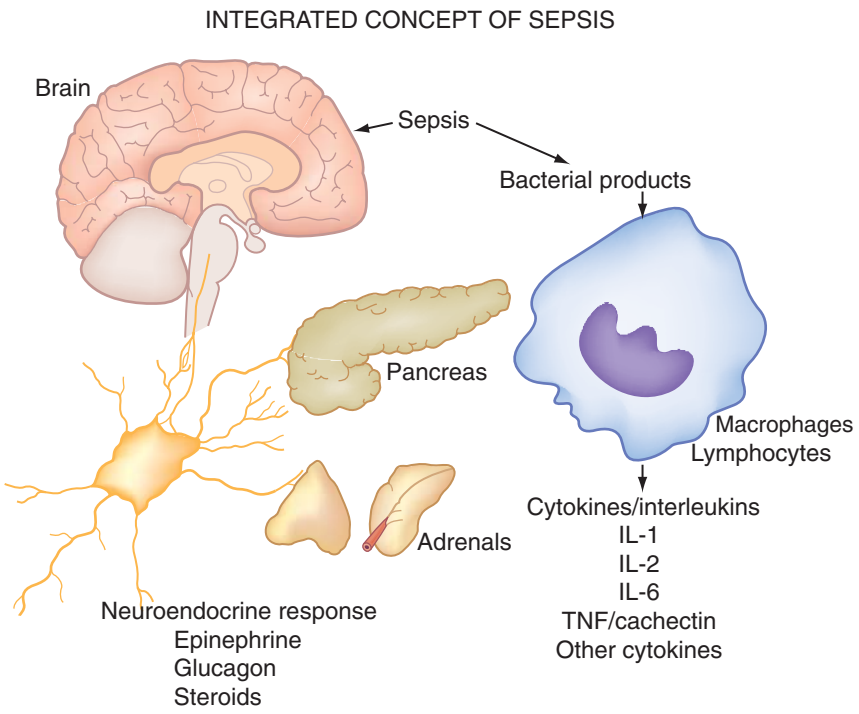


Figure 7-5 An emerging concept of the response to stress and sepsis. In previous years the neurosympathetic response to sepsis was emphasized, with the secretion of epinephrine, glucagon, and corticosteroids—the so-called counter-regulatory hormones. It is now clear that this is but half of the efferent limb and that cytokines are extremely important. IL, interleukin; TNF, tumor necrosis factor.

Role of Cytokines and Other Mediators in the Response to Sepsis

Many of the systemic manifestations of sepsis are mediated by cytokines, levels of which rise in the blood in infection and other inflammatory states such as burn injury (see Fig. 7-5) (for a complete discussion of the biology of cytokines and inflammation, the reader is directed to Chapter 4). Clowes, a general surgeon, in 1983 proposed for the first time that a so-called proteolysis inducing factor (most likely an interleukin split product) was responsible for increased muscle proteolysis and hepatic protein synthesis in sepsis, and this proposal stimulated broad interest in the cytokines as mediators of these processes. Although probably more than 100 products of macrophages exist, attention has focused largely on only a few, primarily interleukin-1 (IL-1), IL-6, TNF, and interferon-γ (IFN-γ). Enterocytes, in addition to inflammatory cells, may also serve as a source of these cytokines. In muscle, activation of proteolysis by TNF and other cytokines appears to depend, at least in part, on activation of a nuclear transcription factor termed NF-κB that serves as a common signaling pathway for inflammation. An increasingly commonly held view is that cytokine release is an appropriate response to a modest-sized insult but that sustained enormous cytokine release is deleterious and may contribute to the so-called multiple organ failure syndrome, the end-stage physiologic state accompanying sepsis.

Elucidation of the roles of particular cytokines in the activation of muscle proteolysis during sepsis has proved difficult. Although many of the cytokines mentioned have, when administered in recombinant form to intact animals, been shown singly or in combination to activate the ATP-dependent ubiquitin-proteasome pathway of muscle proteolysis,[25] in isolated muscle preparations their actions are less clear. Interestingly, unlike IL-1, TNF, or IFN-γ, IL-6 does not induce changes in muscle mRNA for ubiquitin,[25] and this is consistent with the observation in Dr. Fischer's laboratory that in IL-6–deficient mice the sepsis-related acceleration in proteolysis still occurs. One important factor present in intact animals but perhaps lacking during in vitro experiments is the corticosteroids. Studies from Dr. Fischer and Dr. Hasselgren's laboratory strongly suggest that in septic animals, glucocorticoids are required for full activation of the ubiquitin-proteasome pathway in muscle and thus appear to be a permissive factor for the response to cytokines[19] and in particular TNF, whose actions are blocked by RU-486, a glucocorticoid antagonist. Inhibition of TNF production in sepsis and other conditions may be of benefit in inhibiting muscle wasting. For example, recent experiments with a xanthine derivative, torbafylline, demonstrated inhibition of proteolysis via the ubiquitin-proteasome pathway and prevented muscle wasting in animal models of cancer cachexia and sepsis.[26]

Both IL-1 and TNF elicit the release of prostaglandin E_2 from muscle. Although prostaglandin E_2 had been proposed to be critical for increased muscle proteolysis in septic models, no decrease in ATP-dependent proteolysis or ubiquitin mRNA levels occurred in muscles from

endotoxin-treated rats that received naproxen, a potent inhibitor of prostaglandin E_2 production. To summarize both in vivo and in vitro studies, prostaglandins do not appear to be necessary for the rise in muscle proteolysis during infection.[11]

Another signal for increased proteolysis in muscle during systemic infection is fever. Studies of the influence of temperature on protein degradation and synthesis in isolated muscles by V. Baracos and A. Goldberg in 1984 demonstrated a linear increase in the rate of proteolysis but relatively unchanged protein synthesis. Therefore, in febrile animals, the rise in body temperature induced by cytokines and their direct catabolic effects on skeletal muscle appear to act synergistically to induce amino acid release and promote muscle wasting.

The effects of cytokines on the liver are complex. IL-1 is associated with increased hepatic protein synthesis of some of the complement intermediates, whereas synthesis of transferrin is steroid dependent. IL-6 appears to increase the synthesis of certain α-glycoproteins, but undoubtedly other cytokines are involved as well.

Role of Oxidizing Agents

Oxidizing agents such as nitric oxide (NO) and hydroxyl radicals are generated in a variety of tissues and play important roles in metabolic regulation. NO, a mediator of diverse physiologic processes, is a short-lived free radical gas and oxidant derived from arginine by nitric oxide synthase (NOS).[27] Three NOS isoforms have been identified in cells. Endothelial and neuronal NOS (ecNOS and ncNOS) are constitutively expressed and are Ca^{2+}-calmodulin dependent, whereas the largely inducible Ca^{2+}-independent NOS isoform (iNOS) is expressed in immunologically activated cells. A classic action of ecNOS is the cyclic guanosine monophosphate–dependent vasodilation mediated by the endothelium, whereas ncNOS-derived NO functions as a neurotransmitter in numerous pathways. NO reacts avidly with oxygen-derived free radicals, thiols, and the active metal centers of proteins, and a complex chemistry governs its functions in cell signaling and in altering metabolic activity. Of the three isoforms, iNOS is most important because once it is induced by lipopolysaccharide, cytokines, or other factors, large and sustained amounts of NO may be produced. The increase in NO production in sepsis has been proposed to mediate increased hepatic protein synthesis, killing of pathogens, and programmed cell death (apoptosis).[28] Various studies have also shown that skeletal muscle produces NO and that NOS activity in this tissue is influenced by contraction[29] and cytokines. In fact, our recent studies in incubated muscles have shown that NO donors or hydroxyl radicals activate proteolysis by up to 80%.[30] These mediators may therefore be important for the accelerated muscle proteolysis during strenuous exercise or ischemia, after muscle injury, and in inflammatory states.

Cachexia of Cancer

Patients with neoplastic disease may suffer profound weight loss and generalized cachexia. Many factors probably contribute to this response, including reduced food intake, altered metabolic rate, endocrine abnormalities, and the effects of anticancer treatments, but various cytokines and other circulating factors have been identified that undoubtedly play a role, such as TNF, IL-1, IL-6, and IFN-γ.[31] Anorexia is common, even when the tumor is small, a finding suggesting deranged central nervous system satiety mechanisms (see later). Marked muscle wasting is a debilitating feature of advanced cancer. In rats bearing tumors, severe muscle wasting occurs, apparently mediated by TNF and resulting primarily from an increased rate of ATP-dependent proteolysis with increased levels of mRNA for ubiquitin and subunits of the proteasome, especially in the pale muscle fibers, which atrophy most profoundly. However, additional proteolytic pathways may also be activated and different cytokines or other circulating factors are frequently implicated in the genesis of cachexia.[31] One other factor implicated in some types of cancer cachexia is proteolysis-inducing factor (PIF). This substance was identified first in tumor-bearing mice and, when injected into healthy mice, produced profound weight loss. Purified PIF induces catabolism in muscle cells and activates the ubiquitin-proteasome pathway in muscle.[32] PIF has also been found in the urine of a large proportion of patients with weight loss secondary to pancreatic cancer, and treatment with eicosapentaenoic acid (EPA), which blocks the formation of 15-hydroxyeicosatetraenoic acid by PIF in muscle cells, inhibits weight loss even in those with advanced disease.[33] However, whether these mechanisms have broad applicability in cancer remains unclear.

New Concepts in the Regulation of Body Energy Expenditure

In the past decade, exciting insights have been achieved in interrelated areas of mechanisms regulating body size and resting energy expenditure, satiety, and the metabolic phenomena thought to be relevant to aging.[34] These findings have relevance to diverse disease entities, including the etiology of insulin resistance (e.g., in sepsis), type II diabetes mellitus, and morbid obesity. One surprising realization has been that adipose tissue is not just a storage depot for calories, but via a complex network of hormonal and neuronal signals, this tissue also plays an important role in endocrine regulation. Beginning with the discovery by J. Friedman in 1994 of the adipocyte-derived circulating hormone leptin, adipose tissue is now known to be an important source of endocrine mediators, including TNF, angiotensinogen, resistin, and adiponectin. In conjunction with gut hormones such as ghrelin, cholecystokinin, PYY, and insulin, the adipocyte-derived hormones interact in the brain, in particular at the arcuate nucleus, to control food intake and energy expenditure. In the arcuate nucleus, two sets of neurons appear to interact with opposing effects. Activation of agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons increases appetite and metabolism, whereas activation of POMC/CART neurons has the opposing effect of inhibiting eating, in part by causing the release of α-melanocyte–stimulating hormone (α-MSH), a satiety signal. Such mechanisms are clearly relevant to understanding the inanition accompanying advanced cancer, and some

evidence suggests that appetite-promoting agents such as ghrelin may find clinical use in this regard. How these newly described regulatory pathways influence the metabolism of particular nutrients or nitrogen balance remains poorly understood.

Recent discoveries in aging research appear to be connected, if indirectly, to the metabolic signaling pathways described earlier. It is now well accepted that in experimental animals and lower organisms, dietary caloric restriction enhances longevity and may have other desirable effects such as a reduction in primary tumors. Similar genetic mechanisms may underlie such responses, beginning with the discovery by L. Guarente and coworkers of the *Sir2* gene in yeast and the discovery by G. Ruvkun and colleagues of the daf-2 genetic pathway in *Caenorhabditis elegans*. These mechanisms appear to involve changes in nicotinamide adenine dinucleotide (NAD)-dependent functions such as histone acetylation, in insulin signaling, and in cellular responses to reactive oxygen species generated in the mitochondria. These exciting studies will undoubtedly contribute to our future understanding of overall metabolism, carcinogenesis, and free radical–induced injury.

FUNDAMENTALS OF ARTIFICIAL NUTRITION

General Indications for Nutrition Support and Choice of the Route of Administration

Indications for nutritional support should consider the following:

1. The patient's premorbid state (healthy or otherwise)
2. Poor nutritional status (current oral intake meeting <50% of total energy needs)
3. Significant weight loss (initial body weight less than usual body weight by 10% or more or a decrease in inpatient weight by more than 10% of the admission weight
4. The duration of starvation (>7 days' inanition)
5. An anticipated duration of artificial nutrition (particularly total parenteral nutrition [TPN]) of longer than 7 days
6. The degree of the anticipated insult, surgical or otherwise
7. A serum albumin value less than 3.0 g/dL measured in the absence of an inflammatory state
8. A transferrin level of less than 200 mg/dL
9. Anergy to injected antigens

Box 7-1 Methods of Nutritional Assessment

- Clinical history
  - Weighing, subjective assessment
- Body composition analysis
  - Bioelectrical impedance, exchange of labeled ions, neutron activation analysis
  - Cross-sectional imaging (magnetic resonance imaging, computed tomography)
- Indirect calorimetry
  - Oxygen consumption, determination of respiratory quotient
- Anthropomorphic measurements
  - Ideal body weight, skinfold thickness
- Biochemical measurements
  - Albumin, transferrin, prealbumin
- Measurement of nitrogen balance
- Measurements of immunologic function

Each practitioner must choose the criteria in a given patient. Obviously, in critically ill patients, nutritional supplementation should be undertaken more readily than in patients who are less severely stressed. Finally, when patients are either malnourished or in the postinjury stressed state, there is no obvious harm and there may be a clinical benefit to the initiation of immediate enteral feeding, particularly in more critically ill patients (see later).

Two routes of administration are possible: the enteral route, via the stomach or preferably the small intestine, and the parenteral route. The enteral route is considered to be more physiologic in that the liver is not bypassed, thereby allowing this organ to efficiently process and store various portally supplied nutrients, and the release of gut hormones and insulin is facilitated, presumably leading to more efficient nutrient disposal in the periphery. However, despite these and other putative advantages, the relative benefits of enteral versus parenteral nutrition in humans remain unclear (see Controversies in Artificial Nutrition later).

Nutritional Assessment

Nutritional assessment is a process by which changes in body nutritional composition are estimated, in part to predict risk for surgery or other stressful therapeutic activity. Ideally, valid methods of assessment should facilitate patient selection for instituting artificial nutrition and for determining the efficacy of nutritional interventions. Although functional measures of lean body mass, such as skeletal muscle strength, respiratory and cardiac performance, hepatic synthetic function, renal status, and immunologic reactivity, seem most desirable, in practice, such approaches have proved difficult (see later). Acceptable studies of nutritional assessment techniques should be randomized, prospective, and blinded. However, most published studies are retrospective for selected patients, usually those judged to be severely at risk. Studies that emphasize hepatic synthesis of short-lived or immunologically active proteins and those that measure neutrophil function may be more successful in identifying patients at risk for infection. In several studies, a careful history plus physical examination by a seasoned clinician yields the same accuracy as extensive testing for the estimation of nutritional risk, particularly when functionality is assessed (Box 7-1).

Clinical History

Weight loss, anorexia, weakness, inability to carry out normal functions, or a disease process that interferes with

intake, such as esophageal carcinoma, should alert the examiner to the possibility of malnutrition. Certain disorders such as burns, sepsis, head injury, and pancreatitis are particularly catabolic and must be anticipated to raise caloric requirements significantly. The clinical criteria described earlier for the degree of acceptable body weight loss and duration of inanition must be calculated. Finally, on physical examination, muscle wasting, loose or otherwise abnormal skin, the edema of hypoproteinemia, weakness, loss of body fat, and pallor should suggest the diagnosis of malnutrition.

Body Composition Analysis

Accumulation of lean body mass is the principal objective of nutritional support; thus, determination of lean body mass is the most appropriate means of nutritional assessment. Such determinations are usually available only on a research basis.

Bioelectrical Impedance

This method estimates total body water and lean muscle mass by measuring electrical resistance at various surface locations. Though simple to perform, the values derived are often inaccurate and poorly reproducible. In addition, although bioelectrical impedance may be accurate in a normal individual, its accuracy in patients with abnormal body composition has not been verified.

Displacement

Probably the most sensitive determination of lean body mass is displacement. Various body components are estimated by displacement of water volume.

Exchange of Labeled Ions

Total body water may be determined by the administration of tritiated water. Lean body mass is estimated by exchangeable potassium (^{42}K) and extracellular water by total exchangeable sodium (^{22}Na). Shizgal suggested that a ratio of exchangeable sodium to exchangeable potassium greater than 1.2 is an indication of the increased extracellular water and decreased body mass accompanying malnutrition. Shizgal also proposed derivative ratios to estimate total body fat, but because of compounded error, these ratios are probably inaccurate.

Neutron Activation Analysis

This technique is accurate but requires sophisticated apparatus in which the body is bombarded with activated neutrons. Nitrogen, indicative of lean body mass, is then measured. Other ions may also be determined.

Total Body Counters

These large devices measure spontaneous decay of naturally occurring isotopes such as ^{40}K, which reflects lean body mass. However, these measurements are not suitable for patients who are ill because subjects must remain stationary within the counter for prolonged periods.

Magnetic Resonance Imaging

Magnetic resonance imaging may accurately measure lean body mass, although most current work has focused on energy metabolism and the relationship between high-energy phosphate stores in starvation and refeeding. For example, in rats, phosphocreatine is decreased after 6 to 8 days of starvation. Other studies suggest a possible decrease in ATP synthetic efficiency in the starved muscle, presumably secondary to insufficient stores of phosphocreatine to maintain ATP.

Computed Tomography

Computed tomography (CT) with three-dimensional reconstruction can yield accurate values for organ size and volume. Radiographic tissue density can also be used to monitor the response to therapy. For example, studies by Buchman and associates have shown that the hepatic steatosis that commonly occurs during long-term TPN administration can be at least partially reversed by supplementation of the TPN solution with carnitine or choline, as shown by a reduction in hepatic fat content (with increased radiographic density) on serial CT scanning.[35] Other workers have related hepatic steatosis to an abnormal portal vein insulin-to-glucagon ratio, and in experimental animals hepatic steatosis can be cleared by administration of glucagon (see later).

Indirect Calorimetry

Indirect calorimetry, performed with a bedside metabolic cart, is being used increasingly to measure energy balance and to estimate caloric requirements. The measurement is carried out with the patient in the resting state, and in general, 15% should be added for activity. Oxygen consumption can be determined directly and caloric expenditure calculated. In addition, if carbon dioxide production is measured simultaneously, the respiratory quotient (RQ) can be estimated for assessment of overfeeding. An alternative method for determination of oxygen consumption involves placement of a pulmonary artery catheter. If cardiac output is measured by thermodilution and the oxygen content in arterial and mixed venous blood is measured, the Fick equation can then be used to calculate V_{O_2}. In certain patient populations, particularly after severe burn injury, direct measurement of V_{O_2} has proved very useful in estimating caloric needs because in these patients, standard formulas such as the Harris-Benedict equation (see Practical Approach to Artificial Nutrition later) often prove particularly inaccurate.

Metabolic carts can also determine which fuel is being consumed in a clinical setting. An RQ of 1 indicates pure carbohydrate utilization, 0.8 indicates pure protein oxidation, and 0.7 is consistent with pure fat utilization. Theoretically, the RQ with lipogenesis can be as high as 9. Although an RQ greater than 1 is rarely seen, such data are indicative of overfeeding of glucose or fat, or both, whereas an RQ less than 0.7 indicates ketogenesis. Without such measurements, when fat is administered, indirect measures of utilization, such as the absence of plasma lipemia and the presence of ketone bodies, are necessary to confirm efficient metabolism. Although indirect calorimetry is an attractive approach, a recent multicenter study of RQs derived by this method suggests that in practice, low sensitivity and specificity may

limit its efficacy as an indicator of overfeeding or underfeeding.[36]

Anthropomorphic Measurements

These parameters are controversial with regard to normative values and their relevance to nitrogen depletion. Characteristic measurements include the creatinine-height index, triceps skinfold thickness, and arm muscle circumference. Although these values may be proportional to muscle or fat stores, they do not reflect function. A more practical anthropomorphic approach is the calculation of ideal body weight (IBW), particularly when usual body weight, or weight of the patient before the onset of illness, is unknown. IBW can be found in standardized tables developed by the insurance industry that relate height to expected weight, or IBW can be estimated by the following equations:

- For males: 106 lb for the first 5 ft and 6 lb for each inch thereafter.
- For females: 100 lb for the first 5 ft and 5 lb for each inch thereafter.

Because these tables were derived from population norms in the 1950s, before the current trend toward obesity in Americans, they tend to underestimate weight. However, in keeping with the general principle of avoiding excessive provision of calories during artificial feeding, use of the IBW for calculating caloric needs is not harmful and is commonly done (see Practical Approach to Artificial Nutrition).

Functional Studies of Muscle Function

Because many of the tests described earlier are not readily available, muscle strength has been evaluated either by handgrip dynamometry, force-frequency characteristics, or the rate of recovery from fatigue after electrical stimulation of the ulnar nerve. When properly conducted, such studies provide a functional counterpart of severe protein-calorie malnutrition, and they may be used to assess for a beneficial response to nutritional or other anabolic interventions. For example, an ongoing study at Beth Israel Deaconess Medical Center suggests that handgrip strength may improve in elderly patients administered growth hormone. In most studies, however, patients with deficits in hand dynamometry are easily identifiable by other means such as a simple functional history, physical examination, or global nutritional assessment. The importance of functional studies was recently emphasized by the work of Herridge and colleagues (see the accompanying editorial also), who demonstrated residual muscle wasting and weakness for up to 1 year after discharge from the intensive care unit (ICU) and treatment of acute respiratory distress syndrome (ARDS).[37]

Biochemical Measurements

A variety of biochemical approaches have been described for determining malnutrition. Though useful, such methods are often inaccurate and do not usually give added value when compared with a clinical approach to nutritional assessment.

Serum Proteins

Measurement of serum proteins, in particular albumin, is often used as an index of malnutrition, with an albumin concentration of less than 3.0 g/dL being the usual indicator. The half-life of albumin is as long as 14 to 18 days, and for this reason other more short-lived proteins, such as prealbumin (half-life 3-5 days) or transferrin (<200 mg/dL, half-life 7 days), have been proposed as more sensitive indicators of rapid changes in nutritional status. However, the meaning of the lowered serum albumin concentration in patients who are malnourished and at risk has always been controversial. Some investigators have attributed the low serum albumin to decreased synthesis, possibly as a result of low-grade sepsis or stress, and others have attributed it to increased degradation. In a model of long-term sepsis, von Allmen and associates[38] found that whereas albumin synthesis was decreased for the first 24 hours, after 4 days' synthesis this protein actually rose to normal levels. These results suggest that decreased albumin synthesis because of down-regulation may not be tenable in long-term malnutrition. In malnutrition one generally expects an increase in extravascular volume. With greater extravascular volume, a greater amount of albumin is likely to be present in the extravascular space, where it appears to be degraded more rapidly. Thus, increased albumin in the extravascular space with an increased rate of degradation may well explain the lowered serum albumin in patients who are at risk.

