Nutrition for the Hospitalized Patient

Basic Science and Principles of Practice

edited by
Michael H. Torosian

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Marcel Dekker, Inc. New York • Basel • Hong Kong

Library of Congress Cataloging-in-Publication Data

Nutrition for the hospitalized patient : basic science and principles of practice / edited by Michael H. Torosian.
p. cm.
Includes bibliographical references and index.
ISBN 0-8247-9292-0
1. Diet therapy. 2. Hospital patients—Nutrition. 3. Nutrition. I. Torosian, Michael.
RM216.N838 1995
615.8'54—dc20 94-43115
CIP

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the address below.

This book is printed on acid-free paper.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2

PRINTED IN THE UNITED STATES OF AMERICA

To Dorothy and Harry Torosian,
my parents,
for their constant patience, support,
and lifelong commitment to education

Foreword

It is fairly commonplace for patients to be admitted to hospitals with varying degrees of malnutrition. In some of the more deprived areas of the world, this is usually due entirely to starvation. In this country, however, there are many reasons for malnutrition. In the past, many people suffered from vitamin deficiencies before these were well identified. Today, some are admitted with cachexia due to advanced cancer, others are burn victims, and still others suffer from chronic sinus draining such as empyemas. Many other examples can be cited. Recently we have begun to recognize that hospital regimes often cause malnutrition and this is paticularly true where there has been some degree of deprivation before admission. A classic example, of course, is the chronic ulcer patient with a scarred and stenotic pylorus. Such a patient is often admitted after having lost a good deal of weight from anorexia and vomiting. Several days may be spent in various studies, some of which may require withholding food for a day at a time. For example, with this type of patient it is often desirable for the stomach to be empty prior to surgery and this may require a few days of gastric draining with rinsing. To this end, the patient may be on gastric suction for 48–72 hours. Surgery involves blood loss and excites a catabolic response, and some surgeons may want the stomach to rest for a few days before feeding is resumed. Thus, multiple factors may augment a food nitrogen deficit that was already established at the time of admission.

This volume addresses such problems from both a theoretical and a practical point of view. As its title suggests, this book is appropriately divided into two parts. Part I, "Basic Science," is really a crisp review of the science of nutrition by a series of widely known experts. Part II, "Principles of Practice," begins with nutritional assessment and a new statement on nutritional requirements in various states of health and disease. Chapters are devoted successively to the contrasting techniques of enteral and parenteral feeding, followed by chapters on total parenteral nutrition solutions and enteral feeding formulas. Vascular access and enteral feeding techniques are covered, followed by a discussion of the complications frequently encountered in the use of these methods. A series of chapters

on nutrition and specific clinical problems, e.g., sepsis, cancer, gastrointestinal disease, and burns, provides insight into the management of these conditions. The chapter on preoperative nutrition support is based, in part, on an extensive group study in nine VA hospitals. And, finally, several chapters focus on cardiac and pulmonary disease, renal failure, newborns, pregnant women, AIDS patients, and neurologically impaired patients, respectively.

I would like to call attention to three chapters, in particular, perhaps because these subjects have been less covered in the past. First, the chapter on immunonutrition, by John Daly and Arnold Hill, focuses on the role of the macrophage in resistance to infection through its influence on B cells, T cells and T helper cells, and natural killer cells and the relationship between nutrition and immunity.

Second, the chapter on alternative lipids, by Manjakkollai Veerabagu, George Blackburn, and Edward Mascioli, introduces a good bit of new material or material that is less well known to many people who make extensive use of intravenous feeding techniques.

And third, the chapter on anabolic hormones, by Thomas Ziegler and Danny Jacobs, covers this topic in considerable depth and, in addition, keeps the discussion closely related to malnutrition as one sees and appreciates it in the modern hospital setting.

While much of the long-term parenteral and enteral nutrition will necessarily be given at home, the more severe cases of malnutrition will usually be hospital based and it is here that home programs will largely be planned. This volume gives a very complete background of the present status of therapeutic nutrition. It provides thoroughly practical techniques of assessing patients who require special attention, information as to how these requirements are best met, and a description of the pitfalls that may be encountered.

In this book, Dr. Torosian has provided a comprehensive overview of the subject. He has chosen the contributors wisely, based on their expertise in their respective fields. The volume will be of interest as a compendium on therapeutic nutrition and, at the same time, as a useful handbook when applying these principles to practice.

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Preface

Over the past 30 years, a revolution has occurred in the basic science research and clinical practice of nutritional support of the hospitalized patient. During this period, we have witnessed a tremendous increase in the understanding of critical metabolic events that occur at the host, organ, cellular, and molecular levels. This basic knowledge has led the way for the development of specialized nutritional support not dreamed of only a few years earlier. The concept of nourishing patients entirely by the parenteral route has become a reality—primarily through the pioneering efforts led by Dr. Jonathan E. Rhoads and colleagues at the University of Pennsylvania. Furthermore, we now recognize that nutritional support accomplishes much more than simply providing nutrients to prevent malnutrition—i.e., it affects host immunity, cytokine response, and hormone secretion essential for preventing morbidity in critically ill patients.

This book is organized into two parts based on my concept of the development of nutritional support for hospitalized patients—"Basic Science" and "Principles of Practice." The Basic Science chapters deal with concepts of macro- and micronutrient metabolism that are clinically relevant for the provision of nutritional support to patients. Carbohydrate, protein, lipid, vitamin, and trace element metabolism are reviewed in detail and emphasize biochemical processes that are critical to clinical illness and health. The impact of nutrients on wound healing, host immunity, and cytokine response is significant and chapters dealing with these phenomena constitute the foundation for active basic and clinical research. State-of-the-art chapters review the use of alternative lipids, amino acids, and anabolic hormones in specific clinical situations.

The section on principles of practice brings research concepts from the section on basic science into clinical reality. Basic concepts of enteral and parenteral nutrition, nutritional assessment, nutrient solutions, and practical aspects of providing nutritional support are reviewed. Nutritional support of specific clinical populations is extensively reviewed in chapters covering critical care and sepsis, cancer, perioperative support, gastrointestinal

disease, burns, cardiac and pulmonary disease, renal failure, newborns and pediatrics, pregnancy, AIDS, and the neurologically impaired patient. Current chapters that discuss the effect of nutrition on aging and disease prevention are important components of this book. Nutritional support complications and home nutritional support are extensively reviewed. Finally, the cost-effectiveness and legislative challenges of nutritional support are discussed and are clearly essential to integrate this rapidly evolving field into today's complex health care environment.

I wish to express my sincere gratitude to each of the contributors for the diligence and accuracy with which they prepared the chapters. It is a distinct pleasure for me to have worked with and known each of them—I take great joy in their personal friendship and in my respect for their professional talents. They are all clearly experts in their fields and have made tremendous scientific and clinical contributions to the care of the hospitalized patient receiving nutritional support.

This book is as dynamic as the extraordinary revolution in nutritional support that it recounts. We should no longer view nutritional support with tunnel vision—it is not simply the provision of protein and calories to patients to prevent malnutrition. We must expand our perspective of nutritional support to consist of comprehensive, metabolic support of the hospitalized patient. Metabolic therapy of the future will include anabolic hormones, cytokines, metabolic blocking agents, nutritional pharmacology, immunity-enhancing agents, specialized amino acid formulas for specific disease states, alternative lipid substrates, and other designer molecules. The next era of metabolic support of the hospitalized patient promises to be just as exciting as the past.

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Nutrition for the Hospitalized Patient

1

Carbohydrate Metabolism

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INTRODUCTION

Carbohydrates are simple sugars or polymers of sugars that can be hydrolyzed to simple sugars by the action of enzymes in the digestive system. Dietary carbohydrate presently comprises 40–45% of the calories consumed by the average American and consists of 60% starch, 30% sucrose, and 10% lactose. Sucrose (table sugar) and lactose (milk sugar) are disaccharides composed of glucose and fructose (sucrose) and glucose and galactose (lactose). About half of the ingested carbohydrate is digested to glucose and the rest mainly to fructose and galactose. The principal product of carbohydrate digestion and the principal circulating sugar is glucose, which is taken up by the body cells and metabolized for energy. The normal fasting level of glucose in peripheral venous blood, determined by the highly specific glucose oxidase method, is 60–80 mg/dl. In arterial blood, the glucose level is 15–30 mg/dl higher than in venous blood.

The amount of carbohydrate in the adult body is about 300–400 g. Of this, 100 g are stored as glycogen in the liver, another 200–250 g are present as glycogen in skeletal, cardiac, and smooth muscle, and about 15 g consist of the glucose in the blood and extracellular fluid. The carbon skeletons for the synthesis of the nonessential amino acids in the body are provided by carbohydrates. Each gram of carbohydrate when oxidized yields, on the average, 4 kcal. Administered glucose solutions (dextrose) provide 3.4 kcal/g dextrose.

