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Nutrient Metabolism and Support in the Normal and Diseased Liver

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Introduction

The liver plays a dual role in nutritional wellbeing. First, it contributes to nutrient assimilation through the synthesis of bile acids. At the time of a meal, as the gallbladder contracts, bile acids are released into the gut lumen. These bile acids enable lipids to be absorbed efficiently. Second, the liver plays a major role in substrate metabolism and allocation. It maintains nutrient blood levels at a constant level despite variations in substrate availability. It is therefore not surprising that damage to this vital organ has a tremendous impact on nutritional status.

Role of the Liver in Normal Nutrient Metabolism

Carbohydrates

Certain cells such as neutrophils, erythrocytes, and platelets are obligate utilizers of glucose. Therefore, during periods when glucose is not ingested, such as an overnight fast, glucose requirements continue. Many organs that use glucose during the fed state use fatty acids when supplies of glucose are low. It is estimated that carbohydrates account for 45% of the resting energy expenditure in overnight-fasted humans.[1] In this setting, the liver accounts for about 90% of the glucose released into circulation. Earlier studies suggested that approximately three-quarters of that glucose comes from glycogen, its liver storage form; however, a more recent study determined that glycogen contributes only about one-third to hepatic glucose production during the first 22 hours of fasting.[2] The remaining portion comes from gluconeogenesis.[1,2] *Gluconeogenesis* is the formation of glucose from precursors such as lactate, pyruvate, glycerol, and the gluconeogenic amino acids (mainly alanine, glutamine, and glycine). Gluconeogenesis is regulated by hormones and facilitated by a drop in insulin level and a rise in glucagon secretion, characteristic

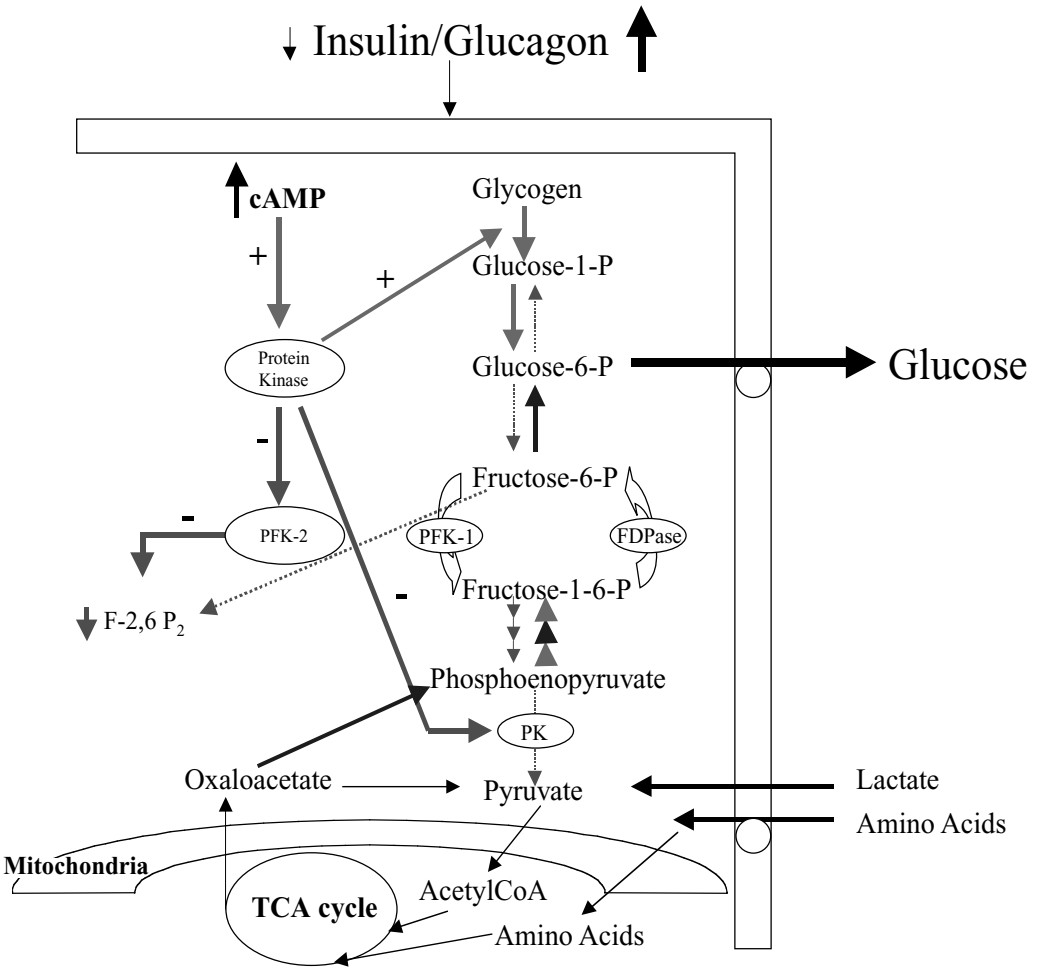

FIGURE 58.1
Hormonal regulation of glucose homeostasis in the liver. During fast, the insulin/glucagon ratio decreases. This stimulates an increase in cAMP in the hepatocyte. cAMP activates cAMP-dependent protein kinase, which activates glycogen phosphorylase. This enzyme leads to the breakdown of glycogen and the formation of glucose-1-phosphate. Protein kinase also inactivates phosphofructokinase-2 (PFK-2). PFK-2 catalyzes the conversion of Fructose-6-Phosphate to fructose-2, 6-bisphosphate (F-2, 6 P_2). F-2, 6 P_2 is an important activator of Phosphofructokinase 1 (PFK-1). The impaired activation of PFK-1 slows glycolysis and favors the conversion of Fructose-1-6-P to Fructose-6-P and ultimately favors the formation of glucose. Protein kinase also interferes with the conversion of Phosphoenopyruvate (PEP) to Pyruvate, by blocking the enzyme pyruvate kinase (PK). This favors the formation of Fructose-1-6-P and ultimately glucose. Glucagon also stimulates gluconeogenesis, in part through carrier mediated uptake of alanine, the major gluconeogenic amino acid. This and other gluconeogenic amino acids enter the TCA cycle with the resultant formation of Oxaloacetate (OAA). OAA is converted to PEP and proceeds toward the formation of Glucose-6-P and ultimately glucose. (Adapted from Brodsky IG. In: *Modern Nutrition in Health and Disease,* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore, 1999, p. 699.)

of the fasted state. The drop in insulin decreases the activity of pyruvate kinase (Figure 58.1). This "blockage" drives the equation back to Glucose 6-phosphate and ultimately increases hepatic output of glucose.

In the fed state, metabolic and hormonal signals change the liver's response to carbohydrates. It is estimated that between 25 and 45% of an oral glucose load is taken up by the liver. This percentage may increase as the carbohydrate load increases.[1] Glucose taken up by the liver is largely used to replenish the glycogen depleted after an overnight fast.

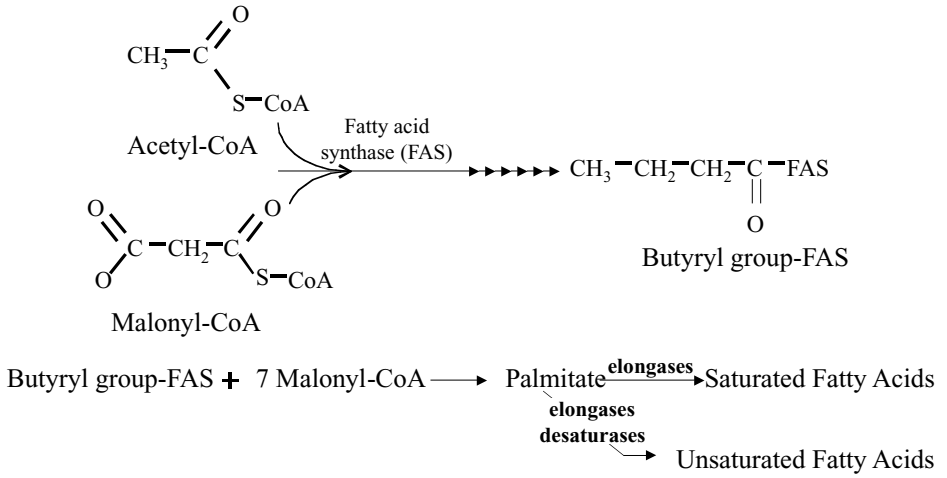

FIGURE 58.2
Fatty acid synthesis. Acetyl-CoA combines with Malonyl-CoA in the presence of the fatty acid synthase complex. Then through a series of condensation, reduction, dehydration, and translocation steps, a four-carbon, saturated fatty amyl compound is formed. Seven more cycles take place to form plasmatic acid (C16: 0). Other fatty acids, both saturated and unsaturated, can be formed using a series of elongates and desaturases.