Nitrogen Balance

Measurement of nitrogen balance is a tedious technique that requires determination of all integumentary, wound, and excretory losses. Overall, such measurements tend to be inaccurate and will often favor the erroneous conclusion that positive nitrogen balance has been achieved. In the clinical setting, nitrogen balance is determined by measuring 24-hour urinary and GI losses. Because most patients receiving parenteral nutrition do not eat, stool nitrogen can be assumed to be 1 g/day, or it can be disregarded altogether. The 24-hour urine collection must be accurate, as monitored by measuring urinary creatinine. The value for the rate of nitrogen loss is compared with nitrogen intake, and nitrogen balance is thus obtained. Therefore,

$$\text{Nitrogen balance} = \text{Intake} - \text{Loss (urine 90\%, stool 5\%, integument 5\%)}$$

or

$$= (\text{Protein intake [g]}/6.25) - \text{Urinary urea (g)} - 2 \text{ (for stool and skin)} - 2 \text{ (for nonurea nitrogen)}$$

Measurement of Protein Breakdown

Nitrogen turnover, particularly that of lean body mass, can be estimated by urinary excretion of 3-methylhistidine, as described earlier. However, 3-methylhistidine measures not only the breakdown of muscle but also the breakdown of a more rapidly turning over protein pool derived from the gut and skin, thus invalidating it as a

measurement of turnover of skeletal muscle protein alone. Short of actual in vitro measurement in isolated muscle tissue (see earlier), common in vivo approaches to the measurement of protein breakdown include pulse-chase and other isotopic methods that involve the infusion of ^{15}N-labeled amino acids and other metabolites. All these methods, unfortunately, are highly derivative and subject to a variety of artifacts.

Measurements of Immunologic Function

Delayed cutaneous hypersensitivity or anergy, most commonly tested by delayed reaction to skin recall antigens, was widely used in early studies of nutritional assessment and is a manifestation of cell-mediated immunity. Although most studies showed a statistical relationship between anergy and mortality, investigators have concluded that delayed cutaneous hypersensitivity is without value for measuring specific nutritional or operative risk. In contrast, more recent data suggest that when skin testing is carefully performed by trained personnel and done at defined times (e.g., on admission rather than at random throughout the hospital course), skin reactivity may have some value. For example, in patients admitted after trauma or with infection, anergy to injected cutaneous recall antigens is associated with high mortality and morbidity. These patients are probably those with severe malnutrition. However, not all malnourished patients are at risk and the defect is immunologic, not nutritional. Furthermore, delayed cutaneous hypersensitivity is complicated by extraneous factors such as surgery, which is followed by immediate anergy in many patients. Patients with cancer are also anergic, and this condition may be reversed after resection. Thus, the significance of delayed cutaneous hypersensitivity must be assessed in concert with other tests. Another method for determining immunologic function in the clinical setting is neutrophil function, but this approach appears to be even less relevant to nutritional status than assays of cell-mediated immunity are.

Specific Fuels

The sources of calories in a normal diet and during artificial feeding are carbohydrate, lipid, and protein. We will discuss each of these fuels, with particular emphasis on their relative roles during IV feeding and adjustments needed for concurrent illness such as diabetes and liver or renal failure.

Carbohydrate

Glucose is the preferred carbohydrate source in traditional TPN. Glucose administration during fasting or stress appears to decrease urinary urea production, the so-called protein-sparing effect, with a minimum of 100 g of glucose per 24 hours being required for this response based on Gamble's classic lifeboat ration studies of the 1940s. It was not until the late 1970s that the metabolism of exogenously supplied carbohydrate was evaluated in detail. The nitrogen-sparing effect of infused glucose was found to occur through two mechanisms. First, hepatic gluconeogenesis is suppressed, so protein need not be broken down to generate gluconeogenic precursors. Second, glucose itself is used as an energy substrate, so fewer amino acids need be oxidized for energy. Wolfe and coworkers showed that maximum suppression of gluconeogenesis is achieved at infusion rates of 4 mg/kg/min (~400 g/day for a 70-kg man) and that glucose infusion beyond this level has minimal effects in further suppressing glucose production during TPN administration in postoperative surgical patients.[39] In this work, although any additional nitrogen-sparing effects of glucose would be expected to be derived from its direct oxidation, at infusions rates higher than 9 mg/kg/min all glucose was degraded by nonoxidative pathways, specifically, those leading to net synthesis of lipid.

Toxicity of Hyperglycemia and Excessive Calorie Administration

When provided in excess, carbohydrate is converted to fat in the liver, a consequence that is referred to as de novo lipogenesis and probably contributes to TPN-related liver dysfunction (see later). In addition, the accompanying increase in V_{CO_2}, as reflected by an elevated RQ (see earlier), may lead to impaired ventilatory function in patients with already compromised pulmonary status. Finally, the resultant hyperglycemic state, most pronounced with a blood glucose concentration greater than 300 mg/dL, leads to immunosuppression and an increased frequency of nosocomial infections. Hyperglycemia is a prevalent metabolic disorder that can be particularly pronounced in the ICU setting and postinjury state and is clearly exacerbated by excessive administration of dextrose.

The immunosuppressive effects of hyperglycemia have been well studied. In vitro data suggest that hyperglycemia leads to immune cell dysfunction as a result of impaired chemotaxis, adherence, phagocytosis, and bactericidal function. In prospective studies, tight postoperative glycemic control has been shown to significantly decrease nosocomial infections in diabetic patients. In the ICU setting, fastidious glycemic control achieved through intensive insulin therapy has been shown to dramatically improve patient outcomes.

In the prospective, randomized study of Van den Berghe and colleagues,[40] 1548 cardiac surgery ICU patients were randomized to either standard glycemic control (to maintain blood glucose at 180-200 mg/dL) or tight glycemic control (insulin infusion to maintain glucose at 80-110 mg/dL). All patents were fed 25 kcal/kg by either enteral or parenteral routes. By maintaining blood glucose in the 80 to 110 mg/dL range, these investigators demonstrated significant improvement in various clinical outcomes and a 42% decrease in overall mortality. This landmark study highlights the importance of maintaining normoglycemia during feeding because otherwise, the benefits of nutritional intervention may be negated by the detrimental consequences associated with the hyperglycemic state. In contrast, in a more recent publication in which a nonsurgical ICU population was studied,[41] Van den Berghe and coworkers failed to demonstrate improved mortality with vigorous glycemic control, and the incidence of clinically significant hypoglycemia attrib-

utable to aggressive insulin use was appreciable. In our own cardiac surgical unit, where maintenance of normoglycemia is prioritized, the incidence of mediastinitis is very low, although other initiatives were undertaken simultaneously.

In an effort to avoid the potential complications of overfeeding, one reasonable short-term option is the practice of hypocaloric feeding. The clinician must often balance the optimal administration of nutrition with a patient's overall clinical status. One could easily envision the desire to limit the volume of TPN received by a diabetic patient with difficult-to-control blood sugar, by a massively volume overloaded patient in renal failure who is not being dialyzed, or by a patient with poor oxygenation who is being maintained on high ventilatory support. In this setting it appears reasonable to provide goal protein (1.5 g/kg/day, see later) while limiting total calories to approximately 1000 kcal/day. This practice will decrease net protein catabolism while still allowing mobilization of endogenous fat stores to close the expected caloric gap and will limit excessive volume administration. This approach is particularly acceptable when applied over a limited time course such as 1 to 2 weeks and in the obese patient population, who have an abundance of lipid available for mobilization, but it is not a viable option for standard nutrition support. It is also unclear whether hypocaloric feeding in patients with renal failure has a similar outcome as nutritional supplementation with essential amino acids and hypertonic dextrose (see later).

Additional Sources of Dextrose

One must be careful to recognize all sources of exogenous dextrose administration, in addition to the patient's feeding solution, because significant amounts of dextrose can be found in the following:

- IV fluids containing 5% dextrose (50 g/L)
- Medications mixed in 5% dextrose instead of normal saline
- Patients undergoing continuous venovenous dialysis, who often have 5% solutions as return fluid
- Patients undergoing peritoneal dialysis with dextrose in the dialysate.

Alternative Carbohydrate Sources

Carbohydrate sources other than glucose have not achieved popularity in the United States. Fructose, which some investigators have proposed for use in glucose resistance, may cause fatal lactic acidosis. The polyalcohols xylitol and sorbitol also undergo transformation to glucose, but xylitol may be hepatotoxic and has probably contributed to several deaths in the literature. Glycerol, another potential source of glucose, is potentially advantageous in that it may be sterilized in solution with amino acids, without caramelization, and its osmolality is low. The safety as well as efficacy of glycerol was studied in patients recovering from major trauma or surgery.[42] In one group, nitrogen equilibrium was achieved with combined lipid and glycerol administration. However, glycerol in large doses may cause renal failure in experimental animals, and thus caution is appropriate.

Lipid

In starvation, fat provides the bulk of calories in the form of free fatty acids and as ketone bodies manufactured by the liver from long-chain fatty acids. Net lipolysis during fasting or stress is promoted by steroids, catechols, glucagon, and some cytokines and is extremely sensitive to inhibition by insulin. Under normal circumstances or in moderate stress, fat and carbohydrate are indistinguishable with respect to their positive effects on nitrogen balance, with 25% of nonprotein calories as fat seemingly being optimal for hepatic protein synthesis. What is not clear is at which point in stress or during sepsis that fat utilization becomes impaired. Most investigators agree that whereas hepatic manufacture of ketone bodies is reduced early in sepsis, fat clearance remains relatively normal until comparatively late, even though fat oxidation is clearly impaired at a previous stage. Many sources of lipid are available for IV use.

Nomenclature and Structure of Fatty Acids

Fatty acids consist of a carboxyl group with a hydrophobic carbon side chain of variable length. The convention for describing fatty acid structure is X (the total number of carbons, including the carboxyl carbon): Y (the total number of unsaturated bonds). So-called desaturases remove two hydrogens to yield a methylene group (double bond between carbons), whereas so-called elongases insert two sequential carbons into an existing fatty acid chain. The most abundant fatty acids contain 14 to 22 carbons, and 16 and 18 predominate. The most common saturated fatty acids are palmitic (C16:0) and stearic (C18:0) acids, with oleic acid (C18:1) being the most common monounsaturated fatty acid. Further complicating fatty acid nomenclature is the "n" or "ω" (omega) numbering system used to describe unsaturated fatty acids. Both "n" and "ω" are interchangeable and refer to the number of carbons between the terminal noncarboxyl carbon and the closest double bond. For the example of oleic acid, because the solitary double bond occurs adjacent to the 10th carbon thus leaving nine carbons at the end of the side chain, the complete nomenclature is C18:1 n-9 or C18:1 ω-9. For the polyunsaturated essential fatty acid linoleic acid, there are two double bonds with six terminal saturated carbons, which gives rise to C18:2 n-6. Lengthening of an unsaturated fatty acid side chain to produce longer derivatives of the essential fatty acid precursors linoleic and α-linolenic acid requires sequential cycles of two-carbon elongation followed by desaturation. These synthetic enzymes prefer substrates with terminal carbon chains of the n-3>n-6>n-9 configuration, in that order, which gives rise to the n-3, n-6, and n-9 series of polyunsaturated fatty acids (PUFAs). The most complete nomenclature for naming unsaturated fatty acids also includes the location of the double bonds. For the preceding example of linoleic acid, the double bonds are after the 9th carbon and the 12th carbon. The most complete description for linoleic acid is therefore C18:2 Δ9, 12, or in the "n" system, C18:2 n-6.

Long-Chain Triglycerides

Safe administration of IV lipid became a reality in the late 1970s when an emulsion (Intralipid) consisting of soybean oil and egg lecithin and containing predominantly long-chain triglycerides (LCTs) became commercially available in the United States. Though initially administered as a source of essential fatty acids (linoleic acid and α-linolenic acid), these n-3 and n-6 LCT emulsions now serve as a valuable caloric source in parenteral alimentation. Lipid emulsions are particularly versatile because they are calorically dense (9 kcal/g) and can be safely infused via a peripheral vein. Their role as a supplemental caloric source is particularly valuable when blood sugar is difficult to control or when carbohydrate administration reaches safe limits.

Medium-Chain Triglycerides

Because of the potential adverse effect of LCT emulsions (see later), alternative lipid fuels have been considered. In comparison to LCTs, medium-chain triglycerides (MCTs), which contain only 8 to 10 carbons, are cleared more rapidly from plasma, are oxidized more rapidly, do not require a carnitine-dependent transport system to enter liver mitochondria, and are more soluble in TPN solutions. MCTs may also have a favorable effect on protein metabolism leading to improved nitrogen balance. However, MCTs can be neurotoxic in patients with cirrhosis who cannot adequately clear them, and overall, mixed MCT-LCT emulsions are thought to be most desirable. Mixed emulsions may be of particular benefit in patients with inflammatory disorders because they contain approximately 50% fewer n-6 LCTs than the traditional Intralipid does. Such LCTs may serve as precursors of potentially deleterious prostaglandins (see later).

Structured Lipids

Structured lipids are a synthetic triglyceride molecule in which medium-chain and long-chain fatty acids are esterified to the same glycerol backbone. The composition of the three fatty acid side chains can vary randomly or can be chemically defined by a specific enzymatic re-esterification process. Studies have proved structured lipids to be safe and to carry the metabolic advantages seen with MCT-LCT physical mixtures. Future studies will determine their role in the routine clinical setting.

Essential or Unsaturated Fatty Acids

Unsaturated fatty acids can be classified as monounsaturated or polyunsaturated, depending on the location of their double bond. The three families of PUFAs (n-3, n-6, and n-9) start as the essential 18-carbon unsaturated fatty acids α-linolenic acid (C18:3 n-3) and linoleic acid (C18:2 n-6) and as the nonessential oleic acid (C18:2 n-9). Both linolenic and linoleic acids are abundant in plants but do not occur naturally in animal tissue. Via sequential steps of elongation and desaturation, the n-6 precursor linoleic acid is converted to arachidonic acid, whereas the n-3 precursor α-linolenic acid is converted to EPA and docosahexaenoic acid (DHA) (Fig. 7-6). As indicated earlier, these desaturase and elongase enzymes are found predominantly in the liver and have as their order of preferred substrate n-3>n-6>n-9. This process is under tight control and the enzymes δ-5-desaturase and δ-6-desaturase appear to be key regulatory points. Interestingly, EPA, the intermediate in the n-3 pathway, appears to be inhibitory for the action of these desaturases on substrates of the n-6 pathway, and therefore elevated levels of EPA can negatively regulate the synthesis of arachidonate. EPA and DHA can be derived only from the direct ingestion of nutrients such as fish oil, where they are abundant, or by synthesis from dietary α-linolenic acid.

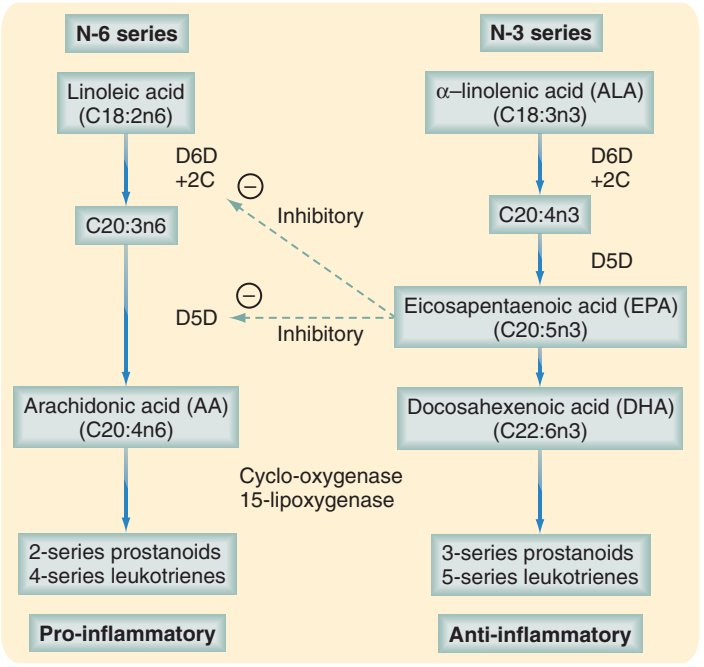


Figure 7-6 Pathways for the synthesis of essential polyunsaturated fatty acids. The important intermediate species leading to formation of the prostanoids and leukotrienes are shown. 2C, two-carbon elongation; D6D, δ-6-desaturase; D5D, δ-5-desaturase. The essential fatty acid precursors linoleic (n-6 series) and linolenic (n-3 series) acid are found only in plants, whereas the n-3 series intermediates eicosapentaenoic acid and docosahexaenoic acid are present at high levels in fish.

Arachidonic acid and EPA are precursors of the eicosanoids, namely, the prostaglandins, thromboxanes, and leukotrienes. More specifically, arachidonic acid is the precursor of the 2-series of prostaglandins and thromboxanes and the 4-series of the leukotrienes. EPA and DHA are the precursors of the 3-series of prostaglandins and thromboxanes and the 5-series of leukotrienes. Therefore, at the level of the cyclooxygenase and lipoxygenase enzymes, which are critical for eicosanoid synthesis, there exists competition between arachidonic acid and EPA. With the ingestion of fish or fish oil, the primary dietary source of ω-3 fatty acids (or alternatively, the n-3 fatty acids), EPA and DHA levels rise and these lipids can displace arachidonic acid in the membranes of cells active in eicosanoid synthesis, namely, platelets, erythrocytes, neutrophils, monocytes, and liver cells. As a result, with ω-3 fatty acid administration there are the following:

1. Decreased production of prostaglandin E_2 and its metabolites
2. Decrease in the production of thromboxane A_2, a potent platelet aggregator and vasoconstrictor
3. Decrease in leukotriene B_4, an inducer of inflammation and potent inducer of leukocyte chemotaxis and adherence
4. Increase in thromboxane A_3, a weak platelet aggregator and weak vasoconstrictor
5. Increase in prostacyclin PGI_3, an active vasodilator and inhibitor of platelet aggregation
6. An increase in leukotriene B_5, a weak inducer of inflammation and weak chemotactic agent.[43]

Accordingly, administration of the ω-3 fatty acids (α-linolenic acid or its products EPA and DHA) may produce an environment in which the inflammatory response, if not halted, is modulated or down-regulated to a less profound provasoconstrictive and prothrombotic state.

Recognition of Essential Fatty Acid Deficiency

Deficiency of essential fatty acids may be prevented by the administration of between 2% and 5% of daily calories as either soybean or safflower oil fat emulsion or a minimum of 30 to 50 g of lipid emulsion weekly. Plasma alterations, which occur within 1 week of administration of fat-free parenteral nutrition, include decreases in the n-6 fatty acids linoleic and arachidonic acid and increased levels of the n-9 fatty acid 5,8,11-eicosatrienoic acid, also known as *Mead acid* (C20:3 n-9). These changes result from the relative deficiency of n-3 and n-6 precursors such that the desaturase/elongation enzymes begin to produce products derived from n-9 fatty acids by default. The so-called triene-to-tetraene ratio, or the Holman index, refers to the ratio of Mead acid (20:3 n-9) to arachidonic acid (20:4 n-6) and is normally less than 0.2. If the ratio is greater than this value and other data are suggestive, essential fatty acid deficiency may be suspected. A common clinical sign is dry, flaky skin with small reddish papules and alopecia. Patients with essential fatty acid deficiency absorb essential fatty acids through the skin, but this approach is not practical except in infants. Patients who have excess adipose tissue can live for months without exogenous essential fatty acid administration because they maintain a mobilizable depot of linolenic acid in their adipose tissue.

Omega-3 Fatty Acids in the Clinical Settin

Omega-3 and ω-6 PUFAs are important components of human cell membranes. Their composition within the cell membrane is primarily determined by dietary intake because the ω-3–to–ω-6 ratio changes with changes in dietary consumption. As indicated earlier, the ω-3 fatty acids EPA and DHA play important roles in prostaglandin metabolism, thrombosis and atherosclerosis, immunology and inflammation, and membrane function. Once epidemiologists recognized that the paucity of heart disease in Greenland Inuits was due to a diet high in long-chain n-3 fatty acids, subsequent human studies examining n-3 supplementation have documented their important role in the prevention and treatment of coronary artery disease, hypertension, arthritis, inflammatory and autoimmune disorders, and cancer.