DIGESTION AND ABSORPTION

Carbohydrate digestion is essentially the hydrolysis of di- and polysaccharides in the diet to their constituent simple sugars by enzymes of the digestive juices. Digestion of complex carbohydrates begins in the mouth with salivary amylase, which hydrolyzes starches (amylose, amylopectin, glycogen) to smaller units. Although some hydrolysis of starch

to maltose occurs in the mouth and continues in the stomach until the food mass is acidified, the principal site of digestion of carbohydrate is in the small intestine. Here, pancreatic and intestinal digestive enzymes reduce the complex carbohydrates to dimeric units. The disaccharidases (enzymes splitting the dimers) in the brush border of the intestinal mucosal cells break the dimers into their constituent hexoses. Sucrose is split rapidly by sucrase into glucose and fructose, lactose more slowly by lactase into glucose and galactose, and maltose rapidly by maltase into glucose and glucose. The resulting simple hexose units in the brush border are then absorbed across the adjacent plasma membrane into the cells of the intestinal mucosa. Dietary fiber, on the other hand, is resistant to hydrolysis by human digestive enzymes. However, in the lower intestine and colon, degradation of some types of dietary fiber may occur through the action of bacterial enzymes.

For absorption, the simple sugars must enter the epithelial cell, be transported across the cell, enter the interstitial fluid, and then pass through the walls of the blood capillaries for transport to the portal circulation and the liver and be dispensed according to need to the systemic circulation. Energy-dependent active transport accounts for most of the absorption of glucose and galactose. It is effected by the sodium pump and a mobile carrier system. When intraluminal concentrations of the sugars are high, passive diffusion accounts for a small amount of the total glucose absorbed. Fructose absorption is not energy dependent or rapid; it occurs by facilitated diffusion at rates dependent upon its local concentration.

About 97–98% of the carbohydrate in most American diets is digested and absorbed. Due to the avidity of the intestinal mucosa for uptake of mono- and disaccharides, intake of these sugars and of many other carbohydrates results in rapid and substantial increases in plasma glucose, galactose, or fructose concentrations. These generate a series of adaptive activities to maintain plasma homeostasis. Less drastic adaptive actions may be required when the carbohydrate is taken in the form of foods with starches versus sugars.

METABOLISM OF GLUCOSE

Quantitatively the most important carbohydrate available to the body, whether by synthesis within the body or by absorption from the diet, is glucose, and hence any discussion of carbohydrate metabolism is essentially one about glucose. Once it enters the cells, glucose is normally phosphorylated to form glucose-6-phosphate (G6P) by the catalytic action of hexokinase. The liver contains an enzyme called glucokinase, which has greater specificity for glucose and, unlike hexokinase, is increased by insulin and decreased in starvation and diabetes. The G6P is either polymerized into glycogen (glycogenesis) or catabolized (glycogenolysis), as outlined in Figure 1. The human body contains about 400 g of glycogen, the storage form of glucose, of which 100 g are found in the liver and are available for systemic use. The larger glycogen stores in skeletal muscle are not available to provide glucose to the rest of the body but can be used to supply energy needs of muscle cells. The synthesis and storage of glycogen are physically limited, since glycogen is a very bulky (hydrated) molecule, and it is estimated that not more than 10–15 h worth of glucose energy can be stored as glycogen in the liver. The breakdown of glucose to pyruvic acid or lactic acid (or both) is called glycolysis. Glucose catabolism proceeds in two ways: via cleavage to trioses or via oxidation and decarboxylation to pentoses. The pyruvic acid pathway through the trioses is called the Embden-Meyerhof pathway and

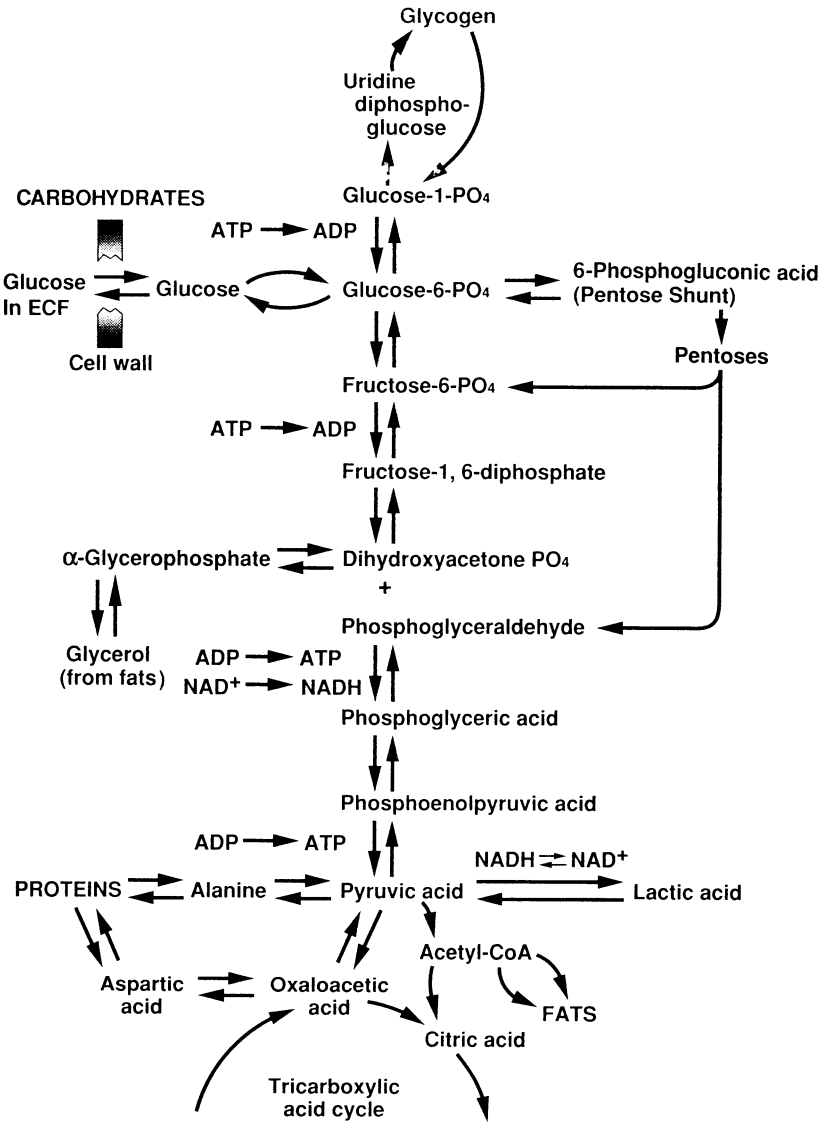


Figure 1 Metabolic pathways of glucose in cells.

the gluconic acid–pentose pathway is known as the direct oxidative pathway or hexose monophosphate shunt (Fig. 1).

Glucose metabolism cannot be completely separated from the metabolism of fats and proteins. On the one hand, proteins are potential sources of glucose, and, on the other, glucose can be converted to acetyl-CoA. Interconversions between carbohydrate, fat, and proteins include the conversion of the glycerol from fats to dihydroxyacetone phosphate and the conversion of a number of amino acids with carbon skeletons resembling intermediates in the Embden-Meyerhof pathway and citric acid cycle to these intermediates by deamination. In this way, and by conversion of lactate to glucose, nonglucose molecules can be diverted to glucose production. Though acetyl-CoA glucose can be

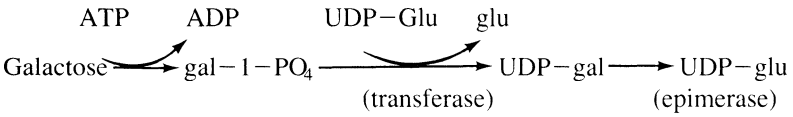
converted to fats, but since the formation of pyruvic acid to acetyl-CoA is irreversible, fats are not converted to glucose via this pathway. Therefore, there is very little net conversion of fats to carbohydrate in the body because, except for the quantitatively minor production from glycerol, there is no pathway for conversion.

GLUCOSE PARADOX

Glucose could be incorporated into glycogen both directly, by passing through G6P and uridine diphosphate glucose, and indirectly, by being metabolized to 3-carbon precursors (lactate, pyruvate), then resynthesized through the gluconeogenic pathway to G6P and then glycogen. The existence of such an indirect, apparently inefficient and energy-wasting pathway has been termed "the glucose paradox" (1,2). Although numerous studies indicate that both pathways are active, it has been very difficult to quantitate the relative contribution of each pathway because of the inability to measure gluconeogenesis and glycogen synthesis accurately in vivo. At least in the transition from fasted to fed, liver glycogen (and fat) synthesis is fueled not directly by glucose but by 3-carbon precursors (2), particularly lactate. The direct pathway appears to dominate in the fed state in humans.