High postprandial glucose levels stimulate the pancreas to release insulin. This decreases hepatic glucose production and increases glucose metabolism and storage. Insulin facilitates the synthesis of glycogen by stimulating the enzyme glycogen synthase. However, the liver glycogen concentration also influences synthesis. As the concentration of this storage form of glucose increases, its rate of formation slows. This phenomenon can occur in spite of high insulin levels and glucose concentrations, emphasizing the fact that this is a limited form of energy storage. It should also be noted that glucose is a relatively poor substrate for glycogen synthesis. Only about 50% of "neoglycogens" come from ingested glucose, while the remainder is derived from gluconeogenic precursors. Thus, the amount of carbohydrates presented to the liver could exceed the ability to form glycogen. Insulin also stimulates glucose oxidation by increasing pyruvate dehydrogenase, which converts pyruvate to acetyl-CoA. When the acetyl-CoA generated by glycolysis is not needed for oxidative phosphorylation, it is converted to fatty acids and ultimately to triglycerides[3] (Figure 58.2).

Lipids and Lipoproteins

The liver synthesizes bile acids from cholesterol. The bile acids are secreted in bile and released in response to a meal. When bile acids are released in sufficient quantities, the critical micellar concentration, they will form micelles. Micelles have a hydrophilic or water-soluble surface, and a lipophilic or lipid-soluble core. Most dietary fat is in the form of triglycerides, which are fatty acids esterified to a glycerol backbone. Triglycerides are a major source of both stored and available energy. As pancreatic lipase cleaves the fatty acids from the dietary triglycerides, these water-insoluble molecules are absorbed into the lipophilic core of the micelle. The micelle provides a conduit through the intestinal unstirred water layer to the lipid-soluble membranes of the intestinal enterocyte. The fatty acid diffuses into the lipid-soluble membrane of the enterocyte (Figure 58.3). Medium chain triglycerides can be absorbed directly into the portal vein and do not need this "micellar intermediate" to facilitate absorption. The bile acids are largely taken up by

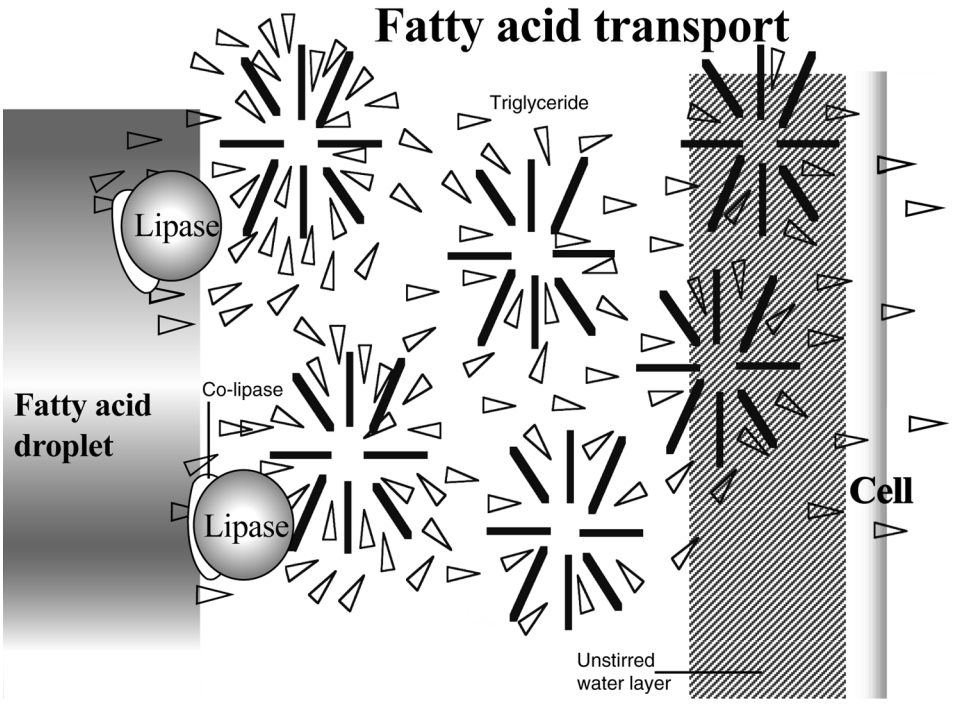

FIGURE 58.3
Fatty acid transport. Co-lipase attaches to the lipid droplet and then binds lipase, the principal enzyme of triglyceride digestion. Lipase then hydrolyzes the ester bonds of the tryglycerides forming free fatty acids. The fatty acids are taken up by the lipophilic inner core of the micelle. The outer core of the micelle is hydrophilic, allowing for this particle to traverse the unstirred water layer of the intestine. The fatty acids in the inner core of the micelle are placed in approximation to the lipid soluble membrane of the enterocyte, allowing for diffusion across the enterocyte membrane. (Adapted from Reference 5.)

receptors in the terminal ileum and transported back to the liver via the enterohepatic circulation. Some unabsorbed bile acids are excreted into the feces.[5]

In the enterocyte, fatty acids are reesterified into triglycerides and packaged into lipoproteins called chylomicrons. Chylomicrons are secreted into the lymphatics, travel through the thoracic duct to the superior vena cava, and are then circulated to target tissues. Chylomicrons are part of the exogenous transport system for lipids. The endogenous system is comprised of three main carriers, VLDL, LDL, and HDL.[5,6] Many of the protein components of these lipoproteins, called apoproteins, are also synthesized in the liver.

The liver can also manufacture triglycerides from fatty acids synthesized by repetitive additions of two carbon fragments, derived from Acetyl-CoA, to malonyl CoA, or from non-esterified fatty acids removed from the blood.[3] Triglycerides synthesized by the liver are transported by the lipoprotein LDL to target tissues. Similarly, cholesterol synthesized in the liver is taken by the LDL carrier to target tissues. Peripheral tissues transport cholesterol back to the liver for excretion by the gallbladder through the action of HDL.

Amino Acids and Proteins

The liver also plays a major role in amino acid homeostasis. Amino acids serve as building blocks of proteins and as precursors to many other important biomolecules, such as purines and pyrimidines. Additionally they can be a source of energy, particularly when they are present in excess of need for visceral or somatic protein synthesis. Amino acids

are either essential or non-essential. The distinguishing feature between these two types of amino acids is the ability of the body to synthesize their carbon skeleton. Essential amino acids have a carbon skeleton that cannot be synthesized *de novo* and must be obtained from the diet.

The first step in the catabolic process of most amino acids is the removal of the α-amino group from the carbon skeleton. This occurs via a pathway known as transamination. In the liver, most of α-amino groups derived from ingested protein, muscle protein, or protein from other tissues are separated from the parent carbon skeleton, leaving a ketoacid and an amino group. This amino group is combined with α-ketogluterate to form glutamate. Glutamate then undergoes oxidative deamination in the mitochondria, yielding the protonated form of ammonia (NH_4^+). The NH_4^+ is a co-substrate in forming carbamoyl phosphatase. It then enters the urea cycle. As ammonia is toxic to animals, the urea cycle enzymes, also located largely in the liver, allow excretion of this harmful metabolite (Figure 58.4). Transamination can also occur between other amino acids. The presence of transaminase enzymes in the liver ensures that the liver is able to conserve essential amino acids and interconvert nonessential amino acids. Although most amino acid catabolism occurs in the liver, the three amino acids with branched side chains (leucine, valine, and isoleucine) are particularly noteworthy. They are oxidized as fuels to be used primarily by extrahepatic tissue, particularly muscle, adipose, kidney, and brain. These extrahepatic tissues contain a single aminotransferase not present in the liver. This acts on all three branched chain amino acids (BCAAs) to produce the corresponding α-ketoacid.

Amino acid carbohydrate skeletons can metabolize to pyruvate or intermediates of the tricarboxylic acid cycle. These can be converted into glucose and are called glucogenic amino acids. These precursors contribute to a process known as gluconeogenesis. In humans, gluconeogenesis occurs largely in the liver, and to a much smaller extent in the renal cortex. Since some tissues in the body are obligate glucose utilizers, this pathway is extremely important during periods of relative glucose deficiency. It maintains hepatic glucose output to glucose-utilizing tissues.[8,9]

The liver absorbs amino acids from plasma to be utilized in protein synthesis. The most abundant plasma protein secreted by the liver is albumin. Albumin is the most important regulator of plasma oncotic pressure and is the principal transport protein for many endogenous and exogenous substances. The liver also produces transport proteins for lipids (lipoproteins), iron (transferrin), and copper (caeruloplasmin) as well as steroid hormone-binding proteins, thyroid hormone-binding proteins, and several vitamin-binding proteins. An equally essential role for the liver is the synthesis of many of the coagulation and fibrinolysis proteins. The liver is also the primary site of synthesis of the complement system that plays an important role in host defense against infectious agents. Finally, it is the major site of synthesis of protease inhibitors, inhibitors of coagulation and fibrinolysis, as well as many other proteins involved in immunomodulation, drug binding, and other aspects of the acute phase response.[10]

Impact of Liver Disease on Nutrient Metabolism

Carbohydrates

Damage to the liver can negatively impact glycogen stores. Since the liver is the major source of glucose production in the fasted state, it would be expected that patients with liver disease might have low blood glucose levels after an overnight fast or a prolonged

