

# Chapter 23

## METABOLIC DERANGEMENTS AND NUTRITIONAL SUPPORT

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### INTRODUCTION

#### METABOLIC DERANGEMENTS IN COMBAT CASUALTIES

Starvation

Exercise

Starvation, Exercise, and Stress

The Effect of Injury

Stages in the Response to Stress

Energy Requirements of Patients With Injuries or Infections

#### NUTRITIONAL SUPPORT

Nutritional Assessment

Parenteral Nutrition

Enteral Nutrition

Assessment of Nutritional Repletion

#### SUMMARY

#### INFECTION CONTROL POLICY AND PROCEDURE GUIDE

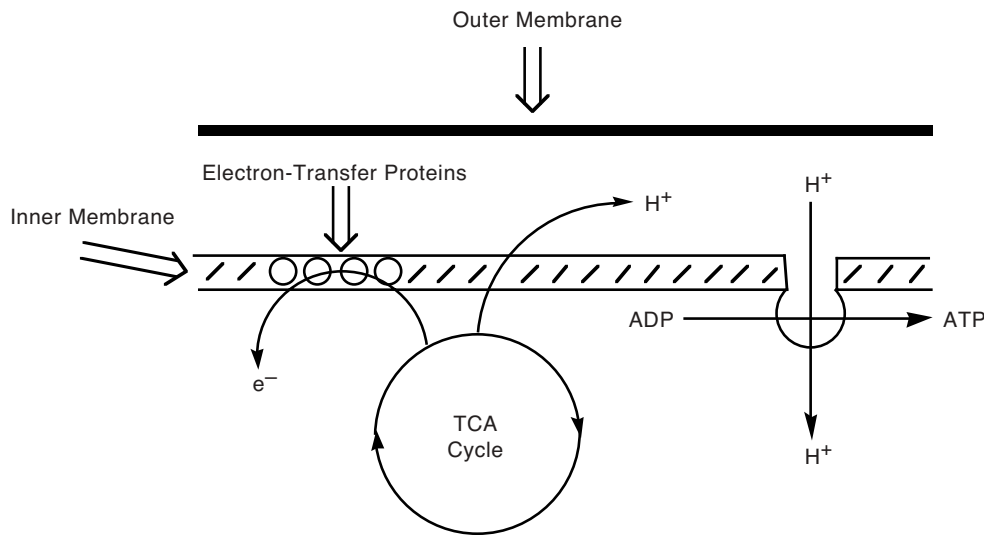
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## INTRODUCTION

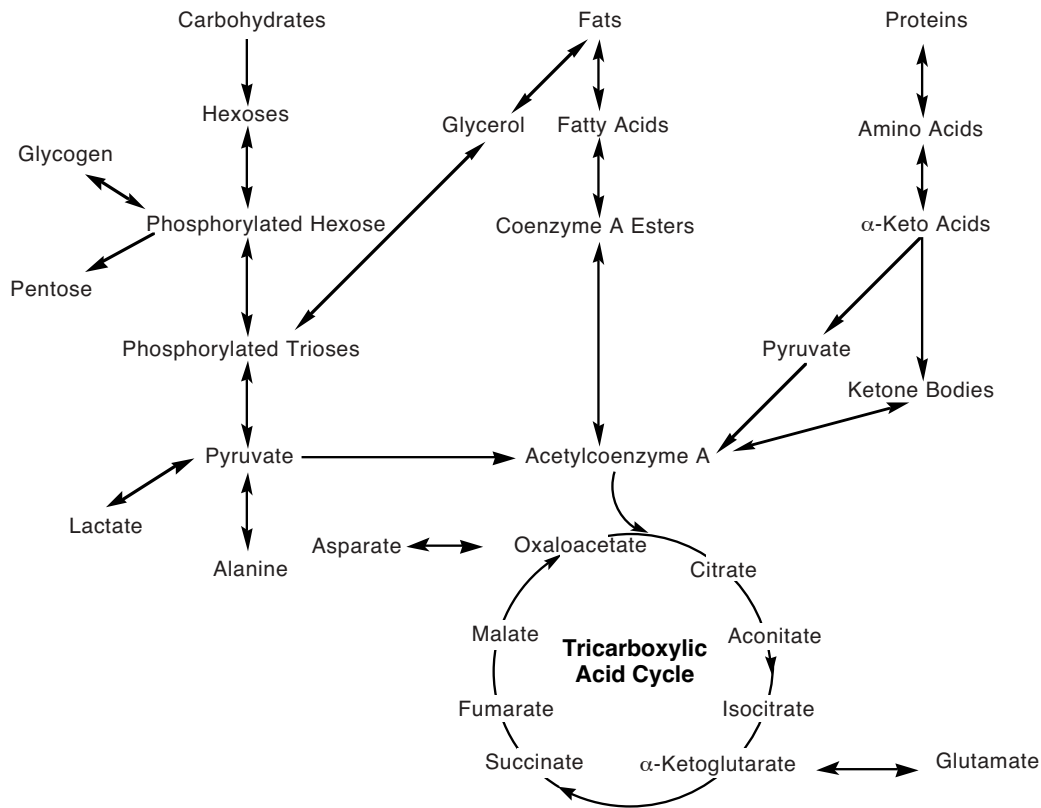
A detailed review of the biochemistry of normal metabolism is beyond the scope of this chapter but a brief review of the more fundamental processes is not inappropriate. Greater emphasis will be placed on recording the gross perversions of normal metabolism that occur during life-threatening trauma—especially when accompanied by sepsis. The remainder of the chapter will describe practical aspects of the nutritional interventions at the disposal of military critical care specialists.

The energy to drive all cellular processes is stored in high-energy phosphate compounds, either adenosine 5'-triphosphate (ATP) or phosphocreatine. These are generated by (a) glycolysis, which occurs within the Embden-Meyerhof pathway, and (b) oxidative phosphorylation, which takes place in the tricarboxylic acid (TCA) cycle in conjunction with the proteins that constitute the respiratory chain. In glycolysis, glucose is broken down into pyruvate or lactate, while the TCA cycle produces carbon dioxide and metabolic intermediates that carry elec-

trons and protons to the chain of respiratory proteins located in the inner membrane of the mitochondria (Figure 23-1). In contrast to glycolysis, in which the enzymatic machinery is found distributed throughout the cytoplasm of cells and can function without oxygen, the complete complement of enzymes needed for the TCA cycle is found exclusively within mitochondria and functions only in the presence of oxygen. As the electrons are passed along the respiratory chain, protons are driven into the space between the inner and outer membranes of the mitochondria, resulting in the development of a proton gradient across the inner membrane. Under the influence of the gradient, protons flow back through the inner membrane, passing through specialized proteins that generate ATP. The electrons combine with oxygen and protons to form water. Oxidative phosphorylation produces the vast majority of the body's metabolic energy: in the presence of oxygen, 1 molecule of glucose can be made to generate as many as 38



**Fig. 23-1.** The *chemiosmotic* theory, illustrated here, is the accepted explanation of how oxidative phosphorylation produces high-energy phosphate compounds. The schematic shows a portion of the wall of a mitochondrion. A characteristic feature of this organelle is a wall formed by an outer and an inner membrane that are separated by a space. The cytochrome oxidation-reduction proteins are located in the inner membrane. The tricarboxylic acid (TCA) cycle produces protons ( $H^+$ ), which are extruded through the inner membrane, and electrons ( $e^-$ ), which are passed along the cytochrome system until they react with oxygen. The protons, which have collected in the space between the membranes, ultimately pass back into the interior of the mitochondrion through specialized proteins embedded in the inner membrane. Here they cause adenosine 5'-triphosphate (ATP) to form from adenosine diphosphate (ADP) and inorganic phosphate. The protons subsequently react with oxygen to form water.



**Fig. 23-2.** The interrelation of the principal classes of metabolites that serve as the source of energy for human activity: carbohydrates, fats, and proteins. The central process is that of the tricarboxylic acid (TCA) cycle, entrance into which is by means of acetylcoenzyme A (acetyl-CoA). The latter substance is made from pyruvate, which comes from the metabolism of carbohydrates and certain amino acids, and from coenzyme A esters formed from fats. Most of the reactions shown are reversible (double-ended arrows) except for the one linking pyruvate and acetyl-CoA. This fact has important implications for understanding the metabolic derangements that occur during severe trauma. Although carbohydrates can be converted into fats, fats cannot be converted directly into carbohydrates. When the supply of carbohydrates to individual cells is inhibited, such as during starvation and when insulin resistance exists, fat catabolism is accelerated to supply acetyl-CoA for use by the TCA cycle. However, an alternative source of glucose is needed to meet the needs of organs that use glucose as the obligatory substrate. The glucose cannot be obtained from fat because the pyruvate–acetyl-CoA reaction is irreversible. The needed glucose is obtained by a process in which alanine is converted into pyruvate. There will also be accelerated entry of amino acids such as aspartate and glutamate into the TCA cycle. In this metabolic state, which is commonly seen following severe trauma, the amino acids needed to form glucose are obtained from the catabolism of protein—but not from fat because of the irreversibility of the pyruvate–acetyl-CoA reaction.

molecules of ATP. By way of contrast, the metabolism of 1 molecule of glucose in the absence of oxygen produces only 2 molecules of ATP.<sup>1</sup>

The ultimate metabolic precursors of high-energy phosphate compounds are complex carbohydrates, which are, for the most part, polymers of six-carbon molecules known as hexoses; fats, which are glycerol–fatty acid esters; and proteins, which are polymers of amino acids (Figure 23-2). The initial steps leading to the formation of ATP involve the breaking down of the complex carbohydrate, fat, and protein molecules into their constituents,

which then form the substrates for oxidative phosphorylation. Hexoses, of which glucose is the most important, are converted to pyruvate, which, depending on the availability of oxygen, is converted either to lactate or to acetylcoenzyme A (acetyl-CoA). Fatty acids as well as the nitrogen-free residue of amino acids also form acetyl-CoA. Acetyl-CoA is the point of entrance into the TCA cycle, where metabolic intermediates derived from carbohydrates, fats, and proteins interact. Amino acids derived from protein in skeletal muscles can be converted to glucose, and excessive dietary inges-

tion of glucose can lead to the formation of fatty acids, which are then stored as fat in adipose tissue. Fat, however, cannot be converted directly to glucose unless the constituent fatty acids either contain an odd number of carbon atoms or have branching chains.

Glucose is the most immediately available energy source and the one in highest demand by the body. A number of tissues, the central nervous system particularly, are obligate glucose users and must have a continuous supply. Fibroblasts and formed elements of the blood such as erythrocytes, as well as the renal medulla, all depend on glucose. Six hundred to 1,000 kcal/d must be provided to these tissues, and glucose is preferentially made available even if the rest of the body must shift to another energy source such as lipid. However, glucose reserves are sharply limited and consist of about 20 g within the body at any given time. More important are the 300 to 400 g glycogen (a polymer of glucose) that are stored in the liver and skeletal muscle. Although the synthesis of glycogen from glucose is easily reversed by the process of glycogenolysis, glycogen is not an optimally efficient storage medium because both its formation and its degradation require the expenditure of energy. In fact, when the synthesis of glycogen stems from noncarbohydrate sources, instead of the usual 3.4 kcal/g obtained from the oxidation of glucose to water and carbon dioxide, a net increase of as little as 1 to 2 kcal additional energy may be produced by the complete oxidation of 1 g of glycogen.

The availability and utilization of carbohydrate are controlled by a complex interplay of hormones, with insulin and glucagon the major factors. Insulin is an anabolic hormone; it reduces plasma glucose levels by (a) increasing glucose transport into cells, whereby glycolysis is stimulated, and (b) increasing glycogen synthesis in liver and muscle. Insulin also blocks gluconeogenesis (wherein amino acids derived from the catabolism of body proteins are converted into glucose) and promotes protein synthesis. Glucagon counters these effects of insulin by promoting glycogenolysis and gluconeogenesis in the liver and lipolysis in the adipose stores. (The latter effect is opposite of that of insulin, which causes fat synthesis.) The ratio of insulin to glucagon controls the balance and is a major determinant of the ability to mobilize energy stores. A high ratio defines an *anabolic* state (ie, more-complex molecules are synthesized from simpler molecules); a low ratio, a *catabolic* state (ie, complex molecules are degraded to simpler molecules).

As previously indicated, the body has the biochemical machinery to use triglycerides and proteins for oxidative phosphorylation once glucose and glycogen reserves are used up (see Figure 23-2). The relative importance of the body's reserves of carbohydrates, fat, and protein as sources of energy is shown in Table 23-1. At any given time, the actual contribution of the carbohydrates, fats, and proteins to overall energy production can be estimated by measuring the respiratory quotient (RQ), which is discussed in Exhibit 23-1 and in greater detail later in this chapter.

Lipids are the most abundant, although not the most readily available, energy source. The average 70-kg soldier has 100,000 kcal stored as lipid (9 kcal/g),<sup>2</sup> and this reserve becomes the principal fuel source during starvation. Fats are broken down into their constituent fatty acids and glycerol, a process known as lipolysis. Two types of lipases act to convert stored lipid to the more readily available fuels glycerol and fatty acid. Hormone-sensitive lipase (activated by adenosine 3',5'-cyclic monophosphate [cAMP], which, in turn, is triggered by catecholamine receptors on the adipocyte membrane) degrades lipids to fatty acids and glycerol. The fatty acids enter the TCA cycle as acetyl-CoA, and the glycerol is either transformed to pyruvate or esterified to triglyceride in the liver. The second lipase, lipoprotein lipase, catalyzes the release of triglycerides from low-density lipoproteins and chylomicrons, an effect that is *inhibited* by catecholamines. The presence of glucose and insulin tends to enhance the effects of lipoprotein lipase.

**TABLE 23-1**  
**ENERGY STORES IN A 70-KG MAN**

Energy Source	Tissue	Energy Stores	
		(g)	(kcal)
Triglycerides	Fat	15,000	100,000
Protein	Muscle	6,000	25,000
Glycogen	Liver	70	280
	Muscle	120	480
Glucose	Throughout body	20	80

Adapted with permission from Linder MC. Energy metabolism, intake, and expenditure. In: Linder MC, ed. *Nutritional Biochemistry and Metabolism with Clinical Applications*. New York, NY: Elsevier; 1985: 290.

## EXHIBIT 23-1

## METABOLIC TERMINOLOGY

Respiratory Quotient (RQ):	The molar ratio of CO <sub>2</sub> produced for O <sub>2</sub> consumed, or VCO <sub>2</sub> /VO <sub>2</sub> . For carbohydrates, this is 1.0 (ie, one mole of CO <sub>2</sub> is generated for each mole of O <sub>2</sub> consumed). For the oxidation of fats, the ratio is 0.7; for protein, 0.82. <i>The conversion of carbohydrate to fat (ie, lipogenesis) can theoretically have an RQ &gt; 8.0.</i> Whenever the respiratory quotient is >1.0, lipogenesis (and therefore overfeeding) is occurring. Remember that changes in the respiratory quotient directly affect PO <sub>2</sub> and PCO <sub>2</sub> . Alveolar PO <sub>2</sub> will fall with a decreasing RQ, for any given level of PCO <sub>2</sub> . PCO <sub>2</sub> will rise with an increasing RQ, and will require a higher minute ventilation to normalize.
O <sub>2</sub> Consumption (VO <sub>2</sub> ):	The amount of oxygen consumed by metabolic processes in 1 min, given as $\text{Minute Ventilation (L/min)} \cdot (\text{FIO}_2 - \text{FEO}_2)$ when the RQ is 1.0.
CO <sub>2</sub> Production (VCO <sub>2</sub> ):	The amount of CO <sub>2</sub> generated by metabolic processes in 1 min, given as $\text{Minute Ventilation (L/min)} \cdot \text{FECO}_2$
O <sub>2</sub> Delivery (DO <sub>2</sub> ):	The amount of O <sub>2</sub> carried to the tissues each minute, calculated as $\text{C.O. (L/min)} \cdot \text{CaO}_2, \text{ or}$ $\text{C.O.} \cdot [(1.39 \cdot \text{SaO}_2 \cdot \text{Hb}) + (0.003 \cdot \text{PO}_2)]$ DO <sub>2</sub> is given in mL/kg/min; about 16 mL/kg/min is normal for adults. Normal VO <sub>2</sub> is about 4 mL/kg/min.
O <sub>2</sub> Extraction Ratio (OER)	The percentage of the delivered O <sub>2</sub> actually consumed in metabolic processes, or VO <sub>2</sub> /DO <sub>2</sub> . This is about 25% in normal adults, and normally decreases as O <sub>2</sub> delivery increases.
Resting Energy Expenditure (REE):	The energy expenditure measured at rest or lying down. REE can be calculated from VO <sub>2</sub> , VCO <sub>2</sub> , and a measurement of metabolized nitrogen (eg, Nu, nitrogen excreted in the urine)*: $\text{REE (in kcal/min)} = 3.581 \text{ (kcal/L)} \cdot \text{VO}_2 \text{ (in L/min)} \\ + 1.448 \text{ (kcal/L)} \cdot \text{VCO}_2 \text{ (in L/min)} - 1.773 \text{ (kcal/g)} \cdot \text{Nu (in g/min)}$

\*REE may be normalized for body surface area or mass by dividing by area in square meters, or mass in kilograms, respectively. Since the contribution of the term 1.773 Nu is small, Bursztein has calculated that a 100% error in measured Nu will be associated with only a 1% error in REE. Therefore, from the practical standpoint, the last term in the REE equation can be ignored, since determination of nitrogen excretion is not necessary to estimate energy expenditure. Source for REE definition and equation: Bursztein S, Elwyn DH, Askanazi J, Kinney JM. *Energy Metabolism, Indirect Calorimetry, and Nutrition*. Baltimore, Md: Williams & Wilkins; 1989: 30, 59, 62.

CaO<sub>2</sub>: arterial oxygen contents; C.O.: cardiac output; FEO<sub>2</sub>: fraction of expired oxygen; FIO<sub>2</sub>: fraction of inspired oxygen; Hb: hemoglobin; PCO<sub>2</sub>: partial pressure of carbon dioxide; PO<sub>2</sub>: partial pressure of oxygen; Sao<sub>2</sub>: oxygen saturation of arterial blood

Insulin inhibits lipolysis; in fact, a high ratio of insulin to glucagon will promote storage of fuel as lipid. Catecholamines, glucagon, and somatotropin (ie, growth hormone) all promote the breakdown of the lipid stores for energy. Steroids will enhance the lipolytic effects of catecholamines and glucagon.

An additional option that the body has to supply glucose or substrates for oxidative phosphorylation is to utilize amino acids, from either ingested or structural proteins, as fuel. There are five points where the carbon skeletons of amino acids can enter the glucose oxidation pathway: as pyruvate, acetyl-CoA, α-ketoglutarate, fumarate, and succinylco-

enzyme A (succinyl-CoA). Protein may be diverted for use as a fuel source, normally as excess dietary protein, or as catabolized structural protein in stress states. Protein yields 4.1 kcal/g.

Normal protein turnover—breakdown and synthesis—is approximately 300 g/d.<sup>3,4</sup> Normal daily protein turnover in skeletal muscle is 100 g/d. Roughly 50 g, which is used to produce digestive juices, and another 20 g of small intestinal lining cells are lost daily in digestion. Eighty to one hundred grams of protein is ingested daily in a typical Western diet. Excess is converted to fuel, and the nitrogen is excreted as urea. Enzymes are continually made, used, and broken down; structural proteins are continually modified; and cells are continually replaced. In normal adults, 15% to 20% of the basal metabolic rate (BMR) is due to metabolism of protein.

Amino acids are transported by a membrane carrier system,<sup>3,4</sup> often against a steep concentration gradient (as opposed to the glucose carrier system). There are seven carriers, specific for different amino acids but with some overlap. Amino acids are constantly being cycled into and out of the cells and transaminated or deaminated for use in cellular processes. Different processes feed these substrates into the cellular plants—hydrolysis of dietary (or structural, in starvation) protein, amination of keto acids, conversion of amino acids and ketoacids to other compounds, use of amino acids for protein synthesis, oxidation of ketoacids—to balance the supply of amino acids with the demand. Most processes involve transamination to glutamate as the common path for transfer.

Metabolism of carbohydrates, fats, and proteins is regulated by a complex neural and hormonal feedback system. The hypothalamus controls both the normal function of the system and the response of the organism to starvation and stress. Stimulation of the ventromedial hypothalamic nucleus by concentrations of metabolic substrates (eg, carbohydrate, lipid, and amino acids), along with input from aortic baroreceptors, renal nerves, and the carotid sinuses, as well as changes in the concentration of hormones are all feedback elements that guide the orchestration of the system by the hypothalamus. When the nucleus is stimulated, sympathetic and parasympathetic outflow increase. The adrenal medulla is stimulated via the great splanchnic nerve. This increase in sympathetic outflow mobilizes substrate (from glycogen stores, lipid pools, and skeletal muscle), in-

creases cardiac output and minute ventilation, and releases insulin and glucagon from the pancreas. Parasympathetic outflow increases absorption of nutrients by the gut. Pituitary hormones—adrenocorticotropic hormone (ACTH), somatotrophic hormone (STH), thyroid-stimulating hormone (TSH), prolactin (PRL), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary, and antidiuretic hormone (ADH) from the posterior pituitary—control utilization of substrate and fluid balance and osmolarity. Insulin is stimulated by the release of  $\beta$ -adrenergic catecholamines, while glucagon is stimulated and insulin is inhibited by  $\alpha$ -adrenergic catecholamines and increased adrenal hormones. Portal blood levels of both insulin and glucagon are significantly higher than systemic levels, as is their utilization by the liver. The ratio of insulin to glucagon concentration dictates whether the response is anabolic or catabolic.

The mobilization of free fatty acids is controlled by an interplay among ACTH, corticosteroids, catecholamines, and glucagon. ACTH also controls the secretion of beta endorphin and melanocyte-stimulating hormone (MSH). This corticotrophin-releasing hormone (CRH)–ACTH–cortisol axis plays a crucial role in our ability to respond to a stressful stimulus. The patterns of response are nearly uniform; only the degrees differ.

The critical importance of the relative ratio of insulin to glucagon cannot be overemphasized. The ratio is one of the chief determinants of catabolism versus anabolism and is responsible for maintaining normal glucose levels in all tissues, particularly the obligate glucose users. Depletion of glycogen stores triggers a shift in the ratio: a fall in insulin levels and an increase in glucagon. The liver responds to this change by increasing gluconeogenesis: amino acids from skeletal muscle protein are stripped of their carbon skeleton to make more glucose. Glucagon activates catecholamine-sensitive lipase in adipose tissues; triglycerides are broken down and the circulating free fatty acids and glycerol are fed to the liver, which catabolizes them to ketones to be used as an oxidative fuel source. When the ratio is reversed, carbohydrate is converted to glycogen and fat for storage of chemical energy, and protein synthesis is stimulated.

Before we move on to specific metabolic rearrangements and nutritional support, the reader should review the metabolic terms and their descriptions in Exhibit 23-1.

## METABOLIC DERANGEMENTS IN COMBAT CASUALTIES

Most patients seen by medical officers in field medical facilities will be members of the armed forces: young, well developed, predominantly male, and with no significant medical history. The typical soldier in the U.S. Army will have entered the combat zone with a large muscle mass and greater-than-normal glycogen stores, but many factors are likely to modify the picture of this healthy, muscular soldier. Of these factors, the most important are starvation, exercise and stress and, in the event of a combat injury, the wound itself. Major W. J. Phillips, Medical Corps, U.S. Army, has published an excellent introduction to this subject.<sup>5</sup>

### Starvation

How does starvation affect metabolism? Glucose is no longer available either from glycogen or from externally supplied carbohydrates, yet several organs such as the brain will not tolerate an interruption in their supply of glucose. After only 8 hours without intake, the body begins to use its glycogen reserves to support the obligate glucose-utilizing tissues—the central nervous system, renal medulla, formed blood elements, and fibroblasts—while the metabolic economy shifts to fatty acid oxidation. Even though energy expenditure may be minimized by a decrease in resting energy expenditure (REE, which is discussed later in this chapter), the available glycogen stores will be depleted within 24 hours. A starved, stressed patient will rapidly catabolize nonvital structural proteins to fuel metabolic processes.

The initial adjustment to an inadequate intake of nutrients is to form glucose from amino acids derived from skeletal muscle protein. Branched-chain amino acids are transaminated to alanine and glutamine, which are “stripped” in the liver for their carbon skeletons to make glucose, or they are used as intermediates in the TCA cycle. A starved patient loses roughly 75 g of muscle protein, or 200 to 300 g of structural muscle tissue, each day. The urea and ammonia generated by this process are excreted by the kidney. The energy for gluconeogenesis comes from catabolism of fatty acids supplied by the lipolysis of adipose tissues.<sup>3,6,7</sup>

Within 1 week, metabolism of fatty acids becomes the principal source of fuel to meet the body's needs. The activation of catechol-sensitive lipase in adipose tissue causes the release of free fatty acids and glycerol. Glycerol is converted to glucose or to

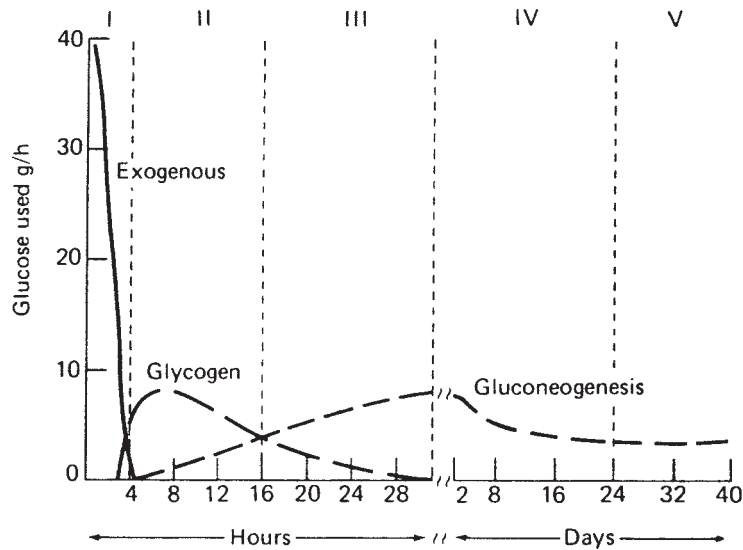
pyruvate, which enters the TCA cycle. A consequence of the accelerated metabolism of fatty acids during starvation is the production of ketone bodies and their increasing use by organs such as the heart and brain in place of glucose. The adaptation of the heart and brain to utilize ketone bodies is of critical importance in prolonging survival during starvation, since it allows for a marked reduction in the glucose needs of the body (perhaps 5% of normal) that otherwise could not be met by gluconeogenesis beyond about 2 weeks (Figure 23-3).