METABOLISM OF HEXOSES OTHER THAN GLUCOSE

Galactose and fructose are the other hexoses that are either absorbed from the intestine or liberated by hydrolysis of lactose or sucrose. Galactose does not affect insulin secretion, and almost all of it enters the liver, where it is converted to glucose by the following pathway:



After phosphorylation, galactose-1-phosphate reacts with uridine diphosphoglucose to form glucose and uridine diphosphogalactose. This uridine diphosphogalactose is then converted to uridine diphosphoglucose, which functions in glycogen synthesis. The latter reaction is reversible, and this is the way the galactose necessary for formation of glycolipids and mucoproteins is formed when dietary galactose intake is inadequate. Since equal amounts of glucose are absorbed with the galactose when lactose is the source, the glucose will be used for immediate energy by most tissues and for glycogen production by the muscles and liver.

Fructose, a ketohexose, is metabolized mainly in the liver to intermediates of the glycolytic pathway, and increased fructose levels in the blood do not evoke a release of insulin. Fructose may be phosphorylated on the sixth carbon atom, competing with glucose for the hexokinase involved, or it may be phosphorylated on the first carbon atom, a reaction catalyzed by a specific fructokinase (Fig. 2). Fructose-1-phosphate is then split into dihydroxyacetone-phosphate (DHAP) and glyceraldehyde. The glyceraldehyde is phosphorylated and along with DHAP enters the pathways for glucose metabolism via pyruvate and acetyl-CoA or enter the pathways for triglyceride (TG) synthesis via α-glycerophosphate. When fructose enters the liver paired with glucose (which usually happens in the dietary situation), it becomes a direct source of carbons for fatty acid and

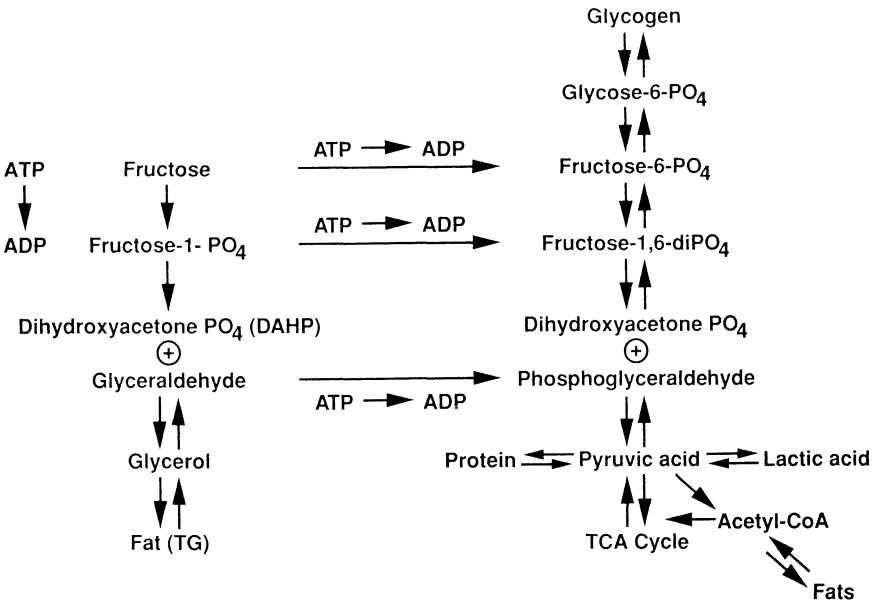


Figure 2 Outline of the metabolism of fructose.

TG synthesis rather than for glucose production. Low-dose fructose administration in fasting humans exerts a pronounced protein-sparing effect and abolishes the characteristic metabolic adaptation to starvation (3). In the presence of fructose, but not glucose, insulin stimulates TG production (4). The rapid oxidation of fructose compared with that of glucose is probably due to its insulin-dependent cellular uptake, followed by its rapid phosphorylation (5). Sucrose supplementation leads to hypertriglyceridemia in humans possibly as a consequence of this disaccharide's fructose rather than its glucose (6). There is no conclusive evidence that physiological amounts of fructose exacerbate copper deficiency or aid in weight control.

CARBOHYDRATE DERIVATIVES

Chemical reaction of sugars lead to the formation of sugar alcohols, amino sugars, glycosides, uronic acids, more exotic sugars (such as fucose, ribose, mannose, and sialic acid), and many complex compounds with proteins and lipids. Glycerol is the 3-carbon alcohol that is formed by the hydrolysis of body TG stores.

Sorbitol, mannitol, and xylitol are sugar alcohols that have energy contents of 4 kcal per g, as does sucrose. They occur naturally in fruits but are also commercially prepared. Xylitol, a 5-carbon polyol, is equally as sweet as sucrose, whereas sorbitol and mannitol are only half as sweet. Slow intravenous infusion of sorbitol, fructose, and xylitol do not alter blood glucose levels, nor do they increase plasma insulin much above basal levels (7). The three principal metabolic effects of infused xylitol are to moderate blood glucose and insulin elevations and to reduce gluconeogenesis (8). Therefore, xylitol is a suitable energy source whenever blood glucose and insulin concentrations are elevated and protein wasting occurs (8), as in injury and sepsis. Ingestion of excessive amounts may produce an osmotic diarrhea.

Inositol is an alcohol related to the hexoses, which occurs in the bran of cereal grains. Ascirlic acid, one of the water-soluble vitamins, is a hexose derivative that can be synthesized by plants and by some animals but not by human beings. Many carbohydrate derivatives are constituents of connective, nervous, and other tissues and are involved in many metabolic functions.

BLOOD GLUCOSE HOMEOSTASIS

One important requirement for all living organisms is to adapt to changes in their environment. Physiological changes are always accompanied by changes in rates of metabolism, which are achieved by metabolic regulations. Humans eat intermittently so that a period of 8–12 h of starvation (overnight) occurs regularly. During this time, the body must utilize fuel stores laid down after previous meals. Glucose levels in plasma are most closely regulated and vary only between 4 and 6 mM (72–108 mg/dl), being the most "buffered" of all fuels in normal humans (9). The glucose taken from the circulation by the cells is constantly replaced by the liver so that the blood glucose level is maintained within this relatively narrow limit. There is a net uptake of glucose by the liver when blood glucose is high and a net discharge when it is low. This "glucostat" function of liver is not automatic but is effected by the actions of various hormones. Elevated blood glucose levels stimulate the pancreas to release insulin, and low levels suppress insulin release. Insulin in turn lowers the blood glucose level by stopping glycogenolysis, promoting glycogenesis, stimulating uptake of glucose by many tissues and converting some carbohydrate to lipid. Glucagon, a pancreatic hormone, is believed to activate glycogenolysis, and epinephrine, produced by the adrenal gland under conditions of stress, increases the rate of glycogen breakdown. Steroid hormones accelerate the catabolism of proteins, thus bringing about gluconeogenesis.

In the kidney, glucose is freely filtered; but at normal blood glucose levels all but a very small amount is reabsorbed in the proximal tubules. When the filtered amount increases, reabsorption increases, but there is a limit to the amount of glucose the proximal tubules can reabsorb. Should the blood sugar level reach 160–180 mg/dl, some glucose will be excreted in the urine (glucosuria). This level, varying from one individual to another, is known as the renal threshold for glucose. Glucosuria does not normally occur due to the efficient handling of the liver. It occurs when the blood glucose is elevated because of relative insulin deficiency (diabetes mellitus) or because of excessive glycogenolysis after physical or emotional trauma or during excessive intake by total parenteral nutrition (TPN).

During exercise the caloric needs of muscle are initially met by glycogenolysis in muscle and increased uptake of muscle glucose. Blood glucose initially rises with increased hepatic glycogenolysis but may fall with prolonged, strenuous exercise. Plasma insulin falls and glucagon rises. After exercise, liver glycogen is replenished by additional gluconeogenesis and a decrease in hepatic glucose output. Insulin levels rise sharply, especially in hepatic portal blood. The insulin entering the liver presumably promotes glycogen storage.