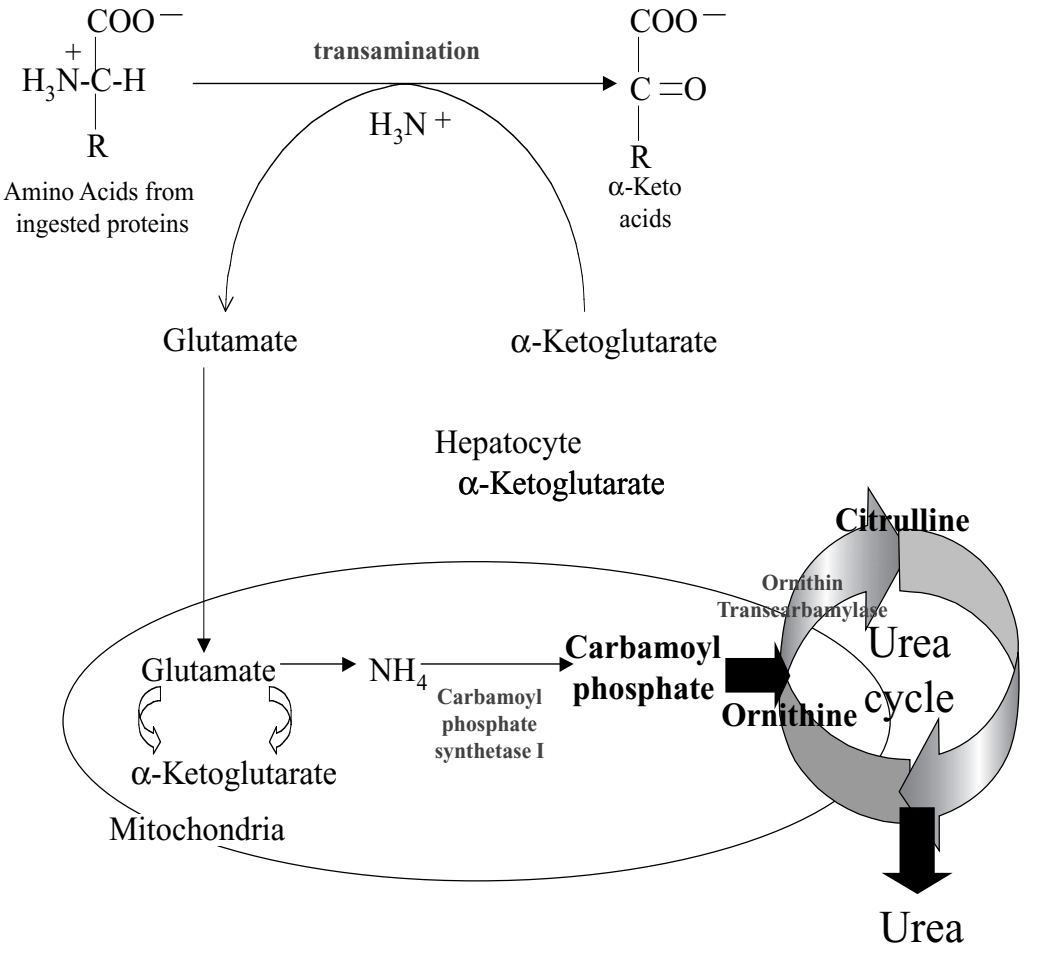

FIGURE 58.4
NH_3 Metabolism. Amino acids from ingested proteins are transaminated to yield NH_3 and α-keto acids. The amino group is then transferred to α-ketogluterate to form glutamate. Glutamate is transported to the hepatocyte mitochondria where α-ketogluterate is reformed with the loss of NH_4. This ammonium group combines with HCO_3 and 2 ATPs to form carbamoyl phosphate. Carbamoyl phosphate enters the urea cycle, is converted to urea after a series of reactions. (Adapted from Nelson DL, Cox MM. In: *Principals of Biochemistry,* 2nd ed, Lehninger AL, Nelson DL, Cox MM, Eds, Worth Publishers, New York, 1993, pg 506.)

absence of oral intake. However, hypoglycemia is rare in liver disease, usually seen only in fulminant hepatic failure or in the terminal stages of chronic hepatic insufficiency. This is probably due to the tremendous reserve capacity of the liver to produce glucose, with approximately 20% of the hepatic mass needed to maintain normal glucose levels in the fasted state.[1]

More commonly, fasting glucose levels in patients with liver disease are normal or high. Despite high levels of glucagon seen in these patients, increased hepatic glucose production does not seem to be a contributing factor. Unless there is coexistent diabetes, studies suggest that hepatic glucose production in liver disease varies from normal to 20-40% lower than normal. However, diabetic cirrhotics with fasting hyperglycemia displayed increased hepatic glucose production, which was not appropriately decreased by insulin.[4]

Since glycogen synthesis is impaired in liver disease and glycogen stores are rapidly depleted in the fasted state, patients with liver disease more rapidly transition to gluco-

neogeneisis and ketogenesis to fill their glucose and energy needs. It is estimated that gluconeogenesis accounts for about 67% of hepatic glucose production, with the remainder coming from glycogenlysis. The rapid switch to a fatty acid/ketone economy for energy needs is an adaptive response, as it decreases reliance on hepatic glucose production. Glucose production by the damaged liver may be limited due to decreased glycogen stores and potentially diminished delivery of gluconeogenic precursors to the liver.[1]

After glucose ingestion, many patients with liver disease have abnormally elevated blood glucose concentrations.[1] In fact, 60 to 80% of patients with cirrhosis are glucose intolerant, and 10 to 30% eventually develop frank diabetes.[4] In a recent study, non-diabetic cirrhotics given a mixed meal had elevated blood glucose levels in spite of a fivefold increase in blood insulin levels.[12] It appears that in these glucose-intolerant patients, both oxidative and nonoxidative glucose disposal is impaired.[1,4] The oxidative impairment of glucose utilization, the less significant of the two abnormalities, is due in part to the preferential utilization of fatty acids seen in this patient population. The generation of Acetyl-CoA from the metabolism of fatty acids inhibits pyruvate dehydrogenase resulting in a diminution of pyruvate oxidation.[4] The nonoxidative utilization of glucose is essentially the formation of glycogen. In spite of hyperinsulinemia seen in these patients, they demonstrate peripheral insulin resistance. As such, glucose uptake by muscle and stimulation of glycogen synthesis is significantly impaired. This accounts for most of the decreased glucose disposal and consequent glucose intolerance seen in these patients, as hepatic glucose production is still normal in the basal state and normally suppressed by insulin.[1,4] In contrast, liver disease patients with diabetes not only have abnormalities with glucose disposal but also are unable to appropriately suppress hepatic glucose suppression, suggesting a relative lack of insulin. Petrides et al. hypothesized that patients with liver disease become frankly diabetic when the pancreatic β-cells cannot meet the increased demand for insulin secretion due to insulin resistance.[4]

Lipids and Lipoproteins

Since cholesterol is excreted from the body through the biliary tree, the total cholesterol level tends to rise in obstructive jaundice. However, in severe parenchymal disease, cholesterol ester levels tend to fall. This latter sign is the result of reduced activity of lecithin cholesterol acyltransferase (LCAT) activity. LCAT is an enzyme synthesized in the liver that catalyses the transfer of a fatty acid from the 2-position of lecithin to the 3 β-OH group to form cholesterol ester and lysolecithin. It plays a key role in the turnover of cholesterol and lecithin. Low levels of this enzyme also alter the lipid composition of lipoproteins.

Plasma triglycerides are often elevated, both in obstructive, and less often in parenchymal liver disease. Triglycerides are normally cleared by the action of peripheral lipoprotein lipases (LPL) and hepatic triglyceride lipases (HTLP). The latter enzyme levels are reduced in liver disease and may account for triglyceride abnormality.[6]

These changes in lipids may effect membrane lipid content, fluidity, and function. They may, in part, explain the abnormalities associated with liver disease in platelet aggregation and in the morphology of red blood cells.[6] These changes in the lipid content of cell membranes effect all cells in the body. The subsequent effects on membrane fluidity and function have been advanced as a possible contributing factor in the hyporesponsiveness of cirrhotic myocardium to pharmacologic or psychologic stress.[7]

After an overnight fast, cirrhotic patients derive a greater proportion of energy from fat oxidation than do controls. This difference in endogenous energy substrate use has been attributed to diminished glycogen stores. After ingestion of a mixed meal, fat oxidation

of cirrhotic patients decreases but still remains elevated compared to controls. The increased reliance on endogenous fat during fasting and the continued high rate of fat oxidation in spite of ingestion of a mixed meal may account for the reduction in body fat stores common in this patient population.[12]

Amino Acids and Proteins

Patients with liver disease often have disturbances in plasma amino acid concentrations, characterized by increased levels of aromatic amino acids and methionine. This is most likely a result of the injured liver's poor utilization of these amino acids as well as portosystemic shunting.[8] Additionally, since the enzymes involved in urea production are largely localized in the liver, urea synthesis, and hence α-amino nitrogen clearance, is lower in cirrhotics compared to controls. In patients with severe decompensated liver disease, the plasma urea level tends to drop and the amount of urea excreted in the urine is reduced. In patients with well-compensated cirrhosis, urea production rates remains stable under basal conditions but maximal urea production capacity is significantly reduced in response to a protein or amino acid load.[8,11]

Chronic alcohol consumption actually increases the synthesis of albumin and constituent hepatic proteins but is also associated with a reduced secretion of these proteins from the liver.[10] However, as liver damage increases, there is a decrease in synthesis of albumin with an apparent significant correlation between its synthesis rate and Childs score (a scoring system based on clinical and laboratory values that is used to demonstrate the severity of the underlying liver disease).[10] Although the albumin is used in many different prognostic scoring systems, it should be remembered that the plasma concentration of albumin is not only dependent on synthesis but also is reliant on the rate of degradation. Additionally, newly synthesized albumin is secreted into the lymph and ascitic fluid, when present, which increases the distribution volume and can contribute to hypoalbuminemia. Therefore, in the acute setting, the serum level of albumin does not purely reflect decreases in hepatic synthesis.