In the clinical setting, the benefits of ω-3 fatty acid administration to surgical patients have been realized when given as a key component of immune-modulating enteral feeding formulas. This topic is discussed in more detail elsewhere in this chapter. The use of IV n-3 lipid emulsions to modulate the immune system is only now being studied in clinical trials in the United States. Because lipid emulsions containing n-3 fatty acids inhibit triglyceride hydrolysis by lipoprotein lipase, fish oil cannot be infused alone or in combination only with LCTs. Instead, n-3 fatty acids must be combined with MCTs and LCTs in a solution composed of 50% MCT, 40% soybean (LCT), and 10% fish oil. Clinical studies in which this combined lipid solution has been administered have confirmed an increase in the ratio of 5-series to 4-series leukotrienes in peripheral leukocytes, an improvement in inflammatory disorders such as atopic dermatitis, and an attenuated inflammatory response in experimental models of both pancreatic injury and acute colitis.[43]

Supplementation of ω-3 may be particularly advantageous in cirrhosis and liver dysfunction. For example, it is well accepted that patients with end-stage liver disease have very low serum and possibly tissue levels of PUFAs. Several investigators have demonstrated low levels of long-chain PUFAs, namely, arachidonic acid, EPA, and DHA, in patients with advanced cirrhosis, and these deficiencies appear to serve as independent predictors of mortality. Patients with end-stage liver disease cannot mount an appropriate inflammatory response when faced with a severe insult or injury, and cirrhotic patients have a well-documented defect in T-cell–mediated immune function. These phenomena may in part be due to a deficiency in second messengers important in the inflammatory cascade, specifically, low levels of long-chain PUFAs and derived eicosanoids. In fact, one of the principal consequences of essential fatty acid deficiency in animals and humans is reduced resistance to infection. As described later (see Metabolic Complications of Long-Term Administration of Total Parenteral Nutrition), ω-3 fatty acids may also be effective in reversing hepatic steatosis in infants with TPN-associated liver disease.[44]

Potential Toxicities of Lipid Administration

Recent reviews of the literature reveal that no adverse effects related to LCT administration have been observed when IV lipids are administered in modest amounts, as long as infusion rates are lower than 0.1 g/kg/hr or 1 kcal/kg/hr. Before this critical level was determined, many adverse effects ensued when LCT solutions were infused at excessive rates and quantities. Lipid accumulating in the liver may inhibit the reticuloendothelial system, the major site of this system, by overloading and impairing Kupffer cell phagocytosis with lipid micelles. The phospholipid-emulsifying agent used in lipid solutions can also interfere with the action of lipoprotein lipase and potentially lead to a clinically relevant hypertriglyceridemic state. Therefore, lipid emulsions are not administered when serum triglyceride levels are greater than 400 mg/dL. The possibility of hypertriglyceride-related

pancreatitis also arises when serum triglyceride levels reach the 800- to 1000-mg/dL range. Excessive lipid may also have deleterious effects in patients with severe pulmonary disease such as ARDS. The downstream prostaglandin products of lipid emulsion precursors, such as thromboxane A_2 or PGE_2, can suppress lymphocyte proliferation and natural killer cell activity while reversing hypoxic vasoconstriction in patients with ARDS, thus further worsening pulmonary gas diffusion, oxygenation, and resistance to infection. Impaired plasma clearance of lipids can result in fat overload syndrome, a particularly significant problem in children manifested as fever, back pain, chills, pulmonary insufficiency, and blocking of the reticuloendothelial system. Fat overload syndrome can result from the administration of a stable fat emulsion over a brief interval or from more modest doses of lipid, which might be physicochemically unstable, and is avoided when fat is administered at a limit of 2 g/kg/day. In infants, up to 4 g/kg/day of fat is tolerated.

Protein

A 70-kg man has between 10 and 11 kg of protein, otherwise referred to as lean body mass. In the fed state, daily protein turnover amounts to between 250 and 300 g, or 3%. The gut is the largest component of this turnover, the source of nitrogen loss being shed enterocytes and secreted digestive enzymes. After digestion of food, all amino acids are absorbed, save 1 g of nitrogen excreted in stool. Although intracellular proteolysis accounts for 50 to 70 g of amino acids being added to the amino acid pool daily, if adequate energy is present, most of these amino acids are reincorporated into protein. The nonessential amino acids can be synthesized from carbon skeletons, and sources of nitrogen such as glutamine can be synthesized through transamination. Twenty grams of plasma protein, 8 g of hemoglobin, 20 g of white blood cells, and a few grams of skin constitute the remainder of total body protein synthesis (see Fig. 7-4). Protein turnover decreases markedly with age. Thus, protein turnover in a neonate approximates 25 g/kg/24 hr and decreases to 7 g/kg/24 hr at 1 year, and in adults, turnover falls to 3 g/kg/24 hr.

Determining Protein Requirements

The minimal intake of protein required for neutral nitrogen balance can be determined empirically by two approaches. The first method involves measuring all nitrogen losses while the human or animal subject is fed a calorically adequate, but protein-free diet. In general, this approach will underestimate the true protein requirement, particularly when a superimposed stressor is present. For example, after several days of a protein-free diet in humans, 37 mg/kg of nitrogen is excreted into urine and 12 mg/kg is lost in feces. Integumentary losses account for another 5 mg/kg, with an additional 2 to 3 mg/kg of nitrogen lost by evaporation, for a total of 56 to 57 mg of nitrogen per kilogram, or in terms of whole protein, 0.34 g of protein per kilogram is lost per day. This latter value is well below commonly accepted norms for the daily protein requirement in humans. A second approach that appears to be more relevant to clinical practice is to determine the minimal quantity of ingested protein necessary to maintain nitrogen equilibrium. When derived in this manner, with various corrections, the average normal requirement is 0.8 g of protein per kilogram, or between 56 and 60 g of protein per day. Trauma, infection, and other catabolic conditions will increase this requirement. In addition, in the postinjury state, the increased rate of whole body protein catabolism appears to be unusually resistant to exogenous supplementation with amino acids. However, this obligate protein loss, driven by the overexpression of catecholamines and cytokines during the systemic inflammatory response, can be offset to some degree by protein administration, with the rate of net protein catabolism decreased to about a fourth of the rate seen in the absence of TPN. The extensive studies of whole body protein turnover by Graham Hill and Robert Wolfe during the 1980s documented that exogenous protein administration of 1.5 g/kg/day achieves maximal protein sparing and that when amounts exceeding this value are administered, no further incorporation of nitrogen into protein is possible, with the excess protein being converted to urea and excreted, at least in relatively normal patients. Accordingly, it is most common to administer protein during artificial nutrition, whether enteral or parenteral, at a value of 1.5 g/kg/day. It is not clear in patients with severe protein loss, such as after major burns, whether limiting protein intake to this level is efficacious, and many centers have attempted to administer even greater amounts of protein (e.g., 2 g/day) to correct measured deficits.

Alterations for Liver and Renal Failure

Patients who are intolerant of nitrogen in the surgical setting usually manifest renal or hepatic impairment, and patients with advanced hepatic failure may have both hepatic and renal insufficiency, the so-called hepatorenal syndrome. Both groups of patients tend to be hypercatabolic, and sepsis is a common accompaniment. In some patients, for example, after an episode of hypotension, a crush injury involving muscle, or dye toxicity in radiologic procedures, the renal failure will, one hopes, be self-limited. In this latter instance the goal is to decrease the rise in blood urea nitrogen (BUN), thus avoiding dialysis, which in turn may add to the mortality associated with an accompanying surgical condition. There are good data in the literature suggesting that essential amino acids are a useful treatment in acute renal failure. In the case of hepatic failure, a BCAA-enriched, aromatic amino acid–deficient solution, given in an effort to avoid encephalopathy but containing sufficient protein in these particularly hypercatabolic patients, is the approach that is also supported by much experimental and clinical data.

Renal Failure

The practice of administering essential amino acids and hypertonic dextrose in a restricted volume, usually in the surgical setting with superimposed acute tubular necrosis, is based on studies published independently in the early 1950s by Giordano and Giovannetti. This work attempted to decrease the frequency of dialysis in chronic renal

failure patients. Substantial protein equivalents are lost during dialysis, but in the surgical setting, dialysis is usually thought to be necessary when BUN approaches 90 or 100 (at which point coagulopathy and other azotemic complications may occur). In addition, encephalopathy may be seen, which may or may not be correlated with the rise in BUN in a given patient. Giordano and Giovannetti found that patients with chronic renal failure who were given protein high in biologic value, such as egg albumin, along with adequate calories required less frequent dialysis. Whether this approach might also decrease damage to the few remaining functioning nephrons by decreasing their filtered load, a concept promoted by Brenner, currently lacks scientific support. According to the Giordano-Giovannetti hypothesis, urea was not an end product, as had been commonly supposed, but diffused into the GI tract and was converted to ammonia by urease-producing bacteria. If one supplied essential amino acids with protein high in biologic value and adequate calories, the hypothesis continued, the ammonia could be reincorporated into nonessential amino acids. Accordingly, a full complement of amino acids would result, thus supporting protein synthesis and adequate nutrition. This hypothesis, however, ultimately proved incorrect. In retrospect, most of the effect of essential amino acids on BUN appears to be the consequence of decreased urea generation resulting from their administration.

Although essential amino acids seemed helpful in the chronic setting, the question was whether they would work in a surgical patient with acute renal failure. A series of studies by Wilmore, Dudrick, Abel, Abbot, Fischer, and coworkers in the late 1960s and early 1970s demonstrated conclusively that when such patients were treated with essential amino acids and hypotonic dextrose, a number of beneficial effects could be demonstrated:

1. Hyperkalemia was improved.
2. Dialysis was averted in patients treated with essential amino acids and hypertonic dextrose, as opposed to hypertonic dextrose alone.
3. Survival was improved, especially in patients with some urine production.
4. There was a lower incidence of pneumonia, GI bleeding, and other complications, thus contributing to the improvement in survival.
5. The incidence of encephalopathy was decreased.

In patients after major procedures, such as repair of a ruptured abdominal aortic aneurysm in which the peritoneum has not sealed, essential amino acids and hypertonic dextrose may also be sufficient to tide the patient over until hemodialysis can be tolerated hemodynamically or, if desired, peritoneal dialysis initiated.

Other investigators, without satisfactory studies, have advocated increasing the complexity of amino acids from the essential eight (namely, the BCAAs isoleucine, leucine, and valine; the aromatic amino acids phenylalanine, tyrosine, and tryptophan; and the sulfur-containing amino acids methionine and cysteine) to include histidine and arginine, semiessential amino acids for which rates of synthesis may be insufficient to support the patient during acute stress. However, by adding these additional amino acids, the ability of the solution to hold the rise in BUN down is diminished. Other practices, such as giving BCAAs in large amounts with standard solutions, have little support in the literature. Using much reduced amounts of standard amino acid solutions, as advocated by some, resulted in one study in considerably worsened survival than in patients treated with essential amino acids. Other studies failed to show any difference in patients given dilute standard solutions or essential amino acids, but numbers of subjects were small.

One should be alert to the possibility of hyperammonemia (e.g., as heralded by mental status changes) in patients receiving only essential amino acids for a prolonged period. In infants, arginine deficiency may develop or the enzymes for conversion of arginine to ornithine may be insufficiently mature. The amino acids histidine, isoleucine, and leucine, if abundant, may suppress argininosuccinate synthetase, which is necessary for the conversion of arginine to ornithine. Whatever the mechanism, when ornithine stores are depleted, it can no longer serve its role as a carrier amino acid in the urea cycle, and as a result, ammonia is no longer detoxified in the liver and hyperammonemia may ensue. Therefore, when essential amino acid solutions are administered, particularly over prolonged periods, it is important that sufficient quantities of ornithine be included and serum ammonia levels monitored. Because this ordinarily does not happen, there is little reason to fear.

When used, the average duration of therapy with essential amino acids in hypertonic (35%) dextrose is generally 10 to 14 days. Once the patient is maintained on dialysis, a more complete amino acid solution is appropriate. In the outpatient setting, protein intake of 0.5 to 0.6 g/kg has been shown to slow the progression of chronic renal insufficiency. However, in renal failure patients with an acute superimposed illness or in those maintained on hemodialysis, protein intake of up to 1.2 g/kg is recommended, with most recent studies supporting improved patient outcome when adequate nutrition is administered, even if more frequent or even daily hemodialysis is required to clear the accumulated urea.

Hepatic Insufficiency

Patients with hepatic insufficiency are protein intolerant as well, but here the result of excessive protein administration is potentially severe encephalopathy. In the surgical setting, most such patients manifest sudden hepatic insufficiency, for example, as a result of cirrhosis with acute decompensation secondary to GI bleeding, sepsis, hepatic resection or transplantation, or portal venous diversion with resulting encephalopathy. The situation is doubly difficult because these patients are hypercatabolic, with a protein requirement of 1.1 g/kg/day, approximately double the minimal 0.55 g/kg/day adequate for a patient with well-compensated cirrhosis. Although it is generally acknowledged that patients with hepatic failure who are receiving IV amino acid solutions tolerate these solutions better than oral protein, most patients with significant liver disease do not tolerate 1.5 or even 1.1 g/

kg/day of amino acids when effort is made to achieve nitrogen equilibrium. Many practitioners confronted with these patients believe that an aromatic amino acid–deficient, BCAA-enriched solution is efficacious, and it is not unusual with such an approach to achieve levels of up to 120 g of amino acids per day, for example, and be rewarded not only by adequate nutrition but also by the absence of hepatic encephalopathy.

The basis for using enriched branched-chain and deficient aromatic amino acid solutions is the so-called false neurotransmitter hypothesis, in which hepatic encephalopathy is not a nonspecific toxic phenomenon, as heretofore had been thought, but instead results from abnormalities in brain synaptic function. The basis for this phenomenon is an abnormal plasma amino acid profile, as demonstrated by James, Fischer, and coworkers in the 1970s. In patients with hepatic failure, decreased circulating levels of BCAAs and increased aromatic amino acids, including phenylalanine, tyrosine, methionine, and tryptophan, appear to result in abnormal amine neurotransmitter products in which norepinephrine and dopamine are replaced by compounds such as octopamine and phenylethanolamine. These so-called false neurotransmitters are postulated to be responsible for the disturbances in consciousness known as hepatic encephalopathy. Accordingly, if the deranged plasma amino acid pattern can be normalized by increasing BCAAs and decreasing aromatic amino acids, the L-system transport pathway of the blood-brain barrier will be presented with an improved amino acid pattern, and a more functional brain amino acid profile will result. Glutamine may also play some role inasmuch as levels of glutamine in the brain reflect the availability of ammonia ion and glutamine is used for exchange of ammonia across the blood-brain barrier. The unified hypothesis of hepatic encephalopathy proposes that the deranged levels of plasma amino acids resulting from decreased hepatic function or anatomic shunting of blood flow, coupled with increased ammonia (glutamine) within the central nervous system, are synergistic in altering transport of amino acids across the blood-brain barrier.

Other workers have suggested the use of increased BCAAs alone in standard amino acid solutions instead of the modified amino acid solution described earlier. However, there is no evidence to support efficacy. The addition of BCAAs to standard solutions also creates a solution containing excessive concentrations of many aromatic amino acids, which with the decreased albumin present in most of these patients, results in increased free plasma and brain tryptophan. Thus, the only formula for which data are adequate is a HepatAmine type of solution consisting of 35% BCAAs and decreased aromatic amino acids. Numerous randomized prospective trials have clearly shown that encephalopathy is well treated by such formulas. Although some trials, particularly one in which glucose was used as the primary calorie source, resulted in increased survival in the group receiving these special solutions when compared with neomycin alone, other trials have not. Furthermore, a large meta-analysis did not support increased overall survival as a beneficial effect of such practices, even though encephalopathy was improved. This topic is further discussed later (see Controversies in Artificial Nutrition).

Plasma Electrolytes

Abnormalities in plasma electrolytes are minimized by careful monitoring. At least 50 mEq of sodium and 20 to 40 mEq of potassium should be administered daily to most patients receiving parenteral nutrition. The daily maintenance requirement is 0.2 to 0.3 mEq/kg/day for calcium, 0.35 to 0.45 mEq/kg/day for magnesium, and 30 to 40 mmol/day for phosphate. Patients who are rapidly anabolic, such as extremely cachectic patients during the initiation of TPN, may require additional potassium, magnesium, and phosphorus (the so-called phosphate steal or refeeding syndrome). One must also be careful to limit sodium and volume administration because these patients are sodium avid and volume overload and congestive heart failure can easily develop. Acid-base imbalance is prevented by adding acetate to TPN solutions when acidosis or hyperchloremia is present, or conversely, solutions are supplemented with potassium chloride when gastric or other GI losses are significant. If potassium chloride is insufficient to prevent metabolic alkalosis, as in patients with gastric outlet obstruction, administration of dilute hydrochloric acid or arginine hydrochloride may also be necessary. In general, in the face of changing fluid and electrolyte requirements, it is generally possible to use the TPN solution to address such needs, unless instability is volatile. However, frequent changes in volume or electrolyte requirements are best dealt with by an alternative route of IV administration to minimize wastage of TPN solutions.

Vitamins and Micronutrients

In the modern era, micronutrient deficiencies in parenteral nutrition are rarely seen but result from inadequate provision of essential fatty acids (see earlier), trace elements, or vitamins (Table 7-4). Such mineral deficiencies are avoided with modern additives, and the available assays for deficiency are often unreliable and not very useful. Therefore, routine testing is not indicated. Some agents require portal passage for metabolic conversion or activation, which is potentially bypassed during parenteral infusion. Furthermore, in short-bowel syndrome or after extensive ileal resection, substances that normally require the enterohepatic circulation for maximal absorption and utilization, such as zinc, copper, manganese, selenium, and many vitamins (cobalamin, folate, and the fat-soluble vitamins A, D, E, and K), are particularly vulnerable. Fat malabsorption, as induced by pancreatic insufficiency, for example, can also lead to inadequate uptake of fat-soluble micronutrients.

Thiamine

Severe thiamine deficiency leads to the classic nutritional disease beriberi, characterized by refractory lactic acidosis as a result of a deficit of the thiamine needed to facilitate entry of glucose into the TCA cycle. The clinical syndrome consists of disturbed mentation, diabetes

Table 7-4 Suggested Dosage of Vitamins and Trace Metals During Severe Illness

VITAMINS AND TRACE METALS	SUGGESTED DAILY DOSAGE
Vitamin	
Water soluble	
Thiamine	25 mg
Riboflavin	25 mg
Niacin	200 mg
Pantothenic acid	50 mg
Pyridoxine	50 mg
Folic acid*	2.5 mg
Vitamin B_{12}†	5 mg
Fat soluble	
A†	5000 µg
D†	400 µg
E†	100 µg
K*	10 mg
Trace Metal	
Zinc	10-20 mg
Copper	0.5-2.0 mg
Chromium	20 µg
Selenium	70-150 µg
Manganese	2-2.5 mg
Iron	25 mg

*Inactivated (oxidized) by addition to hypertonic glucose amino acid solutions.

†Sufficient stores of these vitamins exist, so deficiency states are unlikely during short-term (2- to 4-week) parenteral nutrition. In practice, however, it is wise to provide them.

insipidus, hyperbilirubinemia, thrombocytopenia, and lactic acidosis mimicking sepsis. The plasma amino acid pattern is distorted, with high levels of proline and hydroxyproline. Thiamine deficiency in patients receiving normal amounts of thiamine has occasionally been seen, usually in a depleted patient given a sudden carbohydrate load. Once this condition is recognized, thiamine deficiency is easily treated with 100 mg of thiamine per day. One of the authors (J.E.F.) observed such a case when the Food and Drug Administration withheld the source of multivitamins for several months.

Biotin

Because biotin is ubiquitous, deficiency hardly ever occurs in patients taking anything by mouth, although biotin deficiency has been reported in patients entirely dependent on TPN.

Vitamin D

Deficiency of vitamin D is primarily an issue during long-term TPN administration or in the face of concurrent metabolic bone disease, such as severe osteoporosis (see Metabolic Complications of Long-Term Administration of Total Parenteral Nutrition later). Most standard multivitamin solutions used routinely in TPN contain 200 units of vitamin D. When assayed, aberrations in vitamin D levels (25-hydroxyvitamin D in normal subjects or 1,25-hydroxyvitamin D in chronic renal failure) should be evaluated and levels of parathyroid hormone (PTH) measured concurrently. If vitamin D is to be repleted, oral administration is best (50,000 U/wk for 6 to 8 weeks) because IV replacement can be dangerous, with vitamin D overload and osteomalacia likely.

Vitamin K

In patients who maintain some oral intake in addition to TPN, vitamin K deficiency is unlikely. However, for patients who are entirely dependent on TPN, supplementation weekly with 10 mg vitamin K IV is necessary. In addition, if chronic warfarin (Coumadin) therapy is required, such as for a history of catheter-related superior vena cava syndrome, having a baseline amount of vitamin K in the TPN solution is probably helpful in buffering the inhibitory effect of warfarin on post-translation carboxylation of the coagulation proteins. In this way, large variations in the warfarin requirement can be avoided. Conversely, other practitioners avoid vitamin K entirely under such circumstances.

Zinc

Zinc deficiency may develop in patients who are extremely catabolic or who have excessive diarrhea. Massive diarrhea and malabsorption may increase losses to as great as 10 mEq Zn per liter of stool. Neither plasma zinc nor hair zinc is an accurate reflection of total body stores, which may be markedly depleted even when blood levels appear normal. Three milligrams to 6 mg of elemental zinc per day is required in patients with normal stool losses, and between 12 and 20 mg is required in patients with short-bowel syndrome or excessive diarrhea. Zinc deficiency has numerous manifestations, including alopecia, poor wound healing, immunosuppression, night blindness or photophobia, impaired taste or smell (anosmia), neuritis, and a variety of skin disorders (generalized eruptions, perioral pustular rash, darkening of the skin creases), and is similar to the syndrome of zinc deficiency seen in sheep (acrodermatitis enteropathica).

Copper

Copper deficiency has been observed in a few patients receiving long-term parenteral nutrition and is manifested as microcytic anemia, pancytopenia, depigmentation, and osteopenia. The microcytic anemia may be mistaken for pyridoxine deficiency. In standard mineral solutions used for TPN, up to 2 mg of copper per day is given as the sulfate.

Chromium

Deficiency of chromium is also likely to occur only in patients receiving long-term TPN with minimal or no oral intake. Chromium is necessary for adequate utilization of glucose, and deficiency is often manifested as a sudden diabetic state in which blood sugar is difficult to control, along with peripheral neuropathy and encephalopathy. A total of 15 to 20 µg/day of chromium is adequate to meet daily requirements. To treat chromium deficiency, 150 µg of chromium per day is given for several days.

Molybdenum
This metal is a cofactor for the enzymes superoxide dismutase and xanthine oxidase. The rare deficiency state is characterized by the toxic accumulation of sulfur-containing amino acids and encephalopathy.

Selenium
Selenium deficiency has not been clearly established and is clearly rare. Selenium deficiency may result in diffuse skeletal myopathy and cardiomyopathy (with abnormalities in basement and plasma membranes on muscle biopsy), loss of pigmentation, and erythrocyte macrocytosis.