Six pathways are available for the removal of glucose from the blood stream: (1) continuous uptake for glucose by body cells and its oxidation for energy, (2) conversion and storage of glucose to glycogen by the liver (glycogenesis), (3) synthesis of fats from glucose (lipogenesis), (4) synthesis of numerous carbohydrate derivatives, (5) glycolysis in red blood cells, and (6) glucosuria. A below-normal glucose concentration is known

as hypoglycemia and may occur in certain abnormalities of liver function or when excessive amounts of insulin are produced by the pancreas or when exogenously infused. A blood sugar concentration in excess of normal levels is known as hyperglycemia, which is characteristic of diabetes mellitus and trauma.

HYPOGLYCEMIA

A lower than normal glucose concentration occurs when there is an increase in glucose utilization relative to glucose production. This hypoglycemia results in certain abnormalities of liver function or production of excess insulin by the pancreas. Since the central nervous system is primarily dependent on circulating glucose as a fuel, hypoglycemia may result in central nervous system dysfunction or even death. The prevention or correction of hypoglycemia is critical to survival. Although insulin is the dominant glucose-lowering factor, there are redundant glucoregulatory systems that help preserve the level of this critical fuel in plasma (9–13). Multiple glucose-raising counterregulatory factors collectively constitute a fail-safe system that prevents or minimizes failure of the entire system upon failure of one, or perhaps more, of its components (12).

There is a hierarchy among the glucoregulatory factors. The prevention or correction of hypoglycemia is normally the result of both dissipation of insulin and activation of glucose counterregulatory systems. Among the glucose counterregulatory factors, glucagon plays a primary role. Epinephrine, although involved, is not normally critical, but it becomes so when glucagon is deficient. Thus insulin, glucagon, and epinephrine stand high in the hierarchy of redundant glucoregulatory factors. Growth hormone and cortisol are not critical to the correction of even prolonged hypoglycemia (12) or to the prevention of hypoglycemia after an overnight fast. Glucose autoregulation (hepatic glucose production as an inverse function of the ambient plasma glucose concentration independent of hormonal and neural regulatory factors) may be involved during severe, but not mild or moderate, hypoglycemia. Recurrent hypoglycemia may result in alterations in reduction of hepatic glucose production (13). An impairment in hepatic gluconeogenesis is responsible for the hypoglycemia during sepsis (10). Type I diabetic patients are more vulnerable to hypoglycemia than normal persons (11). The presence of insulin resistance, both at the peripheral and the hepatic level, serves to "protect" the diabetic from hypoglycemia. Hypoglycemia-associated autonomic failure may well be a major risk factor for iatrogenic hypoglycemia in insulin-dependent diabetes mellitus (IDDM) (14). The development of posthypoglycemic rebound hyperglycemia (the Somogyi phenomenon) in the absence of insulin waning in patients with IDDM results primarily from an excessive increase in glucose production due to activation of glucose counterregulatory systems (15). Insulin clearance as well as glucose kinetics during insulin-induced hypoglycemia are identical in trained (athletes competing in elite-class endurance sports) and untrained subjects (16). Intractable hypoglycemia in one patient with colon carcinoma was due to a humorally mediated proliferation of insulin receptors in insulin-responsive cells like circulating mononuclear cells, liver, and muscle (17). Controlled hypoglycemia (gluconeogenic blockade) may be a potential therapy for high-grade tumors sensitive to glucose deprivation (18).

HYPERGLYCEMIA

Following glucose ingestion, endogenous glucose production is suppressed and the body switches from a state of net glucose production to one of net glucose assimilation. This

switch is regulated by both hyperglycemia and hyperinsulinemia. The concept that hyperglycemia per se increases glucose utilization and decreases glucose production is well established (19,20) and this inhibition of glucose production happens in normal humans independent of changes in glucoregulatory hormones (21). Hyperglycemia promotes primarily nonoxidative glucose disposal, while insulin stimulates the oxidation of glucose. Hyperglycemia with fixed basal levels of insulin results in a significant decrease in lipolysis (22). During hyperglycemic glucose clamp studies, the stimulation of insulin secretion is accompanied by a reduction in endogenous insulin clearance (23). Hemorrhagic hyperglycemia, which is caused by insulin resistance, has been demonstrated to have beneficial effects on fluid homeostasis since glucose can assume the role of an important fluid-mobilizing osmole (24). During short-term hyperglycemia, myocardial glucose extraction is enhanced in humans (25), and the majority of the extracted glucose is stored as glycogen. Chronic hyperglycemia tended to potentiate glucose-induced insulin secretion and did not alter the modulating effect of glucose or arginine-stimulated insulin release (26). Adverse effects of hyperglycemia on renal function during normothermic renal ischemia are due to anaerobic glucose metabolism with marked lactate accumulation (27). Mass action of increased plasma glucose during epinephrine-induced hyperglycemia plays an important role in the tissue-enhanced rate of glucose utilization (28). However, brain glucose utilization is not increased, in agreement with another study (29). Hyperglycemia is more marked in major trauma in spite of no exogenous intake of glucose, and it may be the driving force for the accelerated metabolic effects of injury. This posttrauma hyperglycemia is mainly due to an increased hepatic output of glucose and not to a decreased ability of the tissue to extract glucose from the plasma (30).

GLUCOSE TOLERANCE

Body response to dietary glucose infusion is monitored to determine "glucose tolerance," determined by the rate at which the inherent mechanisms for removing excess glucose from the blood perform their functions. Glucose tolerance is usually measured by following blood glucose concentrations 15 min to 2–3 h after an oral load of 50–100 g glucose is given after overnight fasting. Blood glucose level is plotted against time (Fig. 3), and the shape of the curve is determined by (1) the capacity of the body to secrete adequate amounts of insulin; (2) the rate of insulin catabolism; (3) the availability of nutritional factors necessary for insulin binding and effectiveness; (4) the presence of insulin antagonists; and (5) the release of counterregulatory factors, like glucagon, to halt the continuing fall in blood glucose when the actions of insulin have been accomplished.

The degree of insulin release and its effectiveness determine how some blood glucose reaches its peak and the height of the peak attained (normally not more than 160 mg/dl after 30–60 min). These same mechanisms determine the time required for blood glucose to return to normal levels (70–105 mg/dl; 1.5–2.0 h). A high fasting glucose level, a higher than normal and/or delayed peak, and delays in returning to normal are the hallmarks of glucose intolerance and diabetes. When blood glucose level exceeds the renal threshold (160–180 mg/dl), glucose loss in urine (glucosuria) occurs. Repeated episodes of hyperglycemia are the primary cause of the neuropathy, microangiopathy, and other pathologies associated with the diabetic. An overresponse to glucose intake, resulting in a lower peak, a more rapid return, and, in fact, an overshooting so that plasma glucose falls below normal, are the symptoms of hypoglycemia that may precede the development of diabetes.

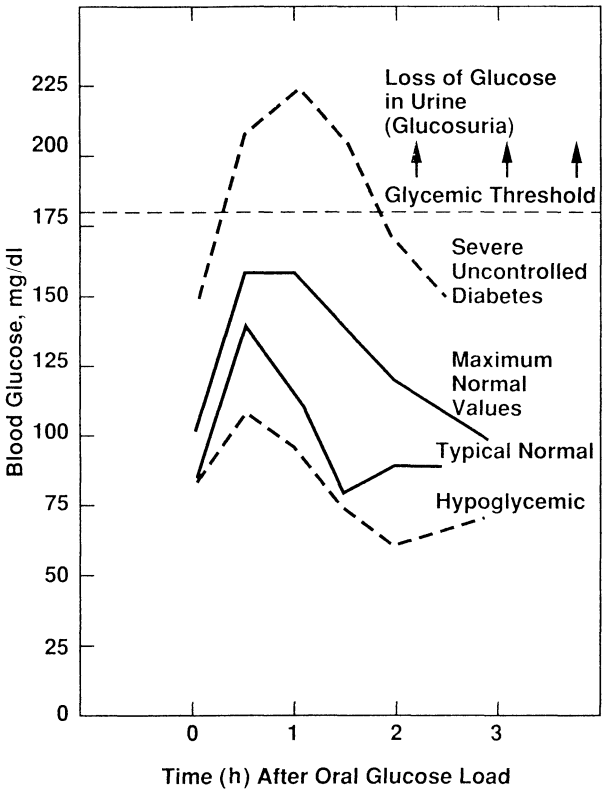


Figure 3 Schematic of glucose tolerance tests.

Understanding the etiology of the various forms of impaired glucose tolerance requires techniques for measuring both pancreatic responsiveness and insulin sensitivity and a means to evaluate their relative contributions to overall glucose tolerance. This is being done by fitting to a mathematical model (minimal model) the data obtained after cold or labeled intravenous glucose tolerance test (IVGTT) (31,32) or during glucose clamp (33). Increased adiposity is not the primary cause of age-related glucose intolerance; both β-cell dysfunction and insulin resistance but not insulin clearance or insulin-dependent glucose disappearance contribute to glucose intolerance in older individuals (34).