The liver is also important in maintaining homeostasis. All clotting proteins, coagulation factors, and inhibitors, and most of the components of the fibrinolytic system are synthesized by hepatocytes except for von Willebrand factor, which is produced by endothelial cells, and megakaryocytes. Liver damage can lead to decreased levels of the clotting factors produced in the liver. It is unusual for fibrinogen to be reduced significantly unless there is concomitant disseminated intravascular coagulation. Overall, liver impairment favors bleeding due to impaired synthesis of coagulation factors and increased fibrinolytic activity. However, it also increases susceptibility to intravascular coagulation resulting from impaired clearance of procoagulant material.[13]

Nutritional Evaluation in Liver Disease

Energy Expenditure in Liver Disease

There is significant controversy about the ability to accurately predict metabolic rates in cirrhotic patients. This is partly because hypermetabolism occurs only when a measured value (indirect or direct calorimetry) is compared to a predicted value. Thus, depending on the methods of standardization and comparison, (i.e., formula equations versus estimates of lean body tissue), the baseline for comparison differs. Common formula equations

that use age, weight, and height are standardized for normal proportioned individuals. They do not make allowances for differences in body compartments that may occur in liver disease. For example, if there is depletion of body fat, a common occurrence in cirrhotics, there is a relative overrepresentation of metabolically active tissue per unit mass. If this were the case, formula equations may predict a lower energy expenditure relative to a measured value. One method to address this potential discrepancy is to correct for lean body mass by using creatinine secretion. Since the secretion of creatinine roughly correlates with the presence of lean body tissue, standardization to this value should help account for discrepancies in somatic protein/fat composition. However, it should be kept in mind that creatine, the precursor of creatinine, is synthesized in the liver. Thus, significant liver disease can compromise the urinary recovery of creatinine and result in an underestimation of the amount of metabolically active tissue. This could subsequently result in an underestimation of lean body tissue and an overestimation of metabolic rate when a measured value is compared to a predicted value corrected for fat-free mass.[14]

Alternatively, fluid retention tends to increase weight or body surface area; formulas that standardize energy expenditure on these values overestimate the predicted metabolic rate compared to a measured value.[15] More recently, researchers have attempted to measure fat-free mass, since this a more accurate indicator of metabolically active tissue. They use this variable in predictive formulas for resting energy expenditure. However, even with these more complicated formulas, only 50 to 60% of the observed variation between measured and predicted values can be accounted for.

Most studies have failed to show significant differences in energy expenditure between cirrhotics and control patients.[14,16,17] However, others, such as in a study by Madden, have demonstrated that the mean measured resting energy expenditure in patients with cirrhosis is significantly higher than in controls when adjusted for body weight. Overall, using multiple predictive formulae, 12% of the patients were considered hypometabolic while 30% were determined to be hypermetabolic. A recent comprehensive study by Müller found a similar proportion of hypermetabolic patients (33.8%). Unfortunately, neither author could identify the hypermetabolic patients on the basis of demographic or clinical variables.[18,19] A possible exception to this is primary biliary cirrhosis patients, in whom worsening disease was associated with increased resting energy expenditure and prolonged diet-induced thermogenesis after a meal.[20]

Müller also demonstrated that increased levels of catecholamines in hypermetabolic patients could be a contributing factor in increased metabolic rate. He further determined that for these patients, a propranolol infusion resulted in a pronounced decrease in energy expenditure.[19]

Clinically, determining hypermetabolism is important for these patients, as they are more likely to present malnourished, and this clinical status may be further complicated by difficulty in nutrient assimilation. Thus, hypermetabolism may further negatively impact outcome. A study assessing preoperative risk factors in patients undergoing liver transplantation associated hypermetabolism and diminished body cell mass (<35% of body weight) with reduced survival after liver transplantation.[21] Given the clinical implications of determining an accurate metabolic rate in cirrhotic patients and the fact that this rate cannot be accurately determined from formulas and clinical variables, many authors are advocating that the metabolic rate should be measured in cirrhotic individuals to accurately determine this value.[18,19]

Prevalence of Malnutrition in Liver Disease

Protein-calorie malnutrition (PCM) is common in advanced liver disease. A summary of five studies using a total of 550 subjects demonstrated a range of PCM from 10 to 100%,

depending in part on the criteria used to determine PCM.[22] In the Veterans Administration Cooperative study on alcoholic hepatitis, malnutrition was a ubiquitous finding and correlated with dietary intake and severity of liver dysfunction.[23,24] In hospitalized patients with less severe alcoholic and nonalcoholic liver disease, the prevalence of PCM ranged from 30 to 40%. It should be noted that much of the data on malnutrition is derived from the alcoholic liver disease population. However, a recent study by Sarin et al.[24] demonstrated that malnutrition in patients with alcoholic and nonalcoholic cirrhosis is very common, and present to the same degree. The patterns of malnutrition appear to be different depending on the underlying liver disease. Patients with nonalcoholic cirrhosis demonstrated decreases in both fat and muscle mass, while those with alcoholic liver disease demonstrated a greater decrease in muscle mass but relative sparing of fat stores. The authors of the accompanying editorial hypothesize that this discrepancy may be due to the "precirrhotic nutritional status" of the patient or to toxic effects of alcohol on meal-stimulated protein secretion. They also speculated that alcohol might lead to changes in intestinal permeability, which could potentially lead to transmigration of intestinal bacteria or toxins with resultant release of proteolytic cytokines.[25] The authors determined that the dietary intake of both groups was reduced to a similar degree.[24]

Nutritional Assessment

The presence of liver disease may affect many of the traditional modalities used to evaluate the nutritional status of patients. Visceral protein stores can be greatly influenced by acute and/or extensive damage to the liver. Liver injury can result in decreases in visceral markers that may be unrelated to the nutritional status of the patient, and may therefore not improve significantly with nutritional intervention. In fact, serum visceral protein appears to correlate better with the degree of liver damage than with the nutritional status of the patient. Chronic liver disease can also cause alterations in cellular immunity and total lymphocyte count independent of protein malnutrition.[22] Furthermore, abnormal immunologic reactivity, again independent of nutritional status, is a prominent feature of chronic autoimmune hepatitis, primary biliary cirrhosis, and possibly viral hepatitis.[27] From a clinical standpoint, a thorough nutritional evaluation should be performed and repeated serially. A bedside assessment of somatic protein stores and subcutaneous fat stores usually provides a reliable nutritional assessment.[26] Other important aspects of this subjective global assessment tool adapted for liver patients included the presence of encephalopathy, edema, weight change, renal insufficiency, constipation, satiety, and difficulty chewing. Anthropometric data, specifically the assessment of fat stores by tricep or subscapular skinfold thickness and the assessment of somatic stores by midarm muscle circumference or body weight to height, can yield valuable information. Assessments should be performed by a skilled person, as there can be problems with reproducibility. Additionally, apparent or subclinical edema can lead to a potential underestimation of the severity of protein and fat losses.[27] The creatinine height index is generally a good indicator of lean body mass in patients with liver disease. However, it, too, has shortcomings, as there is frequently associated renal dysfunction which could impair collection. Furthermore, with severe liver disease there can be a decrease in creatinine formation, as its substrate creatine is synthesized in the liver. Both of these circumstances could result in underestimation of lean body tissue.

In summary, given the numerous limitations of standard nutritional parameters in patients with liver disorders, it is preferable to rely on collective information generated from the use of several parameters used simultaneously and on a serial basis.[27]

Nutritional Intervention in Liver Disease

Background Data

It is well known that patients with chronic liver disease are usually malnourished, and that frequently the degree of malnutrition parallels the severity of the liver disease. Reasons for malnutrition include altered metabolism, malabsorption/maldigestion, anorexia, iatrogenic restrictions, and poor dietary intake. Though there appears to be a correlation between the severity of malnutrition and subsequent morbidity and mortality from liver disease, it is intuitive, though less clear, that nutritional intervention can have an impact. An article by Patek et al., published in 1948, was one of the earliest to evidence that nutritional intervention could impact the course of liver disease. In this study, 124 patients (89% of whom had "significant weight loss") were admitted to the hospital with "hepatic failure." These patients were given a diet of approximately 3500 kcals with 140 gms of protein, supplemented with a vitamin B complex preparation. The supplemented group was compared to historic controls. Although the patients' ability to achieve dietary goals was not mentioned, 49% were described as "clinically improved." This improvement was characterized by 1) a disappearance of ascites, jaundice, and edema, 2) weight gain and strength, and 3) improvement in liver function test results. Furthermore, there appeared to be significant differences in survival between the treated group and historical controls at one and five years.[30] This positive study provided the basis for subsequent studies assessing the impact of enteral, parenteral, and oral supplementation in patients with liver disease.

