UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER

MEDICAL GRAND ROUNDS

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NUTRITION IN THE ICU

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"The doctor of the future will give no medicine, but will interest his patient in the care of the human frame, diet, and the cause and prevention of disease."

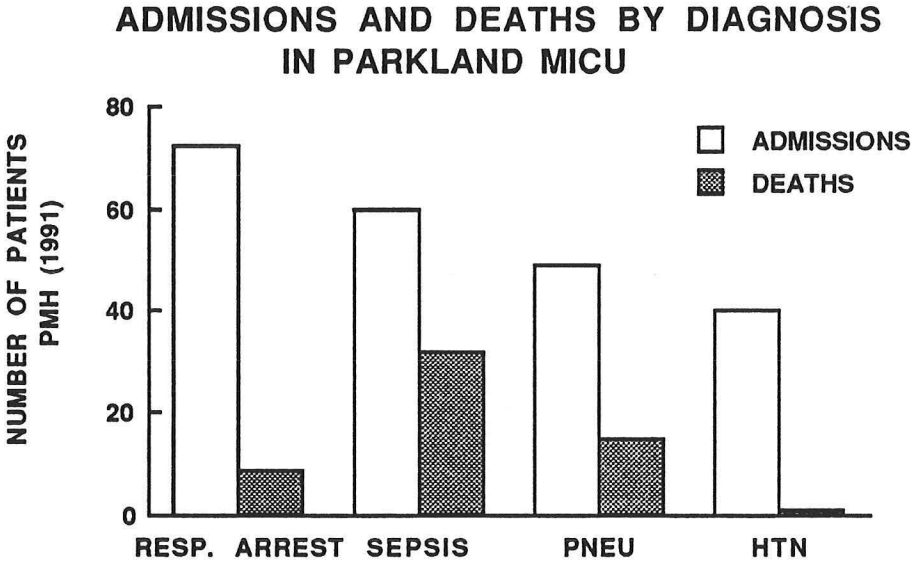
Thomas A. Edison

"I just don't understand those health freaks. I mean, the ancient Greeks ate only natural foods and look at them, they're all dead!"

Goldie Hawn

INTRODUCTION

Great advances in the care of critically ill patients have been made in the last three decades. In the 1960's, there was development and refinement of mechanical ventilation. In the 1970's, the development of the pulmonary artery catheter allowed intelligent manipulation of the determinants of cardiac function. However, despite these advances and the introduction of a multitude of potent antibiotics, sepsis and its complications remain the major causes of mortality in intensive care units.



The Parkland medicine intensive care unit admits between 300 and 600 patients each year. The four most common admitting diagnoses are shown in figure 1. These diagnoses represented 56% of all admissions to the MICU in 1991. Sepsis and pneumonia accounted for 25% of all admissions, however 50% of all ICU deaths occurred in these two groups. The common denominator is infection and sepsis. Infection requiring admission to the intensive care unit carries a mortality approaching 50%. It is surprising that the average age of these patients is less than 50 years and no different than the overall average. The severity of illness as measured by APACHE II scoring is no different than the average for the unit as a whole, however their hospital stay is double that of the rest of the ICU. Thus infection, particularly sepsis syndrome, carries a much higher mortality and morbidity than other illnesses of similar severity.

Sepsis is a disease of cellular function, and as such, it results in significant metabolic derangements. Too often patients fall into a spiral of sepsis, resulting in metabolic disarray which in turn leads to alterations of host defence including immunosuppression, delay in wound healing, and loss of muscle strength. These events can lead to increased frequency of nosocomial infection, inability to be weaned from mechanical ventilation, and increased hospital stay with prolonged convalescence.

Reducing the debility associated with sepsis and other catabolic processes could

potentially enhance recovery and reduce the length of hospitalization. Three general approaches include:

1) Alteration of the stress response
2) Provision of specific fuels
3) Administration of growth factors.

The first approach, alteration of the stress response, holds great promise. Dr. Dal Nogare (1) discussed many of the mediators of tissue damage in his grand rounds on Sepsis in January of this year. Unfortunately, we are not able to alter the stress response sufficiently. This inability was discussed by Dr. Munford in his grand rounds just a few months ago, and in a recent editorial in the New England Journal of Medicine (2). The second approach, to provide general and specific fuels, is the topic of this grand rounds, however I will touch on growth factors as well.

PATHOPHYSIOLOGY OF CATABOLIC ILLNESS

The two major forms of protein calorie malnutrition are termed marasmus and kwashiorkor. Marasmus is simple starvation. It is a chronic disease developing over months or years due to marked caloric depravation. Kwashiorkor or visceral protein depletion is a more acute process that develops over weeks to months. It is usually due to poor protein intake with some, but inadequate, carbohydrate ingestion against a background of acute illness or major surgery or other type of stress. Patients with kwashiorkor often appear well nourished on physical exam but on further examination have major deficits in immune function and in the visceral protein compartment. This is the condition that may develop during hospitalization in patients receiving only isotonic infusions of glucose. A constant infusion of 5% glucose induces a tonic stimulation to insulin secretion. The antilipolytic and antiproteolytic properties of insulin prevent mobilization of fat and skeletal muscles seen in marasmus.

The mediators of the complex systemic responses that are associated with inflammation following infection and injury can be grouped into three broad categories shown in table 1.

MEDIATORS OF THE SYSTEMIC RESPONSES TO INFLAMMATION

HORMONE	CYTOKINE	LIPID MEDIATOR
GLUCAGON	TUMOR NECROSIS FACTOR	PLATELET-ACTIVATING FACTOR
GLUCOCORTICOIDS	INTERLEUKIN-1	THROMBOXANE A_2
	INTERLEUKIN-2	
	INTERLEUKIN-6	
CATECHOLAMINES	INTERFERON γ	LEUKOTRIENE B_4
INSULIN		PROSTAGLANDIN E_2
GROWTH HORMONE		

The cascade of events that occur following sepsis or injury have not been well worked out. The patterns of response depend on the stimulus whether injury, sepsis, burn, or other; and release of a number of mediators is often initiated simultaneously. These three response systems are interconnected by amplification loops and negative feedback control.

It has long been recognized that injured patients have elevations in the "counterregulatory" or anti-insulin hormones: cortisol, glucagon, catecholamines, growth hormone, aldosterone, and vasopressin. The mechanism responsible for these elevations is thought to be at least partially mediated through neuropathways, especially sympathetic stimulation. Catecholamines increase the metabolic rate when infused into normal subjects (3). When cortisol, glucagon and catecholamines are infused together the increases are greater than when the catecholamines are infused alone (4).

Many of the signs and symptoms of inflammation or sepsis occur after cytokines or lipid mediators are administered in vivo. For example, infusion of low doses of tumor necrosis factor in patients with cancer resulted in decreased ferritin levels whereas moderate doses caused fever and elevation of C-reactive protein plasma levels. A much higher dose stimulated the secretion of ACTH and subsequent cortisol secretion with fluid retention. Infusion of larger doses resulted in confusion and hypotension (5). Thus, the infusion of tumor necrosis factor elicits in a dose-dependent fashion many of the signs and symptoms of severe inflammation and sepsis through either direct or indirect mechanisms (6). Tumor necrosis factor and interleukin-1 are both elevated in experimental gram negative septic shock. Tumor necrosis factor has been shown to down regulate gene expression for albumin synthesis in hepatocytes and the administration of cyclooxygenase inhibitors prior to the administration of endotoxin does not block tumor necrosis factor production but does block the systemic effects such as fever, malaise, myalgia, tachycardia and diaphoresis (7). Tumor necrosis factor and IL-1 both increase energy expenditure when administered intravenously into normal subjects (8,9). Interleukin-2 when infused for cancer treatment also increases energy expenditure (10). Interleukin-6 has been shown to be elevated in patients undergoing major surgery and is associated with the acute phase response and reduced hepatic protein synthesis in cancer patients.

IL-1 modulates responses to inflammation including hepatic synthesis of acute phase reactants (11), increases in endothelium adherence, and fibroblast growth (12). It also causes fever, inhibits vasculature smooth muscle contraction (13), and signals T-lymphocyte activation (14). IL-1 also activates the expression of granucyte-colony stimulating factor (15) and granucyte-macrophage colony stimulating factor resulting in leukocytosis (16). Growth factors such as platelet derived growth factor and epidermal growth factor may play important roles in directing body resources to healing injured areas (17-19). It is likely that these mediators are active in the hypermetabolism observed following injury and sepsis.

There are many interactions between these mediators and immunologic function. The most commonly recognized interaction is that between glucocorticoid and cellular immunity. Glucocorticoid causes the release of neutrophils from bone marrow, a decrease in circulating monocytes and macrophages, T-cell sequestration in the bone marrow, lysis of immature T-cells, inhibition of gamma-interferon and IL-1 production, and inactivation of phospholipase A-2 which stimulates prostaglandin and leukotriene production (20). There is much interrelationship between the different mediators. Interleukin-1, gamma

interferon, and IL-6 all cause increases in ACTH release or release of ACTH like substances (21-26).

Normal energy is expended in absorbing and transporting nutrients, in macromolecular synthesis and turnover, and in the process of storing nutrients. Much energy is expended to maintain cellular transmembrane homeostasis such as the sodium-potassium pump. There are also substrate product cycles that expend energy with little net metabolism of substrate. These are the so-called futile cycles and may account for up to 13% of total energy expenditure. These include the cory, glucose to glucose-6- phosphate, fructose-6-phosphate to fructose-1,6-diphosphate, and triglyceride to free fatty acid cycles. Reeds and associates (27) have estimated that protein synthesis accounts for 14-26% of total energy expenditure. The increase in energy expenditure in the injured or septic state has been ascribed by some to the increased protein metabolism seen in these patients (28).

Severe sepsis is accompanied by progressive alterations in oxygen consumption and/or elevation of blood lactate levels (29) despite maintenance of tissue perfusion implying a derangement in cellular metabolism (30,31). Wilson and co-workers (32) observed that patients with depressed oxygen consumption had worse survival than those with hypermetabolism. Forse and associates (33) found that lipolysis following injury is due mainly to beta-adrenergic stimulation while after sepsis it is due to decreased alpha-stimulation. Robin and co-workers (34) pointed out differences between injured and septic patients. In trauma, lipoprotein lipase activity in muscle was increased while that in adipose tissue was decreased. In sepsis lipoprotein lipase activity was decreased in both tissues.

RATIONALE

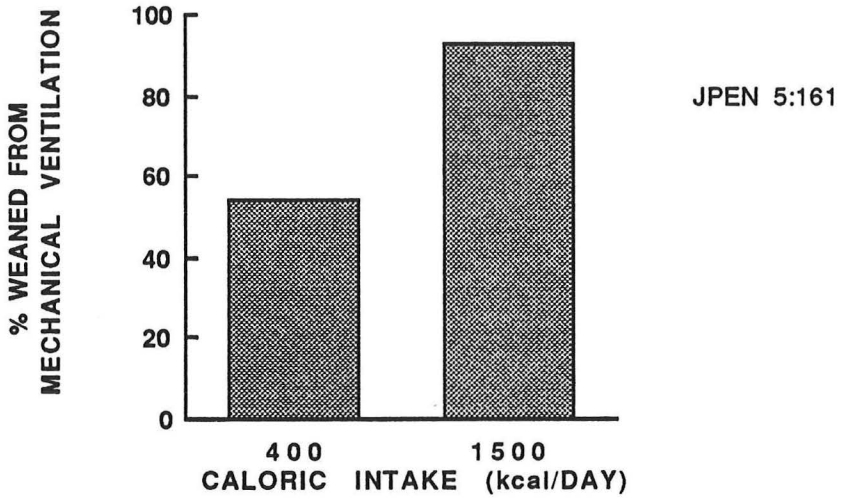
Intravenous nutrition could be said to start in the 1940's when 5% dextrose was administered in 2-3 liters of solution per day. This, however, was a means of replenishing water needs rather than supplementation of nutrition. In the 1950's protein hydrolysates were used intravenously as a means of supplementing nutrition and in the 1960's successful administration of emulsified fat solutions was accomplished (35,36). The use of nutritional support is still controversial and may be difficult since the nutritional needs of the critically ill patient can change very quickly. Organ failure in critically ill patients may produce increased susceptibility to a variety of complications related to nutritional support.

Even after total parenteral nutrition became accessible in the 1970's, several studies showed the prevalence of malnutrition in hospitalized patients to approach 50% (37-39). Malnutrition in the critically ill population in the intensive care unit may be much higher due to the nature of the underlying disease. One study of ICU patients with respiratory failure receiving mechanical ventilation showed that 88% of these patients received inadequate nutritional support while they were in the intensive care unit (40). More recent studies have shown that malnutrition among hospitalized medical patients even now generally remains undetected and largely untreated (41,42). Education about nutritional support is required to reverse the situation. Even in patients who are nutritionally replete a critical illness can result in catabolism and loss of lean body mass and fat.

The effectiveness of nutritional support in decreasing mortality, morbidity, and length of stay in critically ill patients is difficult to prove because so many other factors determine outcome in these patients. The primary pre-existing disease, age, and iatrogenic complications may play a much larger role than catabolism in these patients. As Dr. Dal Nogare stressed in his grand rounds on ARDS last year, it is the ability to treat the underlying disease as well as oxygenate the patient that determines survival. Nutritional support in such patients must be considered adjunctive therapy designed to prevent additional problems caused by malnutrition.

Evidence that nutritional support reduces mortality or morbidity in the critically ill patient is sparse. Bassili and Deital (43) studied the effect of nutritional support on weaning patients from mechanical ventilation as shown in Figure 2.