Iron
Calcium, iron, and other metals are absorbed in the duodenum. Consequently, duodenal bypass (as after a Billroth II gastrectomy) or resection (as after a Whipple procedure) often results in long-term deficiencies of these ions. Iron deficiency can be classified as early (no anemia, serum Fe and ferritin decreased, transferrin increased), intermediate (no anemia, transferrin saturation <15%, ferritin <12 μg/L), or late (hypochromic microcytic anemia). The daily requirement for oral iron is 15 mg/day, 5% to 10% of which is absorbed. Therefore, the parenteral requirement is 1 to 2 mg/day. Despite obligate iron losses from desquamation of skin and gut mucosa, overall there is limited ability to excrete parenteral iron when administered in excess, and iron overload will develop in a significant number of patients given iron routinely. Patients most likely to manifest iron deficiency are premenopausal women (menstruation may increase Fe loss by an additional 1 mg/day), patients receiving more than 50% of their total caloric needs from TPN, patients with chronic GI bleeding (e.g., Crohn's disease in females), and patients maintained on hemodialysis (especially with concurrent erythropoietin therapy). Iron replacement should be avoided in the face of a concurrent inflammatory state or active infection because in these conditions iron utilization is poor and such supplementation may have immunosuppressant activity or may promote bacterial growth. In addition, in short-gut syndrome, some patients appear to carry out iron absorption in the intact duodenum and proximal jejunum too avidly and may be at risk for iron overload. Finally, concurrent inherited hemochromatosis must be recognized inasmuch as 0.2% to 0.7% of the population are homozygotic and 8% to 14% are heterozygotes. Even heterozygotic subjects appear to be predisposed to atherosclerosis, the possible mechanism being iron excess and increased free radical generation. A full discussion of iron deficiency and strategies for iron repletion in TPN is found elsewhere.[45]

PRACTICAL APPROACH TO ARTIFICIAL NUTRITION

A major change in nutritional support over the past decade is the realization that enteral nutrition may be more efficacious, particularly in patients with burns or other trauma, than parenteral nutrition. This topic is explored more thoroughly later in this chapter (see Controversies in Artificial Nutrition) and is discussed briefly earlier as well (see Fundamentals of Artificial Nutrition). Historically, enteral nutrition has not been emphasized as much as parenteral nutrition because it has been assumed that in many disease states the gut will not function to allow adequate nutrient absorption.

In contrast, it is now clear that enteral feeding is often well tolerated, even in severe illness, although it may not provide total nutritional support in all cases. Nonetheless, use of the gut for partial nutritional support probably has significant benefit in areas of immunologic and hepatic function and should be encouraged. As little as 20% of overall nutrient calories administered to the gut was sufficient to show benefit versus TPN alone in certain studies. Therefore, one should approach nutritional support with two goals in mind:

1. To use the gut if possible
2. If total nutritional supplementation cannot be provided by the GI tract, to administer at least 20% of the caloric and protein requirements enterally while reaching goal support with TPN until the GI tract returns to full functionality (Box 7-2)

Box 7-2 General Conditions Suggesting Initiation of Nutrition Support

- Poor nutritional status (oral intake <50% of energy needs)
- Catabolic disease (burn, sepsis, pancreatitis)
- Significant weight loss (>10%)
- Anticipated duration of artificial nutrition longer than 7 days
- More than 7 days' inanition
- Nonfunctioning gastrointestinal tract
- Serum albumin <3 g/dL in the absence of an inflammatory state

Note: Immediate enteral (as opposed to parenteral) feeding in a critically ill patient may be beneficial regardless of the patient's premorbid nutritional status.

Principles of Enteral Feeding

The stomach is the principal defense against an enteral osmotic load. After bolus administration of hyperosmotic fluid, gastric motility is inhibited and gastric secretion proceeds until the gastric contents are isosmotic, at which point transfer across the pylorus begins. The small bowel is less able to dilute and tolerate large osmotic loads when they are administered directly. The small intestine is the principal area for nutrient absorption, with the products of protein digestion (i.e., dipeptides, oligopeptides, and single amino acids) being completely absorbed in the first 120 cm of jejunum. With short or diseased bowel, dipeptides may have an absorptive advantage. Carbohydrate is also absorbed high in the jejunum, with simple sugars being preferred. Complex sugars, such as disaccharides, require additional enzymatic cleavage.

A common difficulty in patients who are ill is acquired lactase deficiency, which often corrects itself in time,

although in the early recovery phase lactose-containing foods may cause diarrhea. Fat is most difficult to absorb because it depends on proper release and mixing of bile and pancreatic enzymes. After gastrectomy, pancreatic resection, or complex upper abdominal operations, such relationships are disturbed, and proper mixing of bile and pancreatic enzymes does not occur. Thus, fat absorption is diminished after a Billroth II gastrectomy and less so after Billroth I procedures. Aside from mechanical issues related to the feeding tube (see later), the most common complications of enteral feedings result from solute overload. Inappropriately rapid administration of hyperosmolar solutions may result in diarrhea, dehydration, electrolyte imbalance, and hyperglycemia, as well as loss of potassium, magnesium, and other ions through diarrhea. If aggressive administration of hyperosmolar solute continues, pneumatosis intestinalis with bowel necrosis and perforation and potentially death will result. Hyperosmolar, nonketotic coma can also occur with enteral feedings as with parenteral nutrition.

Routes for Administration of Enteral Feeding

Patients with a functioning GI tract who cannot achieve adequate nutritional intake orally and are malnourished or at risk for the development of malnutrition are candidates for feeding tube placement. The choice of access route and device must be tailored to the individual by considering the disease process and how long the patient will probably require nutritional support.

Nasoenteric and Postpyloric Feeding

Nasoenteric feeding (gastric, duodenal, or jejunal) is the least expensive and most widely used modality of enteral nutrition. Most commonly, postsurgical patients have nasogastric tubes in place. These tubes are reasonable for the short term because they are typically large bored, do not clog easily, and allow gastric residuals to be checked in assessing GI tolerance. However, the traditional 16- or 18-French nasogastric tube (intended for gastric drainage) is uncomfortable and may promote relatively greater gastroesophageal reflux by holding the lower esophageal sphincter open more than occurs with a narrower tube. Such smaller-caliber feeding tubes (e.g., the Dobhoff tube, 8-10 French) are more comfortable and less erosive to the nasopharynx and esophagus, but they can clog when not carefully maintained and also collapse easily, thus making it difficult to monitor gastric residuals. Though generally considered to be relatively innocuous, nasoenteric feeding tubes are associated with multiple adverse consequences, including tube migration, esophageal and gastric mucosal erosions, pulmonary aspiration, sinusitis, pneumothorax, esophageal stricture, esophageal perforation, and fatal arrhythmias. In particular, feeding tubes with an indwelling removable metal stylet to aid their passage, although used often, appear to be particularly dangerous. In ventilated patients with indwelling endotracheal tubes, malposition in the bronchus with perforation into the pleural cavity seems to be associated most commonly with such stylet-type tubes. A more promising design, though not widely available, is the use of a rigid plastic overtube from which a narrower, soft feeding tube may be deployed after satisfactory gastric positioning. Many of these complications are avoidable with care. For example, aspiration may be minimized by positioning the patient head-up and by monitoring gastric residuals, which should generally be less than 150 mL, although some authors have advocated a more aggressive approach, such as tolerance of residuals as great as 300 to 400 mL.

Many enteral feeding studies are handicapped by the high prevalence of GI intolerance leading to inadequate protein and calorie administration. Such intolerance, in particular that attributable to elevated gastric residual volumes, can affect up to 60% of patients. A variety of approaches have been tried in an attempt to address poor gastric emptying in critically ill patients, including the use of promotility agents such as metoclopramide or erythromycin. Another strategy proposed as a means of bypassing the region of gastroduodenal ileus is postpyloric feeding. Nasoenteric feeding tubes can be placed with their tip positioned in the duodenum or jejunum, either under fluoroscopic guidance or by endoscopic manipulation and visualization. The hypothesis is that the jejunum may be more tolerant of continuous feeding and that by administering nutrients beyond the ligament of Treitz, the risk for aspiration is lessened. However, when these putative advantages have been studied in prospective randomized trials, there did not appear to be any difference when compared with intragastric feeding practices. In fact, in studies involving the use of radiolabeled feeding,[46] regurgitation of postpylorically delivered nutrients and the incidence of actual aspiration or clinically definable pneumonia were no different than in patients fed gastrically. It seems reasonable to assume that in most instances, whether the tube tip terminates prepylorically or postpylorically, because all tubes are introduced nasally, the lower esophageal sphincter is held open regardless, and this is probably the most important mechanism to allow aspiration.

As for feeding tolerance, there also does not appear to be any clear benefit attributable to postpyloric feeding. When aggressive advancement protocols are followed, nasogastrically fed patients, despite having higher gastric residual volumes, receive amounts of enteral nutrition equivalent to those fed nasojejunally. This finding has been confirmed in two separate prospective randomized trials that included 180 patients.[47,48] On the other hand, in postoperative trauma patients, Montecalvo and associates[49] showed that patients who received jejunal feeding attained a significantly higher percentage of their daily caloric goal than did patients fed intragastrically. In conclusion, although the concept of postpyloric feeding remains controversial, it appears reasonable to obtain postpyloric access in patients with specific indications, such as those suffering from significant gastroparesis or with severe pancreatitis (see later). Such access can easily be obtained at the time of surgery directed toward the primary disease process, when a well–carried out feeding jejunostomy obviates most of the risk for aspiration, and will anticipate gastric ileus if sepsis ensues.

Gastrostomy

If long-term access to the stomach will be needed, a permanent gastrostomy can be placed. This goal can be achieved either by the open approach or by percutaneous techniques, the latter using endoscopic, radiologic, or laparoscopic methods. The Stamm gastrostomy, which requires a small laparotomy incision, is the most widely used open technique for insertion of a gastric tube. Either inhalational or, in many cases, awake IV sedation with local anesthesia is an acceptable anesthetic approach for this procedure.

In more recent years, the percutaneous endoscopic gastrostomy (PEG) technique has become the procedure of choice for many patients because it is generally considered less expensive and less morbid, although some studies indicate that open gastrostomy and PEG carry equivalent perioperative risk. Necrosis of the gastric wall, attributable to excessive tension, is a recognized but avoidable complication of percutaneous gastrostomy. Percutaneous gastric tubes can also be placed by the interventional radiologist, which although seemingly less invasive than other procedures for gastrostomy insertion and being used with increasing frequency, actually appears to have a slightly higher incidence of complications and need for open revision than do surgical or endoscopic approaches. On the other hand, for moribund patients or those requiring gastric drainage with no attractive operative approach (e.g., in the face of intestinal obstruction as a result of terminal carcinomatosis), the radiologic technique can be an ideal solution. An important factor limiting any percutaneous gastrostomy insertion is a history of previous upper abdominal surgery, which is associated with the potential for adhesions and superimposition of structures such as the colon between the stomach and the abdominal wall. Perforation of the colon, which may go unrecognized for many days, is a well-described complication of all percutaneous techniques. In such circumstances a Stamm gastrostomy performed via a left upper quadrant incision can usually be carried out. Another drawback of gastrostomy tubes of all types is that they generally do not lie in a dependent position, so it is difficult to aspirate and check gastric residual volumes.

Jejunostomy

Jejunal or small bowel feeding tube access can be achieved by open jejunostomy (either at the time of laparotomy or as a separate procedure), percutaneously by extension through an existing gastrostomy tube (often termed a *G-J tube*), by a laparoscopic approach, or very rarely as a percutaneous jejunostomy placed under fluoroscopic or CT guidance by the interventional radiologist. This latter procedure has an undefined but presumably high frequency of complications and is of dubious value. True percutaneous jejunostomies (as opposed to G-J tubes), though often lifesaving, are complicated more frequently than desired by dislodgement, occlusion, bowel obstruction, and small bowel ischemia. Furthermore, because the small bowel does not accommodate bolus feeding, nutrients delivered to the jejunum must be delivered in continuous fashion while carefully watching for signs of intolerance such as abdominal distention, abdominal pain or tenderness, diarrhea, or constipation. In a critically ill patient, hypo-osmolar or at most iso-osmolar solutions should generally be used. Hyper-osmolar solutions are often not tolerated in critical illness because the bowel is stressed to begin with and such solutions are much more likely to result in pneumatosis, necrosis, perforation, and death.

Management of Tube Tract Infections

A complication common to any percutaneous feeding tube is chronic infection or erosion of the tube tract as it traverses the abdominal wall. As indicated earlier, excessive traction, particularly in the case of PEG, may induce frank gastric wall necrosis and free perforation of the stomach. More commonly, patients may experience chronic drainage, erythema, or excessive buildup of granulation tissue with intermittent bleeding. Factors contributing to such phenomena appear to involve excessive tube motion, the choice of catheter material (latex being less desirable than silicone), and chronic bacterial colonization. Simple hygiene and antibacterial ointment daily usually suffice.

Enteral Formulas and Approach to Feeding Advancement

Mortality from enteral feeding is largely the result of aspiration or, as indicated earlier, occasionally results from hyper-osmolar feeding. Patients should be infused constantly, with the bolus technique reserved for special situations. To prevent reflux and aspiration, patients should be kept at a 30-degree angle because reflux may occur even with postpyloric feeding. In general, there is no commonly agreed on protocol for advancing enteral feeding. For gastric feeding, first osmolality and then volume are increased, usually beginning with solutions that are slightly hypo-osmolar. Most commonly, feeding is started at 10 to 20 mL/hr and gastric residual volumes checked every 4 to 6 hours.

As long as gastric residual volumes remain less than 100 to 150 mL, feeding is advanced in 10- to 20-mL increments until the goal rate is attained. Unfortunately, this conservative protocol often results in unnecessary cessation of feeding and thus leads to slow or inadequate provision of nutrition. Several investigators have had better success when feeding is advanced more aggressively and when standardized protocols that outline rules for feeding advancement and cessation are followed. Such practices, which tolerate gastric residual volumes as high as 250 to 300 mL and increase infusion rates in increments of 20 mL every 2 to 4 hours, have allegedly not resulted in increased complication rates or adverse outcomes. If administration is into the small bowel, volume is increased first, then osmolality. Most patients do not tolerate small bowel administration of tube feeding containing greater than 300 to 400 mOsm, especially when critically ill. Dehydration is prevented by carefully increasing osmolality and using kaolin-pectin (Kaopectate) and opioids to slow the diarrhea, as well

Box 7-3 Indications for Parenteral Nutrition

Primary Therapy

Efficacy shown*
- Gastrointestinal cutaneous fistulas
- Renal failure (acute tubular necrosis)
- Short-bowel syndrome
- Acute burns
- Hepatic failure (acute decompensation superimposed on cirrhosis)

Efficacy not shown
- Crohn's disease
- Anorexia nervosa

Supportive Therapy

Efficacy shown*
- Acute radiation enteritis
- Acute chemotherapy toxicity
- Prolonged ileus
- Weight loss preliminary to major surgery

Efficacy not shown
- Before cardiac surgery
- Prolonged respiratory support
- Large wound losses

Areas Under Intensive Study

Patients with cancer
Patients with sepsis

*Randomized, prospective trials or similar investigations have suggested that such nutritional intervention results in changed (improved) outcome.

as by the addition of free water. Pneumatosis, bowel necrosis, perforation, and mortality usually occur when hyperosmolar feeding persists in the face of voluminous diarrhea or when blood supply to the intestine is inadequate (the so-called challenged bowel), whether caused by reduced cardiac output or atherosclerotic vascular disease.

Enteral Formulas

Many different enteral products are available, and almost all are hyperosmolar (Table 7-5). Most formulas provide 1 kcal/mL, although some higher-calorie formulas (1.5-2 cal/mL) are also available and allow smaller volumes of administration. These high-density formulas tend to have greater proportions of fat and relatively less protein (e.g., Nepro, a formula optimized for renal failure). For patients with normal gut function, an inexpensive tube feeding analogous to a blenderized meal (e.g., a hydrolysate) is well tolerated. Some products have various degrees of complexity ranging from oligopeptides to individual amino acids. The carbohydrate source varies from dextrose to complex starches, the latter solving a major problem in gut feeding—hyperosmolality. Modular diets are those in which the protein, fat, and carbohydrate components can be individually supplied. In patients with reasonably normal gut function, elemental diets (e.g., Vivonex) appear to have no advantage over hydrolysates. Elemental formulations (e.g., dipeptides and oligopeptides) may be more efficiently absorbed in patients suffering from short-gut syndrome or in those with chronic diarrhea, although this idea is unproven. Finally, a recent development is the formulation of tube feeding solutions with potential immune-enhancing properties (e.g., Impact), which is discussed subsequently (see Controversies in Artificial Feeding).

Parenteral Feeding

When enteral feeding is poorly tolerated or impossible to deliver, parenteral nutrition administered safely is the only alternative (Box 7-3). If the parenteral route is chosen, concentrated TPN (>900 mOsm/L) delivered to a large central vein (termed *central TPN*), with the line tip in the superior vena cava, is the preferred method. The potential sources of calories (e.g., carbohydrate, lipid, and protein) have been discussed in detail earlier. In the absence of central access, a less concentrated formula (dextrose not to exceed 5%) may be delivered via a peripheral vein (termed *peripheral TPN*). This latter method is usually for a short term only (4-7 days) and provides less than optimal calories, although nitrogen loss may be retarded. If lipid is included (250-500 mL of a 20% fat emulsion daily) and up to 3 L of dilute solution can be tolerated, peripheral TPN can satisfy the daily caloric requirement. However, the needs of sick patients are rarely satisfied by this approach, and to date, no clinical trials have attributed any benefit to the routine use of peripheral IV alimentation. As discussed earlier, there is some experimental evidence to support the provision of (hypocaloric) amino acids and 5% dextrose or glycerol in an attempt to minimize nitrogen breakdown for limited periods. However, in a European trial by Culebras and coworkers, a limited 14-hour infusion of amino acids and 5% dextrose after operations of modest severity did not show improved nitrogen balance.

Practical Approach to Calculation of the Ideal Parenteral Formula

Physicochemical Considerations

Today, most TPN solutions are administered as a total nutrient admixture (TNA or 3-in-1 solution) with lipid emulsions incorporated into the final solution, as opposed to the older method of a separate piggyback infusion of lipid. The TNA protocol is clinically advantageous because it does the following:

1. Limits the number of central venous catheter violations and chance for contamination
2. Produces a hyperosmolar environment in the TNA solution that protects against bacterial growth
3. Allows continuous infusion, thereby ensuring lipid administration at a safe rate (<0.11 g/kg/hr)

It is important to recognize that TPN is generally compounded in the pharmacy from concentrated stock solutions, which in turn can limit the range of individual solute concentrations achievable. These factors often lead

Table 7-5 Enteral Nutrition Products

DESCRIPTOR	PRODUCT							
	Criticare HN	Vivonex TEN	Peptamen VHP	Impact With Fiber	Impact	Respalor	Nepro	Promod (100 g)
Calories (kcal/mL)	1.06	1.00	1.0	1.00	1.00	1.52	2.00	424
Protein (g/L)	38 (14.4%)	38.2 (15%)	62.5 (25%)	56 (22%)	56 (22%)	75 (20%)	70 (14%)	76 (72%)
Carbohydrate (g/L)	220 (81%)	206 (82%)	104.5 (42%)	133 (53%)	130 (53%)	146 (40%)	215 (43%)	10 (10%)
Fat (g/L)	5.3 (4.5%)	2.8 (3%)	39 (33%)	28 (25%)	28 (25%)	68 (40%)	96 (43%)	9 (19%)
Fat as MCT (%)	0	0	70%	27%	27%	30%	0%	0
Osmolality (mOsm/L)	650	630	300 unflavored/ 430 flavored	375	375	400	665	—
Free water (mL/L)	850	853	840	868	853	770	699	—
Sodium (mEq/L)	27	20	24	48	48	55	37	10
Potassium (mEq/L)	34	20	38	33	36	38	27	25
Calcium (mg/L)	530	500	800	800	800	1000	1370	607
Phosphorus (mg/L)	530	500	700	800	800	1000	695	500
Magnesium (mg/L)	210	200	300	270	270	400	215	—
Vitamin K (mg/L)	131	22	50	67	67	84	85	—
Dietary fiber (g/L)	0	0	0	10	0	0	0	—
Volume for 100% DRI (mL)	1890	2000	1500	1500	1500	1000	947	NA
Comments	Elemental amino acids and peptides, ready to feed, gluten- and lactose-free	Elemental amino acids and peptides, oral or tube feeding, 4.9 g/L glutamine, requires mixing, gluten- and lactose-free	Semielemental high-protein oral or tube feeding, 4.6 g/L glutamine, gluten- and lactose-free	Immune-enhancing tube feeding for critical care; with fiber, high protein, fish oil, RNA, arginine; gluten- and lactose-free	See Impact (no fiber)	For respiratory failure (low carbohydrate, volume restricted), oral or tube feeding, gluten- and lactose-free	For renal failure (low electrolyte, Mg, Pi; volume restricted), oral or tube feeding, gluten- and lactose-free	Protein supplement, gluten-free, low residue; 4.5 g/100 g lactose
Flavors	Unflavored	+ Flavor packets	+ Flavor packets	Unflavored	Unflavored	Vanilla	Vanilla, pecan	NA
Cost per 1500 kcal	$13.50	$13.80	$23.50	$27.00	$25.50	$3.16	$4.90	—

Continued

Table 7-5 Enteral Nutrition Products—cont'd

	PRODUCT							
DESCRIPTOR	Boost	Boost Plus	Boost High Protein	Ultracal	Promote	Promote With Fiber	Probalance	Deliver 2.0
Calories (kcal/mL)	1.01	1.52	1.01	1.06	1.0	1.0	1.20	2.00
Protein (g/L)	43 (17%)	61 (16%)	61 (24%)	44 (17%)	62.5 (25%)	62.5 (25%)	54 (18%)	75 (15%)
Carbohydrate (g/L)	170 (67%)	190 (50%)	139 (55%)	123 (46%)	130 (52%)	138 (50%)	156 (52%)	200 (40%)
Fat (g/L)	18 (16%)	57 (34%)	23 (21%)	45 (37%)	26 (23%)	28 (25%)	40.8 (30%)	102 (45%)
Fat as MCT (%)	0	0	0	40	19	19	20	30
Osmolality (mOsm/L)	590	630-670	650	310	340	380	450	640
Free water (mL/L)	840	780	850	850	830	830	810	710
Sodium (mEq/L)	24	37	40	40	43	57	33	35
Potassium (mEq/L)	43	38	54	41	51	51	40	43
Calcium (mg/L)	1270	850	1010	850	1200	1200	1250	1010
Phosphorus (mg/L)	1060	850	930	850	1200	1200	1000	1010
Magnesium (mg/L)	420	340	380	340	400	400	400	400
Vitamin K (mg/L)	127	68	240	68	80	80	80	250
Dietary fiber (g/L)	0	<4	0	14	0	14	10	0
Volume for 100% DRI (mL)	1590	1180	1060	1250	1000	1000	1000	1000
Comments	Oral supplement only, gluten- and lactose-free	Oral, nutrient dense, may be used as tube feeding, gluten- and lactose-free	Standard high-protein oral or tube feeding, gluten- and lactose-free	Standard tube feeding with fiber, gluten- and lactose-free	Standard high-protein oral or tube feeding, lactose- and gluten-free, low residue	See Promote With Fiber	Higher-calorie (1.2 cal/mL) oral or tube feeding with fiber, gluten- and lactose-free	Volume-restricted oral or tube feeding, gluten- and lactose-free
Flavors	Vanilla, chocolate, strawberry	Vanilla, chocolate, strawberry	Vanilla, chocolate	Unflavored	Vanilla	Vanilla	Many	Vanilla
Cost per 1500 kcal	$1.20	$0.80	$1.20	$3.50	$3.40	$3.40	$2.60	$2.10

MCT, medium-chain triglyceride; DRI, daily recommended intake.