GLUCOSE OXIDATION

The oxidation of glucose is continually taking place within each of the billions of body cells. The end products of this oxidation are CO_2, water, and energy. The cells utilize the energy efficiently by releasing a small amount of it at a time in a series of steps that occur in the mitochondria of the cell. The first step in glucose catabolism is glycolysis, principally an anaerobic phase that results in the formation of two molecules of pyruvic acid from each molecule of glucose. The second phase of glucose catabolism is an aerobic phase that includes the decarboxylation of pyruvic acid to acetic acid, the condensation of acetic acid with coenzyme A, and passage through the tricarboxylic acid cycle (TCA) to yield hydrogen and electrons, CO_2, and water. This is the common pathway for the

oxidation of deaminized amino acids and fatty acids as well as for glucose. Through this cycle about 90% of the energy of the body is produced.

In general terms, the ingested or infused glucose may have one or two immediate fates. It can be oxidized to CO_2 and water, or it can be stored. From thermodynamic considerations alone, it would be impossible for the body to oxidize the large quantities of glucose that it is normally presented with and hence the major portion of it is taken by the tissues and stored. The ability of the body to oxidize glucose is limited and is in the range of 2–3 mg/kg/min (35) in normal humans. The enzymatic steps involved in the glucose oxidation become somewhat saturated at plasma insulin and glucose levels within the physiological range. The route of glucose administration, oral versus intravenous, has no specific effect on glucose oxidation (35). Metabolic glucose clearance is not related to glucose oxidation (36). The progressive increase in the ability to clear glucose from the blood that occurred as intravenous TPN progressed in postoperative patients was not due to an increase in the rate of oxidation of glucose but perhaps stored as glycogen or converted to fat (36). Facilitated glucose disposal after successive glucose loads (the Staub–Traugott effect) can be independent of circulating hormone and free fatty acid levels, but the predominant contribution is oxidative glycolysis (37).

GLUCOSE OVERFEEDING

Glucose overfeeding produces nonprotein respiratory exchange ratios (RQ) greater than 1.0 suggesting net fat synthesis from glucose. Increased carbohydrate oxidation and lipogenesis easily account for the improvement in carbohydrate tolerance during short-term carbohydrate overloading in normal humans (38). On the other hand, in obese subjects, carbohydrate overfeeding does not improve glucose tolerance (39). Resting metabolic rate increased during overfeeding in lean but not in obese subjects and fell during underfeeding in the obese (40). Metabolic clearance rates (MCR) of norepinephrine were similar in the obese compared to lean subjects during both under- and overfeeding. The thermogenic response to exercise was also similar in the lean and obese subjects and was unaltered by carbohydrate overfeeding or underfeeding (40). Lipolytic response to norepinephrine was partially suppressed during overfeeding in both groups. An increase in circulating anabolic hormones (IGF-1, testosterone, and insulin) in response to carbohydrate overfeeding in normal subjects adds strength to the concept that nutritional status can influence hormonal function (41). Even though short-term carbohydrate overfeeding may produce modest stimulation of sympathetic nervous system activity in humans, the increase in thermogenesis induced by overfeeding is neither suppressed by β-adrenergic blockade nor accompanied by an increased sensitivity to the thermogenic effects of norepinephrine (42). Excess calorie intake, without an increase in protein intake, stimulates postabsorptive proteolysis and protein synthesis, and the positive nitrogen balance induced by overfeeding is caused by enhanced postprandial nitrogen retention rather than a change in baseline protein metabolism (43).

Administration of a large glucose load (1.35–2.55 $\times$ REE) to hypermetabolic critically ill patients does not totally suppress fat oxidation as it does in normals (44) and in depleted patients (45). Gluconeogenesis, which is normally suppressed in the presence of high glucose concentrations, persists in traumatized or septic (46) patients. This "glucose resistance" would continue to express itself during high rates of glucose administration (47). Excessive carbohydrate loading also enhances CO_2 production, which may precipitate respiratory distress, especially in patients with borderline pulmonary function (48,49).

These observations imply the need for optimal nutrient supply during the early posttraumatic days. The continued oxidation of fat during high-dose glucose infusion provides an important physiological rationale for providing nonprotein calories in the form of both lipid and glucose.

GLUCOSE METABOLISM AND TUMOR NECROSIS FACTOR

Among the cytokines, which comprise a family of inflammatory mediators induced by infectious stimuli, tumor necrosis factor-α (TNF) has recently gained more attention since it is considered to be the first factor in the cytokine cascade in sepsis. TNF stimulates hepatic glucose production and has a variable effect on peripheral glucose utilization, which is likely to be dose dependent (S0,S1). A relatively low dose of TNF administered to normal human subjects resulted in stress hormone release and a decrease in glucose clearance, suggesting that the putative insulinlike action of TNF may not exist or may be overruled by counterregulatory responses (S0). High doses of TNF invariably caused hypoglycemia, which could be strongly potentiated by removing the counterregulatory effect of adrenal corticosteroids (S1). Lactate, another precursor for gluconeogenesis, has also been reported to increase after systematic TNF administration (S1,S2). Altered glucose metabolism in septicemia may be the result of an interplay between the classical hormones, induced by TNF and other cytokines, on one side, and the cytokine network on the other side (S3). Infusion of TNF induced an increase in substrate availability for gluconeogenesis by stimulating amino acid uptake by the liver. Pronounced increase in the net forearm efflux of amino acids in patients with cancer during TNF infusion suggested redistribution of amino acids from muscle to other tissues such as the liver (S2).

GLUCOSE AND EXERCISE

The uptake of glucose by muscle during exercise is markedly stimulated, and it is rapidly converted to lactate and CO_2. During prolonged exercise the rate of gluconeogenesis is increased due to increases in the activities of pyruvate carboxylase, fructose-1,6-diphosphatase, and glucose-6-phosphatase and diminished activities of phosphofructokinase and particularly pyruvate kinase (S4). The overall hormonal response to exercise creates a metabolic milieu that favors the release of glucose from the liver (glycogenolysis and gluconeogenesis) and the release of fatty acids from adipose tissue (lipolysis). The extent of these hormonal alterations is accentuated as the intensity of the exercise increases and is blunted by physical training (S5). In addition, an increase in activity in the splanchnic sympathetic nerves may also be a contributory factor. During light exercise plasma glucose homeostasis is maintained by a reduction in insulin concentration and/or an increase in glucagon concentration. The blood glucose concentration remains virtually constant during exercise either before starvation or after 4 days of total starvation, and very little is known about this adaptive mechanism (S6).

The influence of exercise on body fuel metabolism extends to the postrecovery period. The hormonal profile seen during exercise (decreased insulin, increased counterregulatory hormones) is rapidly reversed during the first minutes of recovery from acute exercise (S7). The early rise in plasma glucose during recovery is due to an imbalance between glucose production and utilization caused by a more rapid decline than production in the

initial 5 min. The recovery period beyond 5 min is characterized by bidirectional changes in insulin sensitivity in the liver and muscle, which provides a mechanism of muscle glycogen repletion in preference to hepatic glycogen repletion (57).

Physical training induces a greater muscle mass coupled with an enhanced oxidative capacity in muscle. This is associated with a lower rate of terminal oxidation of glucose (resulting in a higher blood glucose concentration) and an enhanced metabolic clearance of lactate (55). Plasma free tryptophan and its ratio to BCAA increase progressively during prolonged cycling to fatigue, and this response is attenuated by glucose feeding (58).

GLUCOSE KINETICS QUANTITATION

Pool model analysis of isotopic (stable or radioactive) data derived after infusing a tracer quantity of glucose and analyzing its pattern of disappearance from plasma and breath has been extensively used in quantifying the rates of glucose kinetics (appearance, oxidation, and recycling) under various pathological considerations (59). Both steady-state and non–steady-state kinetics were assumed. Depending upon the experimental design, single (noncompartmental) or multiple pool models were fitted to the data. Bolus or primed continuous infusion of stable (^{13}C, ^{2}H) or radioactive (^{14}C, ^{3}H) tracer glucoses were used. Recent technological advances in the development of analytical instruments (mass spectrometers for stable isotopes and scintillation counters for radioactive isotopes), the availability of highly enriched tracer isotopes at reasonable cost, and the possibility of replacing the tracers in several positions of the intact glucose molecule made it possible to quantitate the metabolic rates used to elucidate the mechanisms of the biochemical pathways.