Many recent studies have focused on nutritional intervention in alcoholic liver disease. Acute alcoholic hepatitis is a potentially reversible condition, but is associated with high mortality. The majority of patients with alcoholic liver disease who require hospitalization for their disease are moderately to severely malnourished. Malnutrition can contribute to delayed wound healing, increased risk of infection, increased toxicity of alcohol to the liver, reduced protein synthesis, and impaired regenerative capacity of the injured liver.[28,31] Additionally, both human and animal data suggest that poor nutrition combined with alcohol is more injurious to the liver than alcohol alone.[3,31] These factors imply that nutritional intervention may be beneficial in this disease.[28,31] In an early and much-cited trial by Galambos, 28 days of peripheral amino acid infusion resulted in significant improvement in albumin and bilirubin levels in the supplemented group compared to controls. The supplemented group also showed a trend toward improved survival.[33,34]

Mendenhall authored a series of landmark articles on alcoholic hepatitis. A nutritional investigation of patients with alcoholic hepatitis was part of a larger multicentered VA cooperative study of the effects of steroid therapy in the treatment of this disease. In an early study, the patients were categorized into mild, moderate, and severe protein calorie malnutriton (PCM) based on eight parameters that included tests to assess somatic protein stores, visceral protein stores, and delayed cutaneous hypersensitivity. The investigators were able to demonstrate that 30-day and 6-month mortality rates correlated with nutritional category. Perhaps equally important was that patients who moved from one nutritional category to another assumed the mortality associated with their new category.[35] However, it should be noted that this early observation on nutrition and outcome was a secondary endpoint.

The same researchers subsequently designed a study to intercede with nutritional supplements while providing patients with anabolic steroids (oxandrolone). Oxandrolone was used in this population because the researchers believed it would increase anabolism and liver regeneration. In a group of patients defined as having moderate PCM yet adequate

caloric intake (>2500 kcals), oxandralone significantly decreased mortality compared to the placebo group. In addition, patients defined as having severe PCM yet adequate caloric intake had significantly lower 6-month mortality regardless of the use of oxandrolone. Finally, caloric intake during the first month demonstrated a significant inverse correlation, with mortality at six months. It should be noted, however, that as the severity of the liver disease increased, the caloric intake decreased.[29] Unfortunately, it is unclear from this study whether nutritional supplementation, even if the patient accepts and is compliant with this supplementation, will improve the "nutritional category." It is possible that other changes in underlying liver disease also have to occur before nutritional repletion is realized. However, the authors mentioned that there was a "marginally significant correlation" between percent of basal energy expenditure consumed and the improvement in PCM during hospitalization.

These authors published another followup article focused solely on the nutritional indices in this same cohort of patients. The authors were able to identify four nutritional parameters that seem to effect six-month mortality. They included creatinine height index, total lymphocyte count, handgrip strength, and prealbumin levels. The authors suggested that surviving patients tend to improve in most of their measured nutritional parameters, but it is again unclear that either adequate protein or energy intake significantly influences these four variables. Nevertheless, the authors conclude that nutritional therapy improves both prognosis and overall nutritional status. They qualify this statement, however, by stating that the degree of improvement is dependent on the severity of the PCM.[39]

A recent study by Cabre et al. assessed the effects of total enteral nutrition and prednisolone in the treatment of patients with alcoholic hepatitis. Patients were randomized to receive either TEN (2000 kcal/d and 72 g protein via a nasoenteral tube) or prednisolone. The latter group was encouraged to eat a standard hospital diet of approximately 2000 kcals and 1 g/kg of protein. Although no difference was seen in short term or one-year survival, differences in the time to death and cause of death were noted. Deaths occurred earlier in the TEN group (median of seven days). In the prednisolone-treated group, most of the deaths occurred in the immediate six weeks after the end of the treatment period and were largely due to infectious complications. The authors speculate that most of the early mortality may have been caused by inflammatory mediators (thus the early benefit of steroids). The latter mortality may have been caused by changes in the intestinal barrier (supporting the importance of enteral nutrition in maintaining the integrity of the gut barrier). The author suggests that there might be a synergistic effect realized in using both modes of therapy.[41]

The positive effects of nutritional supplementation are not, however, limited to patients with alcoholic hepatitis. In an earlier study, Cabre et al. looked at enteral nutrition in hospitalized cirrhotic patients. The treatment group was given an enteral formula containing 2115 kcal/d with 71 g protein via nasoenteral tube. The control group was offered a standard low-sodium hospital diet supplying 2200 kcals and 70 to 80 g protein. The etiology of the cirrhosis was varied (though largely alcoholic) and there were no differences in Child's scores. All patients in both groups had severe protein energy malnutrition. Although the incidence of major complications was similar in both groups, the Child score improved and mortality fell (47 versus 12%) only in the TEN group. The authors were unable to explain the discrepancy. They suggested that the GI tract stimulation may have decreased the catabolic effect of the injury or resulted in decreased bacterial/endotoxin translocation.[42]

In summary, multiple studies using oral, enteral, and parenteral supplementation have demonstrated only modest improvements in liver function tests and nutritional parameters. A decrease in mortality in nutritionally supplemented patients has not been a consistent or overwhelming finding,[34,40,43-45] though other important facts have emerged. These patients appear to tolerate the protein supplementation, including those with

hepatic encephalopathy. Fluid retention has not been a major problem.[34] It should also be noted that there is no published study demonstrating an adverse effect of nutritional supplementation. These studies point out that nutritional supplementation, though very important, is only one of several factors likely to determine the ultimate outcome in liver disease patients. As this is a factor that can be influenced, at least to some degree, and there do not seem to be untoward effects when used appropriately, attention to nutrition, with supplementation when indicated, should be considered a mainstay in the therapy for these patients.

The use of branched chain amino acids (BCAA) has been advocated in the treatment of liver disease. It has been suggested that 50 to 60% of patients with chronic liver failure will tolerate 60 to 80 g/d of a standard amino acid mixture as part of a parenteral nutrition regimen. The remainder, in particular those with grade III or IV hepatic encephalopathy, seem to respond better to with modified solutions containing BCAA.[54] One rationale for their use in hepatic encephalopathy concerns the high aromatic amino acid (AA)-to-BCAA ratio in the blood of patients with decompensated liver disease. This is primarily due to poor metabolism of AAs by the failing/injured liver. Conversely, BCAAs are deaminated mainly by skeletal muscle, and so have an alternate pathway for their metabolism. Since both of these amino acids compete for the same transmembrane transport system in order to cross the blood brain barrier, the increase in AA/BCAA in the blood favors the transport of AAs. In the central nervous system these AAs can be metabolized to false neurotransmitters (octopamine and phenylethanolamine) and thus contribute to hepatic encephalopathy. Additionally, infusion of BCAAs has been shown to reduce blood ammonia levels.[46] The branch chain amino acids have also been reported to augment protein synthesis in humans. Leucine, or more specifically, its deamination product, βα-keto-isocaprioic acid, is thought to have an important role in stimulating protein synthesis and inhibiting protein degradation.[46,47] Thus, it would seem that a BCAA mixture would be an ideal mode of therapy in patients with liver disease.

Several studies have looked at the use of BCAA in the treatment of hepatic encephalopathy. The largest study was by Cerra et al., who concluded that the BCAA-enriched formula resulted in more rapid and complete recovery from encephalopathy as compared to the standard treatment of neomycin. The treatment group also showed improvements in nitrogen balance and survival. Interestingly, the control group was not given any protein, and their sole source of kcalories was a 25% dextrose solution. Both the BCAA and dextrose solutions were started at 1.5 liters and advanced to a maximum of 3 liters over the ensuing days.[48] Unfortunately, the lack of protein in the control group challenges the validity of the nitrogen balance data and perhaps the mortality differences in these populations.

Overall, studies regarding the use of BCAA in encephalopathy have yielded mixed results.[47,69] A recent meta-analysis by Naylor et al. suggests that BCAA solutions have a significant and beneficial effect on recovery from hepatic encephalopathy, though the authors state that analysis is difficult, given the diversity of the studies involved. The same authors were unable to verify an advantage of BCAA solutions on mortality.[54] Another extensive analysis by Eriksson et al. presented a much more skeptical view of the benefits of BCAA solutions in either acute or chronic encephalopathy. The authors proposed that problems with data analysis, biased assignment of patients to groups in regard to etiology of the encephalopathy, and study design disallowed any firm conclusion that BCAA or their keto analogues were beneficial.[55] Thus, though the use of BCAA-enriched supplements may lead to mild improvement in encephalopathy compared to standard therapy, other positive effects are not consistently demonstrated. The benefits do not seem to justify routine use of this enriched formula at the present time.