Table 7-6 Allowable Additive Supplementation (at the University of Cincinnati Hospital, Cincinnati, Ohio)*

ADDITIVES	AVAILABLE PRODUCTS (INJECTION)	MAXIMAL ALLOWABLE TOTAL PER LITER
Calcium	Calcium gluconate Calcium chloride	9 mEq
Magnesium	Magnesium sulfate	12 mEq
Phosphate	Sodium phosphate Potassium phosphate	15 mmol
Potassium	Potassium chloride Potassium acetate	80 mEq
Sodium	Sodium chloride Sodium acetate	Patient tolerance and/or need
Chloride	Sodium chloride Calcium chloride Potassium chloride	Limited by amount of cation
Acetate	Sodium acetate Potassium acetate	Limited by amount of cation
Insulin	Regular insulin	100 units (in conjunction with fingerstick blood sugar determination)

*Some points to remember: (1) Bicarbonate salts must not be added to parenteral nutrition formulations because they create certain incompatibilities and are ineffective given in this manner. (2) Medicinal agents not mentioned must not be admixed or administered with parenteral nutrition formulations unless compatibility data are available. (3) Phosphate supplementation must be ordered in terms of millimoles of phosphate. Phosphate is available only as the sodium or potassium salt, and when the potassium salt is used for "added" phosphate, it must not exceed the maximum allowable concentration of potassium (i.e., 80 mEq).

to a requirement for greater volumes of solution to be delivered than initially might seem apparent. For example, common stock solutions are 70% dextrose, 10% to 20% amino acids, and 20% lipid. Therefore, for 1 L of solution in the absence of fat, the maximal achievable concentrations are 7% amino acids (70 g/L) and 21% dextrose (210 g/L). These amounts become even lower when fat is added to a 3-in-1 mixture. In addition, the pharmacist must take into account the physical-chemical stability of the 3-in-1 solution with respect to the effect of mineral additives and the relative proportions of caloric sources on the stability of the lipid emulsion and on overall solubility (Table 7-6).

Estimation of Energy Needs

In an earlier section (Nutritional Assessment), a variety of approaches were described to estimate energy needs, including indirect calorimetry, use of the IBW, and calculation by standard methods such as the Harris-Benedict equation. Determination of the resting energy expenditure or basal metabolic rate (BMR) by the Harris-Benedict equation relies on the following formulas:

$$\text{Male BMR} = 66 + (13.7 \times \text{wt in kg}) + (5 \times \text{ht in cm}) - (6.8 \times \text{age in yr})$$

$$\text{Female BMR} = 65.5 + (9.6 \times \text{wt in kg}) + (1.7 \times \text{ht in cm}) - (4.7 \times \text{age in yr})$$

The weight used for this calculation should be the subject's actual body weight. The value obtained for BMR must then be corrected for normal activity, for example, ambulation and the work of breathing (+15%), and for stress. The added caloric expenditure, or relevant stress factor, is 10% for an uncomplicated postoperative patient; 10% to 30% for peritonitis; and 30% to 50% for sepsis, respiratory failure, or trauma. In burns, caloric requirements may be 50% to 100% greater than normal. Additional stress factors include fever (hyperthermia), for which each 1°C increment in body temperature causes a 5% to 8% increase in BMR, and conditions of uncontrolled heat loss, pain, sleep deprivation, and anxiety (Fig. 7-7).

Caloric requirements for TPN administration can also be estimated by using normative values consisting of body weight and the accepted parameter of 25 to 35 kcal/kg/day for the rate of caloric infusion. This latter approach is safe, easy, and the most commonly used in clinical practice. However, because patients can be at, below, or above IBW (as defined in Nutritional Assessment earlier), one must have a method of choosing an appropriate weight that will be used to calculate nutritional goals. This weight is called the *feeding weight* and is calculated by first determining IBW, as found in standardized tables or estimated by using the equations given earlier. Second, IBW is compared with actual body weight (ABW). In comparing IBW and ABW,

- If the patient is underweight, use ABW as the feeding weight.
- If the patient is obese (ABW is >120% of IBW), add 25% of the difference between ABW and IBW to the IBW as the feeding weight.
- If no reliable weight is available, use IBW alone.

Formulation of the TPN Solution

For the calculation of caloric content in TPN, glucose contains 3.4 kcal/g, protein contains 4 kcal/g, and fat contains 9 kcal/g. In general, minimal fluid requirements in the absence of GI or other losses are 25 to 35 mL/kg/day. Using the example of a 70-kg person as the feeding weight, one first calculates the overall caloric goal and the proportion contributed by protein, usually:

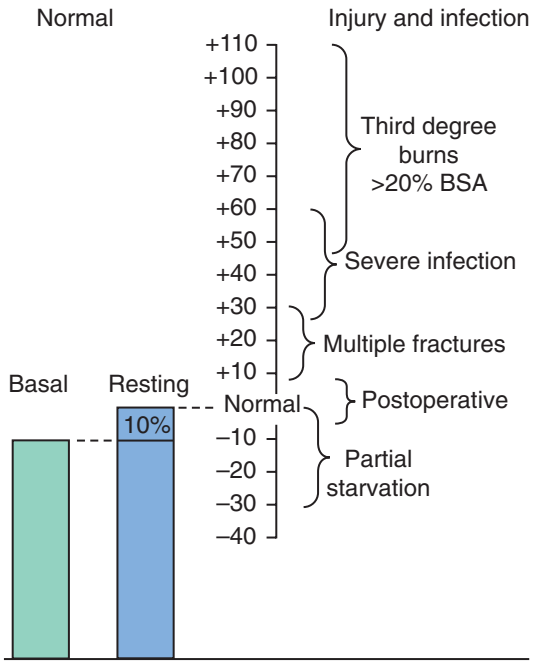


Figure 7-7 **Increases in resting energy expenditure that have been shown to occur during the acute catabolic phase of injury or infection in comparison to the decreases that develop during partial starvation. BSA, body surface area.** (From Kinney JM: The application of indirect calorimetry to clinical studies. In Kinney JM [ed]: Assessment of Energy Metabolism in Health and Disease. Columbus, OH, Ross Laboratories, 1980.)

Total kilocalories (25-35 kcal/kg/day): 30×70=2100 kcal

Protein (1.5 g/kg/day): 1.5×70=105 g amino acids

1. For TPN formulated without lipid (2-in-1 solution):

   Total kilocalories=2100 kcal

   Calories from amino acids=105 g×4 kcal/g=420 kcal

   Remaining calories=2100−420=1680 kcal

   Then make up the difference with dextrose:

   1680 kcal÷3.4 kcal/g=494 g dextrose

   However, remember that as demonstrated by Wolfe (see earlier), 400 g dextrose/24 hr is probably the maximum that can be safely used.

2. For TPN formulated with lipid (3-in-1 solution):

   Total kilocalories=2100 kcal

   Provide 20% of the total calories as

   Lipid=2100×0.2=420 kcal

   Then

   420 kcal÷9 kcal/g=47 g lipid

   Calories from amino acids:

   105 g×4 kcal/g=420 kcal

   Remaining calories:

   2100−420−420=1260 kcal

   Then make up the difference with dextrose:

   1260 kcal÷3.4 kcal/g=370 g dextrose

   Final volume (for 3-in-1, maximally concentrated):

   Amino acids (10% stock solution): 105 g=1050 mL

   Dextrose (70% stock solution): 370 g=528 mL

   Lipids (20% stock solution): 47 g=235 mL

   Total volume=1813 mL/day

The final concentrations (wt/vol) is 5.8% amino acids, 20.4% dextrose, and 2.6% lipid.

For critically ill patients who may have unusually high caloric requirements or who require fine adjustment of the glucose or amino acid content in the TPN solution, it is important to facilitate the clinician's writing of the custom TPN order as just described, if necessary. On the other hand, in the hospital setting most providers have minimal experience managing TPN. For this reason and to avoid the inefficiencies and waste caused by inappropriately formulated TPN, our institution has implemented a weight-based standard TPN ordering process (Fig. 7-8). Values of 25 kcal/kg/day for total kilocalories and 1.5 g/kg/day for amino acids are assumed, and either a non-lipid 2-in-1 formula or a lipid-containing 3-in-1 formula (2% lipid, or 18% of the total calories from lipid) is provided in 10-kg ranges for weight. The order form also provides a suggested schedule for caloric advancement (see later), and the entire process has now been computerized in a Web/HTML-based format. For individuals who desire higher calories, the orders can and should be adjusted upward. In many institutions a very similar, but somewhat different approach to standardized TPN ordering is taken. A uniform, maximally concentrated solution is provided, for example, 7% amino acids/21% dextrose for 2-in-1 formulas, with caloric intake individualized by continuously varying the rate of infusion (versus the step-wise increments described earlier). This latter approach may best minimize wastage of solutions (Fig. 7-9).

Schedule for Advancement

The most important aspect of TPN administration is to ensure that it is delivered in a safe manner, one that prevents the development of hyperglycemia and metabolic derangements (Table 7-7). At our institution, on the first day TPN is initiated as a starter solution containing 70 g amino acids and 150 g dextrose in 1000 mL. Tolerance of the infusion is carefully monitored by assessing blood glucose every 6 hours and electrolytes daily and monitoring for signs of volume overload. If well tolerated, the solution is advanced to the day 2 formula, which consists of 70 g amino acids and 210 g dextrose. On the third day, protein is advanced to goal levels, lipids are added if desired, and dextrose is advanced gradually toward goal amounts by increments of 50 to 100 g/day. If blood sugar rises to levels greater than 150 mg/dL, the dextrose content of the TPN is not increased until glycemic control is secured. In institutions that use a single standard solution, the initial infusion may start at 40 mL/hr and advance in 20-mL/hr daily increments until the desired level of caloric intake is reached.

1954-0711-0279

Beth Israel Deaconess Medical Center
Adult Central Parenteral Nutrition (TPN) Order

Orders must be faxed to Pharmacy daily by 1300 Fax #: 2-8950
PN order has a 24 hr automatic stop time

❒ **DAY 1–2 / STARTER TPN**
A standard parenteral nutrition formulation that can be used initially while assessing glucose and volume tolerance

Amino acid	70 g	
Dextrose	150 g	
Total volume	1000 ml	(providing 800 Kcal)

❒ **DAY 2 AND/OR THEREAFTER: INTERMEDIATE TPN**
An advanced TPN formulation for patients who have demonstrated glucose tolerance to Day 1 TPN. If the patient demonstrates tolerance to this TPN, the patient can be advanced to goal with a Central Standard formula or continued with this formulation for up to 10 days without adverse clinical consequence.

Amino acid	70 g	
Dextrose	210 g	
Total volume	1000 ml	(providing 1000 Kcal)

DAY 3 AND/OR THEREAFTER: CENTRAL STANDARD FORMULAS:
The Central Standard TPNs are weight-based parenteral nutrition formulas providing protein 1.5g/kg/day and 25 kcal/kg/d. Select either the **2-in-1** formula (amino acid/ dextrose) or the **3-in-1** "mixed fuel" formula (amino acid/ dextrose/ lipid) based on the calculated feeding weight. *(See reverse side for calculation. Round to nearest 10 kg.)* For patients with a calculated feeding weight greater than 80 kg or for obese patients (greater than 130% IBW) consult the Nutrition Support Team for patient-specific recommendations.

CENTRAL STANDARD 2-in-1 TPN

	Feeding Weight	TPN Volume	Amino Acid (g/d)	Dextrose (g/d)	Kcal/day
❒	40 kg	1000	60	223	1000
❒	50 kg	1250	75	279	1250
❒	60 kg	1500	90	335	1500
❒	70 kg	1750	105	390	1750
❒	80 kg (or greater)	2000	120	446	2000

CENTRAL STANDARD 3-in-1 TPN

	Feeding Weight	TPN Volume	Amino Acid (g/d)	Dextrose (g/d)	Fat (g/d)	Kcal/day
❒	40 kg	1000	60	170	20	1000
❒	50 kg	1250	75	213	25	1250
❒	60 kg	1500	90	255	30	1500
❒	70 kg	1750	105	298	35	1750
❒	80 kg (or greater)	2000	120	340	40	2000

NON-STANDARD TPN: **Nutrition Support consult recommended.** *See reverse side for general recommendations.*
For patients with liver and/or kidney failure, protein and volume restriction may be required.

❒ Volume _____ ml/d Amino Acid _____ g/d 50% Branched-chain AA _____ g/d Dextrose _____ g/d Fat _____ g/d

ADDITIVE OPTIONS

Vitamin / Trace Element Additives:
Parenteral Multivitamins will be added daily
Trace Elements will be added daily unless specified:
❒ No
Vitamin K 10 mg will be added each Monday unless specified:
❒ No

❒ **Standard elctrolytes**
Total amount below will be added per day.

Na	70 mEq
K	40 mEq
Ca	9 mEq
Mg	10 mEq
Cl	40 mEq
Ac	30 mEq
PO_4	30 mM

❒ **Non-standard electrolytes**
Designate amount to be added **per day.**
NaCl _____ mEq (60–150 mEq/day)
NaAc _____ mEq (as required)
$NaPO_4$ _____ mEq (30–60 mEq/day)
KCl _____ mEq (60–100 mEq/day)
KAc _____ mEq (as required)
KPO_4 _____ mEq (as required)
$MgSO_4$ _____ mEq (10–20 mEq/day)
CaGluc _____ mEq (10–20 mEq/day)

❒ **Other Additives**
See reverse side for general recommendations.
Heparin _____ units
(usual range: 3000-6000 units/day)
Rantidine _____ mg
Insulin _____ units
(Regular Human)
Zinc _____ mg
Other _____

RATE OPTION:
❒ Total volume of solution per 24 hours. Rate of continuous infusion determined by pharmacy-SEE TPN label.
❒ Cycle over _____ hrs. Start at: _ _ _ _
Decrease rate to _____ ml/h at: _ _ _ _ Stop at: _ _ _ _ Plug and flush line with _____ units heparin.

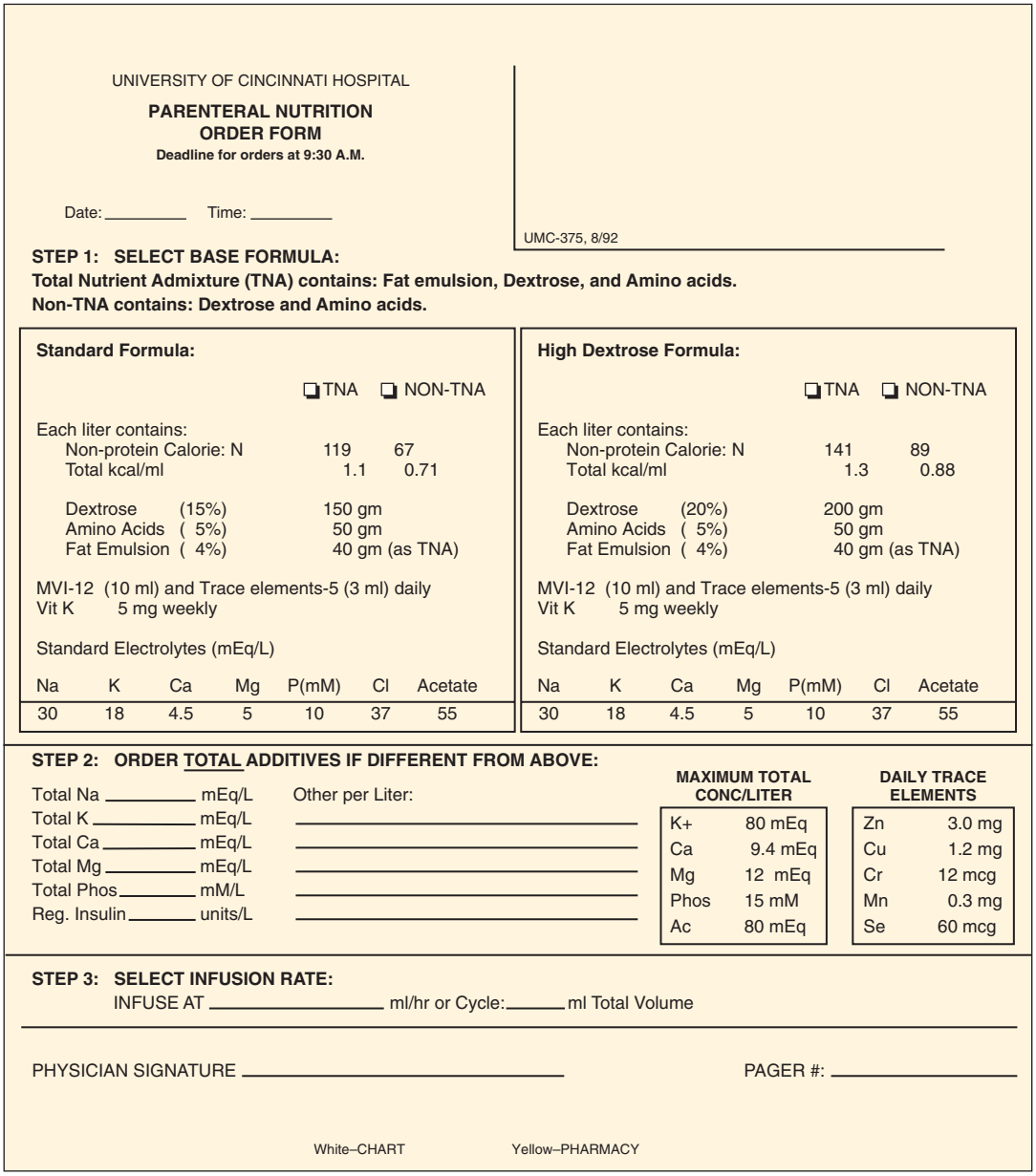
Date: _____ **Physician Signature** _____ **MD** **Beeper:** _____
Time Posted: _____ **by** _____ RN

White - MEDICAL RECORDS Yellow - PHARMACY

Figure 7-8 Order form for the parenteral formulation used at the Beth Israel Deaconess Medical Center, Boston, MA.

Management of Insulin

All patients started on TPN must be provided a subcutaneous sliding-scale regimen for regular insulin administration or, in some cases, an IV regular insulin infusion. The choice depends on the patient's baseline insulin requirement (e.g., concurrent diabetes mellitus) and the presence of factors leading to insulin resistance (steroids, stress), along with the available level of nursing care. In general, it is safe to add an initial 10 units of regular insulin to every bag of TPN because this dose is below the basal rate of insulin production by the pancreatic beta cells and some insulin will be lost as a result of unavoidable binding to plastic components of the infusion equipment. The key to maintaining blood



UNIVERSITY OF CINCINNATI HOSPITAL

PARENTERAL NUTRITION ORDER FORM

Deadline for orders at 9:30 A.M.

Date: _____ Time: _____

UMC-375, 8/92

STEP 1: SELECT BASE FORMULA:

Total Nutrient Admixture (TNA) contains: Fat emulsion, Dextrose, and Amino acids.

Non-TNA contains: Dextrose and Amino acids.

Standard Formula:

❑ TNA ❑ NON-TNA

Each liter contains:

Non-protein Calorie: N	119	67
Total kcal/ml	1.1	0.71
Dextrose (15%)	150 gm	
Amino Acids (5%)	50 gm	
Fat Emulsion (4%)	40 gm (as TNA)	

MVI-12 (10 ml) and Trace elements-5 (3 ml) daily
Vit K 5 mg weekly

Standard Electrolytes (mEq/L)

Na	K	Ca	Mg	P(mM)	Cl	Acetate
30	18	4.5	5	10	37	55

High Dextrose Formula:

❑ TNA ❑ NON-TNA

Each liter contains:

Non-protein Calorie: N	141	89
Total kcal/ml	1.3	0.88
Dextrose (20%)	200 gm	
Amino Acids (5%)	50 gm	
Fat Emulsion (4%)	40 gm (as TNA)	

MVI-12 (10 ml) and Trace elements-5 (3 ml) daily
Vit K 5 mg weekly

Standard Electrolytes (mEq/L)

Na	K	Ca	Mg	P(mM)	Cl	Acetate
30	18	4.5	5	10	37	55

STEP 2: ORDER TOTAL ADDITIVES IF DIFFERENT FROM ABOVE:

Total Na _____ mEq/L
Total K _____ mEq/L
Total Ca _____ mEq/L
Total Mg _____ mEq/L
Total Phos _____ mM/L
Reg. Insulin _____ units/L

Other per Liter: _____

MAXIMUM TOTAL CONC/LITER

K+	80 mEq
Ca	9.4 mEq
Mg	12 mEq
Phos	15 mM
Ac	80 mEq

DAILY TRACE ELEMENTS

Zn	3.0 mg
Cu	1.2 mg
Cr	12 mcg
Mn	0.3 mg
Se	60 mcg

STEP 3: SELECT INFUSION RATE:

INFUSE AT _____ ml/hr or Cycle: _____ ml Total Volume

PHYSICIAN SIGNATURE _____ PAGER #: _____

White–CHART Yellow–PHARMACY

Figure 7-9 Order form for the parenteral formulation used at the University of Cincinnati Medical Center, Cincinnati, OH. The variety of solutions minimizes the chance of error and enables one to handle almost any metabolic situation. The various possible contents of each solution are given.

sugar in the normal range lies in the following maneuvers:

1. Never increase the amount of dextrose in the TPN solution until blood sugar is well controlled (i.e., <150 mg/dL).
2. Determine the amount of sliding-scale insulin administered over the previous 24 hours and add half to two thirds of that amount to the new TPN solution for the ensuing 24 hours.
3. When advancing the dextrose content of the TPN solution, advance the insulin concentration proportionally. For example, if a TPN solution contains 200 g dextrose and 10 units of insulin and the dextrose will be advanced to 300 g, add 15 units of insulin to the solution. Be quick to convert to a constant insulin infusion if it is difficult to gain control with subcutaneous insulin, especially in the setting of critical illness.