EFFECT OF NUTRITIONAL SUPPORT ON WEANING FROM MECHANICAL VENTILATION



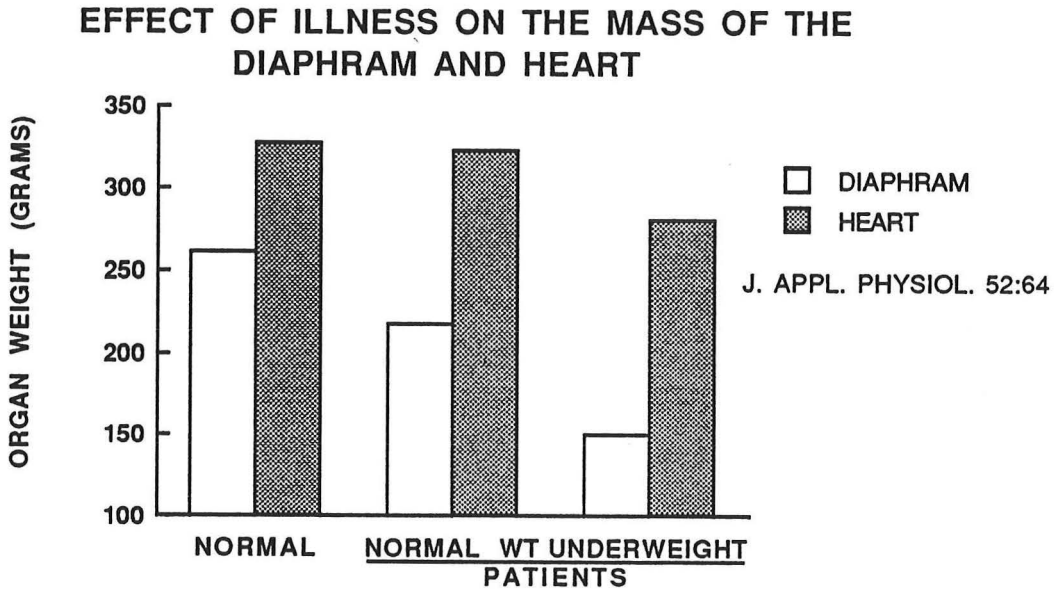
They noted that only 54% of patients fed with 400 kilocalories per day of carbohydrates on mechanical ventilation successfully discontinued whereas 93% of those given total parenteral nutrition to around 1500 kilocalories per day were successfully weaned. Even though this study was not randomized it does suggest that feeding patients may improve the ability to discontinue mechanical ventilation.

DESIGNING A NUTRITIONAL REGIMEN

1) ENERGY REQUIREMENTS
2) PROTEIN REQUIREMENTS
3) NONPROTEIN REQUIREMENTS
4) CALORIE-NITROGEN RATIO
5) ELECTROLYTES
6) VITAMINS
7) TRACE ELEMENTS
8) FLUID REQUIREMENTS
9) ROUTE OF ADMINISTRATION
10) DISEASE SPECIFIC CONSIDERATIONS

Designing a nutritional regimen requires the consideration of a number of factors outlined in Table 2. It is best to take a systematic approach to individualizing a regimen for the critically ill patient. Standardized nutritional regimens are available in most institutions and because of cost and time savings physicians are encouraged to utilize these products. This approach has been shown to achieve nutritional goals sooner than non-standardized regimens (44). However, caution must be used since these standardized regimens will fail to meet some patients' needs and will exceed the needs of others.

Lung defense mechanisms are altered in malnutrition along with a compromise in immunologic function (45-48). Effects have also been shown in the antioxidant defense system and in surfactant production (49-51). There is an increase in respiratory morbidity associated with starvation. Many deaths from starvation are accompanied by pneumonia. It has been demonstrated that there is a marked decrease in the number of sigh breaths in hospitalized patients with malnutrition (52) as well as a decrease in functional residual capacity (53,54). These alterations may predispose the patient to atelectasis and infection. Respiratory muscle function is altered by malnutrition. Diaphragm weight and maximal inspiratory mouth pressures have been shown to be decreased in malnutrition (45). Starvation or any other condition that reduces the metabolic rate also reduces ventilatory drive (55).



Until the 1940's it was thought that the heart was spared during starvation. Figure 3 shows the effect of illness on the mass of the diaphragm and heart. There were three groups of patients; one of normal weight patients who had suffered a sudden death such as cardiac arrest, and two other groups of patients (normal and underweight) who had a more prolonged hospital course. There was relatively little change in the mass of the heart with prolonged illness even if the patient was underweight. However, the diaphragm suffered a decrease in mass with prolonged illness and even more so if the patient was underweight during the prolonged illness (56). Keys and his associates showed, however, that the heart was not spared from the effects of malnutrition. Their study involved 32 young men who voluntarily lost 25% of their body weight over a six month period. The

study showed that undernutrition was associated with a decrease in heart rate, arterial and venous pressures, stroke volume, cardiac output, cardiac index, metabolic rate, oxygen consumption as well as arterial and venous oxygen content (57).

Most studies addressing the nutritional support of critically ill patients is found in the surgical literature. Burns, trauma and post-surgical sepsis are well represented in the literature and have been shown to benefit from hyperalimentation or nutritional support. However, there is a paucity of studies in the medical literature concerning nutritional support of medicine patients. Nevertheless, nutritional support in the intensive care unit has become the standard of care across the country. Extrapolation from data obtained in surgical patients or studies done with experimental animals may not be ideal, however it is often all we have to guide us in applying nutritional support to our ICU patients. Most of the studies would apply to any patients regardless of the cause of injury or metabolic derangement.

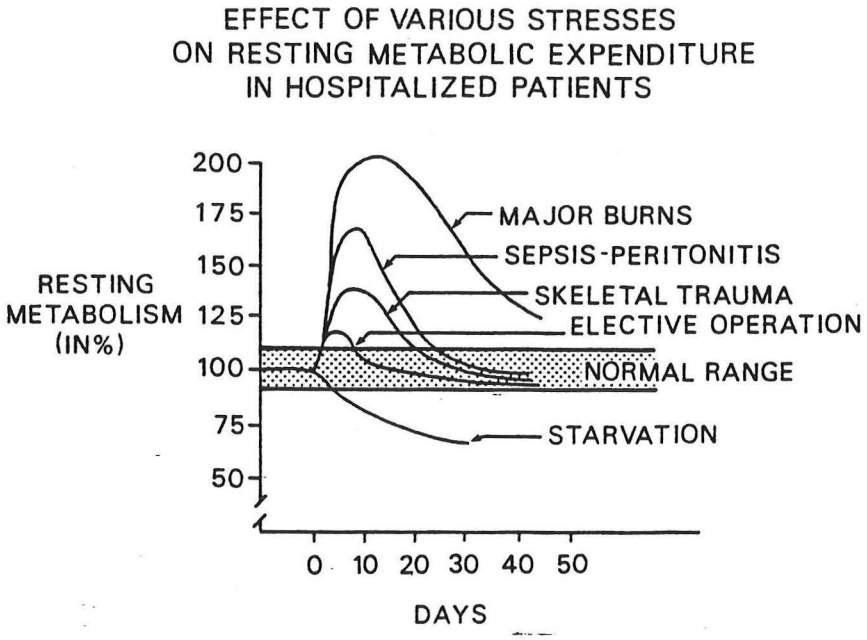


Figure 4 shows the effect of various stresses on resting metabolic expenditure in hospitalized patients. These studies were done in surgery patients of various ages and with various conditions (58). As can be seen from the graph, the increase in energy expenditure in hospitalized patients occurs very rapidly and may be prolonged lasting 2-3 weeks in the sepsis peritonitis group. The question arises whether this can be applied to medicine patients in the medicine intensive care unit. A study by Liggett and Renfro looked at 73 consecutive ventilator supported patients with various primary diagnoses in a medical intensive care unit (59). Energy expenditure was measured using the Fick equation with a pulmonary artery catheter to estimate oxygen consumption. This was then compared to the Harris-Benedict equation for resting energy expenditure. They found that the measured and predicted energy expenditure for patients with various conditions was not significantly different with the exception of septic shock which was 20% above the predicted resting energy expenditure for that group of patients.

The current approach to the nutritional support of critically ill patients is to

provide nutrients that are necessary during health. As physicians, we try to insure that the macronutrients and micronutrients are not rate limited. We do this by increasing the quantities administered to critically ill patients. Hence, the term hyperalimentation. However, sepsis and other catabolic diseases may alter the requirements for specific nutrients. If the patient is given these required substrates this might greatly facilitate the patient's anabolic response to life- threatening disease.

CALCULATION OF NUTRITIONAL NEEDS

The initial step in designing a nutritional regimen is to determine the patient's caloric needs. This includes calculating how much energy the patient is expending and then deciding whether the patient needs to maintain, gain or lose body mass as fat or lean mass. Energy expenditure depends on a variety of factors including age, sex, body mass, disease state, and degree of activity. Measurement of total energy expenditure during a 24 hour period is difficult to accomplish. Therefore, the energy expenditure during a reference state such as at rest is measured or estimated and the result is modified to produce an estimated total energy expenditure. A number of reference states are in use. The basal metabolic rate (BMR) is defined as the metabolic rate measured on awakening in the morning after an overnight fast with a subject in a thermoneutral environment. This measurement is virtually impossible in a patient in the intensive care unit who is receiving continuous infusions and who rarely sleeps through the night. A more useful reference state is the resting energy expenditure (REE), which is defined as the metabolic rate measured while the patient is at rest, defined as lying supine with eyes open and able to respond (60). The REE is usually 5-10% greater than the BMR because of diet induced thermogenesis even in ICU patients receiving simply 5% dextrose solution. This has been termed the specific dynamic action of food stuffs (61,62).

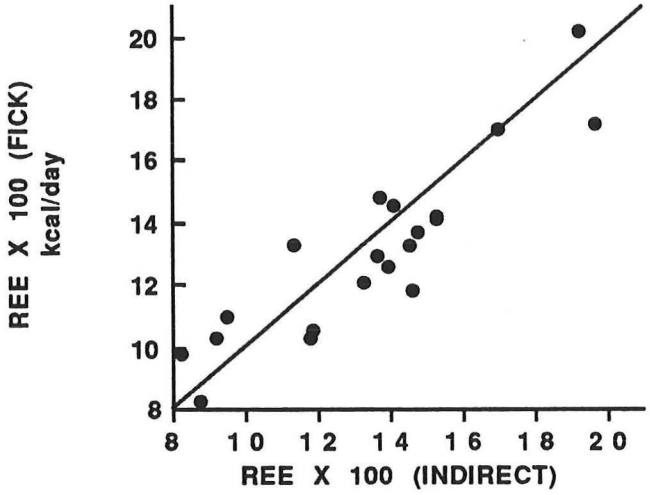
The level of energy expenditure can be calculated with formulas or normograms or determined by using measurements of energy expenditure. The gold standard is direct calorimetry which is very difficult to do, even outside of an ICU setting. It involves measuring the heat production of the patient in a thermal body box. Fortunately, energy expenditure or heat loss is correlated with oxygen consumption and carbon dioxide production (63-65). Therefore, measuring one or both of these parameters, which is called indirect calorimetry, is a measure of energy expenditure. These measurements are usually obtained through what is commonly referred to as a metabolic cart, usually a computer hooked to gas analyzers all arranged on a cart that can be placed at the bedside. These instruments can be expensive, in the range of forty thousand dollars, and require some specialized training for accurate use. These factors place the metabolic cart beyond the reach of many community intensive care units. Calculation of basal metabolic rate and energy expenditure can also be obtained with the use of a pulmonary artery catheter measuring cardiac output, arterial and mixed venous oxygen pressures and thereby calculating oxygen consumption and energy expenditure via the following formula:

$$EE = Q \cdot Hgb\ (S_a0_2 - S_v0_2) \cdot 95.18.$$

where: EE = energy expenditure
Q = cardiac output
Hgb = hemaglobin
SaO2 = arterial oxygen saturation
SvO2 = mixed venous oxygen saturation

This calculation has been shown to be accurate compared to the metabolic cart as shown in Figure 5 (59).

COMPARING INDIRECT AND FICK MEASUREMENTS OF RESTING ENERGY EXPENDITURE



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There are many estimates for daily energy requirements. A rule of thumb is 20-30 kilocalories per kilogram for minimally ill patients, 30-40 kilocalories per kilogram for moderately stressed patients and 40-50 kilocalories per kilogram for critically ill patients (63,66). Resting energy expenditure can be better estimated using formulas based on age, sex, body size, and adjusting this value for the patient's physical activity or severity of illness. There are hundreds of equations utilizing variables such as weight, height, and age to predict energy needs. The most widely used formula is the Harris-Benedict equation developed from oxygen consumption measurements establishing standard resting metabolic rates for both men and women shown below.

HARRIS-BENEDICT EQUATION

DAILY REE (MALE) = 66.5 + 13.7(W) + 5.0(H) - 6.7(A)

DAILY REE (FEMALE) = 655 + 9.6(W) + 1.8(H) - 4.7(A)

W=WEIGHT(Kg) H=HEIGHT(cm) A=AGE(YEARS)

Caloric requirements can be affected by many factors such as physical activity, body temperature agitation and extent of injury (67).