Fats become the primary fuel, with the utilization of lipid becoming a major adaptive response, conserving protein. Protein catabolism declines as the body's energy needs are increasingly met by catabolism of fat. As simple starvation continues, the rate of catabolism decreases from roughly 300 g of muscle tissue per day to 150 g/d. In simple starvation, the intake of carbohydrate can spare protein to some extent. How are these responses to starvation brought about? The fall in glucose causes a fall in insulin, with a consequent, although lesser, inhibition of lipolysis. Glucagon rises as insulin falls, accelerating both lipolysis and glycogenolysis.

What are the systemic medical effects of starvation for a significant period (ie, longer than several days)? All organs are affected by the loss of structural, and often of functional, proteins. The lungs lose the ability to clear bacteria, connective tissues degenerate, and emphysematous changes are the result. Respiratory muscles atrophy. The heart dilates, and, after a time, focal necrosis and fibrosis appears, with myofibrillar degeneration. Red and white blood cell counts fall with decreased production of erythropoietin (ie, erythropoietic hormone) and stem cells. The gut, which has more rapidly dividing cells than any other organ, loses mass out of all proportion to its size as it atrophies. The liver and kidneys lose mass, and the liver begins to accumulate fat. The immune system becomes less and less able to respond to infection, as the number of T helper cells declines and polymorphonucleocytes lose their chemotactic abilities. If hypermetabolism is added to simple starvation, then the catabolism of protein predominates, and the changes discussed are far more profound.

### Exercise

The metabolic consequences of exercise depend on both the duration and the intensity of the exer-



The Five Phases of Glucose Homeostasis

	I	II	III	IV	V
Origin of blood glucose	Exogenous	Glycogen Hepatic gluconeogenesis	Hepatic gluconeogenesis Glycogen	Gluconeogenesis, hepatic and renal	Gluconeogenesis, hepatic and renal
Tissues using glucose	All	All except liver Muscle and adipose tissue at diminished rates	All except liver Muscle and adipose tissue at rates intermediate between II and IV	Brain, red blood cells, renal medulla; small amount by muscle	Brain at a diminished rate, red blood cells, renal medulla
Major fuel of the brain	Glucose	Glucose	Glucose	Glucose, ketone bodies	Ketone bodies, glucose

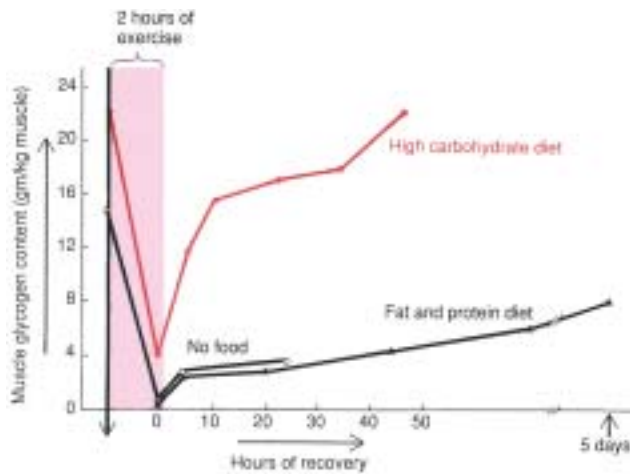
**Fig. 23-3.** The amount of glucose consumed and its source depend on the phase of alimentation. In the immediate postabsorptive phase, exogenous glucose forms the major source and is consumed by all tissues (I). Within 3 to 4 hours of eating, glycolysis of liver glycogen is the major source of glucose (II). The major source of glucose after 24 hours is gluconeogenesis from amino acids released by the catabolism of skeletal muscle protein (III). When fasting progresses to starvation, glucose consumption is increasingly restricted to red blood cells and the renal medulla (IV). During starvation, glucose consumption by the brain progressively falls, as the brain increasingly uses ketone bodies as its major source of energy (V). Whatever glucose is produced comes from gluconeogenesis. Reprinted with permission from Linder MC. Energy metabolism, intake, and expenditure. In: Linder MC, ed. *Nutritional Biochemistry and Metabolism with Clinical Applications*. New York, NY: Elsevier; 1985: 291.

cise. The most intense exercise (eg, running at maximum speed carrying full combat gear) causes muscle ATP and phosphocreatine to be totally consumed in less than 1 minute. If the exertion, albeit at a reduced rate, is prolonged beyond 10 seconds, muscle glycogen stores begin to be broken down to glucose, which, in turn, is metabolized to lactic acid. Anaerobic metabolic pathways—and especially the breakdown of muscle glycogen—are the primary energy source for maximum-intensity exercise that lasts less than several minutes. The amount of glycogen available in muscle is the major metabolic

determinant of performance during short, high-intensity exertion. In normal circumstances, about 80% of the lactic acid formed during anaerobic exercise is converted rapidly back to glucose; the remainder enters the TCA cycle where it will be metabolized to carbon dioxide.

Only when the duration of high-intensity exercise exceeds 3 or 4 minutes does aerobic metabolism become the predominant source of high-energy phosphates. During prolonged exercise under aerobic conditions, the initial major source of energy is liver glycogen, followed by fatty acids. Neverthe-





**Fig. 23-4.** Restoration of muscle glycogen levels after vigorous exercise very much depends on the consumption of a diet high in carbohydrates. A similar degree of glycogen repletion will not occur when most of the calories are provided by a diet rich in fats and proteins. Reprinted with permission from Fox EL. *Sports Physiology*. Philadelphia, Pa: WB Saunders; 1979: 69.

less, glycogen depletion occurs with long-distance running or prolonged marching with a full combat load, even given the steady-state conditions of aerobic energy production. Reconstitution of depleted glycogen becomes an important determinant of further exercise performance. Restoring muscle and liver glycogen stores to normal greatly depends on the types of food consumed after the exercise (Figure 23-4). Thus, the combination of prolonged exercise and nutritional deprivation may seriously degrade exercise performance.

### Starvation, Exercise, and Stress

Starvation is simply the lack of nutrient intake. Few inflammatory mediators are released, and the body responds to exogenous replacement. But now we add moderate stress in the forms of sleep deprivation, anxiety or even fear, cold or heat, and arduous physical exertion—a combination especially likely to occur during military operations. Starvation puts humans into glycogenolytic and gluconeogenic metabolic modes, the latter being ultimately suppressed by the development of lipolysis and the formation of ketone bodies. Unfortunately, exercise and stress interfere with this adaptation. Stress increases glucose utilization out of proportion to total energy expenditure, while it also increases energy expenditure. Glycogen stores are

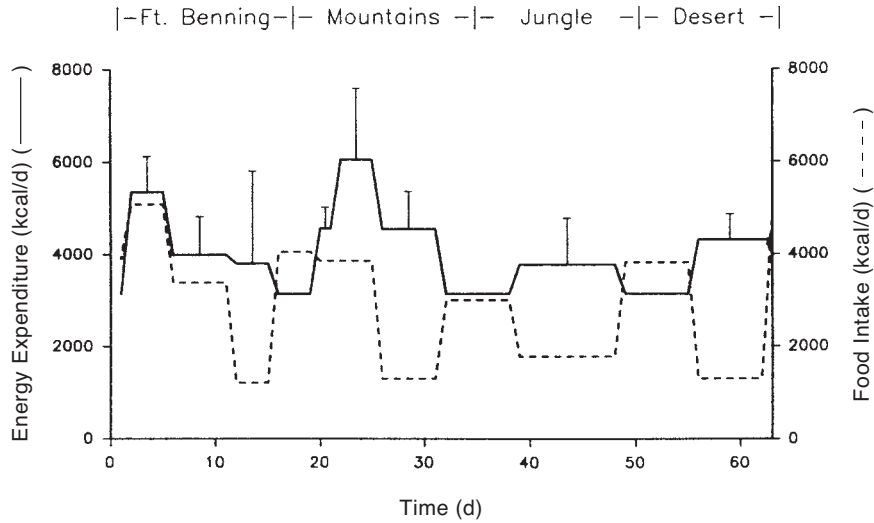
depleted more rapidly. Increased levels of glucagon, catecholamines, and cortisol—hormones that characterize the human response to stress—accentuate gluconeogenesis. Fat is no longer the primary energy source; the body utilizes protein stores instead. Each day, 250 g of fat and 3- to 4-fold that amount of muscle tissue are catabolized to produce new glucose.

Actual measurements of these derangements during combat operations are next to impossible to make for obvious reasons. Fortunately, however, the U.S. Army Research Institute of Environmental Medicine (USARIEM) has studied the effects of starvation, exercise, and stress during the U.S. Army's Ranger Training Course.<sup>8</sup> This is the training exercise that most closely mimics real combat. The training course is extremely arduous; typically, only 40% to 50% of its students pass. The course lasts 62 days and is carried out in four phases in geographically and climatically diverse settings: at Fort Benning, Georgia, and in mountain, jungle, and desert environments in Georgia and elsewhere in the United States.

In the USARIEM study, which was published in 1992, the mean weight loss of Rangers in training over the 62-day course was  $12.1 \pm 3.4$  kg (range 6.5–20.6 kg), which corresponded to a median weight loss of 15.6% of initial body weight. Body fat fell from about 15% of body weight at the beginning of the training to about 6% at the end. Fat-free mass (an index of muscle tissue) fell an average of 4.6 kg. These reductions in body mass were clearly due to the marked imbalance between total body energy expenditure (which averaged  $4,010 \pm 830$  kcal/d) and estimated food energy intake (which averaged  $3,930 \pm 290$  kcal/d) (Figure 23-5). Peak energy expenditures during the mountain phase were estimated to exceed 6,000 kcal/d. By way of contrast, an average, unstressed man requires about 2,000 kcal/d, and an unstressed woman about 1,800 kcal/d.

The combination of inadequate caloric intake, stress, and exercise caused profound endocrine disturbances (Figure 23-6). As expected, the level of insulin and insulinlike growth factor (IGF-1) showed significant decreases, which suggest the magnitude of the ongoing protein catabolism. The cortisol level increased and although glucagon was not measured, we may assume that it also increased since glucagon's role, like cortisol's, is to mobilize the body's noncarbohydrate energy reserves. Not shown on the graph, but of considerable interest, is the nearly 1,000% increase in growth hormone (ie, somatotrophin). The homeostatic importance of

**Fig. 23-5.** Energy balance during the 2 months of the U.S. Army Ranger training course. Solid lines represent estimated energy expenditure, while broken lines represent estimated energy intake. Except for the brief periods of transition between the training phases, the Rangers ate fewer calories than they expended. Reprinted from Moore RJ, Friedl KE, Kramer TR, et al. *Changes in Soldier Nutritional Status and Immune Function During the Ranger Training Course*. Natick, Mass: US Army Research Institute of Environmental Medicine; 1992: 51. USARIEM Report T13-92.

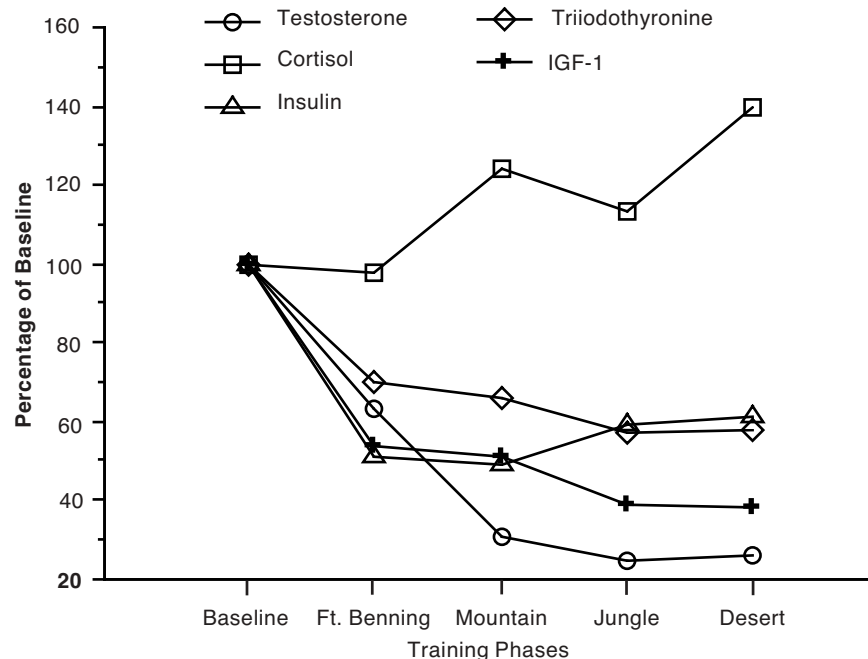


this alteration is unclear, since growth hormone has anabolic effects and, in fact, is increasingly used for that purpose in nutritionally depleted catabolic surgical patients.<sup>9</sup>

Other consequences of the combined starvation, exercise, and stress that characterize the Ranger Training Course, and military operations in general, are loss of strength in large muscle masses such as the thighs (no doubt due to the generalized loss of lean body mass) and dramatic evidence of a loss of cell-mediated immune function. Such indices of T lymphocyte function as phytohemagglutinin-

stimulated proliferation and interleukin-2 (IL-2) production were reduced by one half. Production of IL-6 fell to a similar extent. These derangements are clinically relevant: 50% of the population studied were treated with antibiotics for infection. The cumulative effects of starvation, exercise, and stress can have tragic, unintended consequences. On 15 February 1995, four Ranger students at Fort Benning died from hypothermia after a water-immersion portion of their training. Ironically, the official recommendations that had been prepared on the basis of the USARIEM study had emphasized that

**Fig. 23-6.** Measured changes in the levels of various hormones during the 62-day U.S. Army Ranger training course. Data are given as percentages of the baseline values. The elevation of cortisol and the depression of insulin are consistent with stress and starvation. The actual concentration of testosterone approached the level found in castrated men. However, the cause in the Rangers is not testicular dysfunction but rather a profound suppression of the elaboration of pituitary gonadotropin. Data source: Moore RJ, Friedl KE, Kramer TR, et al. *Changes in Soldier Nutritional Status and Immune Function During the Ranger Training Course*. Natick, Mass: US Army Research Institute of Environmental Medicine; 1992: Table 23, p 68. USARIEM Technical Report T13-92.



the normal thermogenic response to mild cold is impaired during massive weight loss.

Given the extreme psychological and physical stresses and the less-than-ideal circumstances for eating and resting associated with prolonged exposure to combat—or even just living in the combat zone—the metabolic, endocrine, and immune derangements found in USARIEM's Ranger study are to be expected. The importance of weight loss in soldiers should not be underestimated. The extensive slide collection of the Wound Data Munition Effectiveness Team (WDMET) database that was compiled during the Vietnam War contains few photographs of combat casualties who show either significant obesity or who have a muscular mesomorph body habitus. Many of the soldiers portrayed in the WDMET database appear to be significantly malnourished (Figure 23-7).<sup>10</sup> Medical officers must expect to treat soldiers who are not in optimal nutritional status when wounded. Furthermore, in every war in which the United States has been a combatant, U.S. forces have cared for children, the elderly, and prisoners of war. This must be kept in mind when nutritional support is planned, because such potential casualties are likely to manifest some degree of starvation.

### The Effect of Injury

When even a peripheral injury of an arm or leg is added to starvation, mediators are released, catecholamines levels increase further, thyroid hormone is elevated, and cardiac output, oxygen delivery, and oxygen extraction all increase. If the injured soldier is not resuscitated adequately, oxygen delivery may fall and anaerobic metabolism be initiated. Further inflammatory mediators will be released. Should the wound be of the trunk, the

metabolic stresses would be the same, but with this larger body compartment will come more tissue damage; greater blood loss; higher levels of inflammatory mediators; and greater risks of inadequate resuscitation, infection, and organ failure.<sup>11-13</sup>

The chain of metabolic events set in motion by injury is complex. Not only are there direct effects of the injury on tissue, but the body responds with a cascade of direct effects (the immediate response to the injury, including the steps the body takes to protect itself from further injury) and indirect effects (those effects on metabolism resulting from the injury and the direct effects the injury sets in motion).

The body's immediate responses to an injury are (a) the activation of the sympathetic nervous system and (b) a secondary discharge of catecholamines from the adrenal medulla. Cardiac output, and thus the delivery of oxygen to the tissues, increases, and the oxygen extraction ratio also rises as tissue metabolism increases. The release of thyroid hormones, in response to the catecholamine surge, is responsible for 50% to 60% of this increase in metabolism. As the rate of biochemical reactions increases, the core body temperature increases—but owing to homeothermic compensatory changes, not to the extent predicted by the inverse of van't Hoff's law (ie, a reaction rate increases 7.2% for each 1°F rise in temperature). The extent to which the temperature rises is proportional to the severity of the illness.<sup>13,14</sup> An increase in motor activity, whether due to running, shivering, thrashing secondary to pain, seizures, and so forth, usually accompanies these responses and further increases both metabolism and temperature.

The indirect effects of stress and injury on the body are more subtle but play as great a role in altering metabolism. Stress acutely suppresses



**Fig. 23-7.** Five months after he arrived in Vietnam, this soldier was killed by a bullet that transected his upper spinal cord. His degree of malnutrition was not unusual. Photograph: Wound Data and Munitions Effectiveness Team slide collection.

pyruvate dehydrogenase, decreasing the amount of pyruvate available for formation of acetyl-CoA, and eventually of ATP. Glycogen stores are depleted quickly. Oxidation and phosphorylation may uncouple, resulting in a markedly less-efficient metabolism. ATP production decreases, but the production of heat rises as the efficiency of the TCA cycle decreases. Futile cycling of substrate via the Cori cycle occurs; at the site of the injury, glucose is metabolized to lactate, which is then transported back to the liver, where it is converted back to glucose. This process produces heat but no net gain of ATP. Oxygen consumption increases, and the body appears to enter a state of hypermetabolism.<sup>13,14</sup>

The release of the counterregulatory hormones—glucagon, cortisol, and ACTH—further promotes the situation. Cortisol increases gluconeogenesis to 6- to 10-fold higher than the baseline. Peripheral proteins are catabolized, and the amino acids are taken up by the liver. Free fatty acids are mobilized from lipid pools and transported to the liver, where glucagon stimulates the use of the carbon skeletons of amino and fatty acids for gluconeogenesis. Release of inflammatory mediators, such as IL-1, IL-6, and the tumor necrosis factor (TNF), further drives the breakdown of protein and lipid while promoting the waste of fuel resources in futile paths such as the Cori cycle.<sup>11,13,14</sup>

So what do we find when we consider the casualty? A young, previously healthy patient, whose higher-than-normal physiological reserves have been affected not only by his recent health and nutrition but also by complicating stresses such as cold or heat, anxiety, pain, volume loss, and infection. In general, heat is tolerated better than cold, and a warmer environment is a better one for the casualty. The presence or absence of military air superiority will determine evacuation times, and in many cases, the adequacy of resuscitation. The length of time to evacuation, continued pain, volume depletion, and so forth, all effect the production of catecholamines, thyroid hormones, cortisol glucagon and ACTH, and the inflammatory mediators, all of which, in turn, affect the metabolism of the patient.

“Fatigue poisons” (ie, elevated levels of catecholamines, counterregulatory hormones, and inflammatory mediators brought on by the stress of combat or the prolonged stress of waiting for combat) take their toll. Metabolism becomes less efficient, receptors for catecholamines and thyroid hormones down-regulate, glycogen stores *slowly* deplete, and gluconeogenesis and ketosis are present at con-

tinual low levels. Catecholamines initially increase both oxygen consumption and delivery, although inflammatory mediators, as well as the catecholamines themselves, may interfere with both cardiac output and the peripheral distribution of blood flow. Arteriovenous shunting may actually decrease oxygen delivery to the tissues. The key to metabolic control is adequate and continuing resuscitation to prevent both damage to enzyme systems and cells and the formation of free-radical oxidation of tissues.<sup>15</sup>

Other factors (predominant among them volume depletion and concomitant hypoperfusion of tissues) trigger or amplify a hypermetabolic response to stress and injury. The initial state of the injured patient, and the adequacy of initial and continuing resuscitation at the first and second echelons and during evacuation rearward, will determine the efficiency of organ function, the generation of inflammatory mediators, and the subsequent medical course of the patient. Cold and high glucose loads may each promote a subtle diuresis that may be overlooked during extended transport or if there are large numbers of casualties. A significant limb injury, delayed evacuation, and volume depletion worsened by hypothermia may combine to create a hypermetabolic state that will result in multiple organ failure and death weeks after the injury.

### Stages in the Response to Stress

Stress, whether emotional or physical (from illness, injury, or infection), induces specific patterns of metabolic response in the body. The patterns presumably evolved as a survival advantage, a means to deal with overwhelming stimuli. They work reasonably well most of the time but often at great expense to the patient, as Shakespeare knew: “Diseases desperate grown by desperate appliance are reliev’d, or not at all.”<sup>16</sup>

### The Immediate Response

The immediate response to stress is modulated by the sympathetic nervous system, hypothalamus, pituitary, and adrenals. The hypothalamus orchestrates the activation of the sympathetic nervous system and stimulates the release of pituitary hormone and the production of glucagon by the pancreas. ACTH released by the pituitary increases the production of cortisol and other steroids; these, in turn, increase the breakdown of skeletal muscle protein and the turnover of protein in the liver, as well as the breakdown of hepatic glycogen for glu-

cose release. Catecholamines increase available glucose by acting on skeletal muscle to increase protein turnover, on lipid storage cells to release free fatty acids, on the pancreas to increase output of both glucagon and insulin, and on the liver by promoting glycogenolysis and gluconeogenesis. Steroids and glucagon also act to promote gluconeogenesis.<sup>12-14</sup>

Trauma causes a mobilization of resources to deal with the injury, inducing a hypermetabolic state in which oxygen and substrate consumption are greater than normal the availability of ATP does not necessarily increase correspondingly. Oxidative phosphorylation makes available, in the form of ATP, about 40% of the energy that is available in glucose. The remainder appears as heat. Unfortunately, the normal efficiency can be reduced by the uncoupling of oxidation and phosphorylation as well as by the appearance of futile cycles, which consume oxygen and substrate but yield little net gain in energy except for the production of heat necessary for thermostasis.<sup>17</sup> It is apparent that this state will often be induced when the casualty is in a preexisting stressed state and has limited reserves for the new demands. The changes are different from those of starvation but are similar to those seen in the stressed state, although of a much greater magnitude.

The state of hypermetabolism has been known by a variety of names, including sepsis, sepsis syndrome, autocatabolism, and most recently as the systemic inflammatory response syndrome (SIRS). This syndrome is discussed in detail in Chapter 24, The Syndromes of Systemic Inflammatory Response and Multiple Organ Dysfunction, but a brief description of mediators and hormone responses is in order here. The hypermetabolic response to stress, especially trauma and infection, is orchestrated by the activation of the neuroendocrine and cytokine systems. The appearance and magnitude of the mediator response depends directly on the severity of trauma, the amount of inflammatory tissue present, and the presence or absence of infection. Mediators (peptide regulatory factors) are produced by macrophages, lymphocytes, and other cells that are reacting to a stress stimulus, and have both paracrine and autocrine effects on other cells, inducing the expression of a variety of genes and the synthesis of several proteins that mediate the inflammatory response. Two of the most important in terms of metabolism are TNF and IL-1.

In addition to its role as an immune modulator, TNF modulates a great deal of the metabolic response of the organism. Circulating levels of TNF-

$\alpha$  and TNF- $\beta$  increase with stress and increase markedly with infection. Bacterial toxins are one of many kinds of stimuli that activate production of TNF in hepatic macrophages and lymphocytes. TNF activates T and B lymphocytes and the production of interleukins (specifically, IL-1 and IL-6), growth factors, and eicosanoids—especially the lipoxygenase and cyclooxygenase pathways of the arachidonic acid cascade.<sup>11,12,15</sup> The production and output of corticotropin, adrenal cortisol, glucagon, and catecholamine are all increased in response. Fever, a fall in white blood cell count, and hypotension are the immediate results, followed by an increase in white blood cells with a relative lymphopenia, an increase in lactoferrin, and a fall in iron stores. Collagenase synthesis increases, with reabsorption of bone and cartilage. Formation of structural proteins other than at the wound site, albumin production, and the synthesis of nonessential proteins all slow dramatically, while acute-phase protein synthesis in the liver, prostaglandin production, and proliferation of fibroblasts at the site of injury all markedly increase. Serum lipids increase as fat stores are catabolized, and amino acid turnover accelerates.<sup>3,11,13,15</sup> Cytotoxic effects on certain cells—the beta cells of the islets of Langerhans, for example—decrease the availability of the anabolic hormones.<sup>3</sup>

IL-1 also has a broad spectrum of activity, from acting as an inflammatory and immune mediator to affecting metabolic, hematopoietic, and physiological functions. IL-1, the “endogenous pyrogen,” is also responsible for fever, elevation of the white blood cell count, increase in the level of colony stimulating factors and other interleukins, and the marked increase in acute-phase protein synthesis by the liver. IL-1 also decreases iron levels; this may be a protective mechanism, as bacteria deprived of iron are less cytotoxic than those with easy access to iron stores. Serum albumin and serum zinc levels drop as zinc (as well as iron) is taken up by the liver.<sup>3</sup> A decrease in appetite is common, possibly due to the decreased serum zinc. The release of ACTH increases the production of adrenal steroids. IL-1, like TNF, is cytotoxic to pancreatic beta cells. Proteolysis is accelerated, as is hepatic uptake of amino acids for gluconeogenesis and acute-phase protein synthesis. IL-1 and TNF act synergistically to produce acute-phase protein synthesis, the immune response, shock, and hypermetabolism as a response to stress, injury, and bacterial invasion. Other interleukins and eicosanoids amplify the response that the phrase “metabolic tide” describes.