An exception to this may be the patient with chronic encephalopathy who is intolerant to increases in protein or standard amino acid solutions. Eriksson's analysis did concede

that in the setting of chronic encephalopathy in which increases in standard protein supplements worsened or precipitated encepahalopathy, BCAA mixtures were better tolerated. A study by Egberts et al. of this population demonstrated significant improvements in psychomotor function, attention, and practical intelligence when stable patients were supplemented with a BCAA-enriched mixture.[50] However, the clinical applicability of these improvements in psychomotor testing has been called into question.[55]

In vitro studies of isolated hepatocytes suggest that the keto acid analogues of BCAAs augment protein synthesis.[51] However, when the effects of these BCAA solutions were evaluated in cirrhotic patients, no such augmentation was seen.[46,52] In an editorial accompanying this paper, Charlton speculated that because the BCAA-enriched infusate lacked sufficient AAs for protein synthesis, the expected protein synthetic response may have been dampened. Alternately, he suggests that relative hyperglucagonemia may shunt amino acids toward gluconeogenesis and thus render them unavailable for protein synthesis. He concluded that these abnormalities may account for the less-than-convincing "improved outcomes" with BCAA-enriched formulas for patients with liver disease.

Nutritional Recommendations

In multiple diverse populations, malnutrition can negatively impact infection, wound healing, and organ function. The great majority of patients who present for liver disease are malnourished, and the severity of their malnutrition has prognostic implications. However, when studies on nutritional intervention in liver disease are considered, it is difficult to ascertain whether nutritional intervention can positively impact the course of the disease. A similar conclusion can be arrived at in most disease states, both acute and chronic, in which nutritional intervention has been critically assessed. This does not necessarily mean that nutritional intervention is not important in the individual patient. The diverse baseline nutritional status in patients (both from a macronutrient as well as a micronutrient perspective), the differences in insult severity, and the myriad of therapies and approaches given to the individual patient, explain why there does not appear to be a guiding light for nutritional intervention. In spite of this, some general recommendations can be made with regard to energy and protein requirements.

Energy Needs

As discussed previously, difficulties in estimating energy expenditure in cirrhotics have been attributed to fluid retention, relative changes in body compartments, and other variables related to metabolic abnormalities in patients with liver disease. Nonetheless, in stable cirrhotics, various studies have measured energy expenditures ranging from approximately 1500 to 2100 kcals/d.[16,18,19] Thus, though the controversy over whether these patients are hypermetabolic compared to controls remains unanswered, the absolute energy requirements in these patients do not appear to be excessive. Furthermore, in the acute setting, increases in the metabolic rate are influenced by many variables including the severity of the insult, the presence of infection, and medications that the patient may be receiving. These latter variables further complicate accurate extrapolation of energy needs from formula equations. REE, or resting energy expenditure, is measurement of the body's daily energy expenditure, not involving activity or caloric intake. REE with indirect calorimetry remains the most accurate and practical way of estimating total caloric needs. In the absence of indirect calorimetry, the simplest and most accurate predictive formula is the Schofield formula. This formula, referenced by Madden et al.,[18] varies significantly by age. In men between the ages of 30 to 60 it is as follows:

$$(11.48 \times \text{wt}) - (2.63 \times \text{ht}) + 877.57$$

Most interventional studies have used a caloric intake of 2000 to 3000 kcals. In the VA cooperative study, a level of 2500 kcalories and above was considered adequate therapy. Alternately, values ranging from 25 kcals/kg/d (stable cirrhotic) to 45 kcals/kg/d (post-operative cirrhotic) have been proposed.[22] Excessive caloric delivery is not beneficial, as it can create metabolic and respiratory stresses. High caloric delivery may also involve increasing the fluids given to these usually fluid-restricted patients. Additionally, nutritional repletion is not usually accomplished during hospitalization in the current medical climate. Energy goals should thus be directed at maintenance without causing metabolic abnormalities.

Perhaps more important than delivery of a caloric load is the mixture of the kcalories provided. In an interesting study by Chanda and Mehendale, rats subjected to a hepatotoxin demonstrated a decrease in hepatocellular regeneration and tissue repair when given 15% glucose in drinking water.[56] Conversely, in a similar experiment, rats given palmitic acid and L-carnitine were protected against similar doses of that hepatotoxin. The authors suggest that the regenerating liver uses fatty acids as the main source of cellular energy. The increased demand for cellular energy in the form of ATP needed to support hepatocellular division is essentially derived from fatty acid oxidation.[57]

It is also interesting to note that the two outwardly "negative studies" doing BCAA supplementation in a test group were compared to a control group on a lipid-based formula. It is possibile that the lack of efficacy in these studies was due to the lipids conveying some advantage to the control group, thus decreasing by comparison the effectiveness of the BCAA solution in the treatment group.

Other interesting animal data suggests that lipids, specifically saturated fatty acids, may offer protection against alcoholic liver injury. Nanji et al. found that diets enriched with saturated fatty acids (palm oil) reverse the pathological changes induced by ethanol. Conversely, omega-3 fatty acids (fish oil) do not improve the severity of alcohol-induced injury. The authors suggest that the protective effects may be explained in part by differences in lipid peroxidation. Dietary fat helps to modify the expression of cytochrome p450 2E1, which contributes to NADPH-dependant lipid peroxidation. The animals fed the diets rich in saturated fatty acids demonstrated less induction of the CYP2E1 enzyme system.[58] Alternately, the protective effect may be through positive changes in eicosanoid metabolism manifested as an increase in the prostacycline-to-thromboxane B_2 ratio. In previous studies, these authors found that decreases in this ratio preceded the production of pathologic liver disease.

Saturated fats are probably not the only nutrients that may have a protective effect against liver disease. Lieber found that baboons maintained on a chronic ethanol-enriched diet supplemented with polyunsaturated phospholipids (55 to 60% of which was polyunsaturated phosphatidylcholine [PPC]) were protected against alcohol-induced fibrosis. In a similar study, the animals were given a purer extract, comprising 94 to 96% phosphatidylcholine. The researchers found that these baboons given ethanol for up to eight years did not develop cirrhosis or septal fibrosis when fed this supplemented diet. Leiber proposed that the phosphatidylcholine directly affects collagen metabolism and opposes oxidative stress.[3,59,60] Unfortunately, supplementing fat does not appear to be the entire answer. In a rat model, Lieber also found that in the setting of chronic alcohol consumption, increased triglycerides in the diet results in increased fat accumulation in the liver.[3] Extrapolating from animal data, it would therefore seem that in the setting of alcoholic liver disease, 25 to 35% of the total kcalories should be derived from a mixture of these lipids. Thus, it would appear that the type as well as amount of fat are important considerations in supplementing patients with liver disease.

Protein supplementation in the patient with acute liver injury is probably the most controversial aspect of macronutreint nutritional supplementation. These patients usually demonstrate somatic protein wasting and decreases in muscle strength, immune reactivity, and protein synthesis. These deficiencies may in part be due to diminished protein stores. Also, repair of injury, extrapolated from other clinical settings, requires adequate protein. Finally, it has been assumed that liver regeneration is delayed when there is insufficient protein.[3]

In their studies of nutritional intervention in patients with alcoholic liver disease, Mendenhall et al. have stated that all patients with alcoholic hepatitis achieved positive nitrogen balance with 1.2 g/kg of protein. Additionally, this intake of protein was well tolerated in spite of severe liver disease. Encephalopathy was observed in 20% of patients, but its occurrence did not correlate with protein intake.[39] In patients with chronic liver disease, Lieber states that positive nitrogen balance can be attained with a protein intake of 0.74 g/kg. Thus it appears that the stringent protein restrictions often imposed on hospitalized patients with liver disease can be eased. Protein provisions in the range of 0.6 to 0.8 g/kg can usually be safely given during the acute setting, increasing protein delivery as tolerated to at least 1.2 g/kg. It should be noted that the protein supplemented in Mendenhall's study, and the basis of his recommendations, was enriched with BCAA. Although there have been no definitive studies comparing tolerability of standard amino acid mixtures to BCAA, it is possible that an individual patient with acute liver injury may tolerate a larger quantity of protein if supplemented with BCAA supplementation. Thus, clinical surveillance is important when increasing protein load in these patients.