The characteristics of whatever predictive equation is used should be known. These include whether the equation predicts resting, basal or total energy expenditure, the population the equation was derived from, and how well the equation predicts the energy expenditure of the type of patients being assessed. The Harris-Benedict equation was derived from resting energy expenditure measurements of normal subjects rather than patients and may or may not accurately estimate the metabolic rate in different groups of patients in the intensive care unit as shown in Table 3.

ACCURACY OF HARRIS-BENEDICT

PATIENT	ACCURACY	REFERENCE
NORMALS	WITHIN 10% IN 90%OF GROUP	HARRIS 1919
HOSPITAL	WITHIN 10% IN 80% OF GROUP	FEURER 1984
ICU (SURGICAL)	AVERAGE 4.6%,RANGE 70-126%	CARLSSON 1984
ICU (SURGICAL)	AVERAGE 3.8%, RANGE 70-140%	WEISSMAN 1986

The original description by Harris and Benedict in 1919 was made in normals and the accuracy was described as within 10% of the measured value in 90% of the group (68). Feurer in 1984 compared the Harris-Benedict equation to measured energy expenditure in hospital patients and the accuracy fell to within 10% in only 80% of the group (69). The variation between actual and estimated energy expenditure can be even greater in the intensive care unit as shown by Carlson in 1984 who found a range between 70% and 126% of the estimated energy expenditure (70). Likewise, Weisman in 1986 found a range between 70 and 140% of the estimated energy expenditure by the Harris-Benedict equation (71). The use of "stress" factors developed in spontaneously breathing patients must be used with caution in patients in the intensive care unit. The stress factors are designed to account for the hypermetabolic state generally present in post-operative infected, injured or burned patients (58). Medical ICU patients tend to be relatively less hypermetabolic because of lack of spontaneous respiration, sedation, and/or induced paralysis (59). Because fluid retention is so common in the intensive care unit the weight factor of the formulas is commonly falsely elevated giving an inaccurate estimation.

The usual practice is to estimate the resting energy expenditure in patients and add a percent increase above that value to give a fudge factor for the degree of catabolism from stress or trauma or infection. However, this may not be applicable to patients without septic shock in a medicine intensive care unit (59).

Once the REE is determined it must be modified to obtain the total energy expenditure (TEE). The difference between TEE and REE is called the activity factor (72). The activity factor for patients in the intensive care unit is 5-10% (71), and higher in more mobile hospitalized patients. The metabolic rate is lower during sleep and sedation (60,73) but is increased in patients with major changes in clinical condition such as surgery, or the development of sepsis.

Caloric intake should differ based on the goals of nutritional support. Prevention of losses to lean body mass require 1.25-1.30 times REE to be administered. This factor takes into account the activity factor of 5-15% plus a factor of daily variation in nutritional needs which is around 15%. If repletion of lean body tissue is needed, then additional caloric intake is warranted, however weight gain should be limited to 0.5-1.0 kilograms per week. The composition of the weight gain depends on the type of nutrient as well as the caloric content. Patients in a stressed state do not readily gain body mass because of altered substrate utilization. In such patients it is important not to attempt weight gain since overfeeding can cause problems.

NUTRITIONAL ASSESSMENT

The primary goals of nutritional assessment are to assess the pre-existing nutritional state, the length of nutritional support that is needed and the severity and type of illness affecting the patient. Nutritional assessment should include a history, including acute weight change, underlying illness including diabetes, renal, lymphatic, cardiac, pulmonary, gastrointestinal function and any food allergies that are present. The physical exam should include an assessment of whether the patient has malnutrition or obesity. Signs that are helpful include temporal wasting, sunken cheeks, subcutaneous fat levels, cheilosis, skin drooping, muscle mass, jaundice and ascites (74). There are numerous laboratory markers that have been used for making nutritional assessment. These include albumin, transferrin, pre-albumin and retinol-binding protein. Many of the criticisms of these markers, particularly for albumin, is that it has a very long half-life (75). Transferrin also has a fairly long half-life (76) whereas pre-albumin and retinol binding protein have shorter half-lives. They are subject to fluxes in serum concentration due to other than nutrition related decreases. Somatic indices such as creatinine height index and 3-methyl-histidine have been used but depended on renal function and are not reliable with a creatinine clearance less than 20 milliliters a minute (77). This leaves the clinician to apply any or all of these to individual patients to try to come up with some nutritional assessment of the patient. Other modalities of nutritional assessment also include delayed hypersensitivity skin test (78), such as mumps candida, trichophyton or streptokinase streptodornase, serum antibody response to immunization, and total lymphocyte counts as well as CD4 and CD8 counts (79). The predictive properties of various measures in the nutritional assessment are shown in Table 4.

PREDICTIVE PROPERTIES OF NUTRITIONAL ASSESSMENT

	SENSITIVITY	SPECIFICITY
ALBUMIN (<3.5g/dl)	0.50	0.91
DTH (ANERGY) <5mm	0.15	0.95
<10mm	0.52	0.69
LYMPHOCYTES (<1500)	0.43	0.66
TRANSFERRIN (<150mg/dl)	0.57	0.78
CREATININE-HEIGHT (<90%)	0.88	0.45
PROGNOSTIC NUTR. INDEX (>40)	0.88	0.45
CLINICAL ASSESSMENT (HIGH-RISK)	0.82	0.72

It can be seen that none of the measures have sufficient sensitivity and specificity to be clinically useful. Various prognostic nutritional indices have been developed (80). However, these are probably more accurate in the assessment of stable patients scheduled to undergo elective surgery than in critically ill patients in the medicine intensive care unit (81). A study by Baker and associates compared the ability of two clinicians to discern malnutrition by history and physical examination compared to the use of anthropometry, biochemical and isotope whole body composition studies (74). Patients were grouped using simply the history and physical as being normal, mildly malnourished, or severely malnourished. This subjective global assessment was just as good as the anthropomorphic measurements including laboratory studies and body composition studies in predicting patient outcome.

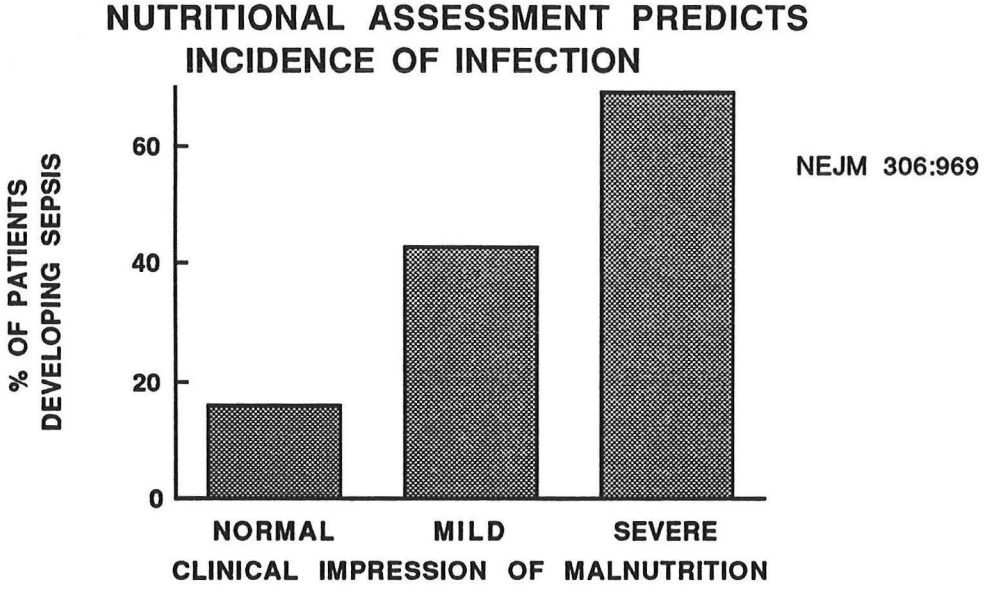


Figure 6 shows that this clinical nutritional assessment predicted the incidence of infection in hospitalized patients (74). The clinical impression of malnutrition was associated with the percent of patients developing sepsis during their hospital course. The percent developing sepsis ranged from less than 20% in the patients assessed as being normal to over 60% in the severely malnourished patients. This nutritional assessment also predicted the clinical outcome as hospital stay. Again, the more malnourished patients had a longer hospital stay implying a longer recovery or convalescence.

This study points out that the general clinical impression of the patient being normal, mild, moderately or severely malnourished is a reproducible and valid technique for evaluating the nutritional status of patients. A carefully obtained history and physical examination are often sufficient for a nutritional assessment.

Malnutrition has been shown to alter immune function. Protein calorie malnutrition is a frequent cause of immunodeficiency in patients (the most common prior to AIDS). This is demonstrated by the morbidity and mortality related to the initial skin test reactivity in patients evaluated for surgical procedures (79).

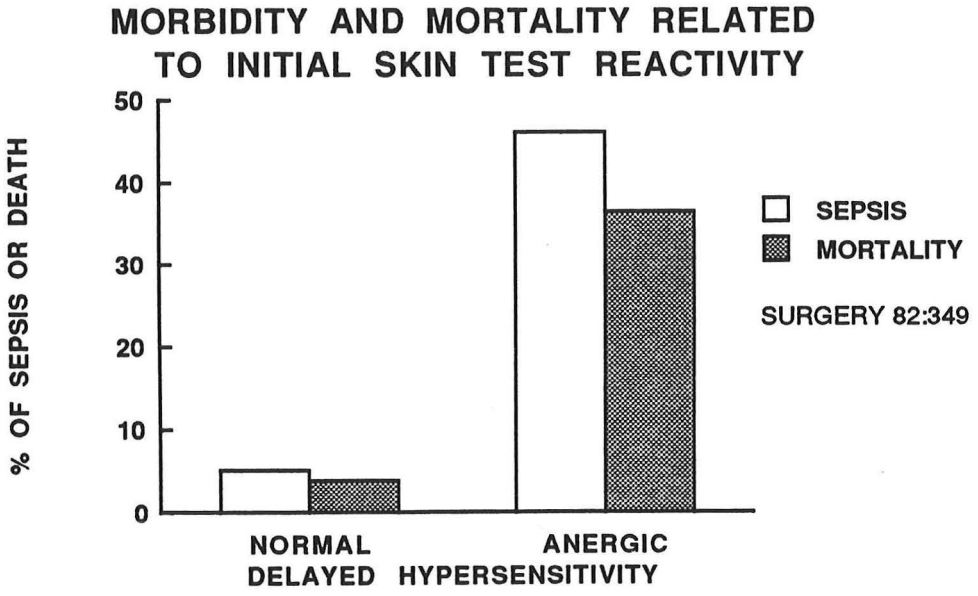
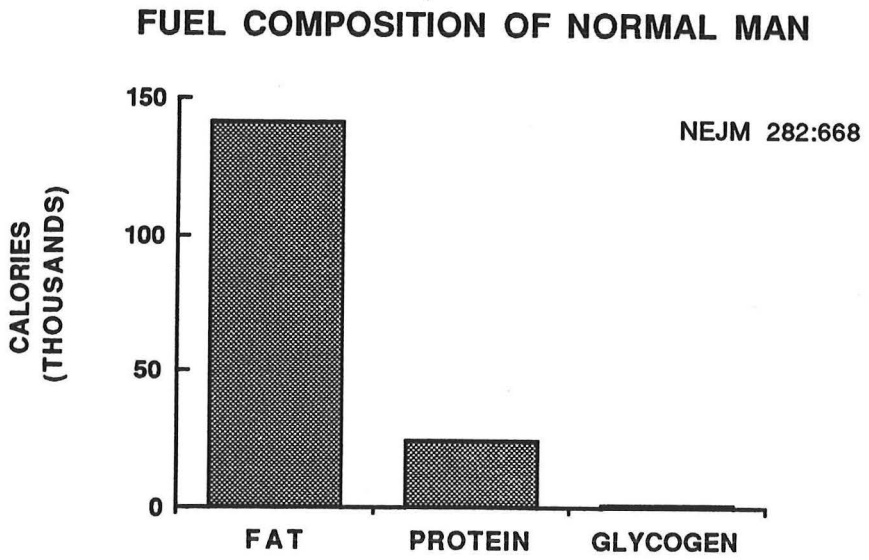


Figure 7 relates the delayed hypersensitivity skin reaction to percent of patients developing sepsis or death during their hospital stay. There is a dramatic increase in both sepsis and mortality in patients who are anergic to skin test antigens.

New diagnostic imaging methods such as computerized axial tomography, nuclear magnetic resonance, and ultrasonography are being investigated as techniques to be applicable to the assessment of nutritional status (82). As well, there are certain isotope dilution assays and in vivo neutron activation analysis that are currently experimental and may hold promise in the future as isotopes become more widely available (83,84). One of the difficulties in assessing nutritional status is the confounding factor of age. Many of the physical and functional changes that are associated with aging are similar to those attributed to malnutrition.



Once the energy needs of the patient has been established, the proportions of protein, carbohydrate and fat can be determined. The fuel composition of normal man is shown in Figure 8. Approximately 1000 kilocalories are stored as glycogen or carbohydrates, about 20,000 kilocalories as protein, about half of which is intracellular, and about 140,000 kilocalories as fat (85,86). In a normal individual it takes only a few days to begin depleting these stores. However, in the injured or critically ill patient this depletion is accelerated markedly (87).