Catecholamines, as well, respond to circulating mediators and the urging of the ventromedial

nucleus of the hypothalamus. Epinephrine and norepinephrine levels increase within 5 minutes of injury, from both sympathetic nervous system stimulation and adrenal output. The degree of response correlates directly with the degree of stress.<sup>13</sup> The catecholamines orchestrate the neuroendocrine response: glucose is released from the breakdown of glycogen, and insulin release is inhibited at the same time glucagon production increases. Serum osmolality rises, which temporarily augments blood volume (although to a lesser extent in the starving or fasting patient). It is unclear to what extent the decrease in insulin affects cellular glucose entry early on, as glucose can enter hypoxic cells without the need for insulin. Certainly, in a hypovolemic, hypotensive patient, many tissues will have some degree of hypoxia. Glucose will also move down a concentration gradient, and as the serum glucose concentration rises, more will enter cells; however, the cells may not be able to utilize the glucose effectively. In addition to the initial decrease in insulin output, the peripheral tissues become less responsive to insulin over time as insulin receptors down-regulate. The shift to a catabolic state brought on by the high levels of TNF, interleukins, catecholamines, steroids, and glucagon causes proteolysis and the release of amino acids from muscle tissue. TNF directly inhibits lipoprotein lipase, decreasing the availability of lipid fuel stores for energy production. Both  $VO_2$  and the metabolic rate increase, an increase that is directly linked to catechol production.<sup>12,13</sup>

Other hormonal balances change, as well. Thyroxine (3,5,3',5'-tetraiodothyronine, known as  $T_4$ ) production does not change, but the conversion of  $T_4$  to 3,5,3'-triiodothyronine ( $T_3$ ) decreases markedly as  $T_4$  breaks down not to  $T_3$  but to the metabolically inactive *reverse*  $T_3$  (3,3',5'-triiodothyronine).<sup>14</sup> This decrease in metabolically active  $T_3$  is one of the causes of the hyperglycemia common to the hypermetabolic state.<sup>18,19</sup> The production of growth hormone increases during stress, which promotes protein synthesis; the increase is enhanced if two stressors occur in a short period, such as a high physical or emotional stress state followed by injury, or injury followed by infection. Arginine vasopressin is released by the posterior pituitary and acts to retain fluid. The adrenal glands pour out corticosteroid in response to ACTH, catecholamines, antidiuretic hormone, and growth hormone, increasing glucose intolerance. Erythropoietin production by the kidney increases, and the renin-angiotensin axis becomes activated.

Once again, the ratio of insulin to glucagon plays a major role. After an initial decrease following stress, insulin levels may rise to far above normal, but they never catch up with the rise in glucagon production and release. The ratio of the hormones is altered to favor catabolism, promoting glycogenolysis and gluconeogenesis. The counter-regulatory hormones, glucagon, growth hormone, catecholamine, and steroids keep glucose levels elevated. It is often difficult to control hyperglycemia even with massive doses of exogenous insulin. Triglycerides are being converted to free fatty acids and glycerol by high insulin levels, increasing lipase activity. This action is overridden to large extent by the counterregulatory hormones but still provides fatty acids to fuel metabolic processes.<sup>13,14</sup>

Immediately after an injury, when blood flow is directed to vital organs in an attempt to preserve oxygen delivery, the insulin response to hyperglycemia is blunted: the beta cells of the pancreas are delayed in responding to hyperglycemia, and the response is less than normal for the level of hyperglycemia. This is due in part to hypoperfusion, and in part to the direct effects of catecholamines and IL-1 and TNF on the beta cells.<sup>13</sup> After resuscitation and stabilization, the insulin response to glucose is normal to increased, occasionally markedly increased. Glucagon, however, has also increased, and the ratio determines catabolism or anabolism. Even when the rise in insulin production outstrips glucagon output, the cells are less responsive to the insulin. Cell-surface insulin receptors down-regulate in response to alterations in growth hormone and cortisol, and there may well be a postreceptor defect similar to that seen in non-insulin-dependent diabetes mellitus.<sup>13,15</sup>

The physiological response of the body to trauma and sepsis has been classically described as having two phases, an *ebb* and a *flow*.<sup>13-15</sup> The *ebb* phase occurs during the first 24 to 48 hours after the stress event, including the initial resuscitation, and is characterized by hypodynamic circulatory and metabolic responses. Cardiac output, temperature, blood volume, and metabolic rate all decrease, as though the tissues are stunned. Lactate levels and body weight (from third-spacing of resuscitation fluids) increase, often dramatically. Data for this phase come from only a small number of patients, and not all experts agree on the presence or importance of the *ebb* phase. While oxygen delivery does decrease, recent data<sup>20,21</sup> show this to be offset by a rise in the oxygen extraction ratio of some tissues. There is general agreement on the *flow* phase, how-

ever. Massive release of epinephrine and norepinephrine push hypercatabolism and the maximum mobilization of nutrients. While the severity of the trauma or sepsis dictates the course, the adequacy of resuscitation dictates the duration of the active phase and the eventual outcome. The shift to an acute-phase response markedly increases the energy needs of the organism, and a massive mobilization of fuels, as well as of structural elements for wound repair, occurs.<sup>15</sup> The flow of substrate generally exceeds the requirements for energy. Tissues adapt to the oxidation of other fuels. These processes will either shift to an adaptive response—*anabolism and repair*—as the stimulus for inflammation is removed, or will continue to multiple organ failure and death.

### *Changes in Organ Beds and Blood Flow*

The response to stress is an adaptive mechanism that makes substrates available to meet the body's metabolic needs. The substrates, however, may not always go where they are needed. Microcirculatory dysfunction is present in many organ beds and may last days to weeks in some. Normal hepatic perfusion is not restored for 2 to 3 days after adequate resuscitation. Both heat production and oxygen consumption of injured tissue rise in the flow phase, due to increased energy expenditure by the heart and breakdown and recycling of lipid and protein—in some cases futile recycling. Oxygen delivery increases and total body oxygen consumption rises, owing to the oxidation of mixed fuels. Carbon dioxide production increases concomitantly, and minute ventilation follows. The increase in total oxygen consumption, however, may not reflect regional blood flow. While in most regions blood flow rises, in some it remains depressed. Both the renal and the splanchnic beds increase their oxygen consumption, generally in proportion to the severity of injury, but changes in the microcirculation may prevent an increase in oxygen delivery. Anaerobic means of ATP production ensue, with increase in tissue lactate. "Adequate" blood pressure does not necessarily mean adequate perfusion. Hypoperfusion is expected in the ebb phase and is vigorously treated. Epinephrine and norepinephrine output rise rapidly in the first 5 minutes after trauma, with elevation of vascular resistance and increased shunting of blood. When this is superseded by the flow phase, the metabolic rate increases and protein catabolism begins. This usually maximizes at 4 to 8 days but persists until the stress stimulus resolves

or the injury is repaired. Hepatic blood flow and oxygen consumption increase shortly after a stress stimulus to allow the liver to meet the increase in metabolic demand. In trauma with inadequate resuscitation, however, or with any combination of sepsis, general anesthesia, or abdominal surgery, hepatic blood flow decreases, limiting delivery of both oxygen and nutrients. Renal blood flow changes in much the same fashion, with a normal increase in glomerular filtration rate to aid in the excretion of toxins and urea. Daily loss of body water generally increases, not only from insensible losses due to fever but also due to this increased glomerular filtration rate and the osmotic load resulting from hyperglycemia and the products of tissue breakdown. While insulin output falls early due to inhibited production in the pancreas, the elevated catecholamines, cortisol, and growth hormone stimulate the alpha cells of the islets of Langerhans to release glucagon in large amounts. High levels of their accustomed fuel, glucose, are made available to all tissues, and the increased serum osmolality helps to augment blood volume. As levels of these catabolic hormones continue to rise after resuscitation, insulin levels rise as well, often to levels severalfold higher than normal. Cell-membrane insulin receptors down-regulate in response, and the hyperglycemia needed for cellular operations under adverse conditions persists. Hepatic adenyl cyclase activates, acute-phase proteins are produced, and both glycogenolysis and gluconeogenesis rapidly maximize.

### *Metabolic Changes in Trauma with Sepsis*

Consider for a moment the massive energy expenditure as the body responds to the stress of trauma or sepsis or both. Some cells must acutely perform many times the normal work of the body by

- producing hormones, inflammatory mediators, and acute phase proteins;
- mobilizing host defenses and producing new neutrophils, lymphocytes and antibodies;
- destroying invading bacteria;
- circulating greater-than-normal amounts of oxygen and nutrients to all parts of the body while removing increased volumes of carbon dioxide; and
- directing nutrients to the wound and producing new protein for granulation tissue, performing repair, and restructuring.

Protein synthesis continues in the face of catabolism, although at a reduced rate; the resources merely shift.

Add to these the metabolic cost of processes necessary to simply obtain fuel when the normal logistics break down—glycogenolysis, proteolysis, lipolysis and gluconeogenesis, generation of urea—and we realize just how *much* energy production is actually necessary, once the “hormonal tide” sweeps in. Add to this the loss in efficiency of glucose utilization. Although clearance of glucose by muscle tissue rises, a lower fraction of the maximum potential energy available from glucose actually appears as useful work, probably because the inhibition of enzymes causes a decrease in the ability of pyruvate to enter the TCA cycle. The increasing amount of pyruvate and increased amounts of lactate, alanine, and glutamine, are carried to the liver, where glucose recycles futilely in the Cori cycle. The high levels of catechols and other mediators support this recycling. Because of the abnormal glucose metabolism, many tissues switch from glucose to fatty acids for fuel, and lipid becomes the primary energy source. Lipolysis occurs despite elevated levels of glucose and insulin. The actual utilization of lipid varies, however, and appears not to be as extensive as would be thought given the elevated metabolic rate. Many tissues cannot utilize lipid effectively, either, and futile cycling of fatty acids to triglycerides and back occurs, at a net energy cost as well as the penalty of fatty deposition in the liver.

Hormone- and mediator-driven muscle breakdown releases amino acids into the circulation, both to increase the precursor pool for visceral protein synthesis and to provide a ready fuel source. Branched-chain amino acids, from structural proteins (skeletal muscle, connective tissues, unstimulated gut mucosa), donate their carbon skeletons for conversion to glucose to support the increased metabolic rate of the liver. Glutamine, alanine, and the aromatic amino acids are readily available for protein synthesis, while the availability of the branched-chain amino acids falls as they are used for fuel. Leucine, released by the catabolism of skeletal muscle, is in large part irreversibly oxidized in muscle. This amino acid is essential to the utilization of other amino acids by the liver; if levels of leucine fall, the liver can no longer efficiently utilize other amino acids. These are broken down and excreted. Total body protein synthesis is reduced, although hepatic protein synthesis rises.<sup>15</sup> Alanine stimulates hepatic protein synthesis, with the synthesis of nonacute-phase proteins (ie, albumin and transferrin) held in check by mediator release from hepatic macrophages. Structural protein, however,

was never intended as an intrinsic energy source except over the briefest time. Trauma initiates an obligatory, normal catabolism over 24 to 48 hours, to provide glucose when glycogen stores are depleted. Further stress stimuli—sepsis, for example—will perpetuate and magnify this response. Lean body mass becomes significantly depleted after 7 to 10 days, placing the patient in a poorer risk group for survival.

### *Shifts in Oxidative Metabolism*

Glucose is the preferred fuel for many tissues, particularly the central nervous system and granulation tissue. The maximum rate of glucose oxidation for most tissues, however, is 3 to 6 mg/kg/min, inadequate for cellular needs under these conditions. Ready supply of glucose is also limited, and new glucose must be slowly mobilized from noncarbohydrate sources. If exogenous calories are provided, with the bulk from carbohydrate, then nitrogen sparing will occur to a much lesser degree than is seen in starvation. The RQ will remain below 1.0, indicating a failure to use glucose as a fuel, or may climb to much greater than 1.0 as exogenous glucose is used to make fat deposits in the liver. Some tissues change over to other fuel sources in an effort to keep up with the demand of the metabolic rate. An RQ of 0.75 to 0.85 generally indicates the use of mixed fuel, most often lipid and protein.

Early response—prior to adequate resuscitation—of oxidative metabolism to trauma or sepsis generally results in an oxygen debt, which itself results from the sum of individual organ decrements in oxygen consumption. Low levels of oxygen consumption are often due to hypoperfusion due to hypovolemia, sepsis, or both; however, hypothermia, malnutrition, and sedation may all contribute and should be considered. Total body oxidative metabolism increases as the hypermetabolic response to a stress state develops. The increase in oxygen consumption in the flow phase represents the increase in total body consumption, and is directly proportional to the severity of injury and adequacy of resuscitation. It peaks between days 3 and 10. Oxygen consumption of individual tissues or organ beds may actually decrease, depending on the state of their perfusion, so the total body oxygen consumption does not necessarily reflect adequate blood flow to all tissues.

As glucose stores are consumed, a shift to lipolysis and proteolysis provides free fatty acids, alanine, and glutamine for the TCA cycle. Unfortunately, a significant portion of the lipid is squandered



to make additional triglycerides, driven by high insulin and glucose levels.<sup>3</sup> Amino acids become the chief fuels for the TCA cycle. While there is an absolute increase in the oxidation of lipid and glucose, the percentage of calories derived from these two sources declines steadily. The rate of endogenous glucose production from all sources increases, but glucose concentrations remain stable, although elevated, because of a matching rise in glucose uptake. Glucose turnover is proportional to total body oxygen consumption, which, in turn, is proportional to the severity of injury or infection. Regional uptake of glucose, though, is related to regional blood flow, and is generally matched by regional lactate release, but is not directly related to regional oxygen consumption. It is the combination of a steep glucose gradient and the diversion of blood flow to regions of inflammation that drives regional glucose uptake. The glucose is often converted to lactate via glycolysis in areas of inflammation, even if oxygen delivery is adequate. As a result, regional oxygen consumption is not predictive of regional glucose utilization.

Serum lactate rises as a consequence of hypoperfusion, but it is a late indicator of that state. Most tissues will tolerate a partial pressure of oxygen as low as 30 torr before excessive lactate generation occurs. Both (a) catecholamines driving gluconeogenesis and glycolysis and (b) decreased hepatic perfusion will raise lactate levels significantly: the first by generation of lactate; the second by limiting clearance.

Endogenous glucose is produced by the liver from a number of precursors. Lactate, alanine, glutamine, glycine, serine, and glycerol are all substrates that can be used to produce glucose, although several of the mechanisms are futile pathways. Since gluconeogenesis consumes energy, the limited ATP generated at the tissue level from the new glucose is balanced by the loss in the liver. The net energy gain for the total body is zero, although the heat produced may be necessary for maintaining thermal neutrality.<sup>17</sup> The site of the wound or inflammation does, however, gain 2 moles of ATP for each mole of glucose consumed, and a few tissues, such as myocardial cells, can utilize lactate directly via the mitochondrial malate shuttle. Alanine can also be converted to glucose and, in fact, is the major source of new glucose. The conversion of alanine to glucose requires the use of ATP and generates urea, the excretion of which requires that further energy be expended. The high-energy phosphate pool gradually shrinks through losses of TCA cycle efficiency and the loss of labile proteins.

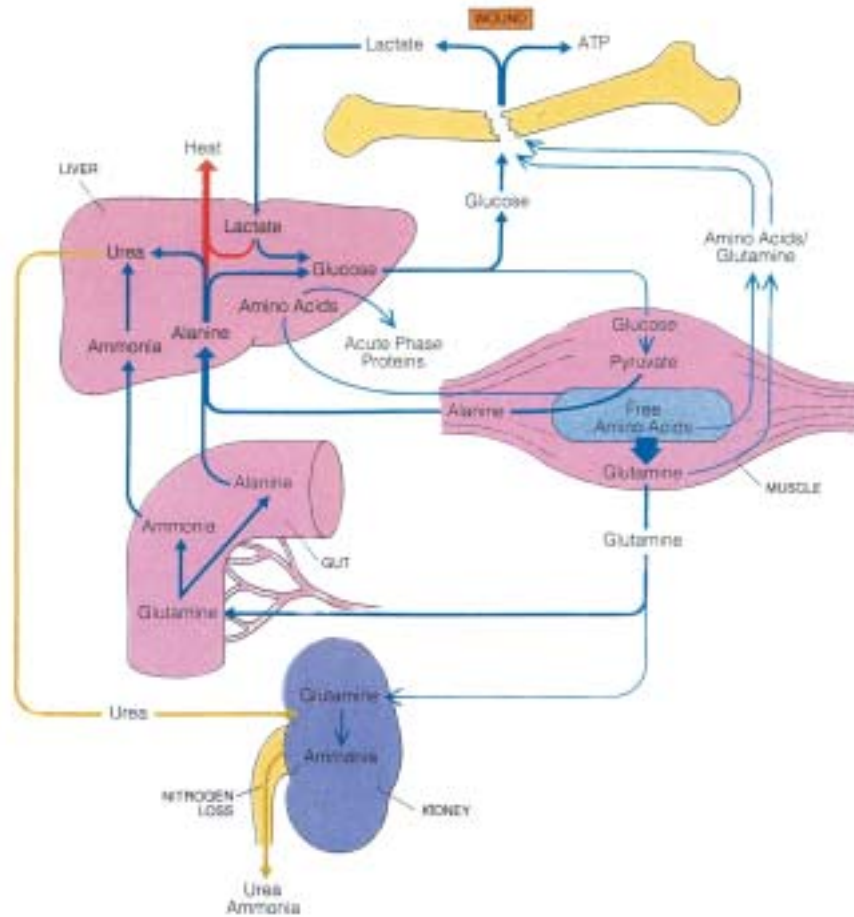
Because of the increased lipolysis that develops a few days after injury, fatty acid deficiencies can occur early. Following trauma, there is a 55% increase in the rate of lipid oxidation; following infection, a 25% increase.<sup>22</sup> The lesser increase in lipid utilization during infection is thought to be due to the impaired activity of lipoprotein lipase by TNF, IL-1, and IL-2.<sup>23</sup> These are not suppressed by carbohydrate feeding, a difference from the oxidation in simple starvation; nor is there an increase in ketones, which are used as fuel under these circumstances. Long-chain, essential fatty acids, linoleic and arachidonic in particular, rapidly decrease after injury. Essential fatty acid deficiency can develop after 2 to 3 weeks, and requires a minimum of 10% of exogenous calories in the form of lipid to prevent.

#### ***Protein Turnover and Preferential Amino Acid Utilization***

Protein turnover increases with stress, and increases dramatically with trauma or sepsis (Figure 23-8). The level may be taken as a measure of the severity of the stress event. As we discussed earlier, glucose stores are used early, leaving the body to depend on lipid calories and, for those obligate glucose-using tissues, on amino acids and glycerol to generate additional glucose. Protein turnover is also increased to free amino acids for production of acute-phase proteins, including TNF and the interleukins, and for wound repair. Both proteolysis and hypermetabolism peak shortly after the onset of the stress state, gradually returning to normal as recovery progresses. The catabolism results in early and rapid muscle wasting.

Branched-chain amino acids from muscle tissue are deaminated and their carbon skeletons oxidized in the TCA cycle for the vastly increased metabolic processes. The rate of protein catabolism can surpass 300 g/d of muscle protein, or nearly 50 g/d of nitrogen lost.<sup>24</sup> Skeletal muscle makes up as much as 80% of the free amino acid pool,<sup>13</sup> with the bulk of this intracellular. A 70-kg man has roughly 87 g of free amino acids in the intracellular space but less than 2 g extracellularly. Protein catabolism is largely an intracellular event, with the changes in skeletal muscle tissue due to changes in the intracellular pools. Breakdown of body protein stores and urinary loss of nitrogen parallels the REE. Hepatic blood flow increases dramatically to meet the hypermetabolic demand. Those amino acids not used to form new protein are deaminated in the liver for their carbon skeletons and their amino groups used

**Fig. 23-8.** Metabolic interrelationships in the wounded casualty. The wound is an obligatory user of glucose, which, for the most part, is derived from amino acids by the process of gluconeogenesis. Glucose is metabolized by glycolysis in the wound, forming lactate. The lactate is then transported back to the liver where it is reconverted to glucose. This process is known as the Cori cycle and, being energy demanding, is one of the determinants of the hypermetabolic state that characterizes trauma. Two amino acids released by the catabolism of skeletal muscle are of special importance: alanine, which is transported to the liver to form glucose; and glutamine, which forms the primary substrate of the intestines. Reprinted with permission from Bessey PQ. Metabolic response to critical illness. Chap 11. In: Part 2. Care in the ICU. In: Wilmore DW, Brennan MF, Harken AH, Holcroft JW, Meakins JM, eds. Vol 1. *Critical Care*. In: *Care of the Surgical Patient*. New York, NY: Scientific American, Inc; 1989: 11-11.



for the synthesis of glutamine and alanine. The concentrations of glutamine and alanine in blood are greater than would be expected from their concentrations in muscle protein, indicating both synthesis in and net release from myocytes. Glutamine has two essential functions: (1) it is the preferred substrate for oxidative phosphorylation in the gut, and (2) ammonium ions from glutamine are used in the kidney to buffer metabolic acids.

Glutamine makes up a large part of the “buffer pool” of amino acids. This nonessential amino acid makes up 5% to 6% of the total body protein, and 60% of the total intracellular free amino acid pool<sup>25</sup> (the eight essential amino acids together make up only 8.4 % of the intracellular pool). Body proteins are not intended to be a long-term energy source. They are structural components, and their loss interferes with a broad spectrum of body functions (eg, locomotion, immunological competence). The level of intracellular glutamine falls rapidly with stress, starvation, and after surgery or trauma, as glutamine is transported to the gut and converted

to alanine to be fed into the TCA cycle in the liver.<sup>4,26,27</sup> The extent of the fall in glutamine levels seen with sepsis parallels the severity of the sepsis. Intracellular concentrations of other amino acids—leucine, isoleucine, valine, alanine, phenylalanine, and tyrosine—rise in stress, trauma, and sepsis, reflecting the catabolism present in the muscle. As they are used to fuel the metabolic engines, levels fall. As the branched-chain amino acid levels decline in sepsis or after severe trauma, the level of aromatic amino acids rises, and the ratio between the two shifts.<sup>4</sup>

Protein synthesis continues even as proteins are catabolized. New cells are built; antibodies, coagulation factors, cytokines, and so forth are elaborated: the shift is from maintenance of general structural elements to defense and wound healing. Probably even more than the neurohormonal controls, the inflammatory mediators are responsible for the degree of hypermetabolic response. When more than 20% of the lean body mass has been lost—generally after 7 to 10 days without nutri-

tional support—insufficient substrate remains to support synthetic function. After 14 days, the wound will be catabolized and is likely to dehiscence. What is left is used as fuel, with decreasing efficiency, until the patient dies.<sup>14,15</sup> Lean body mass cannot be regained so long as the inflammatory mediators are present, although loss of nitrogen can be countered with aggressive feeding. Feeding with a formula high in branched-chain amino acids—leucine, isoleucine, and valine—may ameliorate the protein loss to a greater degree than with standard amino acid formulas. These are preferentially oxidized by muscle, providing nitrogen and energy for skeletal muscle synthetic processes, as well as carbon skeletons for glucose-requiring tissues. Indeed, in the face of insulin resistance and lipase dysfunction, branched-chain amino acids may be the single best source of fuel for a hypercatabolic patient with organ dysfunction.<sup>4,28,29</sup>

As the structural proteins redistribute to areas of increased metabolic need (ie, the visceral organs, macrophages, and wounds) to support acute-phase protein synthesis, nonacute-phase protein synthesis (albumin and transferrin) declines. Hepatic cells release mediators such as nitric oxide, IL-6, and granulocyte-macrophage colony stimulating factor,<sup>11,13,15,30</sup> which maintain the release of inflammatory mediators from the Kupffer cells in an autoamplifying cascade. The effects can persist for days after the initial stress stimulus has been removed, driving the hypermetabolic response. Tissue repair does not begin until late in the flow phase, during the *adaptive* phase, when the metabolic processes organize and regularize. This is the phase when nutritional support is the most effective for rebuilding structural proteins; the body is at last able to respond to exogenous nutrition by increasing cell mass rather than by merely minimizing losses.