Finally, the remainder of patients' energy needs should be met with carbohydrates. As discussed previously, insulin resistance is common in patients with cirrhosis, and this intolerance is further exacerbated in the setting of acute injury. Therefore, providing carbohydrates to the point of inducing metabolic aberrations is not advisable. Cirrhotics may further benefit from complex carbohydrates to reduce insulin requirements. Complex carbohydrates may also be advantageous in the setting of encephalopathy, as they tend to decrease transit time and and lower colonic pH, both of which serve to decrease ammonia absorption from the gastrointestinal tract.[3]

Nutritional Supplements

S-Adenosylmethionine

S-Adenosylmethionine (SAMe) is synthesized by the transfer of an adenosyl group from ATP to the essential amino acid methionine. SAMe serves primarily as a methyl donor. These SAMe-dependent methylations are essential for the biosynthesis of a variety of cellular components including carnitine, phospholipids, proteins, DNA, and RNA, as well as polyamines needed for cell regeneration.[31,61] In addition, it serves as one source of csyteine for glutathione production (Figure 58.5). Furthermore, it has been shown that methionine metabolism is impaired in patients with liver disease and that the activity of SAMe synthase is decreased in human cirrhotic livers.[31,62,63]

The administration of exogenous SAMe should be effective in liver disease. In baboons, correction of ethanol-induced hepatic SAMe depletion with oral SAMe supplementation resulted in a corresponding attenuation of ethanol-induced liver injury.[32,64] Thus, supplementation with SAMe dampens the depletion of hepatic glutathione (GSH) stores. Without supplementation, depletion of GSH leads to inactivation of SAMe synthetase, which would tend to further reduce GSH stores, thereby predisposing to hepatic injury.[32] The studies that have evaluated SAMe supplementation have demonstrated significant improvements in subjective symptoms, serum markers of cholestasis, and hepatic GSH levels.[32,65,66] More recently, Mato et al. demonstrated that SAMe supplementation could improve survival or delay time to transplantation compared to controls. These results demonstrated a positive

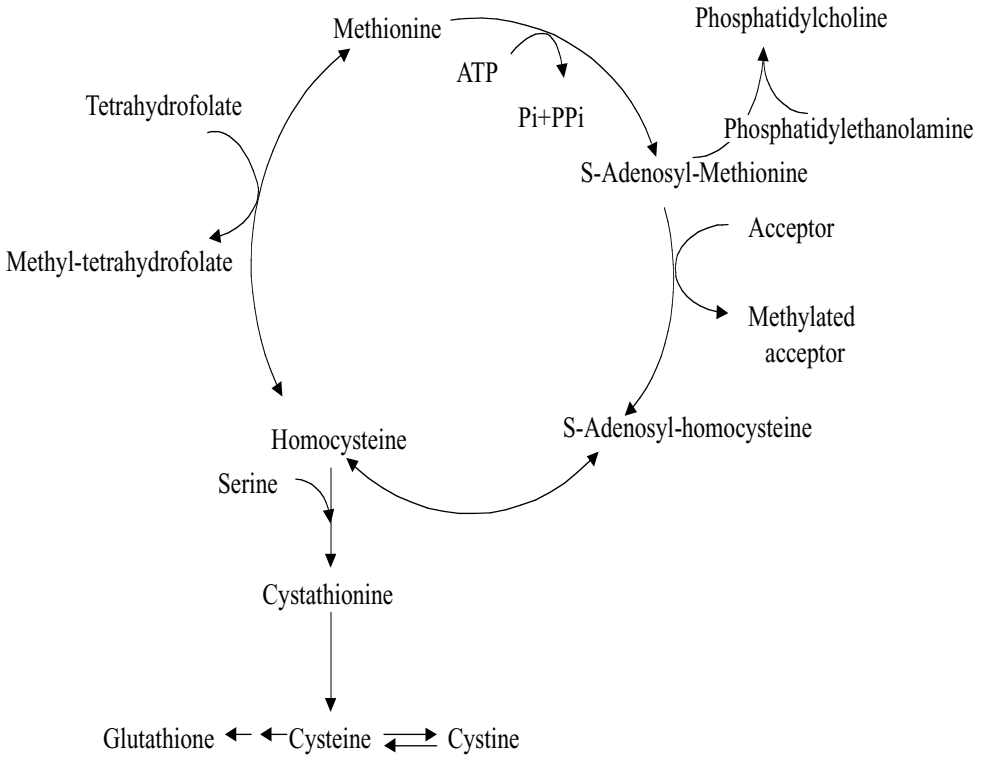

FIGURE 58.5
SAMe synthase. S-Adenosyl-L-Methionine (SAMe) is formed in an irreversible reaction that transfers an adenosyl group from methionine. SAMe is an important donor of methyl groups, and is active in the conversion of creatine to creatinine and of phosphatidylethanolamine to phosphatidylcholine. SAMe is converted to S-adenosyl-homocysteine and then to homocysteine. Homocysteine can combine with serine to form csytathionine which can ultimately be converted to glutathione. (Adapted from Kruszynska YT. In: *Oxford Textbook of Clinical Hepatology,* 2nd ed, Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodes J, Eds, Oxford University Press, Oxford, 1999, p. 257 and Lieber CS. In: *Modern Nutrition in Health and Disease,* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore 1999, pg 1177.)

trend in favor of the supplemented group, but achieved significance only when patients with advanced cirrhotic liver disease (Child C) patients were excluded.[31,67]

Supplementation with SAMe shows significant promise in the treatment of liver disease and will undoubtedly be investigated with larger studies in the future.

Zinc

Zinc (Zn) is the most abundant intracellular trace element. It is involved in a multitude of diverse catalytic, structural, and regulatory functions. Many physiologic functions require zinc, including protein metabolism, normal immune functioning and wound healing, neurosensory function such as cognition and taste, and membrane stability.[68,69] Hypozincemia is common in various types of liver disease.[69] The deficiency is multifactorial and is believed to involve poor dietary intake and impaired intestinal absorption (possibly due to a cytokine-induced intestinal metallothionein, which dampens zinc absorption). Additionally, there is decreased affinity of albumin for zinc in cirrhotics, which might influence bioavailability and lead to increased urinary losses of zinc. Finally, increased cytokine or hormonal concentrations may lead to altered zinc metabolism.[69]

Zinc deficiency may play a role in increasing plasma ammonia levels. Zinc deficiency was shown to decrease activity of glutamate dehydrogenase and ornithine transcarbam-

ylase (OTC), enzymes important in normal nitrogen metabolism (Figure 58.4). Urea synthetic capacity is believed to be reduced in zinc-deficient patients due to reduced OTC activity, as zinc acts as a cofactor in the activity of this enzyme. Zinc supplementation speeds up the kinetics of nitrogen conversion from amino acids into urea in cirrhotics.[11] Zinc deficiency also increases muscle glutamine synthetase and adenosine monophosphate deaminase, enzymes that increase ammonia production from aspartate.[70]

Although zinc deficiency may play a role in some of the altered taste sensations seen in liver disease, it is unlikely to be a major cause of anorexia in liver disease. It is much more likely that the anorexia seen in this disease is cytokine mediated.[69] Conversely, zinc deficiency, at least in part, does appear to play a role in immune dysfunction and perhaps in delayed wound healing. The latter may occur through the effect of zinc on insulin-like growth factor.[69] In regard to protein synthesis, a recent study showed lower serum albumin levels in children undergoing liver transplantation than in other transplant patients in whom serum zinc levels were normal. This correlates with the findings by Bates and McClain, which demonstrated improvement or normalization of serum transport proteins in zinc-deficient patients on parenteral nutrition when supplemented with zinc.[71,72]

Selenium

There are at least eleven selenoproteins; the most well known class is the glutathione peroxidases. These proteins are important participants in the body's antioxidant defenses. Selenium concentrations have been reported to be lower in patients with cirrhosis compared to healthy controls. Selenium deficiency could therefore contribute to the morbidity of cirrhosis. This deficiency could be easily addressed with supplementation. However, a recent study by Burk et al. reported that, though plasma selenium is indeed depressed in patients with cirrhosis, the changes noted in plasma selenoproteins of cirrhotics are not the same as those found in selenium-deficient subjects without liver disease. Functionally, these patients had an increase in the plasma gluatathione concentration, arguing against a true selenium deficiency.[73,74]

Carnitine

Fatty acids are the preferred fuel for patients with cirrhosis. Since carnitine is essential for the mitochondrial use of long-chain fatty acids for energy production, decreased availability of this quaternary amine may lead to energy deficiency in cirrhotics. Deficiency can arise from poor dietary intake or disruption of carnitine biosynthesis, the last step occurring almost exclusively in the liver. Measured levels of carnitine in patients with chronic liver disease can be reduced or increased. The literature suggests that plasma and tissue carnitine levels can be altered in patients with chronic liver disease, depending on both its cause and progression.[75,76]

A recent study by Krahenbuhl and Reichen found that patients with chronic liver disease are normally not carnitine deficient. They also concluded that carnitine metabolism can be disturbed in subgroups of patients with liver disease. For example, patients with alcoholic cirrhosis demonstrated increased plasma concentrations. Patients with primary biliary cirrhosis were able to maintain normal plasma levels of carnitine, but demonstrated increased renal excretion.[76]

Conclusion

It is clear that the relationship between nutrition and the liver is intricate and interdependent. Liver disease can result in anorexia, malabsorption, and abnormalities in nutrient

metabolism leading to a compromise in the nutritional status of the host. This impaired nutritional status can impact negatively on immune function, compromise the ability of the liver to limit the extent of hepatic insults, and retard an appropriate response to injury. Nutritional deficiencies in patients with liver disease can range from subtle abnormalities to advanced protein calorie malnutrition. Some degree of nutritional compromise is invariably present. In treating patients with liver disease, the recognition and aggressive treatment of these deficiencies is paramount. In milder forms of liver disease, this intervention may take the form of nutrient and vitamin supplementation. In more advanced liver disease, aggressive nutritional support, preferably in the form of enteral access and feeding, may be the "controllable" factor that leads to an improved outcome.