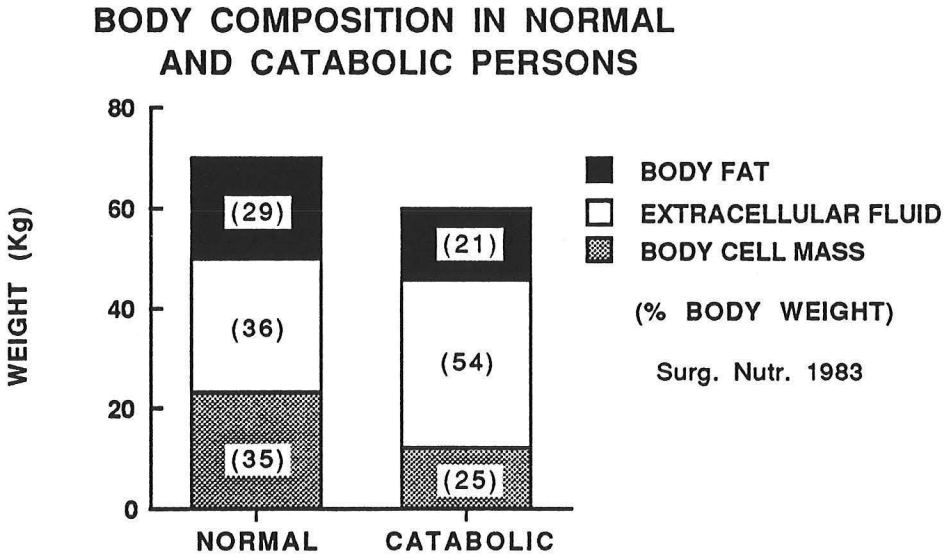
USE OF PROTEIN

The recommended protein intake in a normal American diet is 0.8-1.0 grams per kilogram per day. This protein usually has a biologic value of about 60% (egg protein = 100) and gives a calorie to nitrogen ratio of 170:1. The protein requirements of critically ill patients are increased secondary to catabolism as well as the need to provide substrate for gluconeogenesis and tissue repair. Protein is needed as substrate for acute phase reactant proteins, wound healing, and maintenance or restoration of lean body mass.

The concept of nitrogen balance is defined by the following equation:

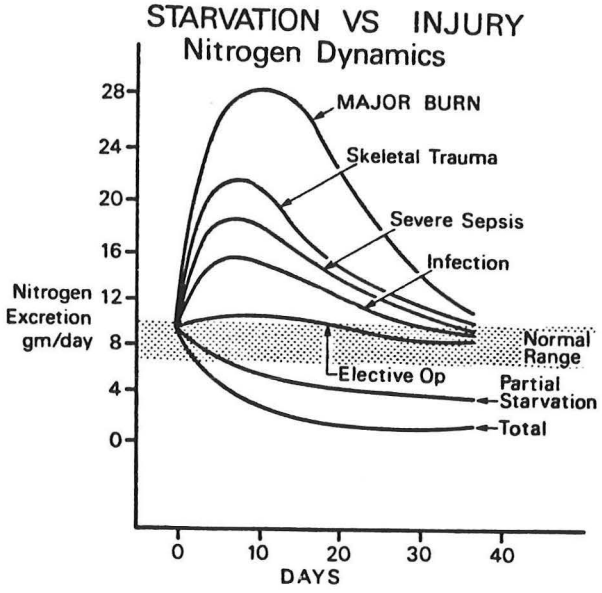
$$N_{bal} = N_{intake} - N_{output}$$

This equation takes on significant meaning when it's known that one gram of nitrogen is equivalent to 6.25 grams of protein. This, in turn, is comparable to approximately 30 grams of wet muscle mass. As an example, if a patient has a net nitrogen loss of 5 grams per day this works out to a loss of muscle mass of 1 pound every 3 days or a little over a kilogram per week which is a 10% reduction in body protein.



The body composition in normal and catabolic persons is shown in Figure 9 (88). Ideally, patients would use fat as their energy substrate however, as can be seen from the graph, body cell mass drops from 35% of body weight to 25% of body weight with a concomitant increase in extracellular fluid. It only takes a few days of starvation to begin to deplete protein stores, however depletion can begin almost immediately and at a much

increased rate during sepsis and catabolic illness as shown in Figure 10 (58). The body's demand for protein during injury or catabolic illness may exceed the supply from the endogenous protein sources of the body.



Studies by Anderson and associates, and Lodner and co-workers show that the nitrogen requirement for balance in stable adults is approximately 0.4 grams per kilogram per day. In nutritionally depleted patients protein requirements may increase to 1.0-1.2 grams per kilogram per day and in septic individuals in their catabolic phase of illness may require 1.25-1.5 grams per kilogram per day with some authors advocating 2 grams per kilogram per day or more (89,90).

The quality of the protein is as important as the quantity of the protein. The distribution of amino acids should be such that they can be used for all types of protein production. One attempt at improving the quality of protein has been the use of branched chain amino acid enriched solutions. These solutions contain up to 45% branched chain amino acids such as valine, leucine, and isoleucine. The rationale behind the use of branched chain amino acids is that in sepsis and trauma both skeletal muscles and the liver have an increased demand for these amino acids. While in vitro studies of these amino acid mixtures were encouraging, clinical studies have failed to show improved nitrogen balance in all but the most severely ill individuals, and an outcome study failed to demonstrate any advantage of the solutions over standard amino acid infusions (91-93).

Patients with hepatic disease resulting in hepatic encephalopathy have elevated levels of aromatic amino acids (phenylalanine, tyrosine, methionine, and tryptophan) while the levels of branched chain amino acids are reduced (94,95). This finding plus the observation that low protein intakes can improve the mental status of these patients led to investigations of the use of branched chain amino acid solutions in these patients. While initial reports were promising several randomized control trials failed to demonstrate clear benefits of the branched chain enriched solutions (96-101). Thus, while there are theoretic

advantages to these solutions these advantages have not been borne out through clinical trials.

In general, large protein intakes can maintain a positive nitrogen balance even in the face of minimal caloric intake (102). However, positive energy balance is important to spare the utilization of protein energy as well as providing glucose, for the function of the nervous system, and essential fatty acids. One way of following the proportion of calories provided as protein versus non-protein calories is to look at the calorie to nitrogen ratio (103). The usual calorie to nitrogen ratio in a normal American diet is 170:1. However, in depleted and moderately ill patients the calorie to nitrogen ratio should be approximately 150:1 and for more critically ill patients the ratio should be about 125:1 although ratios as low as 90:1 have been used in very stressed patients. It is easy to vary the calorie to nitrogen ratio when using parenteral nutrition. However, enteral nutrition products contain total calorie to nitrogen ratios of 150 to 190:1 and it is more difficult to alter the ratio.

USE OF CARBOHYDRATES

Many hospitalized patients unable to eat are "fed" with intravenous 5% dextrose. This "feeding" provides approximately 170 kilocalories of carbohydrate per liter. The rationale for using 5% dextrose is based on the studies of Gamble and associates who were examining the optimal rations for survival at sea (104). These investigators found that small amounts of carbohydrates exhibited protein sparing effects. However, the administration of more than 100 grams per day of carbohydrate did not provide any further sparing of protein in normal subjects. Small amounts of glucose decreased protein loss by reducing hepatic gluconeogenesis. The use of either enteral or parenteral nutritional support has been recognized as life-saving in patients who have curable or controllable disease and who are unable to eat adequately. Substantial help is provided to patients with enteric fistulas, severe enteropathies, small bowel syndrome and severe facial injuries (105-108). One of the advances in burn therapy was the recognition that adequate nutritional intake enhances wound repair (109). In other conditions, however, the use of nutritional support has generated questions with regard to its usefulness.

Nutritional support is frequently used in critically ill patients with the goal of decreasing the utilization of endogenous substrates and attenuation of the rate of catabolism. However, these exogenous substrates are being introduced into an environment where the ability to utilize substrate as well as the rate of utilization often differs markedly from that of normal subjects and unstressed patients (110).

The "typical" American diet contains a caloric distribution of about 40% fat, 40% carbohydrates, and 20% protein. Recent recommendations are to decrease the fat intake to less than 30% of total calories, the balance going to carbohydrates. However, the optimum amounts and proportions for patients in the intensive care unit is unknown. When parenteral nutrition was initially introduced in the United States intravenous lipid emulsion was unavailable. This made dextrose the only non-protein energy source resulting in patients receiving large loads of carbohydrate. Glucose (dextrose) is the carbohydrate of choice for parenteral administration. Other carbohydrate sources such as fructose, xylitol, and sorbitol have been utilized without success (111). Fructose must be

phosphorylated prior to metabolism thereby depleting hepatic ATP levels. It also produces an increase in blood lactate levels. There are problems with dextrose infusions as well. Long- term administration of glucose-amino acid mixtures causes fatty acid deficiency requiring supplemental administration of lipids (112). Large loads of glucose produce side effects such as elevated transaminases and fatty liver. Deposition of fat in the liver with high carbohydrate loads may be due to a decreased ability to mobilize fat from the liver or insufficient capability to produce VLDL (113,114). Large loads of carbohydrates, whether given enterally or parenterally, can produce increased carbon dioxide generation from glucose metabolism (115). This may lead to problems in patients with marginal respiratory function whether these patients are breathing spontaneously, or on mechanical ventilation with a fixed minute ventilation leading to increased carbon dioxide retention and respiratory acidosis. This has been shown in selected patients to actually prevent weaning from mechanical ventilation and a change in non-protein calorie source was associated with successful weaning from mechanical ventilation (116,117).

The maximum rate of carbohydrate oxidation in normal subjects is around 5 mg/kg per minute. However, this decreases under stress to about 3 mg/kg per minute. If calories are provided in excess of these rates then lipogenesis, hyperglycemia, or glycogen deposition can result (118). Presently, the preferred non-protein source of nutrients is a mixture of lipids and glucose. This more closely approximates the normal dietary intake, avoids side effects of large glucose intakes, and supplies lipids which are the main fuel source for stressed patients (119). Nordenstrom et al showed that a lipid glucose combination administered to septic and traumatized patients caused less thermogenesis than with a glucose-amino acid mixture with an equal number of calories (120). These authors also observed less of an increase in urinary norepinephrine excretion. Baker and Rosenberg demonstrated that glucose and lipid mixtures produced fewer hepatic abnormalities (113). Many studies show that nitrogen retention is similar using glucose or glucose-lipid mixtures (121-123). It is important to administer at least some glucose to stimulate insulin which acts as an anabolic hormone and aids in nitrogen retention (124). This also provides sufficient glucose for metabolism by the brain.

In surgery patients there is a greater nitrogen balance per kilocalorie of carbohydrate when the energy intake was below 0.5 x REE than when it was above this level. Also, at low energy intakes carbohydrate was more protein sparing than fat. Fat has similar protein-sparing effects as carbohydrate when the carbohydrate intake is above 150 grams per day (125). Thus, patients should be provided with both carbohydrates and lipids as non-protein calorie sources.

USE OF FATS

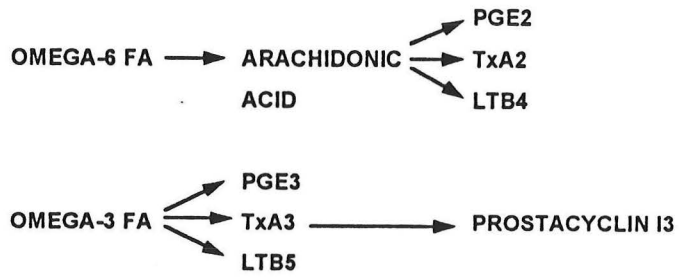
Polyunsaturated fatty acids that have 16 and 18 carbons such as those in soy bean and safflower oils are rich in omega 6 fatty acids (Table 5).

FATTY ACID COMPOSITION OF SELECTED OILS

FATTY ACIDS	OILS			
	SOYBEAN	SAFFLOWER	MCT	FISH OIL
6:0			<2	
8:0			70	
10:0			30	
12:0			<2	
14:0	0.1	0.1		7.0
16:0	10.5	6.7		17.3
16:1w7				8.6
18:0	3.2	2.7		2.7
18:1w9	22.3	12.9		12.9
18:2w6	54.5	77.5		2.1
18:3w3	8.5			0.9
20:5w3				12.8
22:6w3				8.7

These oils are used in the lipid emulsions for most parenteral and enteral feeding of hospitalized patients. Lipids serve as a non-glucose energy source and provide the essential fatty acid linoleic acid (18:2 omega-6) and the presumed essential alpha linolenic acid (18:3 omega-3). The metabolic activity of lipids is shown in Figure 11.

METABOLIC ACTIVITY OF LIPIDS



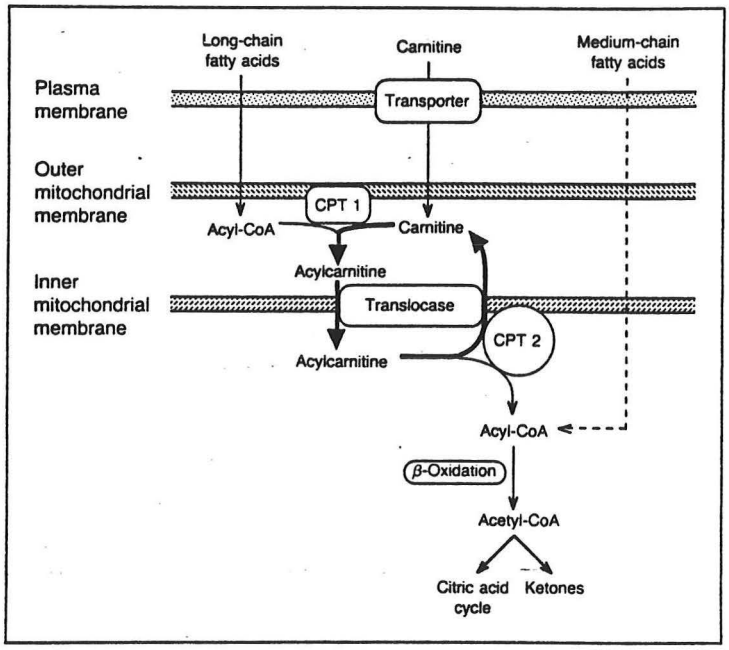
The known essential fatty acid linoleic acid leads to the production of arachidonic acid which is the precursor of the prostanoids and the thromboxanes of the 2 series and of the leukotrienes of the 4 series. These compounds have profound effects on various aspects of the immune response including lymphocyte proliferation, lymphokine secretion, macrophage collagenase synthesis, killer cell activity and tumorcidal activity of activated macrophages (126,127).