### Energy Requirements of Patients With Injuries or Infections

All stress states increase the metabolic requirements of the patient to some degree, which can be estimated by a rule of thumb (Table 23-2). A simple, uncomplicated surgery will increase energy requirements by 5% to 10% over the REE. Multiple trauma or sepsis increases requirements by 30% to 55%; a mechanically ventilated patient with sepsis or trauma has energy requirements 50% to 75% over REE. As a comparison, while doing manual labor, a normal person has energy requirements approximately 100% to 400% above REE. For example, if

**TABLE 23-2**

### PREDICTION OF CALORIC REQUIREMENTS IN STRESSED PATIENTS\*

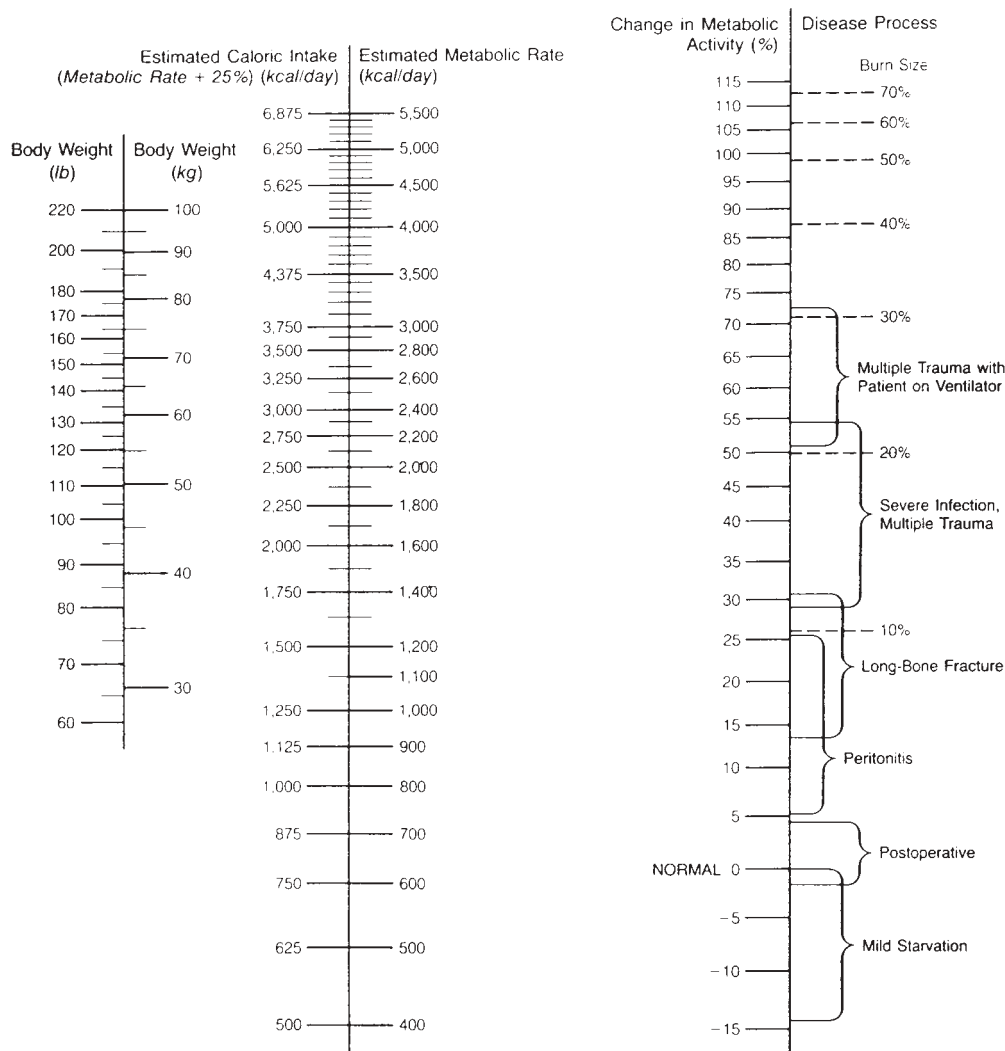
Patient Status	Correction Factor
Confined to bed	1.2 • REE
Ambulatory	1.3 • REE
Fever	(1.0 + 0.13 per °C) • REE
Peritonitis	1.2–1.37 • REE
Soft-tissue trauma	1.14–1.37 • REE
Multiple fractures	1.2–1.37 • REE
Sepsis	1.4–1.8 • REE
Burns (as % TBSA)	
0–20	1–1.5 • REE
10–40	1.5–1.85 • REE
40–100	1.5–2.05 • REE

\*Based on alterations in their metabolic rate  
 REE: resting energy expenditure; TBSA: total body surface area  
 Data source: Zimmerman JE. Nutritional support in the ICU. Lecture presented at Update in Critical Care—1993; April 1993; Washington, DC.

basal metabolism equals 1 kcal/kg/h, and if intense manual labor requires 5 kcal/kg/h (400% above normal), but this level of activity persists for only one fourth or one third of the day, then the manual laborer's energy requirements are approximately 100% higher than normal.

Oxygen consumption rises to match the increase in REE. Normal resting  $\text{VO}_2$  averages 100 to 125 mL/min/m<sup>2</sup>; consumption in a severely stressed patient may be greater than 170 mL/min/m<sup>2</sup> (in general, the higher the consumption can be raised—by altering the available partial pressure of oxygen, available hemoglobin, and cardiac output—the greater the chance for survival). Failure to alter  $\text{DO}_2$  and thereby successfully raise  $\text{VO}_2$  generally ends with a poor outcome.<sup>31</sup>

Energy requirements can be estimated for individual patients in a number of ways; unfortunately, many of the techniques do not lend themselves to battlefield application. Nutritional assessment by intake and weight history is valuable but difficult to obtain in the field. Indirect calorimetry is a moderately useful tool but requires special equipment, a stringent metabolic steady state during measurement, and will only give a “snapshot”—the require-



**Fig. 23-9.** This nomogram provides estimates of the caloric intake required for weight maintenance in patients with various disease processes. If the point that represents the patient's body weight on the scale at left is connected by a straight line to the point that represents the patient's disease process on the scale at right, then estimates for the patient's caloric requirement and metabolic rate can be read off the left and right sides of the middle scale, respectively. This nomogram should be used only for patients from 15 to 45 years of age whose height is normal. Reprinted with permission from Wilmore DW. *Metabolic Management of the Critically Ill*. New York: Plenum Press; 1977: 36.

ments at the time of measurement. Linear-regression formulas frequently overestimate energy requirements. Any of these may be used, so long as the shortcomings of each are borne in mind. Probably the best method of estimating nutritional state and energy requirements, whether in the field or at a fourth- or fifth-echelon hospital, is by a combination of the physical exam and tables that define REE

or BMR based on a combination of body weight and disease process (Figure 23-9). Other specialized tests for nutritional assessment are discussed below.

Medical officers must keep in mind that *REE will change with feeding*. A casualty with a burn to less than 10% of his body surface area will have an increase in REE of 6% to 7% if unfed. Feeding will increase this by a factor of 5; overfeeding will result

in an even greater increase. It requires energy to process fuel and building material. This is known as the specific dynamic effect. A mixed-fuel diet (carbohydrate and fat) will be less costly in terms of energy than an all-carbohydrate or an all-fat diet, and the energy expended to process enteral feeding is significantly less than that used to process parenteral nutrition.

The RQ changes with injury or sepsis. In the stressed state, the RQ is initially between 0.75 and 0.85, reflecting the mixed oxidation of carbohydrates, fats, and proteins in aerobic glycolysis and the TCA cycle. Lipolysis increases, as does release of lactate and pyruvate from muscle tissues, wound tissue, and macrophages and monocytes. The ratio of lactate to pyruvate remains normal, and the redox potential of the mitochondria is unchanged. As SIRS develops, the mitochondria increase their capacity to oxidize the two-carbon fragments being fed to them, and the RQ rises slightly. As organs become less functional, the RQ continues to rise, indicating a net lipogenesis, often aided by over-feeding total calories or carbohydrate.

### *Oxygen Consumption and Oxygen Delivery*

Both oxygen consumption and delivery increase with sepsis or injury, modulated by the elevation of catecholamines. Should sepsis/SIRS progress to shock, both oxygen consumption and REE fall sequentially.<sup>15,21</sup> This progressive decrement in the metabolic response reflects both the maldistribution of blood flow and the impairment of oxygen extraction that are characteristic of the state, as well as an enzymatic failure at the mitochondrial level that inhibits the TCA cycle. The rise of endotoxin levels matches the fall in metabolic rate. As oxygen delivery falls further, an oxygen debt is incurred and lactate accumulates, shifting the ratio of lactate to pyruvate, with a resultant metabolic acidosis.<sup>31</sup> Reversal of the shock state restores the hypermetabolism, driven by catecholamines and inflammatory mediators, but only restoration of adequate oxygen delivery will reverse the oxygen debt and the lactic acidosis.

### *Patterns of Response*

The pattern of response to stress—injury or infection—is standard regardless of the inciting insult, presumably because of a survival advantage to the pattern. The response involves the liver, skeletal muscle, gut, kidneys, and heart, and the wound or

focus of inflammation. The neuroendocrine system and the cytokine-mediator system act interdependently to bring about the characteristic changes, with the neuroendocrine stress response amplified many times by cytokine mediators, and vice versa. Norepinephrine increases endotoxin-induced TNF production, while TNF pushes ACTH and growth hormone production and alters thyroxine conversion, and glucocorticoids feed back to decrease transcription and posttranslational processing of TNF and IL-1.<sup>11,13</sup> The focus of the inflammatory response acts as a physiological arteriovenous shunt, increasing cardiovascular work and restructuring oxygen delivery. It is often a site of tremendous metabolic activity, with killing of bacteria, removal of dead bacteria and necrotic material, and wound repair continuously going on. The focus may be relatively hypoxic and depend on glycolysis for energy, with production of lactate and heat. Lactate and catabolized proteins are transported to the liver, where lactate, glutamine, and alanine are converted to glucose, which is returned to the focus of inflammation. Creatinine, creatine, potassium, and magnesium are all released. The ammonia produced by the catabolism of amino acids helps to neutralize acid loads, which must be excreted by the kidney.<sup>13</sup> Skeletal muscle and the mucosa and smooth muscle cells of the gut are also catabolized for fuel and amino acids. The gut loses its normal immunological function soon after injury, and after that, the ability to mechanically block bacteria and bacterial products from the bloodstream. Stimuli from intestinal bacteria now add to the inflammatory burden. This catabolism cannot be stopped by feeding, but exogenous amino acids can be utilized for both fuel and protein synthesis. (For further discussion of this process, see Chapter 24, The Syndromes of Systemic Inflammatory Response and Multiple Organ Dysfunction).

Should the inflammatory stimulus be removed at this time (by antibiotic treatment, removal of necrotic tissue, wound healing, etc), metabolism enters an *adaptive* phase, where output from the paraventricular nuclei of the hypothalamus decreases, sympathetic activity follows, cortisol and glucose levels fall, and the ratio of insulin to glucagon becomes more appropriate, although still less than normal. Fluids are mobilized, the urinary urea nitrogen decreases and ketones are spilled into the urine. The trend is toward a positive nitrogen balance, although the metabolic rate is still high. Caloric intake may need to be 1.5- to 2-fold higher than the REE to stop protein catabolism, even at this point. The metabolism gradually becomes anabolic.

If the inflammatory stimulus is excessive or prolonged or both, the neuroendocrine and cytokine responses to injury gradually erode the metabolic and immunological reserves. The transition to organ dysfunction comes about from a combination of microcirculatory hypoxia, mediator-induced injury, and toxin-induced injury to cells. Four classic phases have been identified: shock, resuscitation, persistent hypermetabolism (ie, SIRS), and organ dysfunction.<sup>15</sup> Shock and resuscitation affect primarily the microcirculation and the endothelial cells; the success or failure of the initial therapy sets the course for subsequent events. Four to six days after injury or infection, systemic inflammation and altered organ function are seen. Oxygen consumption increases. Oxygen delivery must match for the patient to survive, so cardiac output and minute ventilation follow the rise in oxygen consumption. The RQ is now between 0.78 and 0.82, and the proportion of calories from glucose and fat has dropped. This hypermetabolic pattern will peak in 3 to 4 days, and if the inciting stimulus—infection, persistent perfusion deficit (ie, inadequate resuscitation), local inflammation, or necrotic tissue—is corrected, it should resolve in 7 to 10 days. A portion of these patients, particularly those with prolonged SIRS with shock, will develop a hypermetabolic state that will persist for 14 to 21 days, even if the cause is corrected. If the inciting stimulus remains, the condition will progress to organ dysfunction.

The transition from hypermetabolism to multiple organ dysfunction syndrome (MODS) is usually due to a persistent, often unrecognized, perfusion deficit; a new or resistant focus of infection; or a persistent focus of inflammation. The actual death of a certain mass of cells is probably not the explanation for progressive organ dysfunction; rather, an increasing dysfunction of cellular subsystems to a certain critical point is the likely mechanism.<sup>12,15</sup> Microbial toxins directly inhibit intracellular glycolytic enzymes and intracellular hepatic protein synthesis; mediators such as TNF and IL-1 inhibit lipoprotein lipase, cytochrome P450, and albumin and thyroglobulin production; and products of metabolism in one region (eg, arachidonic acid metabolites) adversely alter metabolism in others. Hydrogen ion shuttles, electron transport systems, and gating proteins are all parts of the clockwork mechanism that enters a state of metabolic dysregulation.

Oxygen consumption becomes flow dependent as the ability to extract oxygen decreases and lactate

production rises. A state of subclinical flow-dependent (inadequate) oxygen consumption may be present in SIRS even without shock, or in the adult respiratory distress syndrome, or pancreatitis, leading to MODS.

If refeeding has not begun by 7 to 10 days, then metabolic failure based on loss of a critical amount of body mass becomes a factor. As the breakdown and redistribution of lean body mass continues and approaches 20%, acute-phase protein synthesis begins to fail. The combination of (a) the loss of structural protein and (b) dysfunction of the remaining systems due to continuing catabolism will in itself cause organ dysfunction, and will also greatly amplify toxin- and mediator-induced organ failure. The transition from a hypermetabolic state to MODS is a significant prognostic event, raising the probability of death from 25% to 40% to 40% to 60% in the early stages of organ dysfunction,<sup>15</sup> to 90% to 100% in the later stages.<sup>15,32</sup> Wound healing and immune function suffer early in organ dysfunction, but impairments of the kidney and liver have the greatest impact on the deranged metabolism. Metabolic requirements are especially increased in uremia. Potassium, phosphates, and magnesium all rise; pH falls; and the patient becomes both volume and protein intolerant. Naturally, hypermetabolism accelerates these processes. Hepatic failure means that the liver no longer efficiently deaminates and transaminates amino acids. Branched-chain amino acids are still used, leading to an imbalance in the ratio between branched-chain and aromatic amino acids. False neurotransmitters are generated, leading to encephalopathy. Effects on lipid metabolism vary, with some patients able to metabolize large amounts of exogenous lipid and others developing severe hypertriglyceridemia (Zieve's syndrome) and, occasionally, pancreatitis.

Treatment of the metabolic derangements—with early, aggressive feeding; correction of flow-dependent oxygen consumption (or maximizing oxygen consumption where it cannot be corrected); and improving perfusion of all organ beds, as measured by tissue pH (ideally) or serum lactate (practically)—assure that morbidity and mortality are markedly reduced. The goal is to overcome the catabolic state, or, where this is impossible, to allow (a) protein synthesis to continue in the face of catabolism and (b) the cellular mechanisms to repair themselves and correct the hypermetabolic state. Enteral feeding, in particular, restores the mucosa of the gut and alters translocation of bacteria and bacterial products.

## NUTRITIONAL SUPPORT

In general, it is easier to feed a malnourished patient—with the proviso that we carefully observe for hypophosphatemia—than a hypermetabolic patient. The results are also more clearly beneficial in the former case. Some recommendations for nutritional support suggest that “nutritional support should be considered if the patient has been without nutrition for 5 to 7 days”<sup>27(p3)</sup> and that “deficits occur in critically ill patients after 7 to 10 days of starvation.”<sup>27(p3)</sup> However, “starvation rarely assists recovery from critical illness.”<sup>33</sup> Most intensive care specialists would begin support 24 to 48 hours after the ebb phase. Nutritional support should be formulated according to the type and severity of the injury or illness, the presence and degree of organ dysfunction, electrolyte abnormalities, and glucose tolerance. Energy requirements are primarily related to age, gender, body size, and activity. In hospitalized, physically intact patients, the REE is the major caloric expenditure (see Figure 23-9).

The magnitude of the increase in the REE in an injured or septic patient is proportional to the degree of injury and the amount of support given. The total energy expenditure (TEE) is the REE plus the thermic effect of food (TEF) and the energy expenditure of activity (EEA). The goal in feeding the patient is weight maintenance, corrected for fluid gains and losses. Generally, 1,800 to 2,200 kcal/d is required for this. Baseline protein requirements are 0.8 grams of protein (or 0.128 g of nitrogen) per kilogram of body weight per day, increasing with the degree of catabolism as established by the severity of trauma. The ratio of nitrogen to calories is roughly 1:150, but may be as low as 1:200 or as high as 1:100. The gut is the preferred route for providing nutritional support, but many times it cannot be used.

### Nutritional Assessment

Several methods are used to assess caloric needs. Indirect calorimetry is in common use and may be easily performed with only a metabolic cart and a trained operator. Unfortunately, it requires that the patient remain in a strict steady-state condition during the period of measurement (eg, no changes can be made in ventilator settings, the patient is not allowed to move). Caloric requirements are based on calculation of oxygen consumption using the Fick method:

$$V_{O_2} = (C_{aO_2} - C_{vO_2}) \cdot C.O.$$

$$V_{CO_2} = (C_{vCO_2} - C_{aCO_2}) \cdot C.O.$$

where  $V_{O_2}$  represents oxygen consumption per unit time,  $C_{aO_2}$  represents arterial oxygen contents,  $C_{vO_2}$  represents venous oxygen contents,  $C.O.$  represents cardiac output,  $V_{CO_2}$  represents carbon dioxide consumption per unit time,  $C_{aCO_2}$  represents arterial carbon dioxide contents, and  $C_{vCO_2}$  represents venous carbon dioxide contents.

When calculated by gas exchange in indirect calorimetry, these become:

$$V_{O_2} = (V_I \cdot F_{IO_2}) - (V_E \cdot F_{EO_2})$$

$$V_{CO_2} = V_E \cdot F_{ECO_2}$$

where  $V_I$  represents the inspired volume per unit time,  $F_{IO_2}$  represents the fraction of inspired oxygen,  $V_E$  represents the expired volume per unit time,  $F_{EO_2}$  represents the fraction of expired oxygen,  $V_{CO_2}$  represents carbon dioxide consumption per unit time, and  $F_{ECO_2}$  represents the fraction of expired carbon dioxide.

The required caloric input can be written as follows<sup>34</sup>:

$$REE \text{ (in kcal/min)} = 3.581 \text{ (kcal/L)} \cdot$$

$$V_{O_2} \text{ in L/min} + 1.448 \text{ (kcal/L)} \cdot$$

$$V_{CO_2} \text{ in L/min} - 1.773 \text{ (kcal/g)} \cdot Nu \text{ in g/min}$$

where  $Nu$  represents nitrogen excreted in the urine.

Even small fluctuations in  $F_{IO_2}$  or  $V_{O_2}$  can alter the value for oxygen consumption. If properly measured, oxygen consumption is quite accurate over the period of measurement, but it is difficult to extrapolate to a 24-hour period in an unstable patient or a patient with varying levels of activity.

Linear-regression-derived “standard” equations generally overestimate caloric needs but may be useful under field conditions. The Harris-Benedict equation,<sup>35</sup> the one most commonly used at military teaching hospitals, uses separate formulas for men:

$$REE \text{ (kcal/d)} = 66.47 + (13.75$$

$$\cdot \text{kg body wt}) + (5.0 \cdot \text{height in centimeters})$$

$$- (6.76 \cdot \text{age in years})$$

and women:

$$REE \text{ (kcal/d)} = 65.51 + (9.56$$

$$\cdot \text{kg body wt}) + (1.85 \cdot \text{height in centimeters})$$

$$- (4.68 \cdot \text{age in years})$$

Probably the simplest, and often the most accurate, method for field use is a combination of standard tables based on body surface area and gender, and a physical examination of the patient. (An even quicker rough estimate: at rest, men consume roughly 25 kcal/kg/d; women, 20 kcal/kg/d.) All caloric estimates are for *nonprotein* calories.

The severity of the trauma or degree of stress increases the requirement for calories. Most critically ill patients require 25 to 35 kcal/kg/d. Patients with severe burns and trauma may require 35 to 45 kcal/kg/d, as may those patients who were severely calorie- and protein-depleted prior to injury. Patients on ventilators—at least those whose ventilation is adequately controlled—have a generally lower requirement, often less than 25 kcal/kg/d (30% of caloric input may be required for ventilation in a nonintubated, critically ill patient).

Protein requirements are initially determined by energy requirements, degree of malnutrition, and severity of injury, then adjusted by following the amounts of urinary urea nitrogen. Generally, the urinary urea nitrogen plus unmeasured nitrogen in the stool (approximately 3 g/d) are taken to be the daily protein requirement. Protein replacement can be guided somewhat more closely by calculating the catabolic index (Exhibit 23-2); the goal is to obtain a low number (< 0 is ideal).<sup>36</sup>

The goals of nutritional therapy are commonsense goals:

- to restore nitrogen balance;
- to provide the appropriate amount of fuel to maintain lean body mass;
- to provide appropriate vitamins, minerals, and trace elements; and
- to avoid overfeeding with any nutrient, but particularly to avoid overfeeding calories.

Excessive calories are converted to fat, particularly in the liver; this shifts the RQ to much greater than 1.0, increasing oxygen consumption and minute ventilation requirements markedly. Caloric overfeeding also depletes potassium and stimulates the release of catecholamines and the formation of lactate, while failing to suppress gluconeogenesis or to alter catabolic or synthetic rates. Overfeeding enterally can result in increased bacterial growth, gas production, and bowel distention.

In general, the sicker the patient, the poorer the accuracy of any of the means of estimating the metabolic rate. Remember also that before any benefits are derived, feeding imposes its own metabolic demands on the patient: increasing oxygen consumption, carbon dioxide production, and ventilatory drive, as well as increasing the workload of the cardiovascular system. A number of empirical correction factors have evolved to improve our ability to estimate calorie and protein requirements of the severely ill. Energy requirements increase 10% to 20% with fever; 30% to 50% with the perioperative state, sepsis, multiple trauma, head injury, or acute renal failure; and 50% to 100% with severe burns or seizures. Energy requirements *decrease* with paralysis, mechanical ventilation, hypotension, and unstressed malnutrition (see Figure 23-9).

As a general guideline, a critically ill patient will consume 25 to 35 kcal/kg/d; this is often useful as a starting point for nutritional replacement. Protein requirements are somewhat simpler to estimate. The nitrogen to calorie ratio should be roughly 1:150, although with severe trauma this may rise to 1:100 (1 g nitrogen is equivalent to 6.25 g protein). In ongoing protein catabolism with a rising blood urea nitrogen (BUN) and increasing ratio of BUN to creatinine, increased calories may ameliorate catabolism to some degree, and a nitrogen-to-calorie ratio of 1:200 may be more appropriate. A greater caloric intake will also be necessary to maintain a positive nitrogen balance at a lower level of protein intake. In general, protein requirements may be estimated by severity of stress.

Acute renal failure, hepatic failure, and MODS all restrict the body's ability to meet its protein

### EXHIBIT 23-2

#### CATABOLIC INDEX

$$\text{Catabolic Index} = \frac{24\text{-h urinary urea nitrogen (UUN) excretion} - (0.5 \cdot \text{dietary nitrogen intake} + 3 \text{ g})}{\text{Calories}}$$

- < 0 No stress
- 0–5 Moderate stress
- > 5 Severe stress

The catabolic index makes two important assumptions:

1. obligatory UUN excretion is 3 g/d, and
2. 50% of ingested protein is utilized.

Data source: Bistrian BR. A simple technique to estimate the severity of stress. *Surg Gynecol Obstet.* 1979;5:54–61.



requirements. Bear in mind that *catabolism* is not sensitive to exogenous amino acids, but *synthesis* is. Protein feeding will not reverse catabolism but will increase the synthetic rate until it catches the catabolic rate and restores the nitrogen balance.

What nutrients are essential in formulating a nutritional support plan? The standard total parenteral nutrition (TPN) formula used at Walter Reed Army Medical Center, Washington, D. C., includes carbohydrate sufficient to provide 50% to 70% of the estimated caloric need (3.4 kcal/g); lipid to provide a minimum of 10% of calories (9 kcal/g) and to prevent fatty acid deficiency (essential fatty acids, chiefly linoleic acid, must make up 1%–2% of total calories, roughly 2–4 g/d); essential amino acids; electrolytes; vitamins; and trace elements (Figure 23-10).

### Parenteral Nutrition

The parenteral route is not the best way to provide nutritional support but is often the only route available when delay would compromise the patient. Standard TPN uses hypertonic glucose—25% or 50%—as a primary source of calories, with a 10% lipid solution to provide additional calories and essential fatty acids. The carbohydrate is oxidized directly, with an RQ of 1.0, while the exogenous lipid is generally added to the fat stores and mobilized as needed to be processed into fatty acids and glycerol. A combination of the two sources provides essential fatty acids, avoids hyperglycemia, stimulates insulin production, and decreases carbon dioxide production. A 6.9% to 10% amino acid solution is added, depending on the formulation, and the resulting mixture diluted to a tonicity of 1,900 to 2,000 mOsm/L. As this solution is administered, via a central line in the superior or inferior vena cava, it is rapidly diluted to a nearly isotonic osmolality. The solution provides 0.85 to 1.1 kcal/mL, and 2 to 2.5 L/d will generally provide adequate protein and calories for any degree of stress.