The most frequently followed methodology (noncompartmental model) for the quantitation of glucose kinetics uses a primed constant continuous infusion (80:1 ratio) of U-^{13}C or U-^{14}C or 1-^{13}C glucose for the determination of the rate of direct oxidation of glucose and 6-^{3}H glucose or 6-6-^{2}H glucose for measuring total glucose production (60). An isotopic steady-state equilibration takes about 2–3 h. The difference between the rates of glucose appearance determined using 6-^{3}H or 6-6-^{2}H and U-^{14}C or U-^{13}C glucoses, in the absence of any exogenous supply of glucose, gives directly the rate of glucose carbon recycling through phosphorylation–dephosphorylation (Cori cycle). Glucose appearance rate in a postabsorptive normal adult is 2.5 mg/kg/min (30,60) and is increased significantly in many pathological states, including severe trauma, burn, and hyperthyroidism (30). Although glucose appearance is markedly enhanced in severe trauma, glucose clearance, oxidation, and recycling are not affected, and this results in hyperglycemia, which seems to be the driving force for the hormonal milieu (30).

GLUCOSE RECYCLING

A substrate cycle exists when opposing, nonequilibrium reactions catalyzed by different enzymes are active simultaneously. Such potential substrate cycles are present in the processes of glycolysis and gluconeogenesis. One such cycle involves glucose conversion to G6P and back to glucose (glucose cycle). Another involves the conversion of fructose-1-phosphate to fructose-1,6-diphosphate and back to fructose-1-phosphate (fructose cycle) and yet another of phosphoenolpyruvate to pyruvate and back to phosphoenolpyruvate. High-energy phosphate bonds in ATP are involved in glucose substrate cycling, with the net result being the production of heat. There is no change in the amount of

either the substrate of the product, but energy expenditure is increased in order to resynthesize the ATP, which results in loss of heat energy. This so-called "futile" cycling provides a unique and rapid mechanism to accelerate metabolic pathways in times of urgent need and to improve sensitivity of metabolic regulation.

The use of isotopic tracers allows the quantitation of the rates of glucose cycling as described before. The activity of glucose recycling in healthy and sick humans has been summarized (30), and the compiled data are shown in Table 1. Newborn infants exhibit the highest recycling rates of glucose, accounting for about one third of glucose production in the fasting state. Normal adults recycle 10 ± 2% of their glucose production, and aging has little effect on glucose kinetics. Prolonged fasting does not increase the absolute amount of glucose recycled, although glucose production is decreased appreciably. Glucose kinetics is not much affected in colorectal cancer patients. In chronic uremia and acromegaly the glucose production and clearance rates are not different from normals but the recycling rate is increased. The production and clearance rates of glucose are decreased in hypothyroidism with no change in the recycling compared to normals. In obese subjects with noninsulin-dependent diabetes mellitus (NIDDM, or Type II) the rates of endogenous glucose production and Cori cycle activity are increased compared to the rates observed in obese subjects with normal glucose tolerance. In insulin-dependent diabetes (Type I), during the normoglycemic state the rates of endogenous glucose production and recycling are comparable to those found in nondiabetic controls, but during the hyperglycemic state both of these rates are increased, with a decrease in clearance and no change in oxidation. Hypermetabolic states such as hyperthyroidism, thermal injury, and acute trauma result in hyperglycemia with enhanced glucose production. In contrast to acute trauma patients, severely burned patients recycled and oxidized more glucose. Anaerobic glucose metabolism by the cutaneous burn wound with increased lactic acid production may be a partial reason for the increased Cori cycle activity. On the other hand, the absence of an increased activity of Cori cycle in acute trauma patients indicates the efficient utilization of the available glucose for tissue uptake at the time of increased demand. The absolute amount of glucose recycled in trauma victims is 0.07 mg/kg/min, similar to unstressed normals. This is energetically wasteful but represents only a trivial amount of energy lost: 20 kJ (4.5 kcal) per day.

SUMMARY

Among the carbohydrates, glucose is a necessary major energy source and a potent regulator of metabolic and physiological functions with extensive mechanisms for close regulation of blood glucose concentration. How the liver regulates the synthesis and utilization of glucose has been studied intensively by biochemists and physiologists for decades. Metabolism of glucose consists of an interrelated series of biochemical reactions facilitated by specific enzymatic activities, which are under the influence of hormones secreted by the pancreas and the adrenal, pituitary, and thyroid glands.

It has long been appreciated that insulin is the glucose regulatory hormone; it suppresses glucose production and accelerates glucose utilization, thus lowering the plasma glucose concentration. In contrast, glucose counterregulation could be accomplished by hormonal signals, neural signals, glucose autoregulation, or a combination of these mechanisms.

Glucose metabolism cannot be completely separated from the metabolism of fats and proteins. A decrease in carbohydrate metabolism is accompanied by an increase in fatty acid oxidation. Only a small amount of carbohydrate is stored in the body in the form of

Table 1 Basal Glucose Kinetics in Healthy and Sick Humans

Status	Concentration (mg/dl)	Appearance (mg/kg/min)	Recycling (mg/kg/min)	Oxidation (mg/kg/min)	Clearance (ml/kg/min)	Recycling (% turnover)	Oxidation (% turnover)
Healthy							
Normal: newborn infants (4–5 h to 2 days)	50 ± 5	5.02 ± 0.12	1.87 ± 0.22	2.67 ± 0.10	11.7 ± 0.2	36 ± 4	53 ± 2
Normal: young adults	90 ± 4	2.75 ± 0.13	0.26 ± 0.08	0.87 ± 0.09	3.12 ± 0.08	10 ± 2	31 ± 3
Normal: elderly	92 ± 2	2.18 ± 0.05	0.28 ± 0.03	0.96 ± 0.07	2.36 ± 0.05	13 ± 2	44 ± 3
Normal: obese[a] (nondiabetic)	97 ± 1	2.09 ± 0.05	0.14 ± 0.01	1.54 ± 0.15	2.15 ± 0.05	7 ± 0.4	74 ± 7
Normal: obese[a] (fasting 3–4 weeks)	69 ± 4	0.88 ± 0.04	0.15 ± 0.03	—	1.28 ± 0.06	17 ± 3	—
Sick							
Cancer: colorectal (Duke C & D)	96 ± 3	2.46 ± 0.59	0.34 ± 0.26	—	2.56 ± 0.61	14 ± 2	—
Uremia: chronic (undialyzed)	79 ± 10	2.19 ± 0.53	0.73 ± 0.13	—	2.77 ± 0.67	32 ± 4	—
Acromegaly (normal glucose tolerance)	85 ± 3	2.18 ± 0.15	0.44 ± 0.08	—	2.76 ± 0.13	20 ± 4	—
Hyperthyroidism	100 ± 11	3.94 ± 0.16	1.39 ± 0.09	—	3.9 ± 0.2	35 ± 6	—
Hypothyroidism	88 ± 9	1.77 ± 0.56	0.20 ± 0.22	—	2.0 ± 0.6	11 ± 12	—
Diabetes: Type I							
Normoglycemic state	106 ± 7	2.15 ± 0.13	0.16 ± 0.04	1.52 ± 0.16	2.02 ± 0.12	7 ± 2	71 ± 7
Hyperglycemic state	189 to 274	2.86 ± 0.28	0.31 ± 0.11	1.54 ± 0.22	1.51 ± 0.15	11 ± 4	54 ± 8
NIDDM (obese)[a]	254 ± 11	3.80 ± 0.24	0.23 ± 0.02	1.50 ± 0.09	1.58 ± 0.15	6 ± 1	42 ± 4
Burn: 60% BSA	123 ± 11	4.25 ± 0.28	0.87 ± 0.28	1.26 ± 0.11	3.51 ± 0.29	20 ± 4	30 ± 3
Acute trauma	128 ± 7	3.96 ± 0.40	0.24 ± 0.07	0.88 ± 0.09	3.16 ± 0.08	6 ± 1	22 ± 2

[a]Glucose kinetics in obese subjects are normalized to kg of fat free mass (FFM).

Source: Ref. 30.

glycogen. If there is an excess of carbohydrate beyond the body's immediate need, it is converted and stored as fat. In the absence of an exogenous feed, production of glucose occurs at the expense of body protein stores, particularly skeletal muscle. Optimal intake of glucose will spare body protein sources. Humans can be healthy with wide variations in carbohydrate intake. Some carbohydrate is necessary in the diet for the oxidation of fats to proceed normally. As little as 50 g of carbohydrate in the diet will reduce ketosis under normal conditions. Glucose intolerance is the hallmark of the injured state, which results in enhanced glucose production, sustained oxidation, and hyperglycemia. Better understanding of the mechanisms related to glucose kinetics is imperative for the successful management of hospital-bound patients.