Fish oils contain small amounts of the omega-6 fatty acid linoleic acid but substantial quantities of eicosapentenoic acid (EPA) and docosahexaenoic acid (DHA), which are both long chain polyunsaturated omega-3 fatty acids (128,129). EPA is the precursor of the prostaglandins of the 3 series and of the leukotrienes of the 5 series. Leukotriene B5 is less inflammatory and less chemotactic than leukotriene B4 which is formed from arachidonic acid.

EPA also forms thromboxane A_3 which is a vasoconstrictor like thromboxane A_2

but not a platelet aggregator and serves as a substrate for prostacyclin I_3 which is a vasodilator and platelet anti-aggregator (128). This shifts the overall balance toward reduced clotting manifested by prolonged bleeding times and decreased thromboxane production. Fish oils also have been shown to dampen leukocyte function through decreased chemotaxis and decreased production of LTB_4. Omega-3 fats seem to be less inflammatory and more immulostimulatory than fats containing omega-6 fatty acids (128,130). Hence, fish oils offer an alternative energy source during critical illness that may improve immune function by being less inflammatory in conditions of excessive inflammatory response. Prolonged bleeding in the critically ill may be a theoretic clinical concern, however the inflammatory state is characterized by increased procoagulant activity that should counteract this.

Medium chain triglycerides (MCTs) which contain 8-carbon (Octanoic) and 10-carbon (decanoic) fatty acids (Table 4) have been proposed as one alternative to long chain triglycerides (LCTs) (131). The primary sources for medium chain triglycerides are fractions of coconut and palm kernel oils. Medium chain triglycerides offer numerous advantages over long chain triglycerides. MCTs are rapidly cleared from the blood because of their smaller molecular size and greater solubility (131). MCTs are rapidly oxidized and are independent of carnitine for entry into the mitochondria of all tissues (Figure 12, 132). MCTs are less likely to be deposited and more likely to be oxidized in tissues (131).



SPECIFIC NUTRIENTS

One reason for protein breakdown from skeletal muscle during injury or inflammation may center around specific amino acids such as glutamine. Lymphocytes, macrophages, enterocytes, thymocytes, colonocytes, fibroblasts, and possibly endothelial

cells all have a high rate of glutamine uptake but only partial oxidation. For lymphocytes and macrophages the rate of glutamine utilization is either similar to or greater than that of glucose (133). The rates of utilization of both glucose and glutamine are high even in resting lymphocytes and these rates are approximately 25% of the rate of glucose utilization by maximally working perfused heart (134). Almost all the glucose used by these cells is converted to lactate and some of the glutamine is converted to lactate, alanine, and aspartate. Recent work using lymphocytes and macrophages has shown that the quantitatively important pathway for glutamine utilization involves the left-hand side of the Krebb cycle (135). There is conversion of oxoglutarate to oxaloacetate despite the fact that the enzymes for the operation of the complete cycle are present in these cells. The hypothesis of why these cells do not fully oxidize glucose or glutamine is that complete oxidation would provide large quantities of ATP so that the concentration would increase and then feed back inhibition would cause marked decreases in the rates of both glycolysis and glutamine utilization. By having a high uptake and only partial utilization of these substrates, these cells provide optimal conditions for regulation of the use of intermediates of these pathways for the synthesis of purine and purimitine nucleotides during the cell cycle. Any decrease in the rate of glutamine utilization by lymphocytes would be expected to decrease the rate of proliferation in these cells. Complete oxidation rates are low since high rates of oxidation would provide more ATP that would inhibit the rate of glutamine utilization. Therefore glutamine must be used at a high rate by these cells even when they are quiescent. The response of the immune system must be rapid. Hence the rate of glutamine utilization must always be high in order to maintain optimal conditions for response to an immune challenge that may occur at any time (136,137).

Glutamine is made available in the lumen of the intestine from the digestion of protein. However, animal studies demonstrate that little of this glutamine enters the blood stream. The absorptive cells of the small intestine utilize glutamine at a high rate and probably utilize all that is absorbed from the lumen of the gut (138). Glutamine is considered a non-essential amino acid meaning it can be synthesized within the cell. Its presence in the free form in skeletal muscle is extensive, accounting for possibly 50% of the free amino acid in skeletal muscles. This pool is rapidly depleted during stress conditions such as critical illness.

Glutamine in skeletal muscle is considered to be the largest "store" of this amino acid. Glutamine constitutes 60% of the total free amino acids in skeletal muscle and is present in humans at a concentration of approximately 20 mmol/liter intracellular water (135). It has been suggested that the skeletal muscle glutamine pool represents a store of this amino acid for release into the blood stream much the same way that hepatic glycogen acts as a store for blood glucose. It has been shown that changes in muscle glutamine concentration following surgery, sepsis and trauma in human patients approaches 50% (139). A decrease greater than 50% in the concentration of glutamine in muscle may be important because it has been associated with increased mortality (140,141). The conclusion was that this relationship of glutamine pool to blood concentration "reveals an important role of this amino acid in the catabolic response to sepsis" (140). A decrease in the concentration of glutamine in muscle may mean a decrease in the rate of muscle protein synthesis and an increase in the rate of muscle protein degradation which results in a loss of skeletal muscle protein. If the process of muscle glutamine release does respond

to satisfy the demand for glutamine by the immune system, then an abnormally low plasma glutamine level could, via an impaired immune system, be responsible for failure to survive during sepsis, trauma, or burns (135).

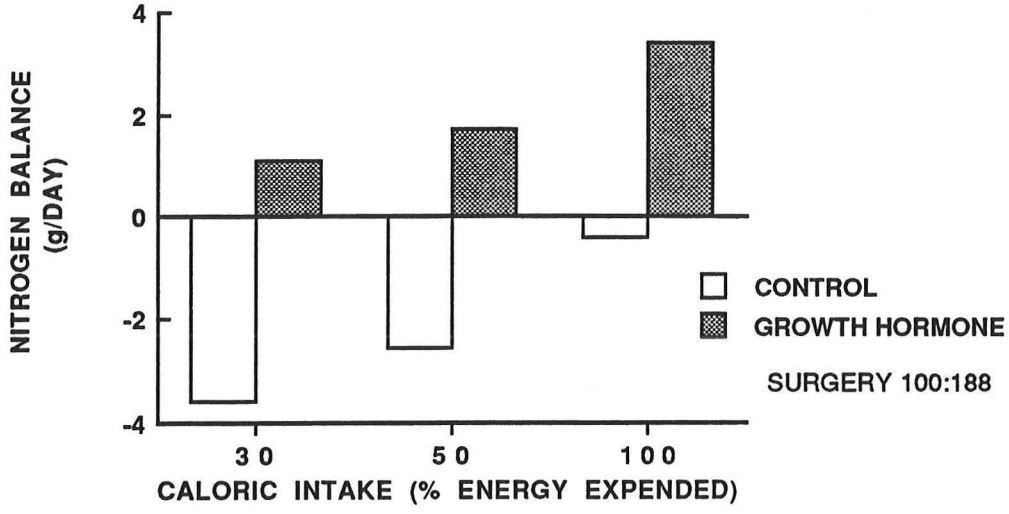
Arginine is another amino acid that could be beneficial in seriously ill patients. When given orally to normal volunteers at a dosage of 30 grams per day, arginine enhanced blastogenesis of lymphocytes in response to mitogen (142). Other studies have shown an increase in immunity, wound healing, and improved nitrogen balance (143). These findings are accompanied by an increase in the plasma concentration of insulin-like growth factor 1 (somatomedin C), and did not occur in animals with hypophysectomy, suggesting that an intact hypothalamic-pituitary axis is required for arginine to exert its beneficial effects. These effects may indeed be related to an increase in growth hormone levels, since arginine is a potent secretagogue for growth hormone, prolactin, insulin, and glucagon (144).

GROWTH FACTORS

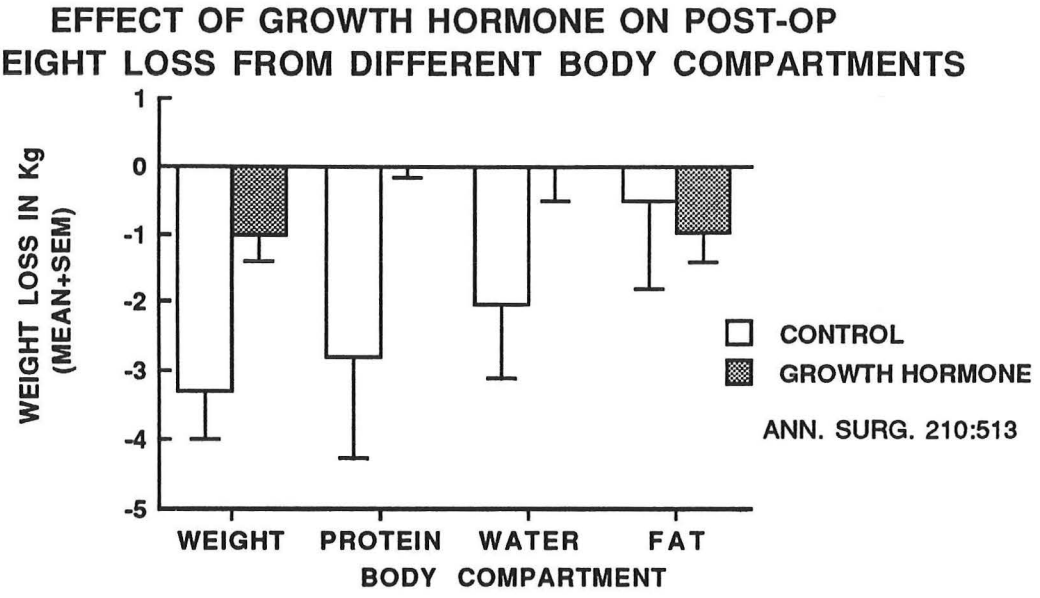
There are many growth factors that have been isolated, purified, their genes sequenced, and are now commercially available in large quantities through the use of recombinant DNA techniques. Many of these growth factors are already in clinical use such as erythropoietin for treatment of anemia in renal dialysis patients, the use of granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor in bone marrow transplant and after chemotherapy, and interleukin-2 as an immune modulator in patients with certain cancers.

One growth factor that holds promise for patients in the intensive care unit is the somatic growth factor, human growth hormone. Initial studies suggested a reduction in protein wasting (145,146). In 1961, Liljedahl and colleagues administered human growth hormone to a group of severely burned patients (146). Nitrogen balance improved as well as an increase in food intake and improved balance of phosphorous and potassium with a decreased catabolism of albumin. The major actions of growth hormone are: to decrease protein catabolism and to promote protein synthesis; to promote fat mobilization and enhance the conversion of fatty acids to acetyl coenzyme A; and to decrease glucose oxidation while increasing glycogen deposition. Manson and Wilmore examined the effect of growth hormone on nitrogen balance during hypocaloric and eucaloric parenteral nutrition as shown in Figure 13 (147).

EFFECT OF GROWTH HORMONE ON NITROGEN BALANCE DURING HYPOCALORIC AND EUCALORIC TPN



Three levels of caloric intake were examined: 100%, 50%, and 30% of the estimated energy expenditure. The nitrogen balance in the control group was negative during hypocaloric conditions but approached equilibrium with adequate caloric intake. In contrast, with growth hormone the nitrogen balance was positive at all levels of caloric intake even at the 30% level. Potassium and phosphorous were also retained along with nitrogen in proportions corresponding to their relative quantities found in skeletal muscle. This nitrogen retention is not short term or transient. Some patients have been maintained on growth hormone for up to 41 days after injury with similar effects on nitrogen balance (148). Clinical efficacy of this approach was evaluated in a placebo controlled, randomized, double-blind trial in patients post-op after gastrectomy or colectomy (149). Some of the results are shown in Figure 14.



The control group lost an average of 3.3 kilograms in the week following surgery. Much of this was lean body mass as evidenced by protein and water loss. The group with growth hormone, however, lost significantly less weight and maintained their lean body mass despite a hypocaloric diet. This effect correlated with muscle strength in that the post-operative hand grip force decreased 10% in the control patients, whereas it was maintained in the patients treated with growth hormone. Administration of growth hormone has also been shown to accelerate wound healing in burn patients (150). Growth hormone in these studies did result in a decrease in the length of hospitalization however at the present cost of recombinant human growth hormone a cost benefit analysis is needed.

ELECTROLYTES

Critical illness results in major alterations in body electrolyte homeostasis and therefore it is essential that adequate amounts of electrolytes and minerals be provided.

The usual electrolyte mineral requirements are shown in Table 6. Careful monitoring of blood electrolyte concentrations is necessary especially during the use of diuretics, nasogastric suction, diarrhea, endocrine abnormalities, hepatic failure and renal problems.