It is important to remember that the insulin added to the TPN solution should cover only the dextrose in the TPN. This insulin should not be used to treat elevated blood sugar resulting from additional sources of dextrose, such as that contributed by an enteral feeding formula administered concurrently. For instance, if the enteral feeding was stopped for any reason, the patient would be at risk for the development of hypoglycemia from the excessive insulin in the TPN solution.

Table 7-7 Suggested Sequence for the Initiation of Parenteral Nutrition Therapy

PARAMETER	DAY 1	DAY 2	DAY 3
Volume (mL/24 hr)	1000	1000-1500	1500-2000
Calories (% of goal)	50%	75%, may add fat	100%
Dextrose (g/24 hr)	100-150	150-200	200-350
Amino acids (% of total)	50%-100%	100%	100%, check BUN
Fat	No	Perhaps	Often (3%-5%, 30-50 g/24 hr)
Insulin	Give separately	Add 50% to TPN	Add 50% to TPN

Note: Electrolytes should begin at a low range (total mEq/24 hr for Na^+=40 to 75, K^+=10 to 40). Insulin is initially given subcutaneously or otherwise separately from the TPN. Half of the preceding 24-hour requirement for insulin can then be added to the TPN solution each day until a stable dosage of insulin in the TPN is reached.

BUN, blood urea, nitrogen; TPN, total parenteral nutrition.

Mandatory Monitoring During Intravenous Nutrition

It is important to monitor a variety of parameters in a patient receiving IV feeding, both to ensure tolerance and to potentially witness a beneficial response (e.g., appropriate weight gain). These parameters are monitored by clinical observations and blood analysis:

Clinical: Daily fluid balance, body weight, evidence of infection

Laboratory:

- *Baseline:* Electrolytes, BUN, creatinine, glucose, calcium, magnesium, inorganic phosphate, liver function (bilirubin, alanine transaminase, aspartate transaminase, alkaline phosphatase), triglyceride, albumin, prothrombin time
- *Every 6 to 12 hours:* Glucose, usually for the initial 3 to 5 days or until stable
- *Daily until stable:* Electrolytes, BUN, creatinine, glucose, calcium, magnesium, PO_4
- *Weekly:* Liver function, triglyceride, albumin, prothrombin time

Catheter Issues in Parenteral Nutrition

Many different types of venous catheters are available for central infusion, and which is most appropriate for a given patient depends on many factors. We focus here on aspects particularly relevant to TPN patients. The most important issue is patient safety. Therefore, avoidance of surgical complications related to catheter placement, avoidance of infection, and prevention of late complications (e.g., thrombosis) are paramount. Current recommendations to aid in the prevention of nosocomial infections attributable to central venous catheters are summarized in a recent publication from the Centers for Disease Control and Prevention.[50]

Catheter Choice and Rationale

In choosing a catheter for TPN administration, the first consideration should be the anticipated duration of therapy. In the inpatient setting, the traditional percutaneous central line, introduced via the subclavian or internal jugular vein and often containing multiple lumens (e.g., the so-called triple-lumen catheter), is most common. As the number of lumens increases, infection rates will rise proportionally, thus arguing in favor of single-lumen catheters when the device is intended solely for TPN administration. A more recent trend is to use peripherally inserted central catheters (PICCs) introduced via the basilic vein, both in the inpatient setting and also for longer-term outpatient therapy. When evaluated in controlled trials, PICC lines show similar rates of line sepsis as traditional central catheters but have an increased incidence of local complications such as leakage, thrombophlebitis, and malpositioning. At best, a PICC line in the outpatient setting has a lifetime of 4 to 6 weeks before malfunctioning or becoming infected. Therefore, for long-term TPN administration, a more permanent solution is needed. The devices available consist of either subcutaneously tunneled central catheters (Hickman, Broviac, Groshong) or self-contained implantable chambers that connect to the central venous system (portacath). The catheter of these devices can be inserted into the vein percutaneously (e.g., the subclavian, internal jugular, or femoral) and then tunneled to the final skin exit site (or to connect to the portacath chamber). Alternatively, access may be obtained by venous cut-down, for example, the cephalic vein within the deltopectoral groove, the external or internal jugular vein, the saphenous vein, or a branch of the subclavian vein within the axilla.

The principle underlying tunneled catheters is that the subcutaneous tract forms a barrier to bacterial encroachment and colonization, thus discouraging a so-called tunnel or tract infection, although a competing mode of infection for these or any other catheters, with resultant bacteremia, is by an intraluminal route. Tunneled catheters are desirable when frequent access is required, or perhaps if a high incidence of infection is anticipated, because they are easily removed. However, these devices are disfiguring and proper care of the exit site usually implies an inability to fully bathe or swim. The portacath is completely subcutaneous and thus obviates some of the limitations of the Hickman design (improved appearance, ability to immerse the body totally). However, when accessed, these devices require percutaneous insertion of a special low-profile needle (Huber needle), which then passes through the self-sealing diaphragm of the device into the chamber. Particularly if accessed frequently, the portacath may have a higher rate of infection and overall rate of failure than tunneled catheters in the setting of TPN, as opposed to other common scenarios such as when used for chemotherapy.

Catheter Sepsis

Catheter sepsis is potentially the most lethal complication in patients receiving TPN.[50] This problem is directly related to catheter care and the incidence of hyperglycemia attributable to TPN and can be reduced to an acceptable minimum of less than 1% per year by attention to detail, avoidance of multiuse catheters, and careful metabolic management. Organisms causing line infections are generally 80% *Staphylococcus* (50:50 *aureus* versus *epidermidis*), 15% yeast, and 5% gram-negative bacteria. Staphylococcal infections are generally related to catheter care, whereas yeast probably reaches the catheter through the gut. Additional factors influencing the incidence of line sepsis include the presence of a percutaneous stoma (e.g., a colostomy or tracheostomy), preexistent malnutrition with an increased susceptibility to infection, corticosteroid administration, recent broad-spectrum antibiotic therapy, concurrent chemotherapy, or severe neutropenia (e.g., in acute leukemia). The absence of a protocol for inpatient line care is also very important because in the ideal circumstance of a hyperalimentation team and a rigid protocol, sepsis rates may be as low as 0.6%.

If fever or signs suggestive of bacteremia develop in a patient receiving TPN, the TPN bottle should be taken down. Blood cultures, both from the central catheter and peripherally, should be performed, and a thorough search should be made for other possible sources of fever, such as pneumonia, an intra-abdominal abscess, the urinary tract, or a wound infection. If the fever persists or blood cultures suggest an infected catheter, the catheter should be removed and the tip cultured quantitatively by rolling it on an agar plate. Such tip cultures are considered positive if more than 15 colonies of organisms appear. Whether a percutaneous central line is simply removed under these circumstances or exchanged over a wire depends on many factors, as does the decision to treat such an incident with antibiotics and for what duration. Fungemia is the most serious type of line infection, with the entry site of *Candida,* the most common fungal pathogen, most probably being the GI tract. It is important to treat colonization with yeast (defined as two positive site cultures, e.g., urine and skin) in a critically ill patient aggressively with either fluconazole or amphotericin to avoid further complications such as line sepsis.

In the instance of a permanent catheter (Hickman, portacath), these devices may sometimes be salvaged in the setting of confirmed bacteremia (usually with gram-negative organisms) by prolonged antibiotic therapy, usually of 2 weeks' duration. For patients receiving long-term TPN who may have limited access options remaining because of multiple previous lines, line salvage becomes even more attractive. For *S. epidermidis* or gram-negatives, antibiotic therapy is effective in 60% to 70% of patients. At times a fibrin sheath at the catheter tip may be a nidus, and dissolution with tissue plasminogen activator or urokinase may be useful. Line tract infections can be more difficult to eradicate. In general, if *Staphylococcus aureus* or yeast is documented on blood culture, the line should simply be removed and IV antimicrobial therapy subsequently administered because these organisms are too virulent and dangerous to treat in lesser fashion. Though beyond the scope of this chapter, additional approaches to the avoidance of line infection are the use of impregnated catheters (e.g., with silver or bonded antibiotics) or the so-called antibiotic lock. The latter consists of antibiotics in high concentration, such as rifampicin, instilled into the catheter at the time that it is disconnected from the infusion, either as prophylaxis or, in some centers, as definitive therapy for line colonization.

Catheter Thrombosis and Other Complications

Catheter failure as a result of clogging and lack of function because of an intraluminal thrombus or a fibrin tip sheath is quite common. This problem can often be corrected by instillation of tissue plasminogen activator or urokinase and can be avoided by administering long-term prophylactic low-dose heparin (usually 6000 U/bag) or by the use of low-dose warfarin (1-2 mg/day), as shown effective in randomized trials.[51] Thrombosis of the great veins (subclavian, superior vena cava) occurs much less frequently, although some series report an incidence as high as 5% to 10%. Signs include upper arm, neck, or facial swelling or pain, or both. When thrombosis of the great veins is suspected, the catheter should be removed, and after confirmation of the diagnosis, thrombolytic therapy should be initiated. Heparin should then be continued, followed by warfarin therapy for 6 months or indefinitely.

Other catheter complications include pneumothorax, vascular injuries (arterial or venous lacerations, delayed arteriovenous fistulas), brachial plexus injury, chronic pain, thoracic duct injury after left-sided cannulation, air embolism, and catheter embolism. Erosion of the catheter into the bronchus, right atrium, or other structures may occur. Septic venous thrombosis is a life-threatening complication, and if antibiotics and anticoagulation are not successful, excision of the involved vein or Fogarty catheter embolectomy may occasionally be successful. Hydrothorax results from catheter malposition and administration of fluid into the thoracic cavity. This problem is particularly common with the more rigid percutaneous triple-lumen temporary central venous catheters, especially when introduced via the left subclavian vein. Such catheters should be 20 cm long, as opposed to the 16-cm catheter manufactured for placement in the right side of the chest or neck. If too short and thus allowing the line tip to terminate or rub against the wall of the superior vena cava, erosion of the catheter tip into the left pleural cavity can result.

Home Parenteral Nutrition

A major contribution of parenteral nutrition has been the ability to maintain patients in a functional state for decades with minimal oral intake. Unlike the continuous-infusion approach appropriate for a hospitalized patient, home parenteral alimentation is generally cycled and performed overnight over an 8- to 14-hour period.

Common Indications for Long-Term Parenteral Nutrition

The most appropriate patients receiving home parenteral nutrition suffer from short-gut syndrome after having lost a large portion of the GI tract either by repeated resections for Crohn's disease or by massive small bowel resection after midgut volvulus or mesenteric thrombosis, or both. Additional indications may include GI motility disorders (chronic pseudo-obstruction, sprue, scleroderma), management of a high-output enterocutaneous fistula, intractable chylous ascites, active Crohn's disease, cystic fibrosis, and chronic pancreatitis. Although home TPN for patients with cancer seems to rarely be indicated (see Controversies in Artificial Nutrition later), Medicare data indicate that an increasing proportion of patients receiving home TPN carry this diagnosis (18% in 1984, 39% in 1988).

The best candidates appear to be those with either (1) a curable malignancy requiring aggressive treatment resulting in anorexia, ileus, or intolerance to GI feeding or (2) a cured patient with residual bowel dysfunction secondary to radiation enteritis or short-gut syndrome. For these patients, survival rates and TPN-related complications appear to be similar to those in TPN patients without cancer. On the other hand, if an incurable cancer is present or the overall prognosis is poor, only 15% of patients placed on TPN will survive 1 year. Human immunodeficiency virus (HIV) infection is a rare indication for TPN, usually in the presence of intractable diarrhea or treatment-related pancreatitis. However, although a prospective, randomized trial showed improvements in global nutritional assessment, subjective health feelings, and Karnofsky performance index in HIV-infected patients receiving TPN for 2 months, there was no difference in survival.[52]

Economic Aspects and Outcome Measures in Home Total Parenteral Nutrition

A variety of statistical sources, including the OASIS (Oley-ASPEN Information System) database, Medicare, and the Mayo Clinic, suggest that the primary disease process of patients receiving home TPN, rather than complications of TPN administration alone, have the strongest influence on survival and rehabilitation. Most deaths are related to the primary disease, with only 8% being related to TPN (e.g., superior vena cava thrombosis, sepsis, or liver failure). For the most favorable candidates, the average rehospitalization rate is one per patient per year, 50% of which are for sepsis, and at least one in six patients will eventually discontinue TPN. Advanced age alone does not appear to be a reason to deny TPN. Overall, the predicted quality of survival at home for several months, rather than a specific diagnosis, seems to be the best justification for prolonged TPN. In view of the profound impact of such therapies on lifestyle, quality-of-life measures are reduced in patients receiving chronic TPN and are comparable to those reported for patients with chronic renal failure treated by dialysis.[53] Home hyperalimentation is a costly proposition. Depending on the area of the United States and the technique used, such costs may run from $30,000 to $60,000 per year for home therapy, with an annual cost of up to $140,000 for hospitalization. Clearly, patient function, rehabilitation, quality of life, and other considerations enter the cost-to-benefit ratio. Patients managed by home TPN who do not have a concurrent or chronic illness are usually extremely well motivated, and many work or have returned to their premorbid situation, or both.

Metabolic Complications of Long-Term Administration of Total Parenteral Nutrition

A variety of problems can arise when TPN is administered over prolonged periods, particularly in patients who have little if any oral intake and are therefore completely dependent on the solution for the provision of essential vitamins, minerals, and fatty acids. The rare deficiency states involving these nutrients and mechanical and infectious disease considerations relevant to the TPN catheter and common in the outpatient population have been discussed earlier.

Liver Disease

Hepatic dysfunction is commonly observed in patients receiving TPN, and these disorders occupy a spectrum ranging from simple elevations in liver function test results to cirrhosis. Most often, if hyperbilirubinemia occurs acutely in a patient receiving TPN, the cause is generally sepsis. Factors responsible for liver disease attributable primarily to TPN administration, as opposed to other causes, remain unclear and are a source of controversy. Hepatic steatosis, cholestasis (presumably from lack of enteral stimulation and reduced release of cholecystokinin), and the presence of chronic inflammation have all been implicated as relevant mechanisms. Predisposing factors include short-gut syndrome (ileal disease or resection), a history of bacterial overgrowth, and recurrent sepsis or a chronic inflammatory state. For example, in a study of patients with severe short-gut syndrome requiring duodenocolostomy, the risk for TPN-induced liver disease appeared to be higher than if some jejunum or ileum remained.[54] However, short-bowel syndrome alone seemed an insufficient risk factor unless combined with a chronic inflammatory state such as Crohn's disease. TPN-specific factors include excessive glucose or insulin administration (with increased hepatic lipogenesis), excessive lipid administration (sequestration in hepatocytes), and alterations in fatty acid metabolism leading to the release of arachidonate-derived inflammatory leukotrienes.[55] For example, a recent study at our institution has suggested that levels of inflammatory mediators such as TNF and C-reactive protein are chronically elevated in patients receiving long-term TPN when compared with normal subjects.[56] One possible mechanism for these alterations is increased generation of inflammatory prostanoids derived from the n-6 fatty acids (e.g., arachidonate), which are prevalent in standard lipid emulsions. However, whether TNF, prostanoids, or other second messengers play a role in the hepatocyte damage occurring in patients receiving TPN is unknown. Nussbaum and coworkers proposed an altered portal vein

insulin-to-glucagon ratio in chronic TPN patients and were able to ameliorate hepatic steatosis in rats maintained on TPN by administering glucagon. Deficiencies in particular nutrients, such as carnitine, choline, taurine, cysteine, and *S*-adenosyl methionine, have also been implicated in TPN-related liver disease. However, although the studies of Buchman and colleagues (see Fundamentals of Artificial Nutrition earlier) have shown that hepatic steatosis and enzymatic abnormalities can be improved by supplementation of TPN solutions with carnitine or choline,[35] these workers have not shown histologic or other evidence for reversal of TPN-induced liver damage. Based on this work, the addition of 1 to 2 g of carnitine to standard TPN, especially during long-term administration, is well tolerated and should be recommended. The use of oral ursodeoxycholic acid (e.g., 500 mg at bedtime or twice daily) is also usually without significant sequelae (although mild diarrhea may occur), and this agent may be useful to help resolve cholestasis when liver function test abnormalities are observed during chronic TPN administration.

In infants dependent on TPN, hepatic dysfunction is a more serious and potentially lethal disease, and it may have a pathophysiology different from that seen in adults. It is frequently associated with cholestasis. Even when enteral feeding is begun and TPN is discontinued, hepatic dysfunction may persist and progress to cirrhosis and death. Whether translocation of gut bacteria or their products across the immature gut, immaturity of other enzyme systems, or other factors may play a role is not clear. The ultimate solution to TPN-induced liver failure in children, if other maneuvers are unsuccessful (e.g., reduced caloric intake, avoidance of inflammation, carnitine supplementation), is combined liver and small bowel transplantation, an extreme intervention with disappointing outcomes at present. Recent exciting work by Puder and associates[44] demonstrated reversal of cholestasis in two infants with intestinal failure and parenteral nutrition–associated liver disease by substitution of a conventional IV fat emulsion with one containing primarily ω-3 fatty acids, thus suggesting that fat emulsions made from fish oils may be an effective means of treating and preventing this often fatal condition. These observations may lend credence to the inflammatory hypothesis discussed earlier. Accordingly, our group is currently testing whether dietary supplementation with ω-3 fatty acids in adult patients receiving long-term TPN may be effective in improving their deleterious pattern of inflammatory mediators and potential liver dysfunction (also see Fundamentals of Artificial Nutrition earlier).

Metabolic Bone Disease

In various studies, 40% to nearly 100% of patients administered TPN over prolonged periods have decreased bone mineral density (BMD) or histologic evidence of bone disease. Some individuals can be shown to have increased urinary calcium or phosphate excretion, decreased PTH levels, or vitamin D deficiency as possible mechanisms, but even in these patients there is poor correlation with BMD.[57] Patients at greatest risk are postmenopausal women, patients with long-standing malnutrition or malabsorption (e.g., Crohn's disease), those with preexisting liver disease, or patients receiving steroids. Some TPN-specific mechanisms postulated to contribute to bone loss are TPN-induced hypercalciuria, in which fixed acids generated by metabolism are buffered by bone calcium carbonate, and calcium diuresis induced by hyperglycemia or excessive sodium. TPN-associated deficiency states, such as calcium or magnesium (magnesium deficiency may decrease PTH release and vitamin D formation), copper (a cofactor for lysyl oxidase and collagen synthesis), boron, or silicon, have also been suggested to play a role. Given that reduced BMD is so common in long-term TPN patients, routine evaluation is probably unnecessary. However, in the patient population at greatest risk, annual assessment of BMD by neutron activation, possibly with measurement of urinary *N*-telopeptides (a marker of bone resorption), is a valid approach. If BMD is markedly decreased (e.g., >2 SD from average), a search for easily corrected problems (vitamin D deficiency, PTH excess or deficiency) is carried out. A relatively new, but unproven intervention in such patients is the use of bisphosphonates, synthetic nonbiodegradable analogues of pyrophosphate that decrease osteoclast-mediated bone resorption. Pamidronate, a second-generation agent shown to be effective in randomized trials in inhibiting postmenopausal osteoporosis, can be administered IV to TPN patients in the outpatient setting (30 mg/200 mL 5% dextrose in water over a 2-hour period) every 3 months, with minimal toxicity.

Artificial Nutrition in Specific Disease States

Pediatrics

Requirements for pediatric patients differ from those for adults. Growth is more rapid, and the distribution of visceral versus lean body mass is considerably different in an infant, who has very little muscle in comparison to an adult. Enzyme systems are incompletely developed, and excessive administration of certain amino acids may result in abnormally high concentrations of potentially toxic amino acids in the brain and perhaps in other viscera. The requirement for protein is far in excess of that for adults and decreases progressively with age. Energy requirements are also greater than for adults but may be decreased by providing a thermoneutral environment. The amount of lipid that can safely be administered is approximately 4 g/kg in an infant, whereas the upper limit of normal in an adult is thought to be 2 g/kg. Whether this difference results from proportionally larger amounts of viscera in neonates, the caloric requirements of whom are largely met by fat, is unclear. Vitamins and trace metals must be carefully administered because the ability to store these substances is limited and the opportunity for toxicity is greater. Venous access is a problem; use of the umbilical artery or vein is mentioned only to be condemned because catheter sepsis at this site is a disaster. In certain catastrophes, such as meconium ileus, gastroschisis, and neonatal enterocolitis, the increased survival now seen is almost certainly the result of aggressive nutritional support, as well as improved perioperative care. However, the contribution of nutritional support

to the survival of low-birth-weight babies, though suggestive, remains unproven. Requirements for nutritional support in infants are presented in Table 7-8.

Pancreatitis

Severe pancreatitis has traditionally been treated with bowel rest and IV feeding on the assumption that gut-derived hormones released with enteral feeding (secretin, cholecystokinin) would have the deleterious effect of stimulating pancreatic secretion, thus worsening pancreatic inflammation. In addition, there is an unfounded belief that lipid-containing TPN may aggravate pancreatitis in some way whereas a 2-in-1 solution will not. Where this has seemingly occurred has been with the use of Intralipid, which raises the possibility that inflammatory mediators derived from n-6 essential fatty acids are the cause (see earlier). However, aside from avoiding severe hypertriglyceridemia, a known precipitant of pancreatitis, there is no evidence to support a negative effect of IV lipid on the course of this disease. Furthermore, pancreatitis is often accompanied by glucose intolerance, particularly when sepsis is concurrent, and in this regard, substitution of fat for dextrose in the TPN solution can be very useful. McClave and coworkers[58] have championed the use of early postpyloric enteral feeding in acute pancreatitis. These workers have provided evidence that decreasing degrees of stimulation of the pancreas occur as the site of feeding descends in the GI tract, and results of randomized trials in acute pancreatitis suggest that jejunal feeding is at least as safe and well tolerated as TPN. Whether early gut feeding in this setting is beneficial in any other way, such as by decreasing the incidence of nosocomial infections (see later), is unproven. However, one of the authors (J.E.F.), in two separate studies in two different institutions, both with rigorous catheter care protocols, found an increased incidence of catheter infection in patients with pancreatitis.