Standard amino acid formulations have 19% to 25% branched-chain amino acids in a balanced mix with other amino acids. Because catabolism of protein in muscle is the primary source of the branched-chain amino acids used by the liver for gluconeogenesis (branched-chain amino acid aminotransferases are primarily found in skeletal muscle), and leucine, in particular, seems to have anticatabolic properties (a dose-dependent ability to decrease catabolism and possibly increase syn-

thesis of muscle proteins as well as improving the synthetic efficiency of the liver), many intensive care specialists recommend using an amino acid formula that is higher in branched-chain amino acids. These modified amino acid formulations contain roughly 45% branched-chain amino acids. While nitrogen balance, and possibly immunocompetence, are improved, a clear improvement in outcome has yet to be shown.<sup>4</sup>

### Replacement Minerals

Minerals must be added to the TPN solution, both to replace those lost during hypercatabolism and owing to the osmotic load of feeding. Magnesium, calcium, potassium, and phosphorus are all used in increased amounts during hypermetabolism. Rather large amounts of magnesium ( $\geq 30$  mEq/d), potassium ( $\geq 100$  mEq/d), and phosphorus (as phosphate, 20–30 mmol/d) are often required. Injury and carbohydrate loads both increase the loss of potassium, as does the fall in plasma magnesium seen after trauma or even elective surgery. Cell membranes become “leaky” after trauma or sepsis, and the intracellular concentration of sodium rises while potassium dips. When the patient improves, extracellular potassium loss accentuates because anabolism drives the uptake of potassium. Hypokalemia can easily result, especially if the patient is diuresing by this time. Seventy to one hundred milliequivalents of a potassium salt is required each day—more if the patient is either hypercatabolic or actively diuresing. Sodium is generally less problematic. One-half to two-thirds normal saline (75–100 mEq/L) is generally adequate to keep plasma sodium in the 135 to 145 mEq/L range. Patients who have received a large sodium load during resuscitation or surgery may more appropriately be given one-third normal saline (50 mEq/L) as a maintenance dose to avert hypernatremia. Sodium input should also be reduced in patients who are actively diuresing, because more free water than solute is lost and these patients can easily become hypernatremic. If frequent adjustments to the sodium or potassium content of the TPN are necessary, it is more practical to establish a lower, fixed amount of each cation for the TPN and to administer additional salt as short-run piggyback intravenous infusions.

Phosphorus is a vital electrolyte, and costly in terms of lessons learned. Feeding the survivors of concentration camps after World War II resulted in an unexpectedly high number of deaths.<sup>37</sup> It took a

MEDICAL RECORD—SUPPLEMENTAL MEDICAL DATA		
For Use of this form, see AR 40-66; the proponent agency is the Office of The Surgeon General.		
<b>REPORT TITLE</b>	<b>OTSG APPROVED (Date)</b>	
ADULT TOTAL PARENTERAL NUTRITION (TPN) & PERIPHERAL PARENTERAL NUTRITION (PPN) ORDER FORM		

Wt: ____ kg/lb Ht: ____ cm/in Age: ____ yr Ward: ____	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%; text-align: center;">[ ]</th> <th style="width: 50%; text-align: center;">[ ]</th> </tr> <tr> <td style="text-align: center;">STANDARD CENTRAL</td> <td style="text-align: center;">STANDARD PERIPHERAL</td> </tr> <tr> <td style="font-size: x-small;">Very concentrated solution for the average patient with perioperative needs (has no free water).</td> <td style="font-size: x-small;">Limited time use via peripheral vein while NPO/advancing enteral nutrition or in perioperative status</td> </tr> <tr> <td style="text-align: center;">(AMOUNT/LITER)</td> <td style="text-align: center;">(AMOUNT/LITER)</td> </tr> </table>	[ ]	[ ]	STANDARD CENTRAL	STANDARD PERIPHERAL	Very concentrated solution for the average patient with perioperative needs (has no free water).	Limited time use via peripheral vein while NPO/advancing enteral nutrition or in perioperative status	(AMOUNT/LITER)	(AMOUNT/LITER)	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th colspan="3" style="text-align: center;">[ ]</th> </tr> <tr> <td colspan="3" style="text-align: center;">'INDIVIDUALIZED CENTRAL/PERIPHERAL'</td> </tr> <tr> <td colspan="3" style="font-size: x-small;">For patients not able to tolerate any of the standard formulations</td> </tr> <tr> <td colspan="3" style="text-align: center;">(Indicate Amount/Day)</td> </tr> <tr> <td style="width: 60%;">PROTEIN</td> <td colspan="2" style="text-align: center;">gm</td> </tr> <tr> <td>PROTEIN SOURCE</td> <td colspan="2"> <input type="checkbox"/> Travasol 10%  <input type="checkbox"/> FreAmine HBC 6.9%  <input type="checkbox"/> Hepatamine 8% <span style="float: right; font-size: x-small;">Suggested</span> </td> </tr> <tr> <td>DEXTROSE</td> <td style="text-align: center;">gm</td> <td style="text-align: center;">Initial</td> </tr> <tr> <td>FAT</td> <td style="text-align: center;">gm</td> <td style="text-align: center;">Amounts</td> </tr> <tr> <td>CALORIES</td> <td style="text-align: center;">cal</td> <td style="text-align: center;">per Day:</td> </tr> <tr> <td>Sodium chloride</td> <td style="text-align: center;">mEq</td> <td style="text-align: center;">(30 mEq)</td> </tr> <tr> <td>Sodium acetate</td> <td style="text-align: center;">mEq</td> <td style="text-align: center;">(70 mEq)</td> </tr> <tr> <td>Potassium chloride</td> <td style="text-align: center;">mEq</td> <td style="text-align: center;">(40 mEq)</td> </tr> <tr> <td>Potassium acetate</td> <td style="text-align: center;">mEq</td> <td style="text-align: center;">(0 mEq)</td> </tr> <tr> <td>Calcium gluconate</td> <td style="text-align: center;">mEq</td> <td style="text-align: center;">(9.6 mEq)</td> </tr> <tr> <td>Magnesium sulfate</td> <td style="text-align: center;">mEq</td> <td style="text-align: center;">(16 mEq)</td> </tr> <tr> <td>Sodium phosphate</td> <td style="text-align: center;">mM</td> <td style="text-align: center;">(0 mM)</td> </tr> <tr> <td>Potassium phosphate</td> <td style="text-align: center;">mM</td> <td style="text-align: center;">(24 mM)</td> </tr> <tr> <td colspan="3" style="text-align: center;">[ ] MINIMAL VOLUME OR [ ] LITERS/DAY</td> </tr> <tr> <td colspan="3">Give: [ ] CENTRALLY OR [ ] PERIPHERALLY</td> </tr> </table>	[ ]			'INDIVIDUALIZED CENTRAL/PERIPHERAL'			For patients not able to tolerate any of the standard formulations			(Indicate Amount/Day)			PROTEIN	gm		PROTEIN SOURCE	<input type="checkbox"/> Travasol 10% <input type="checkbox"/> FreAmine HBC 6.9% <input type="checkbox"/> Hepatamine 8% <span style="float: right; font-size: x-small;">Suggested</span>		DEXTROSE	gm	Initial	FAT	gm	Amounts	CALORIES	cal	per Day:	Sodium chloride	mEq	(30 mEq)	Sodium acetate	mEq	(70 mEq)	Potassium chloride	mEq	(40 mEq)	Potassium acetate	mEq	(0 mEq)	Calcium gluconate	mEq	(9.6 mEq)	Magnesium sulfate	mEq	(16 mEq)	Sodium phosphate	mM	(0 mM)	Potassium phosphate	mM	(24 mM)	[ ] MINIMAL VOLUME OR [ ] LITERS/DAY			Give: [ ] CENTRALLY OR [ ] PERIPHERALLY		
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\* Above standard solutions help expedite initiation of TPN/PPN.  
 \* Determine protein and calorie needs using guidelines page, select solution and indicate # liters which is closest to patient's needs.

\* Above option requires physician determine amounts and volume needed per day and route of administration.  
 \* All orders must reach 4th floor pharmacy by 1300 hours.

ADDITIVES/INSTRUCTIONS
<input type="checkbox"/> Multi-Vitamins 10 mL or ____ per day <input type="checkbox"/> Cimetidine 900 mg or ____ mg per day <input type="checkbox"/> Reg. Human Insulin ____ units per day <input type="checkbox"/> Multi-Trace-5 4 mL or ____ per day <input type="checkbox"/> Famotidine 40 mg or ____ mg per day <input type="checkbox"/> Other: _____ <input type="checkbox"/> Additional Zinc 2 mg or ____ mg per day <input type="checkbox"/> Other: _____ <input type="checkbox"/> Hydrocortisone 5 mg/L Peripheral Soln. <input type="checkbox"/> Other: _____

(Continues on reverse)

PREPARED BY (Signature & Title)	DEPARTMENT/SERVICE/CLINIC	DATE
PATIENT'S IDENTIFICATION (For typed or written entries give: Name—last, first, middle; grade; date; hospital or medical facility)		<input type="checkbox"/> HISTORY/PHYSICAL <input type="checkbox"/> FLOW CHART <input type="checkbox"/> OTHER EXAMINATION OR EVALUATION <input type="checkbox"/> OTHER (Specify) <input type="checkbox"/> DIAGNOSTIC STUDIES <input type="checkbox"/> TREATMENT

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WRAMC OVERPRINT 257  
1 NOV 91

Fig. 23-10. The standard forms used when ordering parenteral nutrition at Walter Reed Army Medical Center, Washington, DC.

## ADULT PARENTERAL NUTRITION GUIDELINES

(Central vein total parenteral nutrition (TPN) and Peripheral vein parenteral nutrition (PPN))

## ADMINISTRATIVE INFORMATION

\*The Standard Formulas specified on the order sheet meet the requirements of the vast majority of patients who do not have significant renal/liver dysfunction.

\*Peripheral Solutions (PPN) are initiated full volume on the first day.

\*One-half of the amount of Central TPN ordered is normally sent on 1st day.

\*Pharmacy sends one 24 hr solution bag at 2000 hr.

\*Orders must be in the 4th Floor Pharmacy by 1300 hr.

\*The last TPN bag is used to discontinue TPN.

\*For assistance call Pharmacy (1421/22), or page: Nutrition Support Pharmacist (#1352), Dietitian (#580), Nurse (#272 or #697), or Physician (#1654).

## 1. DAILY NON-PROTEIN CALORIE (NPC) GUIDELINES:

Give: 25–35 Non-Protein Calories /kg of body weight.

Most patients: 25–30 Cal/kg (30% from Fat)

Hypermetabolic/hypercatabolic patients: 30–35 cal/kg (up to 50% from Fat)

1 gm Dextrose = 3.4 Cal

1 gm Fat = 9 Cal

Avoid giving &gt; 5 mg Dextrose/kg/min or &gt; 2 gm Fat/kg/day

gm Dextrose needed: \_\_\_\_\_ cal/kg X \_\_\_\_\_ kg X \_\_\_\_\_ ÷ 3.4 = \_\_\_\_\_  
   [desired total cal/kg]          [patient's wt.]          [% desired Dextrose cal]  [gm DEXTROSE/DAY]

GM Fat needed: \_\_\_\_\_ cal/kg X \_\_\_\_\_ kg X \_\_\_\_\_ % ÷ 9 = \_\_\_\_\_  
   [desired total cal/kg]          [patient's wt.]          [% desired Fat cal]  [gm FAT/DAY]

— OR USE —

Energy expenditure = The Harris Benedict Equation X Stress Factor X Activity Factor

MALES = [66 + (13.7 X \_\_\_wt in kg) + (5 X \_\_\_ht in cm) - (6.8 X \_\_\_age)] X (\_\_\_SF) X (\_\_\_AF)

FEMALES = [655 + (9.7 X \_\_\_wt in kg) + (1.8 X \_\_\_ht in cm) - (4.7 X \_\_\_age)] X (\_\_\_SF) X (\_\_\_AF)

Stress Factor (SF):

1.0 to 1.3 (maintenance)

Up to 1.5 (for weight gain)

Activity Factor (AF)

Non-ambulatory patient = 1.2

Ambulatory patient = 1.3

## PERIPHERAL NUTRITION SOLUTIONS:

Dextrose: 50–60 gm/Liter (Should provide not less than 150 gm/day)

Fat: 50–62% of cal from Fat      Osmolarity should be &lt; 800

5 mg of Hydrocortisone/Liter helps reduce phlebitis

Approximately osmolarity (mOsm) of a PPN solution = 50 X final % of protein + 100 X final % of dextrose + 150

## 2. DAILY PROTEIN GUIDELINES:

\_\_\_\_\_gm/kg X \_\_\_\_\_ kg = \_\_\_\_\_  
 Total Protein needs: [No. of gm/kg]      [patient's wt.]      [gm PROTEIN/DAY]

Most patients need: 1 – 1.4 gm/kg (via Central or Peripheral vein)

Hypermetabolic/hypercatabolic patients need: 1.5 – 2 gm/kg

Non-dialyzed renal failure patients need: 0.8 – 1 gm/kg

Dialyzed renal failure patients need: 1.0 – 1.5 gm/kg

## 3. AMINO ACID SOLUTIONS: per 100 mL

Have:	Protein	Essential Amino Acids	Branch Chain Amino Acids	mEq Sodium	mEq Chloride	mEq Acetate	mM Phosphate
Travasol 10%: A general purpose amino acid	10 gm	45.3%	19%	0	4	8.7	0
FreAmine HBC 6.9%: For severely compromised patients	6.1 gm	66.7%	45%	1	0	5.7	0
HepaTamine 8%: For hepatic encephalopathy patients	8 gm	55%	36%	1	0	6.2	1

WRAMC OVERPRINT 257  
1 NOV 91

Fig. 23-10 (continued)

## ADULT PARENTERAL NUTRITION GUIDELINES

### 4. DAILY MACRONUTRIENT GUIDELINES:

- Sodium: 60–180 mEq/day, or 40–60 mEq per liter of TPN
- Potassium 80–120 mEq/day, or 40–60 mEq per liter of TPN
- Chloride: 60–180 mEq/day, or 30–60 mEq per liter of TPN
- Magnesium: 12–30 mEq/day, or 8–12 mEq per liter of TPN (0.3–0.45 mEq/kg)
- Calcium: 5–15 mEq/day, or 2–5 mEq per liter of TPN (0.2–0.3 mEq/kg)
- Phosphorus: 10–15 mM /1,000 cal, or approximately: 8–12 mM per liter of TPN  
 Note: 3 mM of K Phosphate has 4.4 mEq K, and 3 mM of Na Phosphate has 4 mEq Na
- Acetate: Balances cations and anions, adjusts acid-base balance of the solution. One mEq of Acetate through intermediary metabolism equates to administration of 1 mEq of Bicarbonate

### 5. DAILY MICRONUTRIENT GUIDELINES:

Daily dose 4 mL, reduce by 50% in non-dialysis renal failure patients

METAL	IV DAILY ADULT DOSE	MULTI-TRACE-5 /4mL
Zinc:	*2.5–4.0 mg	4.0 mg
Copper:	0.5–1.5 mg	1.6 mg
Manganese:	0.15–0.8 mg	0.4 mg
Chromium:	10.0–15.0 mcg	16.0 mcg
Selenium:	20.0–60.0 mcg	80.0 mcg

- \* An additional 2 mg per day is suggested for highly catabolic states
- \* Significant G.I. fluid loss requires an additional 12 mg Zinc/L of TPN

### 6. DAILY FLUID GUIDELINES:

Normal TPN patient requires approximately 1 mL per cal

### 7. DAILY ADULT MULTIPLE VITAMINS:

- Provide a minimum of 10 mL/day
- 10 mg of Vitamin K should be given intramuscularly q Monday for patients not receiving anticoagulants.

### 8. INSULIN IN ADULT PARENTERAL NUTRITION:

If adding insulin to nutrition soln., add a max of 50% of previous days total insulin usage

#### Suggested Insulin Sliding Scale:

- Finger Stick: Insulin Dose (q 6 hr)
- 150–249 mg% 2 Units Reg. Human Insulin
- 250–300 mg% 4 Units Reg. Human Insulin
- 301–350 mg% 6 Units Reg. Human Insulin
- 351–400 mg% 8 Units Reg. Human Insulin
- > 401 mg% draw STAT Serum Glucose and NOTIFY PHYSICIAN

### 9. NUTRITIONAL STATUS INDICATORS:

Degree of malnutrition:	Mild	Moderate	Severe	Notes:
Albumin (mg/dL)	3.0–3.5	2.1–3.0	< 2.1	half-life 18 days, affected by hydration status, blood loss, etc
Transferin (mg/dL)	150–200	100–150	< 100	half-life 8 days, affected by iron deficiency, chronic infection
Prealbumin (mg/dL)	Males: 19–39 mg/dL and Females: 19–30 mg/dL			half-life 1.9 days, indicator of catabolism, synthesis, and liver function. Obtain a baseline value before initiating TPN/PPN
Steady state nitrogen balance = [nitrogen in (gm protein ÷ 6.25)] – [24 hr Urinary Urea Nitrogen (UUN) in gm ÷ 4 gm]				

Fig. 23-10 (end)

while to realize that these patients were already phosphorus depleted, and had adjusted to a low-calorie, low-protein diet. Feeding with a high-calorie, high-protein diet consumed what phosphate they had left: ATP levels fell; 2,3-diphosphoglycerate levels fell; red blood cells could no longer unload oxygen; glucose-dependent organs could no longer effectively uptake glucose; and the patients died. Thirty years later, phosphate depletion was rediscovered when critically ill, catabolic patients were placed on TPN before the vital role of phosphorus was appreciated.<sup>38,39</sup>

Increased amounts of phosphorus are lost in the urine after trauma and sepsis, and even after routine surgery. Levels decrease further with early postoperative feeding, as glucose enters cells as glucose-6-phosphate, and as ATP levels fall in hypercatabolism. Phosphorus is the major intracellular anion; the normal intracellular concentration of phosphorus is 75 mEq/L. The plasma concentration is far less, 1.0 to 1.5 mEq/L, or 2.3 to 4.5 mg/dL (or 1–1.4 mmol/L; there is considerable lack of consistency in reporting results with this anion).

An extracellular phosphorus level of less than 1.0 to 1.2 mg/dL will cause respiratory weakness and usually cardiac arrest when it reaches 0.8 µg. Intravascular hemolysis, white blood cell and platelet dysfunction, myocardial dysfunction, and central nervous system dysfunction (including ataxia, seizures, and coma) all result from phosphorus depletion. Unfortunately, the serum phosphate levels do not accurately reflect intracellular depletion and are not a perfect guide for replacement. In addition, the phosphorus content of lipid solutions, or of phosphate in lipid solutions, may not be bioavailable, and the replacement therefore is less than predicted.

The phosphorus content of salts (sodium or potassium) is expressed in millimoles: 15 mmol of potassium phosphate provides 15 mmol of phosphate. The cations in the salt are, however, expressed as milliequivalents: 15 mmol of potassium contains 22 mEq of potassium. The fact that the cation and phosphate have different valences must be borne in mind when replacing phosphorus. Generally, 15 to 30 mmol of the salt per day mixed with the TPN provides adequate maintenance phosphorus. Sodium or potassium phosphate may be given as a piggyback intravenous infusion, at a rate of 15 to 30 mmol over 2 to 4 hours. Infusion rates more rapid than this may cause intravenous precipitation of calcium phosphate and hypocalcemia, and, if potassium phosphate is used, hyperkalemia.

### Trace Elements

Trace elements are the catalysts and cofactors that drive the cellular machinery; defects in these impair protein synthesis and cellular energetics. More than nine elements are considered essential, but deficiencies in only five are likely to present problems in the intensive care setting (see Figure 23-10). Little is known of the changes that levels of these undergo in metabolic stress due to trauma or sepsis.

Iron is one trace element that is generally not replaced.<sup>27</sup> Inflammation, fever, and intravascular endotoxin are associated with a fall in serum iron levels. Lactoferrin and transferrin both bind iron when release of inflammatory mediators occurs, activating granulocytes. This binding of iron is essential for normal immune function, at least partly because the body makes iron unavailable to invading bacteria.<sup>40</sup> Peritoneal or retroperitoneal blood, intravascular hemolysis, and other conditions that make hemoglobin available to bacteria are all associated with an increased incidence of sepsis.

More than 200 enzymes essential to metabolic function depend on the availability of zinc. Carbohydrate, lipid, protein, and nucleic acid metabolism all depend on an adequate level of zinc, although “adequate” may be difficult to define in the critically ill. Inadequate amounts of tissue and plasma zinc can impair normal wound healing, platelet aggregation, neutrophil chemotaxis, and transformation of lymphocytes. Obvious signs of deficiency (eg, poor appetite, malabsorption with diarrhea, mental depression) are not uncommon in the critically ill, and not specific. The scaly, hyperpigmented dermatitis may be a late finding and may be misdiagnosed. Normal oral zinc intake is 10 to 20 mg/d, of which 20% to 30% is absorbed. Normal losses are 0.5 mg/d in urine, at least 0.5 mg/d in perspiration, and 2 to 3 mg/d in the gastrointestinal tract. Loss of zinc accelerates in bowel disorders, as absorption depends on intact enterocytes; malabsorption, inflammatory bowel disease, massive small-bowel resection, and pancreatitis all are associated with higher losses and decreased absorption. Alcohol abuse and chronic (or massive) diuretic use also accelerate zinc loss, and patients may present with already low or low-normal zinc stores. Patients with burns and acute renal failure also show increased zinc loss. Urinary zinc losses increase in critical illness, in association with the increased nitrogen losses, and IL-1 release causes a rapid decline in serum zinc as the liver takes up large amounts of the

mineral. Zinc accumulates in the liver as metallothionein, which is used to produce  $\alpha_2$ -macroglobulin, a protease inhibitor, as a check on the inflammatory reaction. The maintenance dose of zinc is 2 to 4 mg/d added to the TPN solution. In patients who are highly stressed or catabolic or both, however, an additional 2 mg/d should be added. There is some suggestion<sup>41</sup> that nitrogen balance may improve with zinc repletion.

Copper is another mineral that is depleted by bowel disorders. Short-bowel syndrome, jejunioileal bypass, malabsorption, enterocutaneous fistulae, and biliary obstruction all lose copper. An increased hepatic synthesis of ceruloplasmin in infection or inflammatory states, mediated by IL-1, acutely drops serum copper levels. Prolonged administration of zinc, because of the increase in metallothionein, also lowers copper levels. Copper is required for the normal function of cytochrome oxidase and superoxide dismutase, two vital enzyme systems in our patient population. Normal daily replacement dose is 0.5 to 1.5 mg/d.

Manganese is also required for a number of enzyme reactions, and is generally added to trace element formulas. This element should be avoided in biliary obstruction.

Chromium improves glucose tolerance in the critically ill and allows maximum enhancement of the initial reaction of insulin with its receptor. Adding chromium has little effect on glucose tolerance in patients who are not chromium deficient, but improves it in those who are. Chromium, like zinc, decreases in acute renal failure.

Selenium is required at the catalytic site of glutathione reductase. Its role is to help reduce organic hydroperoxides and lipoperoxides resulting from stress, sepsis, and ischemia. Selenium deficiency impairs immune function by (a) impairing the ability of granulocytes to kill bacteria and (b) damaging granulocytes by the excess accumulation of hydrogen peroxide, which damages the free radical-generating system in those cells. The functioning of T helper cells is also impaired by selenium deficiency. In the lungs, glutathione reductase scavenges oxygen-derived free radicals, offering some protection against damage from these radicals, particularly in patients who require high  $FIO_2$ . Selenium is excreted renally, and is also lost in burn and wound exudates, bowel fluids, and enterostomy fluids or enterocutaneous fistulae. The daily requirement is 20.0 to 60.0  $\mu$ g. Higher doses are generally required for higher stress states; however, ingestion of more than 1 mg/d may cause toxicity. Replacement of 50 to 200  $\mu$ g/d is considered adequate.

## Vitamins

Vitamins are small, organic molecules that are needed in tiny amounts for the normal function of metabolic processes. In general, the metabolic machinery needed for their synthesis is lacking in humans, and a prolonged, deficient intake of a given vitamin will ultimately result in a characteristic and sometimes dramatic clinical syndrome such as scurvy due to a lack of ascorbic acid (vitamin C) and beriberi due to a lack of thiamine (vitamin B<sub>1</sub>). Members of the U.S. military who are deployed to a combat zone are most unlikely to manifest evidence of vitamin deficiencies. However, some degree of vitamin intake is indicated. Without *any* intake, body stores of water-soluble vitamins (C and the B group) will disappear within 4 to 5 months.<sup>42</sup> Fortunately, data from the Ranger Training Study indicate that consumption of the U.S. Army's meals ready to eat (MREs) maintained normal serum levels of vitamins A, C, B<sub>1</sub>, B<sub>6</sub>, and B<sub>12</sub> over a 2-month period.<sup>8(Fig 20, Fig 21)</sup>

Nevertheless, the normal daily requirement of certain vitamins (eg, vitamins A, certain members of the B group, and especially C) may be increased by as much as 3- to 10-fold in the severely injured.<sup>43</sup> In addition, vitamin supplementations have subtle effects that may possibly be beneficial, such as the increased mobility of polymorphonuclear neutrophils in trauma patients brought about by high doses of either  $\alpha$ -tocopherol or vitamin C.<sup>44</sup> Recommended vitamin doses are given in Table 23-3.

Care should be taken to prevent overdosing, especially when administering fat-soluble vitamins such as A and D. Large doses—10-fold greater than the recommended dietary allowances—of the water-soluble vitamins such the B complex and C appear not to be associated with toxicity.