ELECTROLYTE AND MINERAL REQUIREMENTS

MINERALS	AMOUNT
SODIUM	>60 mEq/DAY
POTASSIUM	>60 mEq/DAY
CALCIUM	10-15 mEq/DAY
MAGNESIUM	8-20 mEq/DAY
PHOSPHATE	20-40 mEq/DAY

Magnesium is the second most abundant intracellular cation in the body (after potassium). Magnesium is a co-factor for all enzyme reactions that involve ATP and is also involved in the membrane pump that maintains electrical excitability in muscle and nerve cells (151). There is no reliable measure of total body magnesium status. Over half of the total body stores of magnesium are located in bone and nearly all the rest is in the intracellular compartment. Only 0.3% of the total body magnesium is found in the serum (2.6 millimoles) (151). Serum magnesium levels show little or no correlation with intracellular magnesium levels, making serum magnesium an unreliable measure of total body magnesium balance (152). The diagnosis of magnesium depletion must often be made on clinical grounds. Magnesium depletion should be suspected whenever there are decreases in potassium, phosphorous, sodium, or calcium (153,154). Magnesium supplementation in patients with acute myocardial infarction has been shown to reduce the incidence of arrhythmias. Ryzen, et al demonstrated that 53% of the patients residing in a coronary care unit had low levels of magnesium in lymphocytes, even though only 7% of these patients had a low serum magnesium (155).

Magnesium replacement for patients with symptomatic magnesium depletion and normal renal function should be 1 milliequivalent per kilogram for the first 24 hours and 0.5 milliequivalent per kilogram per day for the next 3-5 days. About twice the estimated magnesium deficit of 1-2 milliequivalents per kilogram is replaced because 50% of the parenteral dose will be lost in the urine despite significant magnesium depletion (156).

As patients go from a catabolic state (negative nitrogen balance) to an anabolic state (positive nitrogen balance) there is an increased need for the intracellular electrolytes phosphate, potassium, and magnesium. The enteral products are often low in sodium and hyponatremia can occur if additional sodium is not provided either intravenously or enterally.

FLUID STATUS

The fluid requirements and volume status of the critically ill patient is very important. Since many ICU patients are fluid restricted it is useful to use concentrated nutrient solutions especially when parenteral nutrition is used. Parenteral solutions made with 20% lipid emulsion, 15% amino acid solution, and 70% dextrose provide 1.3-1.5 kilocalories per milliliter. There are several enteral products that are calorically dense as well (e.g. Isocal HCN, 2 Cal HN, and Magnacal), which contain 2 kilocalories per milliliter. These enteral products however have a elevated osmolarity (590-690 mOsm/l) which may lead to more gastrointestinal problems than the less concentrated solutions. In patients experiencing diarrhea from enteral feeding, paregoric can be added to the enteral solution, however fluid management must aim to prevent dehydration. There is an obligate urea excretion during the administration of amino acids particularly in large amounts which may cause a significant osmotic diuresis. In general, for every gram of nitrogen metabolized 80-100 milliliters of water is needed (157).

TRACE ELEMENTS

Trace elements are essential components of many enzyme systems and are necessary for normal physiologic function. Trace elements shown to be essential in humans include iron, zinc, copper, chromium, selenium, iodine, and cobalt. In addition, manganese, molybdenum and vanadium may also be important (158-161). A list of the enteral and parenteral dosages for these trace elements are shown in Table 7.

TRACE ELEMENT REQUIREMENTS

ELEMENT	ORAL	INTRAVENOUS
ZINC	10-15 mg	2.5-4.0 mg
COPPER	1.2-3 mg	0.5-1.5 mg
CHROMIUM	50-200 μg	10-15 μg
SELENIUM	50-200 μg	40-120 μg
MANGANESE	0.7-5.0 mg	0.15-0.8 mg

Zinc is required for growth and healing. It is part of the enzyme superoxide dismutase which controls oxygen radicals that form peroxide. Zinc is also required for mobilization of vitamin A from its stores in the liver, nucleic acid synthesis, and lymphocyte transformation. ICU patients are commonly deficient in zinc because of such predisposing factors as diarrhea, diuresis, malnutrition, alcoholism, chronic renal failure, burns, and chronic debilitating diseases (162). The deficiency syndrome increases susceptibility to infection. The diagnosis requires a decrease in plasma zinc levels and replacement may require a daily dose of 4 mg elemental zinc (163).

Selenium is a co-factor for glutathione peroxidase, an enzyme that converts hydrogen peroxide to water, preventing the formation of the highly destructive hydroxyl ion. A deficiency of selenium and therefore glutathione peroxidase carries an increased risk of oxygen toxicity. Many enteral feeding formulas do not contain the recommended daily requirement of 50 to 200 micrograms per day.

Chromium is a co-factor for the action of insulin. Chromium deficiency can produce insulin resistance and progressive hyperglycemia. Normal serum chromium levels are 0.04-0.35 micrograms per milliliter (164).

Selenium, zinc, chromium, copper and manganese should be routinely added to total parenteral nutrition solutions. Most commercial products for use enterally contain adequate amounts of trace elements when used as the source for nutrition. Patients with large fluid losses through the gastrointestinal tract often require additional zinc. Iron is not usually needed by critically ill patients who generally have adequate iron stores.

VITAMINS

Vitamins serve as enzyme co-factors in many metabolic pathways and thereby play a crucial role in substrate utilization and host defense. These functions are vital to critically ill patients and must therefore be provided in any nutritional support of these patients. Unfortunately the amount of vitamins required for optimum health even in normal individuals is largely unknown. The recommended daily dietary allowance (RDA) for various vitamins was determined by the Food and Nutrition Board of the National Research Council. When this council reconvened however they could not decide whether the RDA represented intakes for optimum health or intakes to prevent dietary deficiency states. There is now a move to formulate a required dietary index of vitamins which will represent the minimum requirement for prevention of deficiency disease states. In the mean time we are left with very little data on which to formulate optimal vitamin intake even in normals much less critically ill patients. While the RDA can give us a rough guide there are several vitamins for which data exists that shows that the RDA is insufficient in either normals and/or critically ill patients.

Vitamin K is not added to most nutritional products but may be needed in increased quantities in critically ill patients. Most vitamin K in normal individuals is obtained through the gut from vitamin K producing intestinal flora. However, in critically ill patients receiving broad spectrum antibiotics this flora is altered and subsequent vitamin K deficiency can result. ICU patients should have the prothrombin time monitored and supplemental vitamin K given as needed in a weekly dose.

Thiamine or vitamin B1 catalyzes reactions involving aldehyde groups and is particularly important in the conversion of pyruvate to acetyl-CoA and carbon dioxide. Deficiency states of this vitamin include beri beri, Wernicke Korsakoff syndrome, neuropathy and psychoses. Approximately 45% of the population does not meet the recommended daily allowance for vitamin B1 as shown in Table 8 (165).

PRIOR NUTRITION

NUTRIENT	% OF POPULATION NOT MEETING RDA
B-6	80%
Mg	75%
CALCIUM	68%
IRON	57%
A	50%
B-1	45%
C	41%
B-2	36%
B-12	36%
B-3	33%

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Alcoholics have a high prevalence of a deficiency state of this vitamin. The requirements for this vitamin are proportional to the carbohydrate intake and symptoms of deficiency states may not be manifested until carbohydrate feeding is given. Therefore, many patients in the ICU may require replacement therapy which would be much more than the 1-3 milligrams of recommended dietary allowance.

Vitamin E is the major, if not the only, chain-breaking antioxidant in membranes (166). It acts as an antioxidant to scavenge free radicals by blocking the peroxidation of polyunsaturated fatty acids. Vitamin E has been shown to be important in protection against oxidant stress, immune cell function, and immune cell proliferation(167-169). Most patients in the ICU have marginal or deficient levels of vitamin E and often their only source of vitamin E is from the lipid solutions (170). Parenteral lipid solutions contain polyunsaturated fatty acids which provide several different isomers of tocopherol (vitamin E). For instance, intra-lipid provides only 10% of the total vitamin E concentration as alpha tocopherol the rest is provided as beta, gamma, and delta tocopherol isomers. These other isomers are orders of magnitude less effective than alpha tocopherol in the role as a free radical, chain-breaking antioxidant in cell membranes (170). Vitamin E measurements using colorimetry or fluorometry cannot distinguish between the different isomers of vitamin E and would therefore overestimate the vitamin E status of patients. High pressure liquid chromatography can distinguish the various isomers and is the method of choice for monitoring tocopherol status in the intensive care unit (171). The vitamin E status within the cell membrane is markedly influenced by the available plasma tocopherol pool such that the distribution of isomers given will show up in the cell membrane. Even high concentration supplements of alpha tocopherol in the presence of these other isomers will not increase significantly the alpha tocopherol content of the cell membranes (170). Providing selenium, which is necessary for the production of glutathione, vitamin C, and certain sulfated amino acids such as cysteine act to supplement vitamin E activity (172). It's been shown that patients with adult respiratory distress syndrome (ARDS) have low plasma vitamin E levels as well as a deficiency of alveolar fluid glutathione, suggesting an increased need for vitamin E and selenium which may

delay onset of respiratory failure (172,173).

The importance of ascorbic acid or vitamin C in humans has begun to be characterized more extensively, particularly the biochemical properties. Ascorbic acid accelerates hydroxylation reactions in a number of biosynthetic pathways. The most widely appreciated role of ascorbic acid is that of a co-factor for prolyl and lysyl hydroxylases in the biosynthesis of collagen. Ascorbic acid is important for optimal activation of prolyl hydroxylase, hydroxylation of peptidyl proline, an enhanced secretion of procollagen that contains hydroxyproline. Procollagen produced in the absence of vitamin C is unstable and does not show the same tertiary structure as collagen produced in the presence of vitamin C (174).

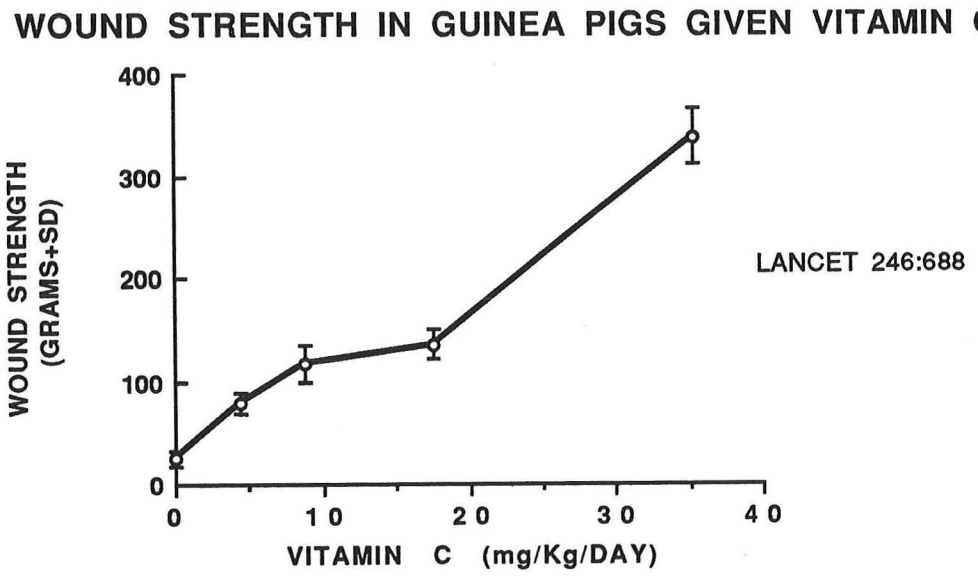


Figure 15 shows the relationship of wound strength in guinea pigs given various dosages of vitamin C. It can be appreciated that there is an increase in wound strength with increasing vitamin C administration (175). Vitamin C has been shown to influence various aspects of the immune system including lymphocyte transformation and motility and function of polymorphonuclear leukocytes (176,177).

Dr. Linus Pauling postulated nearly two decades ago that the recommended daily allowance grossly underestimates the amount of ascorbate necessary for optimum health in humans (178). There are numerous in vitro studies suggesting that higher intakes of vitamin C may be optimal. These include measurements of intracellular ascorbate levels in lymphocytes and saturation levels for renal tubular reabsorption of ascorbate. Many of these concepts in the biology and biochemistry of ascorbic acid are summarized by Levine (174).

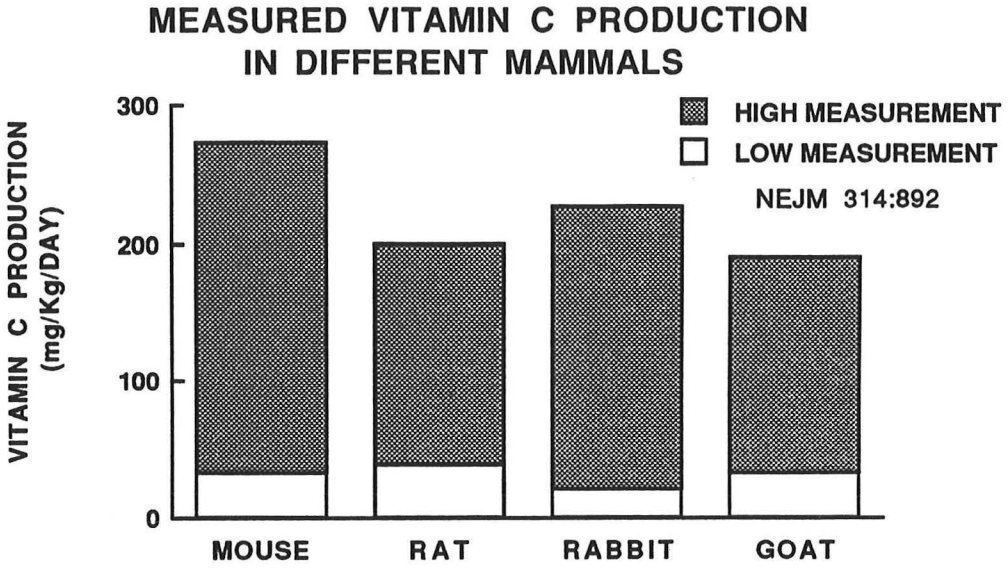


Figure 16 shows the measured vitamin C production in different mammals in milligrams/kilograms/day. If these levels are normalized for 70 kilograms of (average human) weight the low measurement corresponds to approximately 2 grams per day while the high measurement is between 15 and 20 grams per day (179).