Table 7-8 Nutritional Requirements in Infants

Protein (g/kg/day)	
Newborn to 6 mo	2.5-3
6-12 mo	2.0-2.5
School age	1.75
Adolescent	1.2
kcal/nitrogen	150:1
Calories (kcal/kg/day)	
Newborn or premature infant	120
Infant ≤10 kg	100
Infant 10-20 kg	100+50
Infant >20 kg	100+50+20
Fat	? 35% of calories (≤3.5g/kg/day)
Electrolytes (mEq/kg/day)	
Na^+	24
K^+	1-2
Urine Na^+:K^+	>1.0 adequate
Trace elements (per day)	
Term infants	
Ca^{2+}	500-600 mg/L
Mg^{2+}	50-70 mg/L
P	400-450 mg/L
Zn	800 µg/L
Cu	100 µg/L
Children >1 year	
Ca^{2+}	200-400 mg/L
Mg^{2+}	20-40 mg/L
P	150-300 mg/L
Vitamins (per day)	
A	2000 IU
C	80 mg
D	400 IU
B_1	1.2 mg
B_2	1.4 mg
B_6	1.0 mg
E	7 IU
Niacin	17 mg
Dexpanthenol	5 mg
Folic acid	40 µg
B_{12}	50 µg
K	200 µg

CONTROVERSIES IN ARTIFICIAL NUTRITION

Advantages of Enteral Versus Parenteral Feeding

It is increasingly being accepted that enteral feeding is associated with improved clinical outcomes when compared with parenteral feeding alone and, furthermore, that early enteral feeding (i.e., after surgery or traumatic injury) is more efficacious than when such feeding is delayed. In addition, enteral feeding solutions for critically ill patients are now commonly formulated with conditional nutrients thought to have special properties for enhancing immune function, reducing inflammation, and improving nitrogen balance. However, this area of inquiry is confused by a lack of clarity in proposed mechanisms and by potentially overlapping or unrelated explanations for the effectiveness of a given intervention. For example, in studies proposing a benefit with arginine supplementation (see later), does this agent improve immune function directly, or does it promote anabolism by enhancing growth hormone or insulin release, with a nonspecific secondary improvement in immune and other physiologic functions? Moreover, when immune function appears to be improved by a nutritional intervention (the most common claim), does this mean that a specific biologic effect was documented, or as in most studies, was simply the overall incidence of infection or another clinical parameter such as length of stay in the ICU studied? Finally, if the frequency of infection is lessened by enteral feeding, is it because of some laudatory effect on the permeability of the intestine to bacteria, or are the relevant mechanisms more poorly defined?

Translocation Hypothesis and the Role of Gut Mucosa

Translocation is a process by which live bacteria or their by-products (e.g., lipopolysaccharide) gain access to the lymphatic system or portal circulation by passing across the intestinal mucosa. This phenomenon is now fairly well accepted to occur in animal studies after burns and

perhaps in hemorrhagic shock, but not in other catabolic states such as starvation alone. Whereas translocated bacteria are normally cleared by the lymph nodes, bacterial products persisting in the portal or systemic circulation under pathologic conditions are postulated to contribute to hepatic dysfunction, nosocomial infection, and multiple organ system failure.[59]

One problem with the translocation hypothesis as a whole is that any beneficial result of enteral feeding or dietary supplementation with particular nutrients (e.g., glutamine; see later) is automatically attributed to an improvement in gut mucosal integrity, often with little or no evidence. Conversely, increased substrate supply to the liver and improved hepatic acute phase protein synthesis may be another mechanism by which outcome is improved by enteral feeding. Alexander and coworkers[60] provided the initial evidence that gut feeding early in burn injury in guinea pigs and subsequently in human patients could ameliorate the usual catabolic response. The working hypothesis was that gut feeding prevented bacterial translocation, with a resultant decrease in the release of catecholamines and other negative stimuli, and thus prevented catabolism. In trauma patients, several prospective randomized studies suggest that early gut feeding lowers mortality and septic complications (see later).[61] Kudsk and colleagues,[62] in a series of studies in traumatized patients, concluded that early jejunal feeding results in a lower rate of sepsis than in patients receiving parenteral nutrition, but their results remain controversial because of differences in nutrient administration and glycemic control (see later). These authors promoted the concept of total mucosal immunity, that is, improved barrier function of gut, respiratory, and nasal mucosa, and provided some evidence that this immunity is mediated through IgA.

Although it is probably true that a breakdown in gut mucosal integrity leading to bacteremia can occur in patients close to death or in those with defined ischemic colitis, clinically significant loss of gut mucosal integrity has been demonstrated only in patients with burns, trauma, and perhaps hemorrhagic shock. In addition, although bacterial translocation probably does occur in humans, there is little evidence that it is either reduced by the use of enteral nutrition or increased in patients given parenteral nutrition (as suggested by some). It is also interesting to note that in humans supported with parenteral nutrition, remaining without enteral feeding has no substantial effect on mucosal architecture or permeability,[63] whereas chronic starvation and malnutrition do. Furthermore, when illness results in increased intestinal permeability, there remains no clear association between changes in permeability and actual bacterial translocation.[64]

Benefit of Early Enteral Feeding Versus Parenteral Nutrition

It is often said that enteral nutrition is safer and more efficacious than the parenteral route. However, a preliminary note of caution is raised from observations in experimental animals, which concluded that outcomes of enteral and parenteral nutrition were equivalent when animals with catheter sepsis were eliminated. Numerous studies have shown that it is safe to feed the gut in the immediate postoperative period and that this practice does not place the integrity of intestinal anastomoses at risk. Early feeding has been studied primarily in two patient populations: those who have undergone GI surgery and traumatically injured or critically ill persons.

A recent meta-analysis reviewed 11 prospective randomized controlled trials that compared the practice of early enteral feeding with no oral intake (NPO) after elective GI surgery.[65] This analysis of 837 patients concluded that there is no clear advantage to keeping patients NPO postoperatively and that early feeding may be of benefit in decreasing infections and shortening postoperative length of stay. However, closer evaluation of these data reveals that the length of stay was reduced by only 0.84 days, and although there was an increase in any type of infection in the NPO group, when considered individually, no difference was found in the incidence of anastomotic dehiscence, wound infections, pneumonia, intra-abdominal abscess, or mortality. In 2001 Marik and Zaloga performed a meta-analysis of 15 randomized controlled trials involving 753 subjects in which early was compared with delayed enteral nutrition in critically ill surgical patients.[66] Early enteral nutrition was associated with a significantly lower incidence of infection (relative risk reduction of 0.45) and reduced length of hospital stay (2.2 days less). There were no differences in noninfectious complications or mortality. The authors concluded that early initiation of enteral feeding was beneficial, but this result must be interpreted with caution because of substantial heterogeneity between studies.

The studies that compared enteral and parenteral nutrition in the trauma population,[61,62] as discussed earlier, concluded that enteral nutrition was superior because of an attenuated inflammatory response and a decrease in septic morbidity. When these studies are examined more closely, it is clear that patients who were fed enterally usually received significantly less calories than those fed parenterally. This discrepancy of relative overfeeding in the TPN groups led in many instances to hyperglycemia, presumably predisposing patients to immune dysfunction and nosocomial infection. Thus, poor glucose control alone may account for the observed differences in outcome. In more contemporary studies in which feeding is carefully advanced in a manner that avoids hyperglycemia and groups are fed equivalent protein and calories, there appears to be little difference in clinical outcome between the enteral and parenteral routes of feeding.[67] Enteral nutrition can also endanger patient safety in unique ways. Deaths in persons receiving enteral nutrition are often due to aspiration, for example, when gastric motility is suddenly impaired with the onset of sepsis. One death from aspiration is equivalent to the mortality over 2 to 3 years of a well-operated parenteral nutrition program despite the danger of catheter sepsis, which in well-operated units is now less than 1% to 3%.

In conclusion, when possible the gut should be used preferentially for the following reasons:

1. Enteral feeding is much less expensive, with cost as low as $25 to $50 per day as compared with up to $200 per day for parenteral nutrition
2. It probably improves hepatic function and mimics the normal ingress of nutrients to the liver
3. Gut mucosal integrity is probably maintained, particularly in patients with burns and hemorrhagic shock
4. Enteral nutrition may have beneficial effects on nonintestinal mucosa, possibly mediated by IgA secretion by the liver

It seems fair to say that when delivered appropriately, both forms of nutritional support can be expected to improve organ function, immune competence, and wound healing equally in appropriately selected patients. The two forms of nutrition should be considered complementary; patients should be fed both enterally and parenterally to ensure adequate delivery of protein and calories, with the goal of progressively converting to full enteral feeding when safely tolerated by the patient.

Modulation of the Immune Response by Diet, or Immunonutrition

Major injury, whether traumatic or induced by surgery, results in significant suppression of immune function, which may influence patient recovery. Specific nutrients, such as arginine, nucleotides (discussed later), and ω-3 fatty acids (see Fundamentals of Artificial Nutrition earlier), have been shown to modulate the host response in experimental animals, with potential improvements in immune function. The working hypothesis is that clinical use of a solution containing increased amounts of arginine stimulates T lymphocytes and provides a substrate for the generation of NO, whereas the inclusion of ω-3 fatty acids promotes the synthesis of more favorable prostaglandins and inclusion of RNA nonspecifically enhances immune competence. A variety of clinical trials have evaluated the efficacy of enteral formulas supplemented with such immune-modulating substances.

In 1992 Daly and coworkers[68] (also see Daly et al., 1988[69]) were the first to study the clinical effects of immune-enhancing diets by prospectively randomizing 85 patients undergoing surgery for upper GI malignancies to either a standard (Osmolite) or experimental (Impact) enteral formula. Postoperative nutrition was delivered via a jejunostomy tube starting on day 1 and continuing until the seventh postoperative day. Patients administered the immune-modulating diet experienced a significant improvement in both postoperative wound healing and infectious complications, along with a shorter length of hospital stay. A potential flaw in this study is that although patients were fed isocalorically, the diets were not isonitrogenous (15.6 versus 9.0 g of nitrogen per day), thus leaving it possible that the findings may be partially explained by greater protein administration in the subjects given Impact. A prospective, randomized, double-blinded, multicenter study of 296 critically ill ICU patients was conducted by Bower and associates[70] in 1995. Subjects stratified as having either sepsis or systemic inflammatory response syndrome were administered enteral feeding within 48 hours of the precipitating study entry event (trauma, surgery, new onset of infection) that consisted of Impact or a control diet (Osmolite HN). Feeding formulas were not equivalent because the patients given Impact received more nitrogen and fewer calories. There were no statistically significant differences noted overall. However, patients stratified as septic and receiving the immune-modulating formula experienced a significant reduction in hospital length of stay (by 10 days) and a reduction in acquired infections. On subgroup analysis, the patients who received a minimum of 821 mL/day for at least 7 days experienced the greatest decrease in hospital stay.

Braga and coworkers[71] in 1999 showed fairly convincingly that administration of an immune-enhancing diet perioperatively yields significant clinical benefit. These workers randomized 206 candidates undergoing elective surgery for malignancies of the colon, rectum, stomach, or pancreas to receive either an immune-enhancing formula (Impact) or a control formula that was isonitrogenous and isocaloric. Patients were administered 1 L/day for 7 days preoperatively, followed by jejunal infusions of the same formula postoperatively starting 6 hours after surgery and continuing until postoperative day 7. The immunonutrition group experienced significantly fewer postoperative infections (14% versus 30%) and a shorter hospital length of stay (11.1 versus 12.9 days). These findings did not appear to be influenced by the baseline nutritional status of the patient. The authors concluded that attaining adequate intake before the surgical insult gives perioperative immunonutrition metabolic and immunologic advantages over less aggressive approaches to feeding. Despite this positive finding, subsequent studies were less consistent, and therefore several meta-analyses were performed between 1999 and 2001 to further delineate the efficacy of immune-enhancing diets in clinical practice.[72] Common to these meta-analyses was the universal finding of shorter hospital length of stay and an overall reduction in numbers of infectious complications. Although positive conclusions overall were reached in each of these more recent meta-analyses, the heterogeneity of the data makes broad recommendations about the use of immune-enhancing diets tentative.[73,74] What does appear clear is that if it is possible to give immune-modifying nutritional support early in the course of illness and to give it in rather large amounts, its benefits are more easily detected.[75]

Nutritional Pharmacology: Conditionally Essential and Other Special Metabolites in Critical Illness

Nutritional pharmacology is a poorly defined, but often used term that emphasizes the role of particular nutrients to change the pathophysiology of a disease process, presumably by distinct molecular mechanisms. Early examples include the administration of essential amino acids to patients in acute renal failure and using modified amino acid mixtures for the treatment of patients with hepatic failure.

As just discussed, one major area of potential advance in nutritional pharmacology has been the use of

immunity-enhancing enteral formulas. However, many other proposed approaches in this area remain unproven. In some instances, nutritional pharmacology appears to refer to agents that although not metabolically limiting, may be useful if given in supranormal amounts, for example, the beneficial changes in lipid metabolism induced by ω-3 fatty acids. Another interpretation is the use of substances that may be metabolized with improved efficiency under conditions of stress, such as BCAAs. Yet another definition of nutritional pharmacology involves the concept of *conditionally essential* amino acids, nucleosides, or other substances that presumably become rate-limiting for protein or nucleic acid synthesis during stress but are sufficiently abundant under normal conditions. The classic example of the latter is glutamine, an amino acid easily synthesized in many cells and normally present in high levels in the circulation. However, despite some literature supporting a relative deficiency of glutamine during stress (see the next section), even under such conditions, circulating and intracellular levels of glutamine remain well above the K_m for glutamyl transfer RNA and other relevant enzymes.

Glutamine

Within 24 hours of surgery or trauma, levels of free intracellular glutamine fall in many tissues and do not return to normal until as long as 8 weeks later. The significance of this glutamine export is not clear. Glutamine has received much attention as a fuel for enterocytes. It has been proposed that in pathologic conditions, such as after traumatic injury or during infection, energy production from the glutamine released from muscle is critical for maintaining function of GI and immune cells.[1] Furthermore, it has also been suggested that under these conditions a state of glutamine deficiency may exist and that administration of supplemental glutamine in such circumstances is beneficial.[1] Glutamine's effects in either preventing or healing chemotherapeutic or radiation toxicity and in promoting mucosal regrowth after massive small bowel resection are most impressive when it is given enterally. In severe stress, such as after bone marrow transplantation, beneficial effects of glutamine in decreasing hospital stay, improving nitrogen balance, and decreasing infection have been demonstrated.[76] These effects have been attributed to improved gut barrier function, but improved gut protein and hepatic protein synthesis are equally possible.

Although most studies of gut histology with supplemental glutamine have involved enteral delivery, some investigators have proposed that the addition of glutamine to parenteral solutions may prevent the gut atrophy that often accompanies IV feeding. In certain animal studies, the addition of glutamine to parenteral nutrition solutions resulted in maintenance of small intestinal mucosal thickness, protein content, and DNA when compared with glutamine-free solutions, but other investigators failed to show any difference in gut protein, RNA, or wall thickness.[77] These inconclusive experimental results may explain the lack of enthusiasm for glutamine-supplemented parenteral nutrition in clinical practice. Glutamine is also very unstable when added to TPN solutions, thus limiting its practical use. An additional potential concern in neoplastic disease is the observation that glutamine is preferentially metabolized by many tumors, with the potential for augmented tumor growth.

Another putative beneficial effect of glutamine is improved nitrogen balance, particularly in muscle. Attempts to prevent depletion of free glutamine pools in muscle by glutamine supplementation in parenteral nutrition solutions have shown some glutamine sparing. Glutamine supplementation can also raise levels of TCA cycle intermediates, and although this response does not appear to increase energy production or endurance in healthy skeletal muscle, there is some evidence to suggest improved functioning of ischemic heart muscle.[78] Administration of high amounts of glutamine with parenteral nutrition has been reported to promote protein accretion in skeletal muscle.[1] However, although the marginal improvements in nitrogen balance are statistically significant, they seem unlikely to improve clinical outcome.

Arginine

A deficiency of arginine and dibasic amino acids in the plasma of patients with overwhelming sepsis was observed as early as 1978. Although arginine was thought to be a nonessential amino acid, investigators now recognize that the ability to synthesize arginine in the presence of increased requirements may be exceeded and thus it is probably semiessential. Aside from its metabolic functions, arginine supplementation in critical illness may be beneficial by at least two potential mechanisms: (1) by improving immune function and (2) by stimulating growth hormone and insulin secretion, a recognized action of this amino acid. Arginine is also known to enhance the responsiveness of T lymphocytes to mitogenic stimulation in vitro. In the study of immune-enhancing enteral diets by Daly and associates discussed earlier,[69] T-cell proliferation in response to concanavalin A or phytohemagglutinin was improved in arginine-supplemented patients, although nitrogen balance was no different between the two groups. Such clinical studies are difficult to interpret with respect to effects attributable to arginine alone because additional substances (e.g., fish oil) are usually present in the experimental formulas.

Ketone Bodies

The ketone bodies acetoacetate, propionate, and butyrate have been considerably investigated in experimental studies with respect to their beneficial effect on the gut and especially the effect of butyrate on the ileum and colon. No clinical studies involving exogenous administration of ketone bodies or other short-chain fatty acids are available, however. Acetoacetate, propionate, and butyrate are produced by the fermentation of soluble pectin by colonic bacteria. Because short-chain fatty acids are not synthesized endogenously, the colonic mucosa can obtain these metabolites only from bacterial fermentation. When compared with other fuels, butyrate appears to be the principal energy source for the colonic mucosa, with acetoacetate, glutamine, and glucose following in order of importance. Diminished short-chain fatty acid oxidation may therefore disrupt the colonic mucosal

barrier and presumably, though certainly not proven in human patients, its immune function.

In experimental studies, IV butyrate results in wall thickening and increased protein content of both the colon and the ileum, and short-chain fatty acids derived from soluble pectin prevent and heal chemotherapy-related gut mucosal damage in animals, as well as improve diversion colitis. Some investigators have proposed a deficiency of short-chain fatty acids in colonocytes as a precursor to ulcerative colitis, but evidence to support this concept is lacking.[79]

Branched-Chain Amino Acids

For many years the experimental observations that BCAAs promote positive nitrogen balance in muscle and are preferentially oxidized by this tissue (see Metabolic Adaptations in Catabolic States and Regulation of Nitrogen Balance earlier) have stimulated broad interest in using BCAAs as nutritional supplements in critical illness, particularly for the management of hepatic encephalopathy and uremia. However, despite many attempts, little proof of clinical efficacy for BCAAs is available. As discussed elsewhere in this chapter, BCAAs do appear to be helpful in improving severe hepatic encephalopathy, but only in patients to whom a solution deficient in aromatic amino acids is given. However, in incubated muscles from septic animals or humans, BCAAs do not decrease protein breakdown even when present in pharmacologic quantities (5 mM). IV feeding with solutions enriched in BCAAs appears to reduce proteolysis in experimental animals with sepsis, but in septic patients, prospective randomized trials using solutions high in BCAAs (up to 50% of total amino acids) or containing leucine show marginal efficacy in preventing breakdown of lean body mass, perhaps increasing hepatic protein synthesis slightly, but only in severely ill patients. No difference in outcome was seen. Similar results have been obtained in patients undergoing bone marrow transplantation.

Essential Amino Acids

Most amino acids can be recycled, provided that energy is adequate. Thus, small amounts of essential amino acids with adequate energy are sufficient for nitrogen equilibrium. In infants, 40% to 50% of protein intake should be essential amino acids, whereas in adults in nitrogen equilibrium without stress, sepsis, or trauma, 19% to 20% is sufficient. The percentage of essential amino acids should increase with injury or depletion. The use of essential amino acids in the management of renal failure is discussed elsewhere in this chapter.

Purines and Pyrimidines

These nucleic acid precursors have been proposed to be conditionally essential under conditions of stress, potentially limiting cell division and the generation of new immune or other cells. For example, immune-enhancing enteral formulas such as *Impact* contain mRNA for this reason. However, as in the case of glutamine, it seems extremely unlikely that these nucleotides would ever be rate limiting given the numerous salvage pathways available in the cell to regenerate them.

Who Benefits From Parenteral Nutrition?

Indications for parenteral nutrition may be organized into three categories, depending on the desired outcome:

1. Primary therapy, in which parenteral nutrition is thought to influence the disease process beneficially
2. Supportive therapy, in which nutritional support is important but does not alter the primary disease process
3. Controversial indications or those under ongoing study

In most cases, the efficacy of IV feeding remains controversial because of the limited availability of prospective, randomized trials capable of answering such questions.

Primary Therapy: Efficacy Shown

Gastrointestinal-Cutaneous Fistulas

Patients with GI-cutaneous fistulas represent the classic indication for TPN because in general, increased oral intake increases fistula output. Two longitudinal reviews of fistulas concluded the following:

1. TPN increases spontaneous closure of fistulas.
2. TPN has not resulted in decreased mortality in centers experienced in the treatment of fistulas. The major decrease in mortality in the series at Massachusetts General Hospital and the University of California at San Francisco occurred in the 1960s, probably the result of improved intensive care, including monitoring, respiratory care, and better fluid and electrolyte balance.
3. TPN has probably contributed to decreased mortality in patients with fistulas in most other institutions.
4. Treatment of patients with fistulas has been altered by nutritional support. If spontaneous closure does not occur, patients are in better condition for surgery after being supported by TPN.

Respectable rates of fistula closure are also achieved with enteral nutrition, although these rates are slightly lower than with TPN. Initially, fistula drainage increases and then decreases toward closure. A useful compromise, if total caloric replacement is not possible enterally, is to give 20% to 30% of calories enterally, a method that is likely to give all the benefits of enteral feeding, and to give the remainder parenterally.

Renal Failure

TPN results in decreased mortality in patients with acute renal failure, but controversy persists concerning the amino acid solution to use. In 1973, Abel and coworkers, using a mixture of essential amino acids with hypertonic dextrose, largely in patients with surgically related renal failure, reported a decreased appearance of urea, earlier diuresis, and a statistically significant improvement in survival in treated patients versus those receiving dextrose alone. Other investigators have argued for a more complete amino acid formula and for dealing with the rise in BUN by dialysis. Whereas a few studies have attempted to compare the two formulas, no study with

adequate patients concurrently studied is available. A useful compromise is to use essential amino acids early in an effort to avoid dialysis, but once dialysis is required, a complete formulation is used (see earlier discussion in Fundamentals of Artificial Nutrition).