Both fat- and water-soluble vitamins must be regularly replaced during TPN. Commercial preparations are usually available, and one 10-mL ampule per day of a multivitamin mix added to the TPN will suffice. Vitamin K, 10  $\mu$ g/wk, should be given intravenously, but slowly.

## Delivery of Total Parenteral Nutrition

TPN should be thought of as "preenteral" feeding. It lacks the gut stimulation necessary to decrease bacterial translocation and preserve mucosal structure, but it is often the only way to feed a patient. TPN requires a *dedicated* line. This means that *nothing* else goes through that line, not even a little (including withdrawing blood at 3 AM). When

**TABLE 23-3**  
**VITAMIN REQUIREMENTS**

Vitamin	Units	RDA for Daily Oral Intake <sup>1</sup>	Daily, for the Moderately Injured	Daily, for the Severely Injured	Amount Provided by One Vitamin Pill	Daily Amount Provided by Standard IV Preparations <sup>2</sup>
Vitamin A (retinol)	IU	1,760 (females) 3,300 (males)	5,000	5,000	10,000	3,000 (retinal)
Vitamin D (ergocalciferol)	IU	200	400	400	400	200
Vitamin E (tocopherol)	mg TE	8–10	unknown	unknown	15	10 IU*
Vitamin K (phylloquinone)	μg	20–40 <sup>†</sup>	20	20	0	0 <sup>‡</sup>
Vitamin C (ascorbic acid)	mg	60	75	300	100	100
Thiamine (vitamin B <sub>1</sub> )	mg	1.0–1.5	2	10	10	3.0
Riboflavin (vitamin B <sub>2</sub> )	mg	1.2–1.7	2	10	10	3.6
Niacin	mg	13–19	20	100	100	40
Pyridoxine (vitamin B <sub>6</sub> )	mg	2.0–2.2	2	40	5	4
Pantothenic acid	mg	4–7 (adults)	18	40	20	15
Folic acid	mg	0.4	1.5	2.5	0	0.4
Vitamin B <sub>12</sub> (cobalamin)	μg	3.0	2	4	5	5
Biotin	μg	100–200 <sup>†</sup>	unknown	unknown	0	60

\*Equivalent to RDA

<sup>†</sup>Estimated to be safe and adequate dietary intakes

<sup>‡</sup>Must be supplemented in peripheral venous solutions

IU: international units; RDA: recommended dietary allowance; TE: α-tocopherol equivalent; IV: intravenous

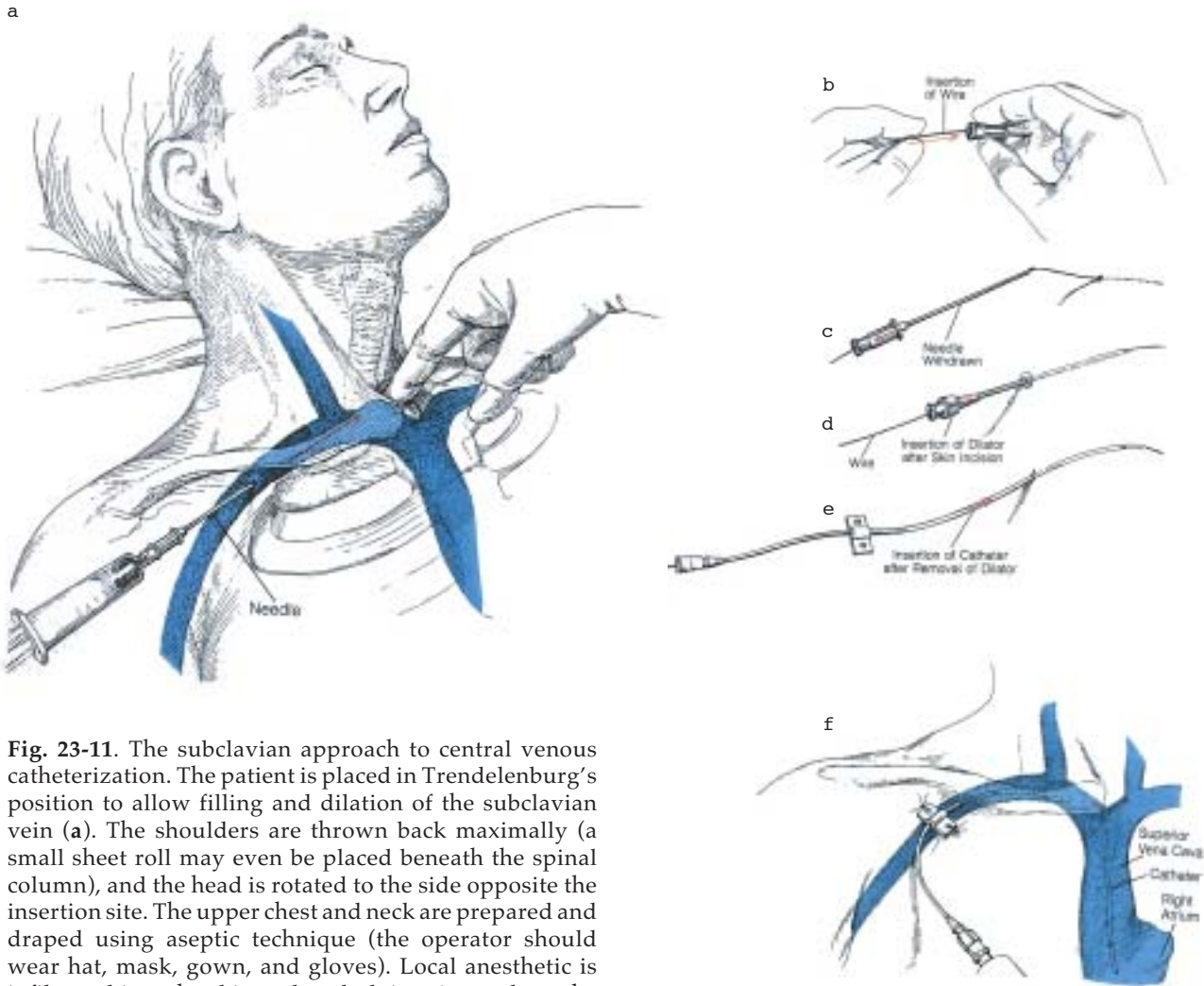
Sources for these values: (1) *Food and Nutrition Board. Recommended Dietary Allowances*. 9th ed. Washington, DC: National Academy of Sciences, National Academy Press; 1990. (2) Nutrition Advisory Group. Multivitamin preparations for parenteral use: A statement by the Nutrition Advisory Group, American Medical Association Department of Foods and Nutrition, 1975. *JPEN*. 1979;3:258.

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protocol is violated, lines become infected. Strict asepsis—cap, mask, gloves, and sterile gown—is required to insert and care for the intravenous line. Insertion is into the subclavian vein where possible, using a modified Seldinger technique (Figure 23-11).

A TPN line may also be inserted using the internal jugular vein or the femoral vein. These sites have slightly higher rates of infection, but as long as no gross soiling of the catheter is probable and strict aseptic technique is used, any difference in infection rate will be minimal. The antecubital fossa veins should be avoided for a number of reasons, among them a high rate of infection.

Single-lumen catheters may be used but are often impractical in the intensive care unit. Most intensive care specialists favor using a triple-lumen catheter, with one port dedicated to TPN. As another alternative, a dedicated infusion port—not the central venous pressure port and *under no circumstances* the pacing port of a Paceport pulmonary artery catheter (manufactured by Edwards / Baxter, Irvine, Calif.), which opens directly into the right ventricle—may be used, with the same protocol as for a single or multilumen central line. The position of the catheter *must* be verified by chest X-ray examination prior to infusion of TPN. Relative contra-



**Fig. 23-11.** The subclavian approach to central venous catheterization. The patient is placed in Trendelenburg’s position to allow filling and dilation of the subclavian vein (a). The shoulders are thrown back maximally (a small sheet roll may even be placed beneath the spinal column), and the head is rotated to the side opposite the insertion site. The upper chest and neck are prepared and draped using aseptic technique (the operator should wear hat, mask, gown, and gloves). Local anesthetic is infiltrated into the skin and underlying tissue along the inferior border of the clavicle at or slightly lateral to its midpoint. The needle found in a standard subclavian catheter insertion kit is attached to a syringe and advanced through the anesthetized area parallel to and beneath the clavicle, but over the first rib. The tip of the needle is aimed at a fingertip pressed firmly into the suprasternal notch. With the needle shaft parallel to the frontal plane of the patient (ie, parallel to the bed), the needle will enter the subclavian vein after advancing about 1.5 to 2.0 in. beneath the skin. Slight negative pressure applied to the syringe will allow the prompt inflow of blood when the vein is entered. The needle is advanced a few millimeters after venous blood is obtained to ensure that the entire beveled tip is within the vein lumen.

As the patient performs the Valsalva maneuver to prevent air embolism, the syringe is removed and the guide wire inserted (b). The wire should advance into the venous system without resistance or pain to the patient. After at least one half of the wire has been advanced into the vein, the needle is removed over the guide wire (c). A small incision is made at the entrance site into the skin, and a dilator is passed over the wire and into the soft

tissue (d). In a well-muscled person, some resistance may be met; the fascia is best traversed by using a screwlike motion and firm, constant pressure on the dilator. As the dilator is advanced, the wire should always remain freely movable within the dilator’s lumen. The dilator is then removed over the wire and replaced by the catheter, an approximate length of which is advanced over the wire into the patient (e). This length can be approximated before insertion by measuring the distance between the insertion site and the point on the sternum at the level of the second intercostal space. The wire is then removed, and the catheter lumen is aspirated free of all air and flushed with saline. The catheter is sutured into position (f), the exit site cleaned, and a dressing applied. Reprinted with permission from Rombeau JL, Rolandelli RH, Wilmore DW. Nutritional support. Chap 10. In: Part 2. Care in the ICU. In: Wilmore DW, Brennan MF, Harken AH, Holcroft JW, Meakins JM, eds. Vol 1. *Critical Care*. In: *Care of the Surgical Patient*. New York, NY: Scientific American, Inc; 1988: 10-15.



indications are those for insertion of any central line: high intrathoracic pressures, platelets less than 50,000, prolonged bleeding time, or elevated prothrombin time/partial thromboplastin time. Under these circumstances, the femoral vein or a surgical cutdown should be considered.

The question of how often to change intravenous TPN lines is controversial. At Walter Reed Army Medical Center, if proper technique is used, we find little difference in infection rates—whether the lines are changed every 3 days or every 5 days. Double-gloving or double-operator techniques give equally low colonization and infection rates regardless of whether the line change is performed over the wire or the catheter is removed to a new location. We use over-the-wire changes every 5 days and culture all catheter tips. We change to a new site only if a line tip is colonized (> 15 colonies). Line dressings are aseptically changed daily. While the practice of leaving lines in until the site is inflamed may have a low incidence of infection under normal peacetime conditions on hospital wards, during wartime, patient care in intensive care units will require regular changes of all central lines, with culture of all catheter tips whenever possible.

At a minimum, glucose and electrolytes must be monitored daily. In unstable or highly catabolic patients, electrolytes, and especially glucose, must be followed more closely, occasionally as often as every 3 hours. Protein, glucose, lipids (therefore total calories), and electrolytes must be reviewed and adjusted daily to fit the needs of the patient. If insulin or potassium requirements grow out of proportion to caloric load or normal daily losses, it is far better to use a baseline amount in the TPN and give additional amounts of hormone or electrolyte as a separate intravenous infusion, than it is to alter the TPN mixture continually.

### ***Complications of Total Parenteral Nutrition***

Complications of parenteral feeding may be grouped into three categories: (1) injury to contiguous anatomical structures during catheter insertion, (2) catheter-related sepsis, and (3) metabolic complications caused by parenteral nutrition. The likelihood of catheter-related complications such as pneumothorax and laceration of vessels in the root of the neck is, to a high degree, determined by the experience of the practitioner and meticulous attention to detail during catheter insertion. Expertise in inserting central lines is *the* essential prerequisite for a low incidence of iatrogenic injuries.

Measures to minimize sepsis arising from a parenteral line depend primarily on the adequacy of nursing care. An excerpt from the *Infection Control Policy and Procedure Guide* developed at Walter Reed Army Medical Center in 1991 is reprinted at the end of this chapter for the benefit of interested readers. The complexity of the control measures serves to remind us why parenteral nutrition is not always feasible in the field echelons of care.

A multitude of metabolic derangements occur during parenteral nutrition. For the sake of completeness, they are listed in Table 23-4, although many are not likely to occur in combat casualties receiving parenteral nutrition. It should be noted that the diagnosis of metabolic complications is somewhat dependent on the availability of an extensive array of laboratory tests, not all of which will be available in deployable medical facilities. Among the more common metabolic derangements are

- hyperglycemia due to too-rapid infusion of glucose, which, if not corrected, can give rise to hyperosmotic nonketotic coma; and
- hypoglycemia due to excessive endogenous or exogenous insulin.

### ***Modifications of Total Parenteral Nutrition***

Certain preexisting medical conditions such as renal, hepatic, and respiratory failure are known to complicate the application of parenteral nutrition. Experience has shown us that modifications in standard protocols for parenteral nutrition are indicated whenever these conditions are present.

***Modifications for Renal Failure.*** Acute renal failure prevents the excretion of the end products of nitrogen metabolism. Urea accumulates from both dietary proteins and endogenous protein catabolism, the measured BUN representing the balance between the increased urea production and the limited ability of the kidney to excrete nitrogenous wastes. Gastrointestinal bleeding and reabsorption of blood nitrogen can markedly elevate BUN in a short time, and this situation is not uncommon in the critically ill.

Protein intake can be decreased in renal failure by reducing exogenously provided amino acids and by providing amino acids of high biological value (Table 23-5). Protein should be reduced to 0.5 g/kg/d when the BUN reaches 60 to 80. Additional carbohydrate calories are supplied, to allow utilization of the elevated nitrogen pool as well as to take advantage of the relative protein sparing provided

**TABLE 23-4**  
**METABOLIC COMPLICATIONS OF TOTAL PARENTERAL NUTRITION**

Problems	Possible Causes	Corrective Measures
<b>Glucose</b>		
Hyperglycemia, glycosuria osmotic, diuresis, hyperosmolar nonketotic dehydration and coma	Excessive total dose or rate of infusion of glucose; inadequate endogenous insulin; increased glucocorticoids; sepsis	Reduce amount of glucose infused; increase insulin; administer a portion of calories as fat emulsion
Ketoacidosis in diabetes	Inadequate endogenous insulin response; inadequate exogenous insulin therapy	Give insulin; reduce glucose input
Postinfusion (rebound) hypoglycemia	Persistence of endogenous insulin production secondary to prolonged stimulation of islet cells by high-carbohydrate infusion	Administer 5%–10% glucose before infusion is discontinued
<b>Fat</b>		
Pyrogenic reaction	Fat emulsion, other solutions	Exclude other causes of fever
Altered coagulation	Hyperlipidemia	Restudy after fat has cleared bloodstream
Hypertriglyceridemia	Rapid infusion, decreased clearance	Decrease rate of infusion; allow clearance before blood tests
Impaired liver function test results	May be caused by fat emulsion or by an underlying disease process	Exclude other causes of hepatic dysfunction
Cyanosis	Altered pulmonary diffusion capacity	Discontinue fat infusion
Essential fatty acid deficiency	Inadequate essential fatty acid administration	Administer essential fatty acids in the form of one 500-mL bottle of fat emulsion every 2–3 d
<b>Amino Acids</b>		
Hyperchloremic metabolic acidosis	Excessive chloride and monohydrochloride content of crystalline amino acid solutions	Administer Na <sup>+</sup> and K <sup>+</sup> as acetate salts
Serum amino acid imbalance	Unphysiological amino acid profile of the nutrient solution; differential amino acid utilization with various disorders	Use experimental solutions if indicated
Hyperammonemia	Excessive ammonia in protein hydrolysate solutions; deficiency of arginine, ornithine, aspartic acid, or glutamic acid, or a combination of these deficiencies in amino acid solutions; primary hepatic disorder	Reduce amino acid intake
Prerenal azotemia	Excessive amino acid infusion with inadequate administration	Reduce amino acid intake; calorie increase glucose calories
<b>Calcium and Phosphorus</b>		
Hypophosphatemia	Inadequate calcium administration; reciprocal response to phosphorus repletion without simultaneous calcium infusion; hypoalbuminemia	Administer phosphorus ( $\geq 20$ mEq potassium dihydrogen phosphate/1,000 IV calories); evaluate antacid or calcium administration or both
Hypocalcemia	Inadequate calcium administration; reciprocal response to phosphorus repletion without simultaneous calcium infusion; hypoalbuminemia	Administer calcium
Hypercalcemia	Excessive calcium administration with or without high doses of albumin; excessive vitamin D administration	Decrease calcium or vitamin D
Vitamin D deficiency; hypervitaminosis D	Inadequate or excessive vitamin D	Alter vitamin D administration
<b>Miscellaneous</b>		
Hypokalemia	Potassium intake inadequate relative to increased requirements for protein anabolism; diuresis	Alter nutrient administration
Hyperkalemia	Excessive potassium administration, especially in metabolic acidosis; renal failure	Alter nutrient administration
Hypomagnesemia	Inadequate magnesium administration relative to increased requirements for protein anabolism and glucose metabolism; diuresis; cisplatin administration	Alter nutrient administration
Hypermagnesemia	Excessive magnesium administration; renal failure	Alter nutrient administration
Anemia	Iron deficiency; folic acid deficiency; vitamin B <sub>12</sub> deficiency; copper deficiency; other deficiencies	Alter nutrient administration
Bleeding	Vitamin K deficiency	Alter nutrient administration
Hypervitaminosis A	Excessive vitamin A administration	Alter nutrient administration
Elevations in SGOT, SGPT, and serum alkaline phosphatase	Enzyme induction secondary to amino acid imbalance or to excessive deposition of glycogen or fat, or both, in the liver	Reevaluate status of patient

SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase  
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**TABLE 23-5**  
**COMPOSITION OF AMINO ACID SOLUTIONS FOR PATIENTS WITH RENAL FAILURE**

	BUN 40–60 mg/dL		BUN 60–80 mg/dL		BUN 80–100 mg/dL	
	Moderate Calories	High Calories	Moderate Calories	High Calories	Moderate Calories	High Calories
<b>Volume</b>						
Amino acids (mL)	500 (mixture high in essential amino acids*)	500 (mixture high in essential amino acids*)	250 (mixture high in essential amino acids*)	250 (mixture high in essential amino acids*)	400 (essential amino acids only)	400 (essential amino acids only)
Dextrose (mL)	500 (50%)	500 (70%)	500 (50%)	500 (70%)	500 (50%)	500 (70%)
Total (mL)	1,000	1,000	750	750	900	900
<b>Contents</b>						
Amino acids (g)	32.5 (3.2%)	32.5 (3.2%)	16.3 (2.1%)	16.3 (2.1%)	20.8 (2.3%)	20.8 (2.3%)
Dextrose (g)	250 (25%)	350 (35%)	250 (33%)	350 (47%)	250 (28%)	350 (39%)
Total nitrogen (g)	5	5	2.5	2.5	3.3	3.3
Nonprotein kcal/g N	170	238	340	476	258	360
Total kcal	875	1,315	913	1,253	932	1,273
kcal/mL	0.9	1.3	1.2	1.7	1.0	1.4

\*70% essential amino acids and 30% nonessential amino acids

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by an increased carbohydrate load in the catabolic patient. Total volume is decreased, to 1 to 1.5 L/d in the anuric or significantly oliguric patient. Parenteral formulations must be modified to decrease phosphorus, magnesium, and, usually, potassium. Electrolyte supplementation must be recalculated daily, based on close monitoring of the patient's electrolytes, as carbohydrate loading and glucose intolerance will produce electrolyte shifts. Chloride intake should be reduced, and the acetate salts of sodium and potassium utilized to a greater extent, to counter the metabolic acidosis that accompanies uremia. Caloric input from fat is reduced, as fats do not have as great a protein-sparing effect as do carbohydrates, and fats contain 15 mmol of phosphate per liter. Trace elements should be decreased, or withheld for 1 to 2 weeks, unless the patient requires dialysis. If the BUN rises to the 80 to 100 range or above, replacing the standard amino acid mixture with a specialized renal failure formulation is justified. These renal failure-specific formulations generally have a higher proportion of essential amino acids.

Patients receiving hemodialysis regularly, or those on continuous arteriovenous hemofiltration (CAVH) or continuous arteriovenous hemodiafiltration (CAVH-D), will not need the severe restrictions in

volume, protein, and fat that patients with renal failure who are not undergoing dialysis receive. Volume is generally liberalized to 2 to 2.5 L/d in patients undergoing dialysis. In noncatabolic patients, protein requirements are 1.0 to 1.5 g/kg/d. Higher protein intake will be required in patients who remain catabolic or are on CAVH or CAVH-D. Caloric requirements also increase for hemodialysis patients and those on CAVH. Patients receiving CAVH-D, however, absorb some glucose from the countercurrent dialysate solution, and caloric input from TPN is often reduced slightly to compensate. In patients on hemodialysis or CAVH-D, folate and the B vitamins must be replaced in greater-than-normal amounts. Increased replacement should be considered in patients in the diuretic phase of acute tubular necrosis, as well.

This late phase of acute tubular necrosis is often marked by hypokalemia and hypomagnesemia, as these electrolytes "wash out" while sodium is, relatively, retained. Close monitoring of electrolytes and frequent adjustments to TPN and maintenance fluids are required during this period.

**Modifications for Hepatic Failure.** The nutritional requirements in severe hepatic dysfunction or hepatic failure depend primarily on the primary disease or trauma, rather than on the hepatic failure

per se. The only exception is acute, fulminant hepatitis, where metabolic demands on the liver must be severely restricted. Protein is often limited in hepatic encephalopathy, but has not been shown to alter outcome in severe hepatic dysfunction or multiorgan failure. Similarly, formulations specific for hepatic dysfunction or failure or both (ie, those high in branched-chain amino acids and low in aromatic amino acids) are often used to offset the elevated levels of aromatic amino acids found in hepatic dysfunction. Like protein limitation, these specific formulations have not effected significant improvements in outcome, although patients remain responsive longer and are somewhat easier to manage metabolically. A reasonable strategy is to provide 1.0 to 1.5 g/kg/d to patients with hepatic failure, until their ammonia levels rise to the point where the encephalopathy worsens, and then to switch to a formula low in aromatic amino acids and high in branched-chain amino acids.

Hepatic failure formulations generally contain no trace elements (see the hepatic amino acid section of Figure 23-10). These must be individually added, based on the needs of the particular patient. Nearly all critically ill patients will require the addition of zinc, but certain trace elements may actually be harmful. Copper, in particular, is best avoided in patients with hepatic failure. Folate and the B vitamins must be supplemented in these patients, as they must also in patients with renal failure.

**Modifications for Respiratory Failure.** Modification of TPN for patients with respiratory failure is somewhat easier. Glucose is oxidized to carbon dioxide and excreted via the lungs. Since the rate of gas exchange is altered by the administration of carbohydrate, changes in minute ventilation requirements with feeding should be noted. Patients with inadequate pulmonary reserve, or with a fixed rate of carbon dioxide excretion (ie, those on mechanical ventilation) are particularly susceptible, as they cannot vary the rate of gas exchange with feeding. While overfeeding calories should be avoided in all patients, those with respiratory insufficiency are particularly sensitive to carbohydrate calories. Fortunately, probably fewer than 10% of mechanically ventilated patients need modification of standard nutritional formulae. In those few who do, a 50:50 division of calories between carbohydrate and fat, with 1 g of protein per kilogram of body weight per day and a 150:1 ratio of calories to nitrogen, is usually adequate. If this is unsuccessful in allowing the patient to wean from the ventilator, a reduction in total calories to 60% to 70% of calculated requirements may be tried briefly.

### Peripheral Parenteral Nutrition

In patients who do not require complete nutritional support but who need a brief period of supplementation, peripheral parenteral nutrition (PPN) may be used. The most significant advantage of PPN is that a peripheral intravenous catheter—albeit a dedicated, single-purpose line—may be used instead of a central catheter. The feeding is necessarily of lower caloric density, generally 0.3 to 0.6 kcal/mL, but 1,200 to 2,300 kcal can be delivered daily.

The singular disadvantage of PPN is that it requires a large volume of fluid, often 2 to 4 L/d. The fluid has an osmolarity between 600 and 800 mOsm/L and should not be given peripherally if greater than 800 mOsm/L. Osmolarity can be approximated as follows:

$$(50 \cdot \% \text{ protein in final mix}) \\ + (100 \cdot \% \text{ glucose in final mix}) + 150$$

Intravenous catheter sites must be changed every 48 to 72 hours, both because of the risk of infection and because of the irritation that a hyperosmolar fluid causes in small veins. A small amount of hydrocortisone (5–10 µg/L) added to the infusion may help to reduce phlebitis. Fat emulsions are given separately, every day or every other day, and should provide 50% to 60% of the calories.

### Insulin

Insulin may be added to both TPN and PPN, generally to a maximum of 50% of the insulin used the previous day. This will never provide—and should not provide—complete insulin coverage. Some of the added insulin will be adsorbed onto the intravenous catheter tubing. Insulin will have to be supplemented by either an intravenous insulin infusion (often the easiest route of administration to use in critically ill patients) or by injecting intermittent boluses of insulin according to a sliding scale (see part 8 of Figure 23-10). An intravenous infusion can be prepared by adding 125 units of insulin to 250 mL of 5% dextrose in water, running 100 mL through the tubing to saturate the tubing and prevent further adsorption, and then beginning the infusion at 0.5 to 1.0 unit per hour. The insulin infusion can be titrated to a blood glucose between 180 and 220 µg/dL. Alternatively, a sliding scale may be based on glucose determinations from finger sticks, with laboratory confirmation every 4 hours. Insulin given according to a sliding scale must be administered subcutaneously because the half-life of regu-

lar insulin is too short when given intravenously, and hourly injections would be required.