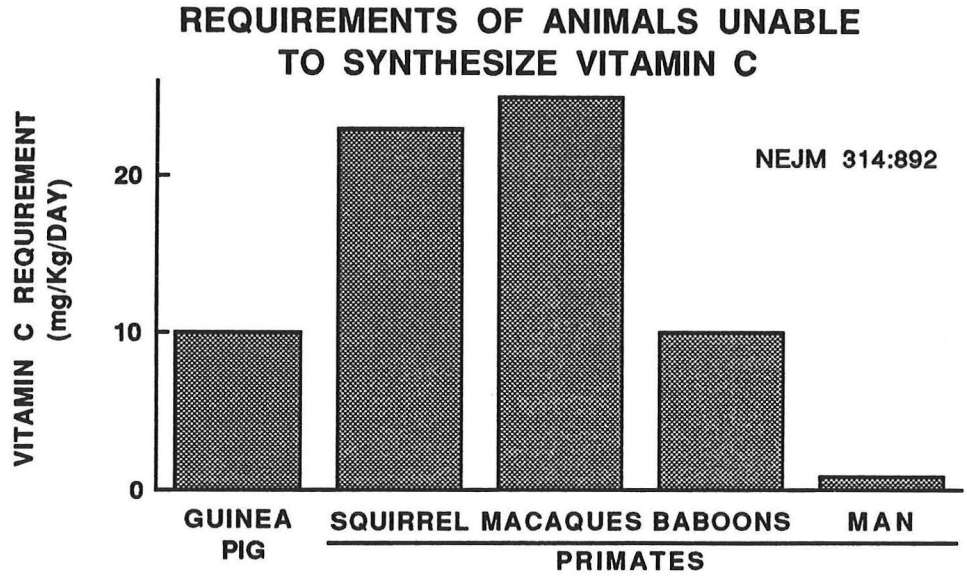
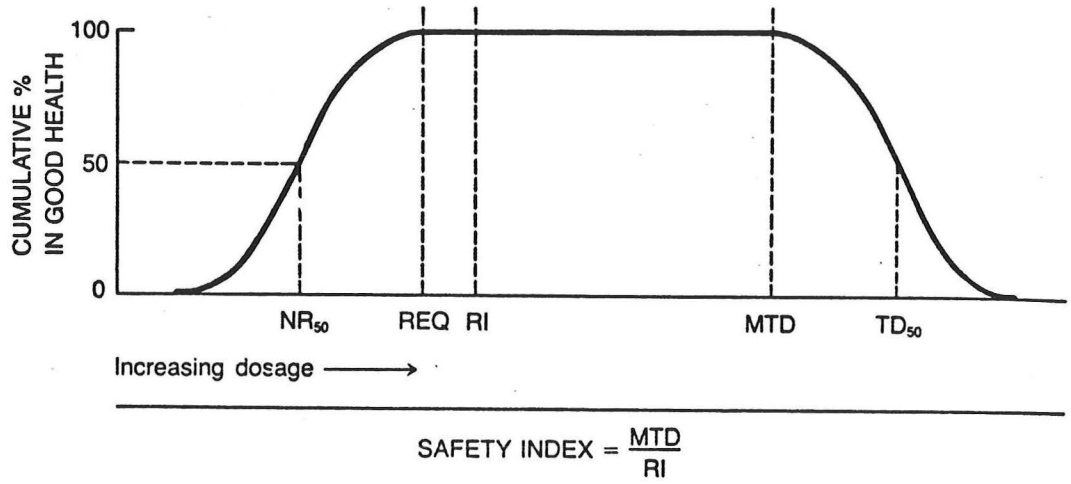


Figure 17 shows the requirements of certain animals unable to synthesize vitamin C including man. Optimum health in guinea pigs has been shown to require 10-16 milligrams per kilogram per day of vitamin C. Optimum health in non-human primates is shown to be between 10 and 25 milligrams per kilogram per day. The requirement in man is shown as 0.9 milligrams per kilogram per day which is slightly above the recommended daily allowance (RDA) for vitamin C. While much of this data is circumstantial it seems

likely that the human requirement for vitamin C for optimum health is significantly above the recommended daily allowance (174).

Vitamin products for use in parenteral nutrition are available and should be used routinely. Vitamins should be infused daily over a long period of time, such as with amino acid solutions, to optimize supply and to avoid exceeding thresholds for excretion. This will insure that the patient has vitamins available when they are needed.

Since the optimum dosages of vitamins are unknown and they are generally regarded as safe it might be reasoned that more is better. However, some measure of toxicity should be used. The usual measure of toxicity in pharmacological drugs is the pharmacological therapeutic index or TI which is defined as the median toxic dose or TD50 divided by the median pharmacologically effective dose or ED50. A proportional relationship similar to this drug therapeutic index has been developed for nutrient supplements. This vitamin safety index is shown in Figure 18. This vitamin safety index ranges from 5-10 for vitamin A to over 1000 for folic acid (180).



NR_{50} = Median Nutritional Requirement
REQ = Requirement
RI = Recommended Intake
MTD = Minimum Toxic Dose
TD_{50} = Median Toxic Dose

NUTRIENT ADMINISTRATION

The route of nutrient administration is a major decision in nutritional support. There is a commonly used dictum introduced by Heinberger that "if the gut works, use it" (181). There is increasing evidence that the route of nutrient administration is of major biologic importance. The enteral route is considered the natural portal of nutrient entry, digestion, and absorption implying that nutrient use would be more efficient when introduced into the gastrointestinal tract. Glucose administered orally produces a more rapid rise in insulin than glucose given parenterally, probably related to secretion of secretin by the stomach (182). The large intestines are important for fluid homeostasis

and micronutrients are more readily administered via the enteral route.

One compelling reason to provide nutrition through the gastrointestinal tract is the observation that the presence of nutrients in the intestine are essential in maintaining normal enteric enzymatic activity and structural integrity (183). It has become increasingly apparent that the intestinal mucosa functions as a major local defense barrier to prevent colonizing bacteria in the gut from invading systemic organs and tissues. This barrier function is complimented by a variety of immunologic mechanisms. These include immune cells within the intestinal wall and mesenteric lymph nodes, intraluminal secretory Iga, and the Kupffer cells of the liver and the spleen (167184).

Any insult resulting in disruption of the intestinal epithelium allows colonizing bacteria to pass through the epithelial mucosa oftentimes leading to infection of the mesenteric lymph nodes and other systemic organs. This microbial migration has been termed bacterial translocation (184). Major mechanisms promoting bacterial translocation include altered permeability of the mucosa caused by hemorrhagic shock, sepsis or endotoxemia, decreased host mechanisms such as immunosuppression, and increased bacterial overgrowth or intestinal stasis. Experimental animals given parenteral nutrition exhibit an increased incidence of bacterial translocation from the gut (185). These studies have shown that diets which lack bulk or fiber are associated with a decreased intestinal bacterial barrier function, and that glutamine is an essential amino acid for mucosal integrity in the gastrointestinal tract (186,187).

Enteral feeding is also associated with greater safety, convenience and economy than parenteral nutrition. Enteral feeding has been shown to be as effective as antacids and H2 blockers in the prevention of hemorrhage from stress-induced gastritis (188). Enteral nutrition avoids problems associated with delivery of parenteral nutrients through venous catheters including pneumothorax, catheter sepsis, and metabolic derangements. Despite these advantages enteral nutrition is often impossible to deliver in the critically ill patient. Enteral feeding is not possible when there is intestinal obstruction, vomiting, ileus, massive gastrointestinal hemorrhage, and high output enteral fistulas. There are many other relative indications for parenteral nutrition.

A large number of the studies comparing enteral and parenteral nutrition were performed in patients with esophageal obstruction where the enteral nutrition was delivered via a catheter jejunostomy (189-191). This enteral delivery system has been shown to be a reliable method of nutrient delivery however nasal enteric tubes are more likely to be used and are associated with much more morbidity. Complications associated with nasal enteric tubes include tube dislodgement, vomiting, gastric distention, and aspiration all of which can result in inconsistent delivery of nutrients (192). The most common problem is diarrhea which may be caused by a variety of factors. Diarrhea is a particularly bad complication since it may result in fluid and electrolyte imbalance, decubitus ulcer formation, and increased wound and urinary tract infections. Kelly et al found a 41% incidence of diarrhea in patients, many receiving nasogastric feedings, staying in an ICU longer than 48 hours (193). Brinson and Kolts observed that of 35 ICU patients with albumin levels below 2.6 grams per deciliter 12 developed diarrhea while no patient with an albumin level above 2.6 grams per deciliter had diarrhea (194).

Enteral feeding is usually associated with more intermittent feeding schedules many times because of gastrointestinal bleeding or the need to make a patient NPO prior

to a diagnostic procedure or because of the need to slowly increase the concentration and volume of the feeding. For this reason, it is not uncommon for patients to develop a cumulative nutritional deficit when enteral nutrition is used. As a general rule if full caloric intake cannot be achieved within 3 or 4 days by enteral nutrition, the parenteral route should be considered. The primary goal should be to provide adequate caloric intake with the route of administration as a secondary consideration.

Parenteral nutrition requires placement of an intravascular catheter. The decision of whether or not to place a central or peripheral intravascular catheter depends on whether parenteral nutrition will be used to supplement enteral nutrition and also how long nutrition will be needed. If nutrition is needed for only a short period of time (1 week or less) or if parenteral nutrition is to be used to supplement enteral nutrition, then peripheral vein catheterization can be used. Large volumes of parenteral nutrition are needed to administer an adequate number of calories through peripheral veins since the peripheral vein can only tolerate an osmolarity of 700-800 milliosmoles per liter (195,196). The patient must be able to tolerate fluid intake over 2 liters per day. Amino acid concentration is limited to 3-4% and fat emulsions are necessary to provide calories with a minimal osmotic load (197).

The infusion of nutrients through a central vein catheter allows the use of solutions with much higher osmolarity. The placement of the central venous catheter is a matter of choice although the infraclavicular subclavian vein cannulation is the most commonly used. Catheter placement should be confirmed with a chest roentgenogram. If approach is through the superior veins the ideal location for the catheter tip is in the mid superior vena cava. A subcutaneous tunnel for the catheter should be considered if parenteral nutrition is to be administered for a prolonged period. It is suggested that the catheter be dedicated only to the administration of parenteral nutrition, to reduce handling and infection. The use of multi-lumen catheters is valuable when other chemotherapeutic agents are to be administered, however these catheters carry a higher rate of associated sepsis. Catheter related sepsis during parenteral nutrition occurs in 5-10% of patients. Specific factors felt to be important in preventing catheter related sepsis are listed as follows (198):

1. Solution preparation under a laminar flow hood
2. Aseptic catheter insertion
3. Strict protocol for management of dressings and infusion apparatus
4. Maintaining a closed infusion system used only for nutrient solutions
5. TPN administration through a single lumen catheter
6. Patient management by a specialized multidisciplinary nutrition/support team

Nasogastric or nasoduodenal tubes are commonly used in the critical care setting, although oral gastric tubes and tube enterostomies placed either in the stomach or jejunum are also used. The nasoenteric tubes should be soft, small bore tubes composed of non-reactive materials such as silastic or polyurethane. Many have weighted tips that enable them to pass into the small bowel with peristalsis although this occurs only about 15% of the time if allowed to pass blindly. The use of metoclopromide and placing patients on the right side may help distal migration. Fluoroscopic or endoscopic guidance may also facilitate placement.

Placement should be confirmed by an abdominal roentgenogram to avoid intrapulmonary and esophageal feeding. Tube placement should be checked often with a chest x-ray because it is not unusual to find the tube displaced into the esophagus. Large bore polyvinyl nasogastric tubes are not recommended for enteral nutrition.

Product	kcal/mL	Protein (g/dL)	Fat (g/dL)	CHO (g/dL)	Osmolality	Volume to Meet RDA
Isotein HN	1.2	6.8	3.4	15.6	300	1,770
Precision NH	1.05	4.4	0.1	21.6	525	2,850
Precision Isotonic	1.0	2.9	3.0	14.4	300	1,560
Precision LR	1.1	2.6	0.2	24.8	530	1,710
Isocal	1.06	3.4	4.4	13.3	300	1,890
Sustacal	1.01	6.1	2.3	14.0	620	1,060
Enrich	1.1	4.0	3.7	16.0	480	1,391
Ensure	1.06	3.7	3.7	14.5	470	1,887
Ensure HN	1.06	4.4	3.6	14.1	470	1,321
Osmolite	1.06	3.7	3.9	14.5	300	1,887
Osmolite HN	1.06	4.4	3.7	14.1	300	1,321
Travasorb HN	1.0	4.5	1.6	17.5	560	2,000
Travasorb	1.0	3.0	1.6	18.5	560	2,000
Magnacal	2.0	7.0	8.0	25.0	590	1,000
Isocal HCN	2.0	7.5	10.2	20.0	690	1,000
Sustacal HC	1.5	6.1	5.8	19.0	700	1,180
Ensure Plus	1.5	5.5	5.3	20.0	690	1,420
Ensure Plus HN	1.5	6.3	5.0	20.0	650	947
Tolerex	1.0	2.1	0.15	22.6	550	2,000
Vivonex T.E.N.	1.0	3.8	0.3	20.6	630	2,000
Critcare HN	1.06	3.8	0.5	22.0	650	1,890
Vital HN	1.0	4.2	1.1	18.5	500	1,500

*CHO = carbohydrate; RDA = recommended daily allowance.