Short-Bowel Syndrome

Repeated small bowel resections for Crohn's disease and major enterectomy after mesenteric thrombosis or volvulus are the major causes of short-bowel syndrome. No randomized prospective trials have been undertaken, but patients with short-bowel syndrome have no alternative to long-term home TPN. Patients receiving home TPN who would otherwise almost certainly have died commonly survive for 10 to 20 years or even longer. Some patients undergo sufficient hypertrophy of the remaining small bowel that the need for home TPN is ultimately decreased or obviated. If a patient is left with 1.5 ft of small bowel anastomosed to the left colon, hypertrophy in 1 or 2 years will, in most cases, enable survival without daily parenteral nutritional support, although twice-weekly supplementation may be necessary. Efforts to promote more rapid hypertrophy of the small bowel by using gut-specific hormones, fuels, and isotonic solutions have been reported.

Burns

The sharp decrease in mortality from 1965 to 1970 in patients with burns was probably the result of aggressive nutritional support. Early aggressive nutritional support in patients with major burns is associated with improved survival,[60] and aggressive enteral feeding within 3 hours of burn injury is increasingly being practiced. Parenteral nutritional support is reserved for those few patients in whom enteral nutrition cannot meet their caloric needs. Moreover, as discussed earlier, nutritional pharmacology is increasingly being used in enteral diets specifically designed for burned patients and most likely has contributed to lower rates of sepsis, fewer days of bacteremia, lower mortality, and shorter hospital stay.[70]

Hepatic Failure

Improved survival is also seen in patients with hepatic failure who are given aggressive nutritional support. Patients with liver disease are often malnourished secondary to excessive alcohol ingestion and decreased food intake and have decreased tolerance to stress. Protein is the important nutritional component that they require, but these patients are specifically protein intolerant if hepatic encephalopathy is present (see earlier discussion in Fundamentals of Artificial Nutrition). Of the seven randomized prospective trials thus far reported, in the five in which hypertonic dextrose was used as the caloric source, branched chain–enriched amino acid solutions were at least as effective as lactulose or neomycin in the treatment of hepatic encephalopathy. In two studies, improved survival was seen. For reasons that are unclear, in studies in which the major caloric source was fat, efficacy for BCAAs was not seen.[80]

Fan and associates[59] randomized 124 patients undergoing hepatic resection for hepatocellular carcinoma. Half the patients received only oral nutrition, whereas the other half received perioperative IV nutritional support with a branched chain–enriched solution. Dextrose and lipid were the caloric sources, with MCTs accounting for 50% of the lipids. A statistically significant reduction in the overall postoperative morbidity rate occurred in the perioperative nutrition group as compared with the control group (34% versus 55%), predominantly because of fewer septic complications (17% versus 37%). In addition, there was a reduced need for diuretic agents to control ascites (25% versus 50%), less weight loss (0 versus 1.4 kg), and less deterioration in liver function as measured by indocyanine green clearance (−2.8% versus 4.8%). However, the difference in mortality (5 of 64 in the perioperative nutrition group and 9 of 60 in the control group) did not reach statistical significance. Thus, during hepatectomy, outcome can be considerably improved by perioperative parenteral nutrition.

Primary Therapy: Efficacy Not Shown

Inflammatory Bowel Disease

In patients with inflammatory bowel disease, oral intake often provokes diarrhea, protein-losing enteropathy, bleeding, and abdominal pain. Although TPN and bowel rest are useful in the treatment of Crohn's disease (particularly disease limited to the small bowel, in which a remission rate of 75% can be expected), such therapy has not been subjected to a randomized prospective trial. The mean duration of remission is approximately 11 months. Patients with colonic involvement do less well; their rates of initial remission and duration are considerably lower than those of patients with small bowel disease alone. Patients with extensive, severe, and chronically recurrent Crohn's disease are suitable for home hyperalimentation, particularly when surgical therapy would leave the patient almost anenteric. Patients with ulcerative colitis should not receive long-term TPN to induce remission because definitive resection with a sphincter-saving operation (e.g., an ileoanal pouch or Soave procedure) produces a long-term cure. On the other hand, TPN for usually less than 2 weeks, in conjunction with IV antibiotics, may allow the rectal mucosa to heal and thus facilitates rectal mucosal stripping.

Anorexia Nervosa

Patients with anorexia nervosa starve to a moribund state, with enormous loss of lean body mass, tissue, and protein. Anorectic patients are difficult to treat and can be self-destructive, for example, by disconnecting their IV lines and thus inviting air embolism. A prospective trial has not been carried out in patients with anorexia nervosa.

Supportive Therapy: Efficacy Shown

Acute Radiation Enteritis or Chemotherapy Toxicity

Acute radiation enteritis or GI complications of chemotherapy, or both, may prevent oral intake. TPN must be administered until the gut mucosa heals and clearly enables the patient to survive. Chronic radiation enteritis with multiple strictures may render the patient a candidate for home parenteral nutrition or, rarely, enteral

feeding with minimal-residue diets, provided that the original neoplasm has been cured. Some data suggest that enteral glutamine may alleviate acute radiation enteritis, chemotherapy-induced mucositis, or intestinal graft-versus-host disease in bone marrow transplant recipients, but because glutamine is a metabolic source for malignant cells, one should be certain that no malignancy persists.

Prolonged Ileus

Prolonged ileus after an abdominal procedure may necessitate a course of TPN until the ileus subsides. Obviously, this therapy is only supportive.

Supportive Therapy: Efficacy Probably Present

Weight Loss Preliminary to Major Surgery (Perioperative Parenteral Nutrition)

Four important questions concern the use of parenteral nutrition in patients experiencing weight loss before major surgical procedures: **(1)** Are operative complications of surgery increased in patients who have lost weight? **(2)** If so, can these patients be identified? **(3)** If these patients are identified, does short-term parenteral nutrition change the outcome? **(4)** If all these conditions are met, what mode of nutritional repletion should be used and for how long?

1. Are surgical complications of major operative procedures increased in patients who have lost weight? In an older review analyzing 18 randomized and nonrandomized studies, Detsky and colleagues[81] concluded that the case had not yet been made for the use of TPN before major surgery. In contrast, a critical Veterans Affairs study, one of the best randomized, controlled, prospective studies available in the entire field of parenteral nutrition, appears to identify a group at risk, namely, patients who lost more than 15% of their body weight before surgery.[82] In this group the incidence of surgical complications was greater and was ameliorated by TPN.
2. Can this group be identified? Observations as early as those of Studley in 1936 suggested that patients with profound (20%) weight loss and a low serum albumin level experienced increased complications and mortality after gastrectomy. Thus, identification of the group at risk requires a careful history and global assessment. A history of greater than 10% or certainly 15% weight loss and an albumin value of less than 3 g/100 mL would place these patients in a high-risk group. Delayed cutaneous hypersensitivity testing by injecting antigens, hand dynamometry, and serum transferrin are confirmatory and optional.
3. Does short-term nutritional intervention change the outcome? It does, provided that nutritional intervention is limited to the group with severe malnutrition and immunologic dysfunction. In the Veterans Affairs multicenter trial,[82] preoperative nutritional intervention for 7 to 10 days decreased operative septic complications in patients who were judged to be severely malnourished and who had lost more than 15% of their body weight. However, in the group stratified as having mild to moderate malnutrition, the decrease in surgical complications was more than offset by the increase in catheter-related infectious complications. The total energy intake of the TPN group was 46 kcal/kg (2944 kcal/day), whereas the ad libitum group consumed 20 kcal/kg (1280 kcal/day). With this degree of TPN-induced hyperglycemia, the immunosuppressive effects would be great enough to negate any potential benefit of preoperative feeding, with the exception of the subgroup that was severely malnourished. Thus, improperly administered TPN increased the risk of catheter- and non–catheter-related infection. Whether fewer calories or a shorter period of preoperative repletion would have resulted in greater benefit to the minimally or moderately malnourished group is not clear.
4. How long should preoperative repletion last? In previous studies, with 3 days of parenteral nutritional support before surgery, the trend was toward decreased sepsis, but statistical significance was not achieved because of the small number of patients. With preoperative repletion, patients begin to feel better at approximately 5 days, a point that generally coincides with an increase in the shortest-turnover proteins, that is, retinol-binding protein and thyroxin-binding prealbumin. In the Veterans Affairs cooperative study,[82] the duration of preoperative parenteral nutrition was between 7 and 10 days, and efficacy was seen. Thus, a period of 5 to 7 days should be used for preoperative nutritional repletion.

Cancer

In the 1980s, the initial enthusiasm for nutritional support in patients with cancer waned as evidence suggested that tumor growth is stimulated by such intervention and that nutritional supplementation of patients undergoing chemotherapy or radiation therapy (or both) might decrease survival or the remission-free interval. This important area is plagued by a lack of uniformity in studies, by the inclusion of both malnourished and normally nourished patients in studies, and by the finding that responses to nutritional support may differ depending on whether the treatment modality is to be radiation therapy, chemotherapy, or resection. The sources of calories supplied in standard feeding regimes may also be inappropriate in a patient with cancer because glucose rather than fat may be used preferentially by many tumors. Randomized prospective trials in patients with cancer have shown efficacy for preoperative IV nutritional support only in severely malnourished patients with upper GI tumors. For example, in the Veterans Affairs study discussed earlier, patients with carcinoma of the esophagus or the gastric cardia benefited from perioperative nutritional support and had decreased mortality and morbidity without apparent stimulation of the tumor.[82] In addition, several studies in patients with cancer have suggested that postoperative nutritional support via so-called immunologically active tube feeding may improve postoperative outcomes in general (see Immunonutrition earlier).

Cardiac Surgery

Patients with cardiac cachexia are at increased risk for complications and mortality after cardiac surgery. The conventional wisdom is based on Starling's pronouncement in 1912 that the heart is spared the ravages of starvation. This is not true. Protein depletion in experimental animals results in decreased myocardial contractility, with distortion of cardiac histology manifested as edema and necrosis of myofibrils, conditions that are not totally reversed even after prolonged nutritional repletion. In the single prospective randomized trial in which nutritional supplementation was begun on the day of surgery (and thus unlikely to show efficacy), no improvement in outcome was seen. A study in which patients with cardiac cachexia about to undergo surgical treatment are subjected to prolonged nutritional repletion has yet to be done. Anecdotal clinical evidence suggests that patients with cardiac cachexia require nutritional supplementation for at least 2 to 3 weeks and perhaps as long as 6 weeks before surgery, a finding supported by experimental evidence. Fluid limitations in such patients require more concentrated solutions.

Respiratory Failure and Requirements for Prolonged Respiratory Support

No evidence indicates that pulmonary function itself, rather than the muscles of respiration, is improved by nutritional support. Although some information is available concerning the metabolic needs of the alveolar cells responsible for surfactant production and gas exchange, a tailored IV solution has not appeared. Whereas weaning from ventilators may improve with nutritional support, a potential deleterious effect of hypertonic dextrose is overproduction of carbon dioxide. Although this phenomenon is extensively discussed in the ICU setting, it is not common; occasionally, in patients with marginal pulmonary function, carbon dioxide overproduction may require replacing glucose with fat to promote weaning from the ventilator. Carbon dioxide production and RQ can be measured in most intensive care settings, as described earlier.

Large Wounds and Other Sources of Nitrogen Loss

Many patients with large wounds such as decubitus ulcers are unable to eat. Provision of nutritional support to improve wound healing is logical, but no randomized studies exist.

HIV Infection

The place of TPN in the treatment of patients with acquired immunodeficiency syndrome is controversial[52] and was discussed in an earlier section in the context of home TPN.

FUTURE DIRECTIONS IN ARTIFICIAL NUTRITION: NOVEL APPROACHES FOR REDUCING CACHEXIA

Besides the primarily nutritional approaches described earlier and designed to promote positive nitrogen balance and improved overall outcome in critically ill patients, additional strategies are available and are a focus of present and future research. Certain initially promising approaches, such as administration of growth hormone, have not been clearly shown to be of clinical benefit, whereas others, such as pharmacologic inhibition of protein breakdown, are in their infancy.

Inhibition of the Stress Response

A variety of approaches have been used to inhibit the actions of the inflammatory mediators and catabolic hormones that are released under conditions of stress and are presumably responsible for protein loss and cachexia. Included in this category are the ω-3 fatty acids, which have been amply discussed in earlier sections and which continue to show promise as therapeutic agents. Unfortunately, alternative strategies, such as the use of neutralizing antibodies to TNF or to endotoxin during sepsis, have either been shown to be ineffective or, in some cases, actually seem to cause increased mortality in clinical trials. An attractive drug is the glucocorticoid receptor antagonist RU-486, but no data are available for this agent in cachectic patients, perhaps in part because of societal unease with the identity of RU-486 as an abortifacient. An important issue for all such approaches is whether the signals commonly thought to be harmful in conditions of stress (e.g., the cytokines) should be interpreted in such a simple manner or, alternatively, whether these mediators serve critical and useful functions during the stress response as well.

Administration of Anabolic Factors

Gut-Derived Hormones

Studies have suggested that glucagon-like peptide-2 (GLP-2) has a robust effect on stimulating gut hypertrophy, DNA, and wall thickness in animals receiving parenteral nutrition. In one of the authors' (J.E.F.) preliminary studies, the effects of GLP-2 have been impressive in the sense that continued administration of GLP-2 in rats receiving TPN results in gut hypertrophy exceeding that seen in orally fed animals. It is hoped that clinical trials will take place within several years.

Growth Hormone and Insulin-like Growth Factors

In experimental studies discussed earlier, growth hormone and IGFs promoted positive nitrogen balance in muscle. Furthermore, the IGFs inhibit muscle proteolysis and stimulate protein synthesis directly (unlike growth hormone), and during systemic administration the IGFs may be less diabetogenic than growth hormone. These agents may also have beneficial effects on lipolysis. These anabolic effects have led to the clinical use of cloned human growth hormone. Pharmacologic levels of this hormone given with hypocaloric TPN to humans can promote positive nitrogen balance in sepsis and after major injury.[1] The increase in protein degradation in isolated muscles after burn injury can also be reversed by IGF-I in a dose-dependent manner,[83] but this effect was not seen in muscles from septic animals, where IGF-I increased protein synthesis but had no effect on protein

degradation rates.[18,83] Although the role of growth hormone in clinical practice remains poorly defined, a cautionary note is raised by a recent clinical trial of growth hormone administration to ventilated ICU patients,[84] in which mortality, the duration of ventilator dependence, and length of stay were seemingly worsened, not improved, by the hormone.

Anabolic Steroids

The increased secretion of testosterone in males at puberty is thought to determine the increased skeletal muscle mass that occurs at this stage in development and is maintained into adult life. Accordingly, suppressing testosterone in healthy young men reduces fat-free mass and fractional muscle protein synthesis, and androgen supplementation to normal physiologic levels in androgen-deficient men leads to increased muscle mass and strength.[85] The potential therapeutic use of testosterone has also been explored in a number of studies. There is some evidence for the use of testosterone to reverse the loss of muscle mass and strength that occurs in normal aging in males.[85] In HIV-infected men with weight loss and low testosterone levels, testosterone supplements led to improved strength, and injections of testosterone after severe burn injury reduced muscle loss by improving protein synthetic efficiency and reducing muscle protein degradation rates.

Catecholamines

Catecholamines appear to exert an anabolic effect on muscle principally by reducing calcium-dependent proteolysis and by increasing protein synthesis. The anabolic effect of catecholamines can also be mimicked by the β_2-adrenergic agonist clenbuterol. Numerous studies in animals have shown that clenbuterol treatment increases carcass and muscle weight, and furthermore, clenbuterol can inhibit wasting caused by hind limb suspension or denervation in rats and can also attenuate cachexia after scald injury. In addition, clenbuterol improved lean body mass and muscle size in animals with experimental tumors while increasing the utilization of lipid.[86] The exact mechanism by which drugs such as clenbuterol promote positive nitrogen balance in vivo remains unclear. For example, a pure β-antagonist, propranolol, was shown by Herndon and colleagues to improve protein balance and reduce energy expenditure in children with severe burns randomized to 2 weeks of oral therapy.[87]

Inhibition of Proteolysis

Pharmacologic Inhibition

An extremely attractive approach to the treatment of muscle wasting is direct inhibition of intracellular proteolysis. As knowledge of the biochemical pathways for protein breakdown in muscle and other tissues grows, the potential for such intervention increases. Low-molecular-weight active-site inhibitors of the proteasome are now available,[12,14] and newer-generation inhibitors have been shown to be fairly safe in humans during initial trials of their use as antineoplastic agents, for example, in treating multiple myeloma. More recently, specific E3s induced in muscle under catabolic conditions have been identified,[15,16] and these enzymes may offer tissue-specific targets for inhibition of ubiquitination and proteolysis during future drug development. Such specificity will probably prove important in avoiding toxicity inasmuch as intracellular protein breakdown has fundamental and pleotropic functions, including regulation of the cell cycle, antigen presentation, and prevention of the accumulation of abnormal proteins in cells.

Lessons From Nature

Muscle proteolysis is suppressed in certain physiologic conditions, including dietary protein deficiency and prolonged fasting.[22] Muscles from such animals are also resistant to many catabolic signals, such as the proteolysis induced by denervation. An improved understanding of the intracellular mechanisms and endocrine signals responsible for these adaptations should suggest new strategies relevant to clinical practice and useful for reducing muscle wasting in ill patients.

SUMMARY

One of the most important therapeutic modalities of the 20th century has been nutritional support, in particular, IV feeding. As investigators are trained who are equally familiar with the operating room and with modern cell biology, the basic mechanisms underlying disease states relevant to surgical patients are increasingly being elucidated at the molecular level. The ability to intervene in and correct nutritional deprivation states that cause significant mortality in patients will continue to improve as our knowledge of nutrition and metabolism becomes increasingly sophisticated.

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Abel RM, Beck CH Jr, Abbott WM, et al: Improved survival from acute renal failure after treatment with intravenous essential L-amino acids and glucose: Results of a prospective, double-blind study. N Engl J Med 288:695-699, 1973.

An early, randomized, double-blinded trial showed improved survival after the application of techniques of parenteral nutrition and administration of a specialized solution to patients with renal failure. The eight essential L-amino acids were administered in hypertonic dextrose to patients with renal failure, and these patients were compared with a group receiving isocaloric hypertonic dextrose alone. Improved survival and perhaps early healing of the renal lesion were seen.

Clowes GH Jr, George BC, Villee CA Jr, Saravis CA: Muscle proteolysis induced by a circulating peptide in patients with sepsis or trauma. N Engl J Med 308:545-552, 1983.

Few articles have inspired as much interest and excitement as this description of a 4200-d protein isolated in the plasma of patients with sepsis. This hypothetic cytokine, PIF, increased hepatic protein synthesis and muscle breakdown. Subsequent experiments revealed that the particular conditions used in these experiments may have contributed to these findings. Nonetheless, this article probably contributed more to research on the effect of cytokines during surgical procedures than any other and inspired a great deal of work over the subsequent years.

Cuthbertson DP: Observations on the disturbance of metabolism produced by injury to the limbs. Q J Med 1:233-246, 1932.

This study may well have begun contemporary nutritional support. This classic description of loss of nitrogen and breakdown of lean body mass after injury is a careful study in a classic tradition.

Dominioni L, Trocki O, Mochizuki H, et al: Prevention of severe postburn hypermetabolism and catabolism by immediate intragastric feeding. J Burn Care Rehabil 5:106-112, 1984.

The first demonstration that changes in gut flora and translocation of bacteria or absorption of bacterial products after thinning of the mucosa in burns contribute to hypermetabolism is presented. With the confirmation of similar results in patients with burns, it is clear that this hypothesis with respect to gut products is operant in other patients as well.

Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE: Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery 64:134-142, 1968.

This is one of the classic articles originally describing high-glucose central TPN from which stems the current popularity of parenteral nutrition in the United States. In this ambitious project, the biochemical requirements for growth in puppies were investigated with astounding results: normal growth comparable to that seen in puppies who were eating freely could be achieved without any oral intake, provided that one infused the necessary nutrients by vein.

Fischer JE (ed): Total Parenteral Nutrition, 2nd ed. Boston, Little, Brown, 1991.

This book represents an attempt to standardize the practical approach to TPN.

Fischer JE (ed): Nutrition and Metabolism in Surgical Patients. Boston, Little, Brown, 1996.

The basic science and practical knowledge relevant to surgical nutrition are presented in one volume. The various chapters also address the efficacy of parenteral nutrition.

Fischer JE, Rosen HM, Ebeid AM, et al: The effect of normalization of plasma amino acids on hepatic encephalopathy in man. Surgery 80:77-91, 1976.

An approach to liver disease and intolerance to protein in patients with hepatic encephalopathy is described. This study represents the culmination of a hypothesis of hepatic encephalopathy depending on altered plasma amino acid patterns, changes subsequently discovered to be amplified by alterations in the blood-brain barrier secondary to the disturbed metabolism in liver disease. It represents an early anecdotal attempt to enable patients with severe hepatic deficiency to receive adequate nutrition at the same time as awakening from hepatic encephalopathy; these patients received increased protein equivalent in the form of a branched-chain–enriched (to 36%) amino acid solution now commercially available as HepatAmine.

Rombeau JL, Rolandelli RH (eds): Clinical Nutrition, 3rd ed. Philadelphia, WB Saunders, 2001.

This is the most recent large textbook on enteral and parenteral nutrition. It is well done and has been updated, with many specialized chapters.

Ryan JA Jr, Abel RM, Abbott WM, et al: Catheter complications in total parenteral nutrition: A prospective study of 200 consecutive patients. N Engl J Med 290:757-761, 1974.

A study of the complications of parenteral nutrition was conducted in a large hospital with one of the first centralized nutritional support teams. This study confirmed that rigid asepsis in the care of catheters and minimizing catheter manipulation were the most important factors in preventing catheter line sepsis.

Wilmore DW, Dudrick SJ: Treatment of acute renal failure with intravenous essential L-amino acids. Arch Surg 99:669-673, 1969.

This study represents the earliest approach to disease-specific parenteral nutrition. The principle of attempting to define the metabolic abnormalities in a given patient and infusing an appropriate nutritional substrate was first proposed in this study. The intravenous equivalent of a Giordano-Giovanetti diet containing only the eight essential L-amino acids (an oral diet of high biologic value) was used.

Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the surgical intensive care unit. N Engl J Med 345:1359-1367, 2001.

This carefully conducted study emphasizes the importance of stringent control of blood glucose for the prevention of sepsis and other complications in critically ill patients.

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