REFERENCES

1. Katz J, McGarry JD. The glucose paradox. Is glucose a substrate for liver metabolism? J Clin Invest 1984; 74:1901–1909.
2. Katz J, Kuwajima, Foster DW, McGarry JD. The glucose paradox: new perspectives on hepatic carbohydrate metabolism. Trends Biochem Sci 1986; 11:136–140.
3. Gelfand RA, Sherwin RS. Nitrogen conservation in starvation revisited: protein sparing with intravenous fructose. Metabolism 1986, 35:37–44.
4. Kazumi T, Vranic M, Steiner G. Triglyceride kinetics: effects of dietary glucose, sucrose, or fructose alone or with hyperinsulinemia. Am J Physiol 1986; 250:E325–E330.
5. Heinz F. Metabolism of fructose in liver. Acta Med Scand (suppl) 1972; 542:27–36.
6. Reiser S, Hallfrish J, Michaelis OE, Lazar FL, Martin RF, Prather ES. Isocaloric exchange of dietary starch and sucrose in humans. I. Effects of levels of fasting blood lipids. Am J Clin Nutr 1978; 32:1659–1669.
7. Pellaton M, Acheson K, Maeder E, Jequier E, Felber JP. The comparative oxidation of glucose, fructose, sorbitol, and xylitol in normal man. J Parenter Enteral Nutr 1978; 2:627–633.
8. Georgieff M, Moldawer LL, Bistrian BR, Blackburn GL. Xylitol; an energy source for intravenous nutrition after trauma. Parenter Enteral Nutr 1985; 9:199–209.
9. Cahill GF Jr. Ketosis. J Parenter Enteral Nutr 1981; 5:281–288.
10. Frizzell RT, Campbell PJ, Cherrington AD. Gluconeogenesis and hypoglycemia. Diabetes/Metab Rev 1988; 4:51–70.
11. Amiel SA, Tamborlane WV, Sacca L, Sherwin RS. Hypoglycemia and glucose regulation in normal and insulin-dependent diabetic subjects. Diabetes/Metab Rev 1988; 4:71–89.
12. Cryer, PE. Glucose counterregulation: prevention and correction of hypoglycemia in humans. Am J Physiol 1993; 264:E149–E155.
13. Davis MR, Shamoon H. Counterregulatory adaptation to recurrent hypoglycemia in normal humans. J Clin Endocrinol Metab 1991; 73:995–1001.
14. Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest 1993; 91:819–828.
15. Bolli GB, Gottesman IS, Campbell PJ, Haymond MW, Cryer PE, Gerich JE. Glucose counterregulation and waning of insulin in the Somogyi phenomenon (posthypoglycemic hypergycemia). N Engl J Med 1984; 311:1214–1219.
16. Kjaer M, Mikines KJ, Christensen NJ, Tronier B, Vinten J, Sonne B, Richter EA, Galbo H. Glucose turnover and hormonal changes during insulin-induced hypoglycemia in trained humans. J Appl Physiol 1984; 57:21–27
17. Stuart CA, Prince MJ, Peters EJ, Smith FE, Townsend CM III, Poffenberger PL. Insulin receptor proliferation: a mechanism for tumor-associated hypoglycemia. J Clin Endocrinol 1986; 63:879–885.

18. Horowitz, GD, Lowry SF, Jeevanandam M, Brennan MF. The metabolic effects of gluconeogenic blockade in tumor-bearing man. Ann NY Acad Sci 1984; 435:432–434.
19. Liljenquist JE, Meuller G, Cherrington AD, Perry J, Rabinowitz D. Hyperglycemia per se can inhibit glucose production in man. J Clin Endocrinol Metab 1979; 48:171–175.
20. Verdonk C, Rizza R, Gerich J. Effects of plasma glucose concentration, glucose utilization, and glucose clearance in normal man. Diabetes 1981; 30:535–537.
21. Sacca L, Hendler R, Sherwin RS. Hyperglycemia inhibits glucose production in man independent of changes in glucoregulatory hormones. J Clin Endocrinol Metab 1978; 47:1160–1163.
22. Shulman GI, Williams PE, Liljenquist JE, Lacy WW, Keller U, Cherrington AD. Effect of hyperglycemia independent of changes in insulin or glucagon on lipolysis in the conscious dog. Metabolism 1980; 29:317–320.
23. Tillil H, Shapiro ET, Rubenstein AH, Galloway JA, Polonsky KS. Reduction of insulin clearance during hyperglycemic clamp. Dose-response study in normal humans. Diabetes 1988; 37:1351–1357.
24. Ljunqvist O, Sandberg E, Nylander G, Ware J. Glucose kinetics in haemorrhagic hyperglycemia. Circulatory Shock 1989; 28:347–356.
25. Wiseneski JA, Stanley WC, Neese RA, Gertz EW. Effects of acute hyperglycemia on myocardial glycolytic activity in humans. J Clin Invest 1990; 85:1648–1656.
26. Leahy JL, Cooper HE, Deal DA, Weir GC. Chronic hyperglycemia is associated with impaired glucose influence on insulin secretion. A study in normal rats using chronic in vivo glucose infusion. J Clin Invest 1986; 77:908–915.
27. Podrazik RM, Natale JE, Zelenock GB, D'Alecy LG. Hyperglycemia exacerbates and insulin fails to protect in acute renal ischemia in the rat. J Surg Res 1989; 46:572–578.
28. Meszaros K, Lang CH, Hargrove DM, Spitzer JJ, Tissue glucose utilization during epinephrine-induced hyperglycemia. J Appl Physiol 1989; 67:1770–1775.
29. Orzi F, Lugignani G, Dow-Edwards D, Namba H, Nehlig A, Patlak GS, Pettigrew K, Schuier F, Sokoloff L. Local cerebral glucose utilization in controlled graded levels of hyperglycemia in the conscious rat. J Cereb Blood Flow Metab 1988; 8:346–356.
30. Jeevanandam M, Young DH, Schiller WR. Glucose turnover, oxidation, and indices of recycling in severely traumatized patients. J Trauma 1990; 30:582–589.
31. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity and β-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 1981; 68:1456–1467.
32. Cobelli C, Pacini G, Toffolo G, Sacca L. Estimation of insulin sensitivity and glucose clearance from minimal model: new insights from labelled IVGTT. Am J Physiol 1986; 250:E591–598.
33. Pacini G, Finegood DT, Bergman RN. A minimal-model-based glucose clamp yielding insulin sensitivity independent of glycemia. Diabetes 1982; 31:432–441.
34. Chen M, Bergman RN, Pacini G, Porte D Jr. Pathogenesis of age-related glucose intolerance in man. Insulin resistance and decreased β-cell function. J Clin Endocrinol Metab 1985; 60:13–20.
35. Jacot E, Defronzo RA, Jequier E, Maeder E, Felber J-P. The effect of hyperglycemia, hyperinsulinemia, and route of glucose administration on glucose oxidation and glucose storage. Metabolism 1982; 31:922–930.
36. Wolfe RR, O'Donnell TF, Jr., Stone MD, Richmand DA, Burke JF. Investigation of factors determining the optimal glucose infusion rate in total parenteral nutrition. Metabolism 1980; 29:892–900.
37. Buchanan B, Abraira C, Hodges L. Potentiation of ^{14}C-glucose oxidation by priming glucose loads: effect of starvation. Metabolism 1984; 33:411–414.
38. Welle SL, Campbell RG. Improved carbohydrate tolerance and stimulation of carbohydrate oxidation and lipogenesis during short-term carbohydrate overfeeding. Metabolism 1983; 32:889–893.