Sliding-scale dosages of insulin often must be adjusted and often have to be imposed on top of a baseline insulin infusion, particularly in hypercatabolic patients who are refractory to the action of exogenous insulin.

### Enteral Nutrition

Enteral feeding has recently come to be accepted as the preferred route for providing nutritional support after trauma or during infection. While there are often reasons that the parenteral route must be used, enteral feeding is the more physiological, and provides several advantages. The gut is an active organ, deeply involved in the processing and regulation of a large number of nutrients, peptides, inflammatory mediators, hormones, and immunoglobulins. It is a major component of host defense against invading microorganisms, both as a mechanical barrier and as a major immune organ, especially during periods of stress. During starvation and the catabolic state induced by trauma or sepsis, the health of the gut relates directly to the health of the organism.

The cells of the intestinal mucosa, the enterocytes, are the most rapidly proliferating cells in the body. Feeding is the primary stimulus—both direct and indirect—for the growth of these cells. Feeding directly stimulates desquamation of the gut lining and enhanced renewal of the enterocytes, while enteroglucagon, gastrin, and other gut hormones indirectly stimulate cell renewal and growth. The gut, in turn, regulates circulating nutrients through mechanisms more complex than the simple digestion and absorption of feedings. Amino acids and glucose released from catabolized muscle are processed by the gut before they are transported to the liver. Glutamine, a “nonessential” amino acid that makes up a large percentage of the amino acids released from skeletal muscle during stress, is the principal oxidizable fuel for the small bowel. Half the glutamine extracted by the small bowel is oxidized to ammonia, which is, in turn, passed on to the liver for processing to new proteins, and which represents a good part of total body protein turnover. During the catabolism that follows trauma or infection, amino acid uptake by the gut accelerates. This acceleration is, to some extent, matched by the increased release of glutamine by catabolized skeletal muscle. During stress, however, consumption outstrips production, glutamine concentrations fall, and the small intestine finally runs short of fuel and substrate.

Mucosal epithelial cells of the colon use glutamine to a lesser extent. The large bowel depends on short-chain fatty acids—chiefly butyric, acetic, and propionic—and keto acids for fuels. The short-chain fatty acids are vital for sodium and water reabsorption by the colon and for cell growth and proliferation. Short-chain fatty acids are produced by bacterial fermentation of polysaccharides. The gut bacteria use less than 10% of the energy of the polysaccharides themselves. The rest of the energy goes to produce large amounts of short-chain fatty acids, with acetate, propionate, and butyrate comprising 83% of the product in a ratio of 1:0.3:0.25. These energy-carrying compounds can then either be absorbed (> 500 kcal/d in a fed gut) or excreted.

Release of inflammatory mediators, the use of antibiotics and histamine type 2 (H<sub>2</sub>) blocking agents, and inadequate provision of enteral calories will each alter the functions and mechanical integrity of the intestine. An intact mucosal barrier and intact immunological function reduce both transmigration of bacterial endotoxin and translocation of enteric bacteria. Endotoxin is normally absorbed across the cell barrier in a controlled fashion and presented to the Kupffer cells for detoxification. Production of stress hormones and the normal catabolic response to injury are modulated. Loss of cell mass because of starvation or increased catabolism diminishes this normal modulation. Continued loss of cell mass or the introduction of hypotension result in cell edema and loss of function, and physically disrupt the barrier by (a) decreasing antibody and mucous production and (b) allowing the tight junctions between cells to open as cells swell or necrose. Both endotoxin and bacteria can move across the barrier unchallenged. A vicious cycle is set in motion: with the decrease of cell mass, concomitant loss of mucosal villi decreases the bowel’s ability to absorb nutrients, which then decreases the production of immunologically and oncologically active proteins, which then further reduces the ability of the bowel—as well as the rest of the body—to function.

Most of the alterations in intestinal function with stress are not inevitable; they can be prevented by enteral feeding. Enteral feeding provides the best means of maintaining the integrity of the intestinal mucosa. Even so simple a measure as exposing the mucosa to a continuous normal saline infusion decreases villous atrophy.<sup>45</sup> Stimulation of enteroglucagon and gastrin by feeding has a trophic effect on stomach and intestinal mucosa. Feeding enterally decreases the elaboration of stress hormones

**TABLE 23-6**  
**ENTERAL FORMULAS AND ORAL SUPPLEMENTS USED AT**  
**WALTER REED ARMY MEDICAL CENTER\***

Product Name	Citrotein	Shakeup	Instant Breakfast (with 8 oz whole milk)	Sustacal	Ultracal	Nutren 1.5
<b>Features</b>	Clear liquid High protein Low-fat orange and punch flavors	High calorie Moderate protein Vanilla, chocolate, and strawberry flavors	High protein Vanilla, chocolate, and strawberry flavors	High protein Vanilla, chocolate, and strawberry flavors	14 g fiber/L; suitable for most tube-fed patients	Calorie-dense to limit volume Vanilla, chocolate, and unflavored
<b>Calories/mL</b>	0.66	1.4	1.06	1	1.06	1.5
<b>Protein g/L (% Cal)</b>	41 (25)	50 g	53 (22)	61 (24)	44 (17)	60 (16)
<b>Carbohydrate g/L (% Cal)</b>	120 (73)	226 g	126 (51)	140 (55)	123 (46)	170 (45)
<b>Fat g/L (% Cal)</b>	1.6 (2)	33 g	30 (27)	23 (21)	45 (37)	68 (39)
<b>Fat Source</b>	Soy oil	Milk fat	Milk fat	Soy oil	40% MCT; 60% soy oil	50% corn oil; 50% MCT oil
<b>Free Water (%)</b>	93		81	84	85	78
<b>mOsm/kg Water</b>	480		670–715	650	310	410–590
<b>Na mg/L<sup>†</sup></b>	710		950–1,200	940	930	750
<b>K mg/L<sup>‡</sup></b>	710		2,150–3,000	2,100	1,620	1,875
<b>P mg/L</b>	1,100		965	930	850	1,050
<b>Ca mg/L</b>	1,100		1,240	1,010	850	1,050
<b>Mg mg/L</b>	420		302	380	340	500
<b>Cal/100% Vit. RDA</b>	1,000		1,200	1,080	1,250	1,500
<b>Our Cost/L</b>	\$3.26		1 pkg = \$0.36	\$2.36	\$3.88	\$3.88
<b>Source</b>	Sandoz		Nestle	Mead Johnson	Mead Johnson	Clintec

\*All WRAMC enteral products contain vitamin K except Citrotein and Instant Breakfast

<sup>†</sup>1 mEq Na = 23 mg

<sup>‡</sup>1 mEq K = 39 mg

MCT: medium-chain triglycerides; LCT: long-chain triglycerides

and the catabolic response to trauma and infection. Glutamine and alanine both improve nitrogen balance. In studies with animals,<sup>27,46</sup> administration of glutamine alone has been shown to increase mucosal cellularity, improve nitrogen balance, and improve outcome; however, glutamine is unstable in solution and is not added to amino acid prepara-

tions used in TPN. Glutamine is in some enteral products, but often not in sufficient amount.<sup>46,47</sup>

**Enteral Formulations**

Enteral formulations may be balanced or disease specific. The latter are, generally speaking, not

Osmolite HN	Isocal	Nepro	Amin-Aid	Peptamen	Lipisorb	Vivonex T.E.N.
Suitable for most tube-fed patients Unflavored	Moderate in protein and electrolytes OK for > 3 years of age Unflavored	Renal. High calorie, high protein For oral or tube feeding	Renal. No electrolytes Essential amino acids	Semielemental Small and large peptides and amino acids Flavor packs available	For fat mal-absorption Whole protein Palatable	Elemental Amino acids Very low fat Usually unpalatable
1.06	1.06	2	2	1	1	1
44 (17)	34 (13)	70 (14)	19 (4)	40 (16)	35 (14)	38 (15)
141 (53)	133 (50)	216 (43)	366 (75)	141 (51)	117 (46)	206 (82)
37 (30)	44 (37)	96 (43)	46 (21)	39 (33)	48 (40)	3 (2.5)
50% MCT; 50% corn and soy oils	80% soy oil; 20% MCT oil	Safflower oil; Soy oil	Soy oil	70% MCT oil; 30% LCT oil	86% MCT; 14% LCT	Safflower oil
84	84	71	74	85	83	84
300	270	635	700	270	320	630
930	530	835	< 345	500	734	460
1,561	1,320	1,060	< 117	1,250	1,251	782
758	530	690	0	700	701	500
758	630	1,380	0	800	701	500
304	210	215	0	400	200	200
1,320	2,000	1,900	No vitamins	1,500	2,000	2,000
\$5.20	\$2.00	\$12.33	\$18.00	\$19.11	\$7.96	\$15.82
Ross	Mead Johnson	Ross	McGaw	Clintec	Mead Johnson	Sandoz

balanced, with nutrients often in their simplest form: amino acids rather than intact proteins of high biological value, or dipeptides and tripeptides; an emphasis on carbohydrate, often as simple sugars, for calories; and essential fatty acids or medium-chain triglycerides for fats. Often, these ingredients are not as easily absorbed or utilized as those in

balanced diets. The formulations are for a single, specific purpose. Renal formulations, for example, contain no nonessential amino acids, the intent being to promote the reuse of the nitrogen in urea. Hepatic formulations are often deficient in aromatic amino acids (phenylalanine, tyrosine, and tryptophan) and contain high concentrations of the

branched-chain amino acids, the opposite of the condition we normally find in the patient with hepatic failure.

Balanced formulations, on the other hand, usually contain carbohydrate and fat in a ratio of 70:30, and provide 1 to 2 kcal/mL. They are generally isotonic, although formulations with a higher proportion of their calories from carbohydrate have a higher osmolarity. Carbohydrates are usually provided as oligosaccharides and polysaccharides or maltodextrins, with fats in the form of medium-chain or long-chain triglycerides. Balanced formulations are often lactose free—as much as possible—since lactase is often markedly decreased in an injured or unused gut. The diarrhea (which is not infrequently seen when enteral feeding is started) more often is caused by bowel-wall edema from a low serum albumin, abnormal bowel flora from long-term antibiotic use, lactase deficiency, or any combination of the three, rather than a “hyper-tonic” formulation. Since there is some variation between formulations, often the substitution of one balanced formula for another will resolve a problem: feeding a formula higher in carbohydrate, often via the stomach, may help patients with steatorrhea; a formula with a higher percentage of calories from fat may help if diarrhea is secondary to a hyperosmolar (eg, a high-carbohydrate) product. Protein is usually provided at a fixed ratio of calories to nitrogen, often 150:1. The proteins most easily absorbed in a balanced formulation are the intact proteins of high biological value (eg, egg albumin) and dipeptides and tripeptides. Amino acids are *not* easily absorbed.

Electrolytes, vitamins, and trace elements are added to both balanced and disease-specific formulations; the amounts obviously vary with specific requirements in the latter. Formulations offer a wide range of caloric, protein, and electrolyte options (Table 23-6).

### **Delivery**

Before enteral feeding can be initiated, the patient’s readiness for such feeding must be assessed. Does the patient have a history of gastroesophageal reflux? Prior aspiration? Is the patient on medication that might promote reflux? The list is a long one and includes a broad range of drug types: theophylline, anticholinergics, calcium channel-blocking agents, catecholamines, vasodilators; in other words, any agent that decreases contraction of the lower esophageal sphincter. Is the patient conscious; if not, does the patient have an

intact gag reflex? Is the gut functional? Does the stomach empty normally, or does ileus or obstruction interfere? How recently has the patient had surgery involving the bowel? Unfortunately, bowel sounds and the passage of flatus are not specific indicators of gut health. If gastrointestinal output from all sources (nasogastric tube, ostomies, and rectum) exceeds 600 mL/24 h, then enteral feeding is less likely to be successful. Gastroparesis, bowel obstruction, ileus, pancreatitis, high-output enteric fistulae, and gastrointestinal bleeding are all relative contraindications to enteral alimentation. The decision to feed enterally or parenterally (or both) will be based on not only the presence of one or more of the above, but also on the extent to which they are present.

The serum albumin level and the extent of bowel edema also play major roles in how well enteral nutrients are absorbed by the bowel. A serum albumin level of less than 2.7 g/dL will often allow enough interstitial fluid to remain in the bowel wall to diminish uptake of enterally provided nutrients, particularly amino acids and hydrolyzed proteins, which may require functional enterocytes for absorption. Similarly, an edematous or dysfunctional colon cannot reabsorb sodium and water properly.

**Surgical Access.** Two surgical procedures can be used to gain access to enteral feeding. First, surgical insertion of a gastrostomy tube may be accomplished either during the initial operative procedure, or may be done percutaneously (via esophago-gastroscopy) a few days after surgery. Once the insertion wound has healed sufficiently—usually 24 hours<sup>48</sup>—gastric feeding can begin. Second, a feeding jejunostomy may be placed surgically, either as a separate procedure or through the gastrostomy tube, and jejunal feeding instituted. The gastrostomy tube may then be used to decompress the stomach, administer medication, and measure gastric residual volumes if gastroparesis is a postoperative problem.

**Access Via a Feeding Tube.** More commonly, however, nasogastric tubes are used. Nasogastric tubes are usually made of polyurethane and are relatively inflexible. They were designed for, and are commonly used for, gastric decompression, but are often used for feeding as a matter of convenience. While feeding into the stomach does have a theoretical advantage in neutralizing gastric pH, this advantage is offset by the wicklike action of the nasogastric tube, which prevents competent functioning of the lower esophageal sphincter and allows gastric contents to reflux into the esophagus. This problem is compounded by gastroparesis or



ileus, although use of a nasogastric tube will allow residual gastric volumes to be followed in these conditions.

One of the simplest and best-tolerated means of providing enteral nutrition is by use of a duodenal feeding tube, inserted either orally or nasally, and passed into the second portion of the duodenum. These tubes are made of polyurethane or silicone rubber and are thin walled and highly flexible. They come with a wire stylet to stiffen them enough to insert, and a combination of the stylet, the patient's position, gravity, and twisting and turning of the catheter as it is inserted will get the tube to the proper position in the duodenum. Duodenal feeding tubes are often designed to be self-passing, with a weighted tip, and once in the stomach and left to their own devices, will pass nicely into the duodenum, provided that the tube has not been taped onto the patient. Always leave some "play" in the tubing (a loop that will allow the feeding tube to traverse the pyloric sphincter). It is often helpful to place the patient with his right side down for several hours. Sometimes, increasing gastrointestinal peristalsis by using a cholinergic drug like Reglan (metoclopramide, manufactured by A. H. Robins, Richmond, Va.), will facilitate placement. However, the medical officer must ensure that the patient does not have a bowel obstruction before Reglan is administered.

**Tube Placement.** An easy method of tube placement, which seems to work most of the time, has been described.<sup>49</sup> After the feeding tube is passed to the stomach with the patient sitting, the head of the bed is lowered and the patient is placed on his right side. The feeding tube is then twisted in a corkscrew motion while it is advanced a distance sufficient to pass into the duodenum. Passage through the pyloric sphincter can often be felt. If resistance is encountered, the feeding tube, with a loop, should be taped to the patient. The feeding tube, now free to advance on its own, passes more often than not. Initial tube placement may be checked by auscultation; however, the position of the tube is always verified by X-ray examination before feedings are instituted.

### **Tolerance to Feeding**

Tolerance to feeding should be assessed by beginning the infusion at a low rate (eg, 30 mL/h) for the first 24 hours. The patient should be closely monitored for abdominal distention or cramping, and for the onset of nausea, vomiting, or diarrhea. Residual volumes may be assessed if a nasogastric

tube is used for feeding, or if a nasogastric tube was left in place when the feeding tube was placed. The relative position of both tubes is important in assessing residual volume. If the feeding tube has slipped back to the duodenal bulb or stomach, or if the nasogastric tube is at the pylorus, then large residual volumes may not accurately reflect the function of the stomach and the bowel.

### **Monitoring**

In general, enteral nutrition requires at least as careful monitoring as parenteral. Tubing must be changed daily, and formula at least every 8 hours, to prevent bacterial overgrowth. Intake and output must be followed as closely as they are in parenteral nutrition. Residual volumes should be checked every 4 hours, initially. The risk of aspiration is significant in enteral feeding; even the presence of two sphincters (pyloric and lower esophageal) between the feeding-tube outlet and the lungs does not completely remove the risk. The head of the bed should be elevated 30° during enteral alimentation, with feeding interrupted, if necessary, to allow for sleeping.

### **Diarrhea**

Diarrhea (passage of more than 300 g or 300 mL of liquid or semisoft stool per day) can develop in up to three fourths of critically ill patients who receive enteral alimentation. As stated before, this is usually due to atrophy of villi, bowel-wall edema, and the use of multiple antibiotics, with consequent disruption of the normal intestinal flora. Pseudomembranous colitis due to *Clostridium difficile* must always be considered. Therapeutic response to diarrhea includes replacement of lost fluid and electrolytes, decreasing the rate of feeding, changing to a different product, and adding Kaopectate (manufactured by Upjohn, Kalamazoo, Mich.; the active ingredients are kaolin and pectin) to the formula. Fifteen to 30 mL of Kaopectate administered every 2 to 6 hours will often slow diarrhea. Kaopectate binds bacterial toxins and is often useful in diarrhea due to bacterial overgrowth. It also apparently stimulates villous trophism (soluble fiber polysaccharides have a similar effect on mucosal growth and function, and have been shown<sup>50</sup> to improve recovery from inflammation). Remember to *flush the feeding tube* afterwards; frequent flushing ensures the tube's continued patency and reduces the need for replacement. Opiates should be avoided, as they may worsen or induce ileus and allow fur-

ther bacterial overgrowth. Water may be added if the patient has a free-water deficit (eg, large insensible losses, hypernatremia due to diuresis), but enteral formulae for diarrhea rarely require dilution, as most are isotonic. Decreasing the osmolarity to 150 mOsm may be tried, but if a decrease in rate and osmolarity and the addition of Kaopectate do not solve the problem, then fat and carbohydrate malabsorption should be assessed with stool fat, D-xylose, and finally breath hydrogen laboratory tests, looking for bacterial overgrowth. Stool specimens should be sent to the laboratory early to be tested for *Clostridium difficile* toxin; if the test is negative but diarrhea persists, then consider evaluation with a flexible sigmoidoscope.

### Maintaining the Feeding Tube

Clogging of feeding tubes can be minimized by flushing the tube with water after use (eg, after administering medication, when feeding bags are changed). Medications in pill form should never be crushed and given through a feeding tube. Pills and tablets should be dissolved in 15 to 30 mL of water, injected into the tube by Toomey syringe, and flushed. Should a clog develop, a small amount of a carbonated cola soft drink injected into the feeding tube may dissolve it.

Feeding tubes tend to migrate and should be adequately secured. They should be taped (always with a loop) to the patient's forehead or cheek; take care not to put pressure on the nares. The tubes may also be more firmly hobbled should their wandering become a problem.

### Assessment of Nutritional Repletion

The assessment and consequences of nutritional depletion are well described: a loss of 40% of total body weight is usually fatal; there are generally accepted "panic values" for electrolytes and micronutrients; and the value of nutritional support is widely accepted. Assessment of nutritional repletion is not so clear cut. The question of *how* to monitor nutritional repletion has been asked by a number of authorities: there is a difference between monitoring structural repletion versus monitoring cell function. Nutritional repletion alters the performance of cells before it restores mass, by altering membrane ion transport and by returning enzyme function to normal. Nuclear magnetic resonance studies using phosphorous 31 labeling have shown a fall in oxidative phosphorylation in malnutrition, implying a decrement in mitochondrial function.

Cell energetics return to a more normal function before protein synthesis restores cell mass but still require 2 to 4 weeks of nutritional repletion in a severely malnourished patient. Three fourths of the energy liberated by the hydrolysis of ATP is used to maintain ion gradients across cell membranes, even at the expense of protein synthesis, in a malnourished patient. Protein synthesis is a metabolically expensive cell function, requiring five molecules of ATP for each amino acid incorporated into a protein. It should come as no surprise that cells take care of their basic requirements first.<sup>51</sup>

As an index of nutritional repletion, serum albumin has a sensitivity of only about 10%. While the half-life of albumin in normal individuals is 18 days, it is much shorter in catabolic patients. Albumin levels fall before significant malnutrition occurs in patients who are starved, stressed, or both, because of ongoing catabolism of nonessential proteins. In the stressed patient, protein production is shifted to acute-phase proteins. Large-scale volume expansion, not uncommon in critically ill patients, also lowers albumin levels significantly. Generally, a level of 2.5 to 3.0 g/dL reflects a mild-to-moderate depletion of the albumin pool, 2.0 to 2.5 g/dL a moderate depletion, and less than 2.0 g/dL a severe depletion, but this assessment may not accurately reflect the patient's overall nutritional status. Albumin rises slowly following nutritional repletion, usually taking weeks to rise in patients receiving TPN. Any earlier rise may be artifactual and due to contraction of the extracellular water pool, rather than to an actual increase in albumin mass. Albumin may actually rise more rapidly with enteral feeding than with TPN, although bowel-wall edema may preclude this route until adequate oncotic pressure is established and tissue edema reduced. Because albumin is necessary to maintain intravascular oncotic pressure, supplementation may be accomplished by continuous infusion at 4, 8, or 12 mL/h to increase serum osmolarity and decrease bowel-wall edema in preparation for enteral feeding. Bolus supplementation of serum albumin is not effective in mobilizing fluid.

Transferrin is also a nonsensitive indicator of nutritional repletion, even though the half-life of transferrin (8 d) is shorter than that of albumin, and therefore turnover is faster. Transferrin is a necessary component of the white blood cell response to infection and inflammation. Levels tend to increase earlier than serum albumin levels with feeding, partly as a reflection of this function. Transferrin levels also increase with iron deficiency, as the protein is no longer bound. Levels between 100 and

150 mg/dL reflect a moderate depletion of the pool; less than 100 mg/dL, a severe depletion.

Thyroxine-binding prealbumin is more sensitive than either albumin or transferrin to nutritional repletion. It has a half-life of 1.9 days and is a fairly useful indicator of catabolism and protein synthesis. The fall in this protein in critical illness may be related to changes in thyroxine levels rather than to malnutrition, however, making clinical application difficult. Normal levels in men are between 19 and 39 mg/dL; in women, 19 and 30 mg/dL.

Similarly, retinol-binding protein is a more sensitive indicator of nutritional repletion than is either albumin or transferrin, but the use of this plasma protein as an indicator has limited utility outside academic medical centers.

Fibronectin levels provide a very sensitive barometer of nutritional depletion and repletion. Fibronectin is rapidly consumed during critical illness, with a corresponding fall in serum levels. Levels peak early with adequate repletion, but after 1 to 2 weeks become relatively useless in assessing nitrogen balance. Most other indices have problems as well.

The Creatinine-Height Index<sup>3</sup> overestimates muscle mass in critical illness, and is sensitive to renal dysfunction. Cutaneous reactivity and lym-

phocyte counts are nonsensitive and nonspecific indices of nutrition, as immune function is affected by multiple factors: infection, uremia, cirrhosis, hepatitis, steroids, burns, hemorrhage, trauma, general anesthesia, and others.

The urinary urea nitrogen test is extremely useful in assessing the catabolic rate, and therefore the physician's ability to balance protein breakdown with nutrition repletion. While it is a gross measure, the nitrogen balance is still the best indicator of the adequacy of repletion of protein. Adequacy of caloric repletion is best assessed by indirect calorimetry.

The problem of providing nutritional support to casualties in the theater of operations has recently been addressed.<sup>52</sup> At present, the limitations of deployed resources may not allow either enteral or parenteral forms of nutritional support; however, both forms should be available in fourth-echelon hospitals. Although parenteral nutrition is probably not possible in the third echelon during a major war, enteral nutrition—being much more feasible logistically—is certainly an acceptable alternative. For this reason, surgeons should be encouraged to insert feeding tubes during resuscitative surgery on all casualties who are likely to require nutritional support.

## SUMMARY

Metabolic interventions are important in the treatment of wounded casualties because the common perception of the soldier as a vigorous, muscular mesomorph obscures reality: combat casualties are frequently nutritionally depleted or even frankly malnourished. Unfortunately, however, the applicability of nutritional therapy for combat casualties is a function of the nature of the deployment. In short but intense conventional wars and in operations other than war, only limited medical assets will be deployed in the combat zone, and they will be used primarily for resuscitative surgery. Casualties who require nutritional support will probably be evacuated for the needed treatment to hospitals at the fourth echelon or in the continental United States. Ideally, however, nutritional support would begin prior to evacuation.

The primary constituents of ingested food—carbohydrates (hexoses, of which glucose is pre-eminent), fats (triglycerides), and proteins (amino acids)—are interconverted by the TCA cycle found within mitochondria. Metabolic intermediates are formed within the mitochondria, which store chemical energy in molecular bonds to be used in

a variety of essential, life-sustaining processes. Metabolic intermediates in excess of the body's immediate energy needs are converted into fatty acids for storage in fat cells, or into glucose, which is stored as glycogen in liver and muscle. Although at any given moment the metabolism of glucose is the major source of the body's energy-supplying intermediates, lipids are the major form of nutrient storage. Proteins can serve as storage deposits for amino acids; their primary role, however, is structural, and protein metabolism results in functional impairment. Interconversion of glucose, fatty acids, and amino acids is not perfect; although glucose can be converted into fat and certain amino acids can be converted into glucose, fatty acids are not easily converted into glucose. During uncomplicated starvation, when glucose is in short supply, free fatty acids (or ketone bodies formed from their partial metabolism) are used by most organs in place of glucose. Low circulating insulin levels are necessary for the metabolic adaptation to starvation.