References

1. Kruszynska YT. In: *Oxford Textbook of Clinical Hepatology* 2nd ed, Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodes J, Eds, Oxford University Press, Oxford, 1999, p 257.
2. Rothman DL, Magnusson I, Katz LD, et al. *Science* 254: 573; 1991.
3. Lieber CS. In: *Modern Nutrition in Health and Disease* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore, 1999, pg 1177.
4. Petrides AS, Vogt C, Schulze-Berge D, et al. *Hepatology* 19: 616; 1994.
5. Jones PJH, Kubnow S, In: *Modern Nutrition in Health and Disease* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore, 1999, pg 67.
6. Harry DS, McIntyre N. In: *Oxford Textbook of Clinical Hepatology* 2nd ed, Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodes J, Eds, Oxford University Press, Oxford, 1999, pg 287.
7. Ma Z, Lee SS. *Hepatology* 24: 451; 1996.
8. Kruszynska YT, McIntyre N. In: *Oxford Textbook of Clinical Hepatology* 2nd ed, Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodes J, Eds, Oxford University Press, Oxford, 1999, pg 303.
9. Nelson DL, Cox MM. In: *Principals of Biochemistry* 2nd ed, Lehninger, Nelson, Cox, Worth Publisher, New York, 1993, pg 506.
10. Gerok W, Gross V. In: *Oxford Textbook of Clinical Hepatology* 2nd ed, Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodes J, Eds, Oxford University Press, Oxford, 1999, pg 346.
11. Haussinger D. In: *Oxford Textbook of Clinical Hepatology* 2nd ed, Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodes J, Eds, Oxford University Press, Oxford, 1999, pg 325.
12. Riggio O, Merli M, Romiti A, et al. *JPEN* 16: 445; 1992.
13. Denninger M. In: *Oxford Textbook of Clinical Hepatology* 2nd ed, Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodes J, Eds, Oxford University Press, Oxford, 1999, pg 367.
14. Schneeweiss B, Graninger W, Ferenci P, et al. *Hepatology* 11: 387; 1990.
15. Heymsfield SB, Waki M, Reinus J. *Hepatology* 11: 502; 1990.
16. McCullough AJ, Raguso C. *Am J Clin Nutr* 69: 1066; 1999.
17. Merli M, Riggio O, Romiti A. *Hepatology* 12: 106; 1990.
18. Madden AM, Morgan MY. *Hepatology* 30: 655; 1999.
19. Müller MJ, Böttcher J, Selberg O, et al. *Am J Clin Nutr* 69: 1194; 1999.
20. Green JH, Bramley PN, Losowwsky MS. *Hepatology* 14: 464; 1991.
21. Selberg O, Böttcher J, Tusch G, et al. *Hepatology* 25: 652; 1997.
22. McCullough AJ, Mullen KD, Smanik EJ. *Gastro Clin N Am* 18: 619; 1989.
23. Mendenhall CL, Anderson S, Weesner RE, et al. *Am J Med* 76: 211; 1984.
24. Sarin SK, Dhingra N, Bansal A, et al. *Am J Gastro* 92: 777; 1997.
25. McCullough AJ, Bugianesi E. *Am J Gastro* 92: 734; 1997.
26. Hasse J, Strong S, Gorman MA, et al. *Nutrition* 9: 339; 1993.
27. Munoz SJ. *Sem in Liver Dis* 11: 278; 1991.
28. McCullough AJ, Tavill AS. *Sem Liver Dis* 11: 265; 1991.
29. Mendenhall CL, Moritz TE, Roselle GA. *Hepatology* 17: 564; 1993.
30. Patek AJ, Ratnoff OD, Mankin H, et al. *JAMA* 138: 543; 1948.

31. Schenker S, Halff GA. *Sem in Liver Dis* 13: 196; 1993.
32. Lieber CS. *J Hepatol* 32(1): 113S; 2000.
33. Nasrallah SM, Galambos JT. *Lancet* ii: 1276; 1980.
34. Nompleggi DJ, Bonkovsky H. *Hepatology* 19: 518; 1994.
35. Mendenhall CL, Tosch T, Weesner RE. *Am J Clin Nutr* 43: 213; 1986.
36. Mendenhall CL, Anderson S, Weesner RE, et al. *Am J Med* 76: 211; 1983.
37. Silk DBA, O'Keefe SJD, Wicks C. *Gut* 29S; 1991.
38. Achord JL. *Am J of Gastro* 82: 1; 1987.
39. Mendenhall CL, Moritz TE, Roselle GA. *JPEN* 19: 258; 1995.
40. Bonkovsky HL, Fiellin DA, Smith GS. *Am J of Gastro* 86: 1200; 1991.
41. Cabre E, Rodriguez-Iglesias P, Caballeria J. *Hepatology* 32: 36; 2000.
42. Cabre E, Gonzalez-Huix F, Abad-Lacruz A, et al. *Gastroenterology* 98: 715; 1990.
43. Bonkovsky HL, Singh RH, Jafri IH, et al. *Am J Gastro* 86: 1209; 1991.
44. Kearns PJ, Young H, Garcia G, et al. *Gastroenterology* 102: 200; 1992.
45. Morgan TR. *Sem Liver Dis* 13: 384; 1993.
46. Weber FL, Bagby BS, Licate L, et al. *Hepatology* 11: 942; 1990.
47. Buse MG, Reid SS. *J Clin Invest* 56: 1250; 1975.
48. Cerra FB, Cheung NK, Fischer JE. *JPEN* 9: 88; 1985.
49. Fischer JE. *JPEN* 14: 249S; 1990.
50. Egberts EH, Schomerus H, Hamster W, et al. *Gastroenterology* 88: 887; 1985.
51. Base W, Barsigian C, Schaeffer A, et al. *Hepatology* 7: 324; 1987.
52. Tessari P, Zanetti M, Barazzoni R, et al. *Gastrology* 111: 127; 1996.
53. Charlton MR, Branched Chains Revisited *Gastroenterology* 111: 252; 1996.
54. Naylor CD, O'Rourke K, Detsky AS, et al. *Gastroenterology* 97: 1033; 1989.
55. Eriksson LS, Conn HO. *Hepatology* 10: 228; 1989.
56. Chanda S, Mehendale HM. *FASEB J* 9: 240; 1995.
57. Chanda S, Mehendale HM. *Toxicology* 111: 163; 1996.
58. Nanji AA, Sadrzadeh SMH, Yang EK, et al. *Gastroenterology* 109: 547; 1995.
59. Lieber CS, DeCarli LM, Mak KM, et al. *Hepatology* 12: 1390; 1990.
60. Lieber CS, Robins SJ, Li J, et al. *Gastroenterology* 106: 152; 1994.
61. Stipanuk MH. In: *Modern Nutrition in Health and Disease* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore, 1999, pg 543.
62. Horowitz JH, Rypins EB, Henderson JM, et al. *Gastroenterology* 81: 668; 1981.
63. Duce AM, Ortiz P, Cabrero C, et al. *Hepatology* 8: 65; 1988.
64. Lieber CS, Casini A, Decarli LM, et al. *Hepatology* 11: 165; 1990.
65. Frezza M, Surrenti C, Manzillo G, et al. *Gastroenterology* 99: 211; 1990.
66. Vendemiale G, Altomare E, Trizio T, et al. *Scan J Gastro* 24: 407; 1989.
67. Mato JM, Camara J, Fernendez de Paz J, et al. *J Hepatol* 30: 1081; 1999.
68. King JC, Keen CL. In: *Modern Nutrition in Health and Disease* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore, 1999, pg 223.
69. McClain CJ, Marsano L, Burk RF, et al. *Sem in Liv Dis* 11: 321; 1991.
70. Mullen KD, Weber FL. *Sem in Liv Dis* 11: 292; 1991.
71. Narkewicz MR, Krebs N, Karrer F. *Hepatology* 29: 830; 1999.
72. Bates J, McClain CJ. *Am J Clin Nutr* 34: 1655; 1981.
73. Burk RF, Levander OA. In: *Modern Nutrition in Health and Disease* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore, 1999, pg 256.
74. Burk RF, Early DS, Hill KE, et al. *Hepatology* 27: 794; 1998.
75. Rebouche CJ. In: *Modern Nutrition in Health and Disease* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore, 1999, pg 505.
76. Krahenbuhl S, Reichen J. *Hepatology* 25: 148; 1996.
77. Brodsky IG. In: *Modern Nutrition in Health and Disease* 9th ed, Shils ME, Olson JA, Shike M, Ross AC, Eds, Williams and Wilkins, Baltimore, 1999, pg 699.
78. Nelson DL, Cox MM. In: *Principals of Biochemistry* 2nd ed, Lehninger AL, Nelson DL, Cox MM, Eds, Worth Publishers, New York, 1993, pg 506.