Some of the many solutions available for enteral administration are shown in Table 9. Enteral feedings are usually classified as polymeric, oligomeric, or modular (199,200). Polymeric formulas are semi-isotonic or hypertonic solutions that contain 100% of the recommended daily allowance for vitamins and minerals when a total daily prescription of, on average, 2 liters is administered. Most have a relatively high carbohydrate/fat ratio, are low in sodium and fiber, and contain intact or almost intact protein. Most are lactose free because of the high incidence of gastrointestinal intolerance of lactose. The protein source is usually egg, soy or lactalbumin that may be intact or partially hydrolyzed. Polymeric diets therefore require the ability to digest protein, carbohydrate, and fats. The osmolarity of these formulas are usually low because of the high molecular weight compounds used. They are fairly palatable and can be used for oral as well as tube feedings, are relatively inexpensive, and adequate for the majority of patients (201).

Oligomeric or elemental diets contain basic molecules that require little or no digestion. They are absorbed almost completely and leave little residue in the colon. They contain either crystalline amino acids or dipeptides and tripeptides, oligosaccharides and disaccharides, minimal amounts of long or medium chain triglycerides, and all essential minerals and vitamins (201). Oligomeric diets require digestion of both carbohydrate and fat and thus require some pancreatic exocrine function. These diets are usually hyperosmolar and can cause diarrhea if delivered too rapidly. They carry an increased cost but may be useful particularly during periods of digestive or absorptive insufficiency (202).

Modular diets are used in patients with unusual dietary requirements. A "module" consists of one or several nutrients that can be combined to produce a nutritionally

complete diet. This type of modular feeding is expensive and complicated however is rarely needed (203).

CONSIDERATIONS FOR SPECIFIC DISEASES

Liver disease presents unique problems for providing nutritional support. The liver is responsible for 20% of the body's basal metabolism. It is important in the metabolism of both endogenous and exogenous carbohydrates, lipids, and proteins with liver disease markedly altering this substrate usage. Patients with different liver diseases such as acute hepatitis, biliary obstruction, cirrhosis, and hepatic encephalopathy require different nutritional management. Important considerations include calorie intake, protein intake, fluid management, hypoglycemia from depletion of glycogen stores, and thiamine, folic acid, and vitamin B 12 deficiencies.

Patients with hepatic encephalopathy represent a dilemma, since these patients usually present with underlying malnutrition and hypoalbuminemia. Minimizing protein intake may improve these patients' mental status but at the cost of further deterioration of their nutritional state. These patients have been found to have an increased level of the aromatic amino acids in plasma and a decreased level of branched chain amino acids (94,95). This has led to the investigation of supplying these patients with branched chain enriched amino acid solutions. However, randomized trials have failed to demonstrate any clear benefits of branched chain enriched solutions, even though initial reports were promising (96-101). Both enteral and parenteral branched chain enriched amino acid solutions are available and may benefit patients refractory to protein restriction and the usual therapeutic measures.

Acute renal failure carries mortality rates of 40-80% when it occurs following trauma, surgery, or sepsis. Extremely high catabolic rates for these patients has been measured, up to 1 kilogram of lean body tissue lost per day. The challenge is to provide nutritional support without inducing uremia, fluid overload, or electrolyte imbalance. Providing small amounts of protein rich in essential amino acids to minimize the production of urea has been investigated, but with incomplete success (204-206). The infusion of glucose and small amounts of only the essential amino acids minimizes nitrogen waste and fluid imbalance and may be indicated in patients for whom dialysis represents a hazard. However, for most patients, there is no proven nutritional advantage to supply nitrogen exclusively as essential amino acids (206). The current recommendations calls for more nourishing solutions providing 1.2-1.5 grams per kilograms per day of approximately equal quantities of essential and non-essential amino acids. The mortality rate remains high underlining the major element in the hypercatobolic response associated with acute renal failure is the critical illness or injury that led to its development. Each hemodialysis treatment results in the loss of 6-9 grams of amino acids and peritoneal dialysis leads to 130-180 grams lost per exchange (207,208).

Patients with severe protracted pancreatitis usually demonstrate a marked degree of nutritional depletion. This observation forms the rationale for intensive nutritional support however part of the medical management is directed to minimizing the stimuli to pancreatic exocrine function. Nutritional therapies have been shown to stimulate pancreatic exocrine secretions in the following descending order of magnitude: oral solid

diets, oral elemental diets, intraduodenal elemental diets, intrajejunal elemental diets, total parenteral nutrition, and fasting. Parenteral feedings are generally prescribed in the early acute phase of severe pancreatitis. Studies indicate that pancreatic enzyme production is not stimulated by intravenous infusions of amino acids or lipids, or by short term TPN therapy with either glucose based or lipid based nutrient solutions (209,210).

Despite the theoretical advantages of TPN, Saxs and associates showed that there was no difference in the number of days to oral intake, the total hospital stay, or the number of complications of pancreatitis when early parenteral nutrition was compared to standard crystalloid infusions (211).

Lipid infusions should be withheld in patients in whom pancreatitis is associated with persistent secondary hyperlipidemia and in those with pancreatitis due to an underlying disorder of lipid metabolism (209). Otherwise intravenous administration of lipids or lipid-based TPN has been shown to be safe and effective.

One relative contraindication to administration of intravenous lipids is acute myocardial infarction or ischemia. Some studies of lipid infusions have been associated with elevated circulating free fatty acid levels (212), and though the acute effect of this on ischemic myocardium is controversial (213), studies exist that suggest that arrhythmias may be precipitated (214) and the area of ischemic damage in acute myocardial infarction may be extended (215).

Taurine supplementation may prove beneficial to patients with several types of heart disease. Taurine is an amino acid that has a role in the conjugation of bile acids and is implicated in the stabilization of the electrical activity of cell membranes and myocardial contractility (216). It is the most abundant intracellular free amino acid, present in millimolar quantities whereas other amino acids are usually present in micromolar quantities. Taurine is generally considered a non-essential amino acid for humans however it is not present in currently available crystalline amino acid preparations and patients receiving TPN develop a significant deficit in plasma taurine levels (216-218).

The respiratory and cardiac systems are unique in that they are required to function continuously without rest. They therefore continually use energy and thus must have a continuous supply of energy. Respiratory muscle function is altered by malnutrition as discussed previously. Malnourished patients exhibit a reduced ability to clear airway secretions. This coupled with a reduced immune function makes these patients especially susceptible to pneumonia.

Acute respiratory failure is the most common admitting diagnosis to the intensive care unit. (see Figure 1) The respiratory effects of nutrition, regardless of the route of administration, include an increase in oxygen consumption ($V0_2$), carbon dioxide production ($VC0_2$), and minute ventilation (VE). The respiratory quotient (RQ) is defined as the ratio of CO_2 produced to that of 0_2 consumed during the course of fuel oxidation. The RQ for glucose is 1.0, for fat is 0.71, for protein is 0.80.

Nutrition in this group of patients must be provided without causing an excessive increase in ventilatory demand. Excessive intake, especially of carbohydrates, in patients who are unable to increase their minute ventilation such as patients with COPD or patients on mechanical ventilation can result in hypercapnia and respiratory acidosis secondary to increased carbon dioxide production (117,219). In patients with COPD it may be necessary to prolong the period of mechanical ventilation to provide adequate nutritional

repletion. When the patient is ready to be weaned from the ventilator a decrease in carbohydrate intake may prove beneficial. Providing calories in excess of requirements can be very troublesome for patients with respiratory failure. Excess glucose has a respiratory quotient greater than 1.0, reflecting lipogenesis. This produces a marked increase in CO2 production.

COMPLICATIONS OF NUTRITIONAL SUPPORT

The administration of parenteral and enteral nutrition can result in a number of complications. These are listed in the following tables and most are either obvious or self-explanatory.

COMPLICATIONS OF ENTERAL NUTRITION

MECHANICAL	METABOLIC
TUBE "KINKS"	NUTRIENT INTOLERANCE
NASOPHARENGIAL EROSIONS	ELECTROLYTE / FLUID IMBALANCES
SINUSITIS, OTITIS	
INTESTINAL OBSTRUCTION	
NAUSEA / VOMITING	NONCOMPLIANCE
ASPIRATION	
DIARRHEA	

COMPLICATIONS OF PARENTERAL NUTRITION

METABOLIC	
GLUCOSE	FAT
HYPERGLYCEMIA	HYPERLIPIDEMIA
HYPOGLYCEMIA	MICROEMBOLISM
	DEFICIENCY
PROTEIN	ELECTROLYTE
HYPERCHLOREMIC ACIDOSIS	POTASSIUM DEFICIENCY
PRERENAL AZOTEMIA	
PHOSPHATE DEFICIENCY	
AMINO ACID IMBALANCES	MAGNESIUM DEFICIENCY
OTHER	CALCIUM DEFICIENCY

COMPLICATIONS OF PARENTERAL NUTRITION

MECHANICAL
VENOUS ACCESS - SUBCLAVIAN VEIN (2-20%)
PNEUMOTHORAX
HEMOTHORAX
CATHETER MISPLACEMENT
THROMBOSIS
INFECTIOUS
ABSOLUTE INDICATIONS FOR REMOVAL
INFECTION AT CATHETER ENTRANCE
SEPTICEMIA
SEPTIC SHOCK

COMPLICATIONS OF PARENTERAL NUTRITION

METABOLIC	
VITAMIN	TRACE METALS (COPPER)
HYPERVITAMINOSIS	LEUKOPENIA
DEFICIENCY	"STEELY HAIR" SYNDROME
VIT. K, FOLATE, B-12	OTHER
TRACE METALS (ZINC)	MANGANESE
ACRODERMATITIS	CHROMIUM - GLUCOSE
HAIR LOSS	TOLERANCE FACTOR
DELAYED WOUND HEALING	
OTHER	

The most common metabolic complication observed in patients receiving TPN is a derangement of serum glucose levels. Ryan observed a 15% incidence of marked hyperglycemia (glucose > 400 mg per deciliter) and a 9.5% incidence of hypoglycemia (glucose < 50 mg per deciliter) among 200 consecutive patients receiving glucose based TPN (220). Hyperglycemia may be a manifestation of overt or latent diabetes mellitus, or it may reflect the reduced pancreatic insulin response to a glucose load, which is routinely observed during starvation, stress, pain, major trauma, infection, and shock (220). Hyperglycemia may also represent peripheral insulin resistance possibly secondary to high levels of circulating catecholamines and glucocorticoids found in conditions of acute stress such as sepsis (220,221). A gradual increase in glucose based TPN, over a 3 day period,

may avoid significant hyperglycemia.

Insulin may be added to the TPN solution as a means of insulin administration and glucose control. This has the advantage that inadvertent alterations in the rate of glucose delivery are automatically accompanied by appropriate adjustments in the amount of insulin administered. The manifestations of glucose intolerance may be averted or ameliorated in patients with persistent hyperglycemia by providing a portion of the non-protein calories as fat (222,223).

Blood glucose levels decrease when the rate of infusion of glucose based TPN is abruptly stopped (221). Wagman and associates studied 48 patients in whom glucose based TPN was discontinued abruptly (224). None of the patients developed symptoms of hypoglycemia, but 4 of the 48 patients had nadir blood glucose levels below 70 milligrams per deciliter, including one patient with a value of 49 milligrams per deciliter. This nadir value consistently occurred within one hour of stopping TPN, thus tapering the infusion rate over 2 hours would appear to be safe.

Gastrointestinal intolerance of enteral nutrition is common and may be manifested by vomiting, abdominal cramping and distention, and diarrhea. Diarrhea is the most common of these although the incidence is variable. Cataldi-Vetcher and associates reported an incidence of diarrhea of only 2.3% (225). In contrast Heymsfield and associates (226) found an incidence of 20% and Silk and associates reported a 25% incidence (227). Much of this GI intolerance has been felt secondary to the infusion of hyperosmolar feeding mixtures. However a variety of other, perhaps more important factors, have been implicated (226-229). The development of diarrhea has been associated with the infusion of cold feeding formulas, prolonged antibiotic administration, other concurrent medications, magnesium containing antacids, fat malabsorption, intestinal atrophy due to malnutrition, lactose intolerance, microbial contamination of nutrient formulas, and most recently serum hypoalbuminemia with low serum colloid osmotic pressure (228,229).

CONCLUSION

The role of nutritional support in the care of critically ill patients is still not fully established. There is much uncertainty over the lack of evidence that nutritional support plays any significant role in improving the outcome of such patients. Our current techniques of nourishment for patients in the ICU is suboptimal and therefore outcome studies using these techniques may result in erroneous results. Providing adequate nutrition requires a multi-disciplinary approach, close monitoring, and frequent adjustments.

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