When stress and physical exertion are superimposed on starvation, not only are overall metabolic

demands increased, but mobilization of fatty acids is also impeded by elevated levels of stress hormones such as catecholamines, cortisol, and glucagon. Hence, when physical stress occurs with starvation, there is an increased need for glucose, which (because of the lack of metabolic machinery allowing free conversion of fatty acids to glucose) can only be obtained through the process of gluconeogenesis: amino acids derived from the catabolism of body proteins are converted into glucose. The need for glucose and the associated accelerated catabolism of protein are even greater when a wound is present, because healing tissue is an obligate consumer of glucose. Protein catabolism is further accelerated when the wound is septic, owing to the formation of mediators of inflammation such as IL-1 and the eicosanoids. Thus, the combat casualty with severe wounds that have become septic is both hypermetabolic (ie, the REE is 30%–60% greater than normal) and hypercatabolic with a negative nitrogen balance (ie, more than 10 g of urea nitrogen is excreted via the urine per day). Paradoxically,

both hyperglycemia and hyperinsulinemia are frequently present, indicating that the hormonal milieu associated with injury and sepsis has induced a state of resistance to the normal biological effects of insulin.

Ideally, optimal metabolic management of the hypermetabolic and hypercatabolic combat casualty requires knowledge of both the REE and the nitrogen balance. Caloric intake can then be set at 30% to 40% of measured energy expenditure, and the amount of nitrogen at 1 g/150 kcal of caloric intake. Since the equipment for indirect calorimetry is not likely to be available in deployable hospitals, a more empirical approach will be necessary there (eg, giving 40 kcal/kg/d, with nitrogen being given in the ratio of 1 g/200 kcal. At least half the total caloric intake should be in the form of carbohydrates. The route of administration will depend on whether the gastrointestinal tract is functional. If it is, the enteral route is preferable since it is safer, cheaper, and, perhaps most importantly, it helps to preserve the integrity of the intestinal mucosa.

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## EXCERPT FROM WALTER REED ARMY MEDICAL CENTER INFECTION CONTROL POLICY AND PROCEDURE GUIDE

For the benefit of the interested reader, the following excerpt is reprinted from Roup BJ, ed. Lieutenant Colonel, Army Nurse; Chief, Infection Control Service, Department Of Nursing. *Walter Reed Army Medical Center Infection Control Policy and Procedure Guide*. 3rd ed. Washington, DC: Walter Reed Army Medical Center; November 1991; previous editions February 1987, June 1989.

### PERIPHERAL AND INTERMITTENT INTRAVENOUS THERAPY

#### I. GENERAL

This SOP establishes WRAMC policy for the insertion and maintenance of peripheral intravascular devices, fluids, delivery systems, and the procedure to be followed in the event of suspected infection.

#### II. SPECIFIC

##### A. IV Insertion

1. Equipment
  - a. IV solution
  - b. IV tubing set, primary
  - c. Steel needle or plastic catheter

(NOTE: Steel needles, eg, butterfly or scalp vein, are recommended over plastic catheters as they appear to cause less phlebitis. Plastic catheters should be used when a secure route for vascular access is imperative or when administered drugs may tissue damage if they infiltrate.)

- d. Iodophor or alcohol for skin prep
  - e. Tourniquet
  - f. Tape
  - g. IV stand
  - h. Waste container
  - i. Sterile dressing (2 x 2 gauze pad or semi-permeable plastic membrane)
  - j. Chux (blue pad)
  - k. Gloves
2. Procedure
    - a. Wash hands with antiseptic soap and water for at least 30 seconds.
    - b. Visually inspect IV container for cloudiness or particulate matter. Check glass bottles for cracks; squeeze plastic bags for air leaks. DO NOT USE IF STERILITY IS SUSPECT.
    - c. Connect tubing to solution container using aseptic technique. Glass bottles require vented tubing; plastic bags require non-vented tubing.

(NOTE: Use of extension tubing, especially 3-way stopcocks is discouraged. Frequent manipulation and open stopcocks provide microorganisms direct access to the blood stream. If 3-way stopcocks are used, the cap covering the unused port should be a Luer-Lok cap or taped in place.)

- d. Fill entire length of tubing with solution and close tubing clamp.
- e. Select venipuncture site in an upper extremity.

(NOTE: The risk of infection with lower extremity cannulation is extremely high. Cannulae inserted into lower extremities should be removed as soon as venous access in an upper extremity is established.)

- f. DO NOT SHAVE insertion site. Remove excess hair by clipping with scissors.
- g. Place Chux under extremity to protect bed linen.
- h. Apply tourniquet and palpate blood vessel. (A tourniquet that is too tight will not allow the vein to distend.)
- i. Cleanse site with prep solution, using friction from center to periphery in a 2" diameter spiral.
  - 1) PREFERRED PREP: Cleanse site with iodophor, eg, Betadine. Allow to dry. DO NOT remove with alcohol. The antimicrobial action depends in part on the continued release of free iodine.
  - 2) ALTERNATE PREP: Cleanse site with isopropyl alcohol for AT LEAST ONE MINUTE and allow to air dry. (Alcohol contact time is the kill factor.)

- j. After the venipuncture site has been prepped, DO NOT touch the skin with your finger unless wearing a sterile glove.
- k. Put on gloves.
- l. Holding the skin taut, insert the needle/catheter along-side the vein, bevel up, about ½ inch from the site of vein puncture. Carefully puncture the vein and thread the needle into it. Observe for blood return. If blood return is present, continue with procedure.

(NOTE: If no blood return is obtained, manipulate the needle carefully to gain entry into vein. If unsuccessful, withdraw the needle, obtain fresh needle, prep skin again, and make another attempt. DO NOT MAKE REPEATED ATTEMPTS USING THE SAME NEEDLE.)

- m. If using plastic catheter, withdraw the needle.

(NOTE: Once the catheter has been withdrawn, do not reinsert it into the catheter as it may sever the catheter and cause it to “float” through the circulatory system.)

- n. Connect filled tubing to needle/catheter hub, release tourniquet, open tubing clamp and adjust flow to appropriate rate of infusion.
- o. Secure needle/catheter with small piece of tape (chevron style). DO NOT place tape directly over venipuncture site.
- p. Apply sterile dressing. Two methods are acceptable:
  - 1) Apply dry, sterile 2 x 2 gauze pad. Secure with tape. Avoid bulky dressing.
  - 2) Apply semi-permeable transparent dressing following manufacturer’s guidelines.
- q. Anchor tubing securely to patient’s extremity.
- r. Record date, time of insertion, type of device and initials of person performing venipuncture on a piece of tape. Attach to IV dressing. Record same information in the clinical record.
- s. Label IV tubing with appropriate dated label (per Department of Nursing/Department of Nursing Administrative Policy guidelines) and record date, time and initials on the label.
- t. Instruct patient to report signs and symptoms of phlebitis, infection or infiltration (pain, burning, redness, swelling, numbness or fluid/blood seepage).
- u. Remove all excess/used supplies and equipment from the patient’s room. Dispose of needles and syringes into plastic sharps container; trash into the waste basket.

#### B. IV Maintenance

1. Inspect IV insertion sites for evidence of phlebitis, pain, infiltration, leakage or blockage at least daily and every time a new IV solution container is hung. If the patient has unexplained fever, pain, or tenderness at the site, the gauze dressing should be removed and the site visually inspected.
2. Change the IV tubing and dressing at the same time the IV site is rotated: EVERY 72 HOURS. Start the IV at another site BEFORE the old set is removed.

(NOTE: This procedure should be accomplished as one maneuver to reduce the amount of manipulation of the system.)

3. When the patient’s physician has determined that sites cannot be changed every 72 hours:
  - a. Meticulous site care should be performed every 72 hours; more often if indicated.
  - b. Document in the clinical records the reason(s) for not rotating the sites, and observations of the site.
4. 250 ml container should be used for “TKO” or “KVO” infusions.
5. Fluid containers must be clearly labeled with patient’s name, added medications, and time-stripped for easy monitoring of fluid volume infused.
6. Fluid container must be changed at least every 24 hours.

#### C. Site Care

1. Remove dressing down to, but not including, chevron tape.
2. Remove old iodophor with alcohol.
3. Cleanse site thoroughly with iodophor solution.

(NOTE: Alcohol may be used for iodophor-sensitive individuals.)

4. Allow to dry. DO NOT remove with alcohol.
5. Redress with sterile dressing.

(NOTE: Site care is to be performed when cannulae are left in longer than 72 hours or when dressing becomes wet or soiled.)



6. Record date of dressing change, date of insertion, type of device, and initials on piece of tape; attach to dressing. Record dressing change in the clinical record with observations of site appearance.

D. Administration of IV Piggyback Medications

1. All piggyback medications should be mixed in the pharmacy.
2. Connect the secondary (piggyback) tubing to the medication container using aseptic technique.
3. Attach secondary tubing to the primary tubing with a needleless connector. Ascertain that connection is secure.
4. Lower the primary infusion container to a level lower than the piggyback container, using the hook provided with the tubing.
5. Set flow rate for proper infusion period.

(NOTE: Infusion periods are listed on the label of all IV piggybacks prepared in the pharmacy.)

6. After infusion of the medication, clamp the secondary tubing, raise the primary container to its original height and leave the secondary tubing connected to the primary tubing.

(NOTE: Secondary tubing can be flushed by lowering the piggyback below the level of the primary bag, flush and drain back into primary tubing.)

7. When ready to administer the next dose, remove the empty bag and replace it with the new one. Fill secondary tubing by lowering the secondary container and opening the clamp on the secondary tubing. Close the clamp and proceed as in 4. and 5. above.
8. When administering more than one medication, and the medications are compatible, follow the procedure outlined in 7. above.
9. When administering incompatible medications, lower the secondary set WITH THE EMPTY MEDICATION CONTAINER ATTACHED and open the clamp on the secondary set. Fluid will flow through the tubing into the previously empty medication container and proceed with steps 4–6 above.

(NOTE: Piggyback tubing is changed every 72 hours, the same as primary tubing.)

E. Administration of Intermittent Infusions

1. Ascertain that the “Heparin Lock” has the appropriate needleless connector component attached.
2. Using a needleless connector component attached to a syringe containing sterile normal saline for injection, connect the syringe to the Heparin Lock and aspirate slightly. If blood return is noted, inject 2–3 cc of normal saline solution to assure patency of the device and to clear device of residual heparin.
3. Attach infusion to heparin lock using a needleless connector component.
4. Infuse medication as ordered.
5. At completion of the infusion, unhook the tubing from the heparin lock.
6. Using a needleless connector component attached to a syringe containing heparin solution, connect the syringe to the heparin lock and flush the lock.
7. Discard tubing. A new set of IV tubing will be used for each infusion.

F. IV Infusion Pumps

1. One piece administration sets are recommended. Follow the manufacturer’s guidelines for set-up and line flushing procedure.
2. IMPORTANT: Check under site dressing for swelling frequently. Use of a pump increases the risk of extensive infiltration if a needle or catheter becomes dislodged.
3. All surfaces of the pump must be thoroughly cleaned when soiled, and between patients, using a housekeeping disinfectant detergent or product recommended by the manufacturer.

G. If IV-Associated Sepsis Is Suspected

1. Culture any purulent drainage around catheter site prior to cleansing the skin.
2. Cleanse skin around catheter with antiseptic to remove skin organisms.
3. Clip off catheter tip with sterile scissors, dropping catheter into DRY, STERILE specimen cup. Request quantitative cultures of the tip. Send to laboratory IMMEDIATELY to prevent drying and death of organisms.

(NOTE: In addition to routine identification data, culture request should include type of specimen (catheter tip), site of catheter (R forearm), signs and symptoms.)

4. A blood culture should be drawn from the opposite arm after carefully prepping the venipuncture site with iodophor.
5. If IV solution contamination is suspected:
  - a. Cap end of IV tubing with a capped, sterile needle.
  - b. Send ENTIRE IV set-up and solution container to the laboratory for culture. DO NOT disconnect any part of the set-up.
  - c. Call Infection Control IMMEDIATELY (phone 782-4350/4351) to alert them of the problem.

(NOTE: The laboratory will NOT culture IV systems without coordination with Infection Control.)

6. Record observations and actions in the clinical record.
7. Complete WRAMC Form 1811, Quality Control and Risk Management Report, and submit through proper channels.

## RECOMMENDATIONS FOR CENTRAL INTRAVASCULAR LINE INSERTION

### I. GENERAL

A. Purpose: To provide guidelines to all personnel involved in performing or assisting with the insertion of a central intravascular catheter.

B. References:

1. Miller, S., Sampson, L.K., Soukup, S.M. AACN Procedure Manual for Critical Care, Philadelphia: W.B. Saunders Co., 1985, pp. 47–53.
2. Hospital Infections Program, Center for Infectious Diseases, CDC, Atlanta, Ga., 1985.
3. Nutrition Support Core Curriculum 2nd ed., C. Kennedy Caldwell, P. Guenter, eds., American Society for Parenteral and Enteral Nutrition, 1988.

### II. SPECIFIC

A. Equipment

- \*Caps
- \*Masks
- \*Sterile gown(s) for physician(s)
- \*\*Sterile gloves (appropriate size)
- \*Sterile drapes
- \*Acetone (10%)/alcohol (70%) swabsticks (2 packs of 3)
- \*Povidone/iodine scrub swabsticks (2 packs of 3)
- \*Alcohol (70%) swabsticks (2 packs of 3)
- \*Povidone/iodine solution swabsticks (2 packs of 3)
- \*1% Lidocaine
- \*4 x 4s
- \*2 x 2s
- \*4-0 silk suture on cutting needle
- \*22g needle (1)
- \*10 cc syringes (2)
- \*20g needle (1)
- \*25g needle (1)
- \*Scissors
- \*Hemostats
- Heparin Solution (100 units per cc)
- Catheter kit for insertion
- Tape
- Alcohol wipes

\*All items contained in Central Venous Insertion Tray

\*\*Size 7½ gloves in Central Venous Insertion Tray

Also need Central Venous Dressing Tray which contains:

- 2 prs sterile gloves (size 7½)
- Acetone (10%)/alcohol (70%) swabsticks (pack of 3)

Povidone/iodine scrub swabsticks (pack of 3)  
Alcohol (70%) swabsticks (pack of 3)  
Povidone/iodine solution swabsticks (pack of 3)  
Skin prep swabstick  
2 x 2 gauze  
Sterile cotton tip applicator  
Scissors  
Masks (2)  
Cap  
Elastoplast dressing

B. Procedure

1. Explain procedure to patient to promote understanding and minimize anxiety. Obtain written consent (Physician).
2. Organize and assemble supplies and equipment at bedside.
3. Wash hands; turn off faucet with paper towel.
4. Place patient in supine and Trendelenburg position of at least 15 degrees. Place a rolled towel between scapulae with head turned away from insertion site. This positioning promotes maximum filling and distention of the subclavian vein to the angle between the clavicle and the first rib. The increased pressure created in the upper thorax also decreases the possibility of air embolism.
5. Place a mask over patient's mouth and nose (and trach). If patient is unable to tolerate a mask, use a towel or drape as a barrier between patient's mouth/nose/trach and insertion site.
6. Don gown, cap, and mask to avoid contamination of site and equipment. Open and prepare insertion tray.
7. Don sterile gloves and begin preparation of skin for insertion. The area to be prepped should extend from above the clavicle to the nipple line and from the shoulder to just beyond the sternal notch. Cleanse with friction using a circular motion from center to periphery. The following order should be observed.
  - a. Start with the acetone/alcohol swabsticks to remove skin fats and oils which may harbor pathogens. It is also effective in removing old tape and glue from previous dressings.
  - b. Cleanse area with povidone/iodine SCRUB swabsticks using same friction and circular motion from center to periphery.
  - c. Remove povidone/iodine with alcohol swabsticks. The povidone/iodine scrub solution is now contaminated with organisms. If left on skin, it will cause irritation because it contains soap. Again, use a circular motion from center to periphery.
  - d. Paint area just prepped with povidone/iodine solution swabsticks. This provides a protective barrier against skin organisms.
8. Apply sterile drapes so that only area not covered is the prepped area.
9. Assist physician in donning mask, cap, sterile gown and sterile gloves.
10. Open catheter kit and drop in sterile tray or allow physician to remove contents.
11. Clean top of heparin flush solution with alcohol wipe and hold for physician to draw up sufficient solution to flush catheter prior to insertion.
12. Physician will insert catheter. Monitor patient during catheter insertion. Assist patient to remain immobile. Notify physician if breaks in aseptic technique are noted. Assist physician as necessary.
13. Catheter should be secured to skin by 4 separate sutures by the physician. This is necessary to minimize movement of the catheter and prevent accidental dislodgement. Line should be sutured in the vertical position. Avoid suturing line horizontally toward the shoulder because of extra stress on the sutures as the patient ambulates.
14. The area around the insertion site and sutures should be repped and an occlusive dressing applied using the following steps:
  - a. Open Central Venous Dressing Tray.
  - b. Don sterile gloves (and cap and mask if not already wearing them).
  - c. Using acetone/alcohol swabsticks remove all blood from around the insertion site and sutures. Blood left on the skin may provide medium for bacterial growth.
  - d. Reprep the skin by using povidone/iodine scrub swabsticks. Use a circular motion and start at the insertion site, then around the sutures.
  - e. Remove povidone/iodine scrub with the alcohol swabsticks starting at the insertion site using a circular motion.
  - f. Paint the area with povidone/iodine solution and blot dry with 2 x 2s. Use the cotton tip applicator to remove any extra solution from under the line.
  - g. Place folded 2 x 2 over the insertion site and line down to and including the sutures. This is to prevent the occlusive dressing from sticking to the line and sutures.

- h. Cut the Elastoplast to fit over the insertion site and sutures. Round all corners and be sure 2 x 2s are completely covered.
15. Remove mask from self and patient. Also remove rolled towel from patient's scapula. Apply skin prep around edge of Elastoplast and tape around the edges of the dressing.
16. Label the dressing with date, time and initials of person doing the dressing.
17. Remove all supplies and wash hands.
18. Ensure that a STAT portable chest X-ray is obtained before ANY infusion is started. The patient is to remain in bed until confirmation of line placement is obtained.
19. Chart the procedure, any problems encountered, patient's tolerance of the procedure, and verification of line placement.
20. Infusions may begin only after verification of line placement. If patient has a triple lumen catheter and is to receive TPN, do not infuse anything through the DISTAL port except TPN. The other two ports may be used to draw blood or infuse other solutions.

### III. RELATED CARE

- A. Assess and monitor the patient and IV site q2h for complications:
  1. Pneumothorax
  2. Hemothorax due to subclavian or innominate artery puncture
  3. Hematoma at the puncture site
  4. Myocardial perforation related to the catheter advancement
  5. Infection
  6. Phlebitis
  7. Thrombosis
  8. Air embolism
  9. Mediastinal fluid infusion (hydrothorax)
  10. Catheter shearing or embolism
  11. Brachial plexus injury during subclavian catheter placement
  12. Osteomyelitis related to subclavian insertion.
- B. Maintain catheter asepsis:
  1. Change central line dressing every 48–72 hours, or whenever the catheter is changed. If a fever occurs, obtain culture of site and blood cultures.
  2. If dressing becomes soiled, disrupted, or non-occlusive, it must be changed.
- C. The patient is to remain supine until line placement is confirmed. Reposition the patient following catheter insertion; elevate the head of the bed. Place the patient in the recumbent position when the IV tubing is disconnected from the catheter to minimize the risk of air embolus.
- D. Monitor the IV flow rate at frequent intervals; all TPN and IV solutions with medications must be infused via an infusion pump (IMED).
- E. Removal of catheter:
  1. The recommended duration of a central line is 72 to 96 hours; however, under certain circumstances, a patient's clinical condition may necessitate a central line remaining in a site for a longer period. This is acceptable if proper documentation by the physician is in the Doctor's Progress Note (SF 509) regarding the circumstances, clinical need and the condition of the central line site, and is accomplished on a daily basis.
  2. At the earliest sign of sepsis, the central line site should be changed in conjunction with other therapeutic measures.
  3. Procedure for removal of catheter when appropriate:
    - a. Apply non-sterile gloves. Remove dressing.
    - b. Remove the sutures, using a suture removal kit.
    - c. Have the patient take a deep breath and hold. Withdraw the catheter out and upward away from the skin.
    - d. Inspect the catheter to make sure it is intact.
    - e. Using a second sterile suture removal kit, culture the catheter tip if infection is suspected.
    - f. Apply pressure to the area to prevent bleeding.
    - g. Apply a sterile occlusive dressing.
    - h. Assess the patient and monitor for complications after catheter removal.

## RECOMMENDATIONS FOR CENTRAL VENOUS CATHETER DRESSING CHANGES

### I. GENERAL

- A. This procedure guideline applies to all personnel involved in performing or assisting with central venous catheter dressing changes and is the procedure used by the Nutrition Support Service, WRAMC.
- B. Frequent use of central lines for monitoring and IV administration of fluids, medications, and/or total parenteral nutrition (TPN) requires a standard and meticulous method of care to minimize the risk of contamination and sepsis. In support of the current literature and national standards, central line dressings will be changed every 24 to 72 hours (depending upon local protocols), whenever the catheter is changed, or when there is drainage and/or sign of infection at the site.

### II. SPECIFIC

#### A. Equipment

- 1 cap
- 2 masks
- 1 clean gown
- 1 roll of tape
- Central Line Dressing Kit Containing:
  - 2 pairs of gloves
  - 1 triple pack acetone-alcohol swabsticks
  - 1 triple pack povidone-iodine scrub swabsticks
  - 1 triple pack isopropyl alcohol swabsticks
  - 1 triple pack povidone-iodine solution swabsticks
  - 1 protective dressing swabstick (skin prep)
  - 1 4 x 5 Elastoplast dressing
  - 2 2 x 2 cotton gauze sponges
  - 1 cotton tip applicator
  - 1 pair scissors

#### B. Procedure

1. Wash hands. Explain the procedure to the patient and/or significant others. Check for povidone-iodine or tape allergy.
2. Organize supplies and equipment at the bedside to decrease the amount of time that the site is open to the air.
3. Don gown, mask and cap. Place the patient in a supine with head turned away from catheter insertion site to decrease potential for contamination by nursing personnel and by patient secretions. Place a mask over patient's mouth and nose (and trach) if patient is able to tolerate. If patient is unable to tolerate the mask, use a towel as a barrier between patient's mouth/nose and insertion site.
4. Open central line dressing kit and don a pair of gloves.
5. Remove present dressing carefully to minimize trauma and prevent accidental dislodgement of catheter. Place soiled dressing in proper trash receptacle.
6. Inspect the skin and catheter site infection, leakage, or other mechanical problems.
7. Don sterile gloves.
8. Cleanse the insertion site with acetone / alcohol swabsticks, working in a circular motion from the insertion site outward to the edge of the dressing border. This removes adhesive material and defats the skin. Repeat 3 times. Do not apply over broken skin.
9. Working in a circular motion from site outward, cleanse the insertion site and distal portion of the catheter with the povidone-iodine scrub swabsticks 3 times to remove bacteria and fungi from the skin and catheter.
10. Working in a circular motion as before, cleanse the site of the povidone-iodine scrub with alcohol swabsticks 3 times to remove the povidone-iodine scrub.
11. Paint a 3 x 6 area from site to periphery with povidone iodine solution swabsticks 3 times. Blot excess or pooled solution. Allow to dry. This provides a protective barrier against pathogens.
12. Place a folded 2 x 2 over the insertion site and line down to and including the sutures. This is to prevent the occlusive dressing from sticking to the line and sutures.
13. Cut the Elastoplast to fit over the insertion site and sutures. Round all corners and be sure 2 x 2s are completely covered.

14. Apply Elastoplast. Paint around edges of Elastoplast with skin prep and tape all around dressing.
15. Tape all connections or ensure that all Luer lock connections are tight. This prevents dislodgement of the tubing from the catheter and reduces the potential for air embolism. Tape edges of dressing, if necessary.
16. Write the date and time of dressing change, and your initials on the dressing. This allows for easy identification and documentation of the interval to change the line and the dressing.
17. Document the dressing change and the condition of the insertion site, the patient's tolerance of the procedure, and any problems encountered in the nursing notes.

C. Related Care

1. Inspect site frequently for signs of infection, inflammation, drainage, and infiltration.
2. Whenever the catheter is changed, the dressing must be changed.
3. IV tubing for TPN must be changed every 24 hours—or every bag change. Dressing should be changed every Monday, Wednesday, Friday or according to local protocol (ie, ICU).

**SUMMARY TABLE FOR SITE, DRESSING, AND TUBING CHANGES**

**I. GENERAL**

- A. Change all IV fluid containers every 24 hours.
- B. Handle all intravascular devices with aseptic technique.

**II. SPECIFIC**

Duration of Site/Needle	Dressing Change	Tubing Change	Documentation of Appearance of Site
Central (Short Term) According to Protocol	48–72 h	24*–72 h	With dressing change
Central (Long Term) N/A	48–72 h	24*–72 h	24 h
Implanted Devices 6–7 d	48–72 h	24*–72 h	24 h
Peripheral, Arterial 72–96 h	48–72 h	48–72 h	24 h
Peripheral, Intravenous 72 h	72 h	72 h	24 h
Piggyback Meds, Continual Infusion 72 h	N/A	72 h	N/A
Piggyback Meds, “Heparin Lock” 72 h	N/A	Each infusion	N/A

\*With every new bag of TPN or every 72 h for all other fluids