39. Grey N, Kipnis DM. Effect of diet composition on the hyperinsulinemia of obesity. N Engl J Med 1971; 285:827–831.
40. Katzeff HL, O'Connell M, Horton ES, Danforth E, Jr., Young JB, Landsberg L. Metabolic studies in human obesity during overnutrition and undernutrition: thermogenic and hormonal responses to norepinephrine. Metabolism 1986; 35:166–175.
41. Forbes GB, Brown MR, Welle SL, Underwood LE. Hormone response to overfeeding. Am J Clin Nutr 1989; 49:608–611.
42. Welle S, Campbell RG. Stimulation of thermogenesis by carbohydrate overfeeding. Evidence against sympathetic nervous system mediation. J Clin Invest 1982; 71:916–921.
43. Welle S, Matthews DE, Campbell RG, Nair S. Stimulation of protein turnover by carbohydrate overfeeding in man. Am J Physiol 1989; 257:E413–E417.
44. Tracey KJ, Legaspi A, Albert JD, Jeevanandam M, Matthews DE, Brennan MF, Lowry SF. Protein and substrate metabolism and parenteral feeding. Clin Sci 1988; 74:123–132.
45. Askanazi J, Carpentier YA, Elwyn DH, Nordenstron J, Jeevanandam M, Rosenbaum SH, Gump FE, Kinney JM. Influence of total parenteral nutrition on fuel utilization in injury and sepsis. Ann Surg 1980; 191:40–46.
46. Long CL, Kinney JM, Geiger JM. Nonsuppressability of gluconeogenesis by glucose in septic patients. Metabolism 1976; 25:193–201.
47. Elwyn DH, Kinney JM, Jeevanandam M, Gump FE, Broell JR. Influence of increasing carbohydrate intake on glucose kinetics in injured patients. Ann Surg 1979; 190:117–127.
48. Askanazi J, Elwyn DH, Silverberg PA, Rosenbaum SH, Kinney JM. Respiratory distress secondary to a high carbohydrate load: a case report. Surgery 1980; 87:596–598.
49. Covelli HD, Black JW, Olsen MS, Beekman JF. Respiratory failure by high carbohydrate loads. Ann Intern Med 1981; 95:579–581.
50. Van Der Poll T, Romijn JA, Endert E, Borm JJJ, Buller HR, Sauerwein HP. Tumor necrosis factor mimics the metabolic response to acute infection in healthy humans. Am J Physiol 1991; 261:E457–E465.
51. Chajek-Shaul T, Barash V, Weidenfeld J, Friedman G, Ziv E, Shohami E, Shiloni E. Lethal hypoglycemia and hypothermia induced by administration of low doses of tumor necrosis factor to adrenalectomized rats. Metabolism 1990; 39:242–250.
52. Starnes HF, Jr., Warren RA, Jeevanandam M, Gabrilove JL, Larchian W, Oettgen HF, Brennan MF. Tumor necrosis factor and acute metabolic response to tissue injury in man. J Clin Invest 1988; 82:1321–1325.
53. Van Der Poll T, Sauerwein HP. Tumor necrosis factor: its role in the metabolic response to sepsis. Clin Sci 1993; 84:247–256.
54. Dohm GL, Newsholme EA. Metabolic control of hepatic gluconeogenesis during exercise. Biochem J 1983; 212:633–639.
55. Calles-Escandon J, Felig P. Fuel hormone metabolism during exercise and after physical training. Clin Chest Med 1984; 5:3–11.
56. Elia M, Lammert O, Zed C, Neale G. Energy metabolism during exercise in normal subjects undergoing total starvation. Human Nutr: Clin Nutr 1984; 38C:355–362.
57. Calles J, Cunningham JJ, Nelson L, Brown N, Nadel E, Sherwin RS, Felig P. Glucose turnover during recovery from intensive exercise. Diabetes 1983; 32:734–738.
58. Davis JM, Bailey SP, Woods JA, Galiano FJ, Hamilton MT, Bartoli WP. Effects of carbohydrate feedings on plasma free tryptophan and branched-chain amino acids during prolonged cycling. Eur J Appl Physiol 1992; 65:513–519.
59. Wolfe RR. Radioactive and Stable Isotope Tracers in Biomedicine. Principles and Practice of Kinetic Analysis. New York: Wiley-Liss, 1992.
60. Wolfe RR, Allsop JR, Burke JF. Glucose metabolism: responses to intravenous glucose infusion. Metabolism 1979; 28:210–219.

2

Protein Metabolism

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INTRODUCTION

Poor nutrition and weight loss, with an attendant depletion of body protein are frequent occurrences in surgical patients. This is a serious problem because many studies have shown that poor nutritional status is generally associated with decreased survival. The protein loss can occur either before surgery as a consequence of the presurgery disease process or as a result of trauma or sepsis. Nutritional support focuses on ensuring that the body's protein metabolism is functioning normally and is capable of responding to the initial injury and the subsequent associated recovery processes. Other chapters in this volume describe the clinical details; the purpose of this chapter is to discuss why so much emphasis is placed on protein metabolism.

Quantitatively, the major site of protein loss is skeletal muscle because muscle is by far the largest single metabolically active protein pool in the body. Half of the protein in an adult is structural protein, principally collagen and elastin (**Fig. 1**). The remainder is about equally divided between skeletal muscle and viscera. Elastin and collagen turn over at negligible rates (half-lives of a year or more), so their turnover is not a factor in either protein deficiency or the response to stress.

Changes in lean body mass and nitrogen balance primarily reflect changes in muscle protein content. Other, smaller systems are also impacted by protein deficiency. Of particular importance to the surgical patient are the immune, respiratory, and gastrointestinal systems. Undernutrition results in decreased immunocompetence (11,13,27) and deterioration of the respiratory system (5). Thus pneumonia is a common complication in malnourished patients (17,22). The gut, which has recently been shown to play an important role in the immune system, also atrophies with undernutrition (13,41).

BODY COMPOSITION

Part of the rationale for being concerned with nutritional status is to determine whether nutrition is a limiting factor in the body's ability to function normally and respond to the

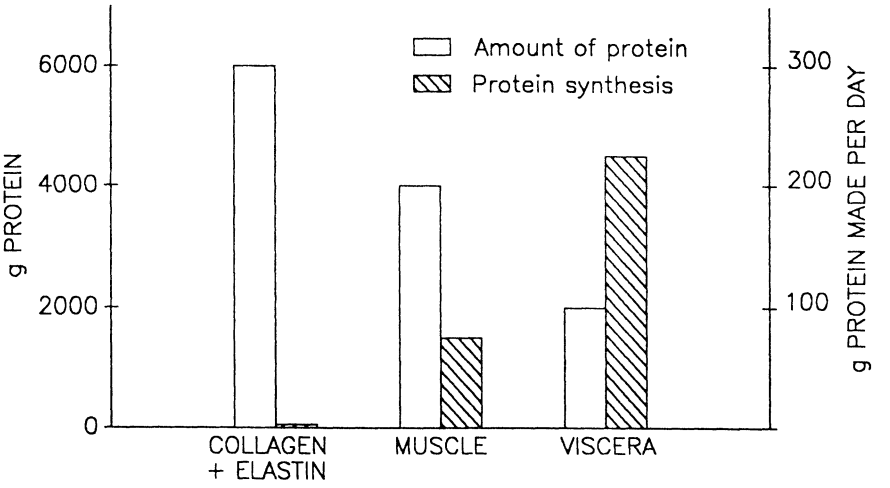

Figure 1 Distribution of protein within the body.

disease and any associated infections. Assessment of nutritional status encompasses the measurement of total body protein, energy reserves (principally fat), vitamins, minerals, and micronutrients. The emphasis is primarily on energy stores and body protein. The most important component is the body protein status. Assessment of body fat content is not a reliable index of wasting because it depends on prior activity levels and dietary habits (18). When surgical patients are described as being malnourished or nutritionally depleted, the inference is that they are protein and usually energy depleted.

Protein is important because of its role in the body. Protein serves both as the machinery and as part of the strucutre of the body. All of the metabolic functions in the body, from cell division to obtaining energy from foodstuffs to host defense mechanisms, are affected by proteins. In addition, some proteins, such as collagen and elastin, are involved in structural support of the body. The role of the other nutrients (fats, carbohydrates, vitamins, and minerals) is primarily, although not exclusively, to support protein metabolism. Death inevitably results when body protein losses approach 30–40% (8,19,28).

Assessment of body protein content is difficult because of the necessity of making the measurements noninvasively with minimal inconvenience to the subject and at low cost. Only neutron activation analysis gives a direct measurement of body nitrogen and therefore an absolute value for body and tissue protein. Dual emission x-ray (DEXA) also gives a highly accurate measurement of body composition. Other methods are less direct, inferring protein status from measurements of body fat or water content.

The more rigorous methods such as neutron activation analysis, DEXA, nmr, total body potassium, and total body water by isotope dilution tend to be technically complex, expensive, and hence impractical in the clinical setting. At the other extreme are anthropomorphic measurements based on such measurements as body weight (especially changes in body weight) and skinfolds. These measurements give reasonable assessment of the status of body composition, particularly if applied to large groups, but need to be treated with caution when applied to individuals. To obtain reliable data on an individual using these methods, it is advisable to make several measurements (e.g., anthropometrics,

body weight, plasma proteins) and draw conclusions from the overall picture. In between are controversial methods such as TOBEC and bioelectic impedance; although they have been extensively validated in healthy individuals, validation in disease states is limited. Despite these caveats, it is not difficult to detect protein depletion when it is specifically looked for.

PROTEIN TURNOVER

It is, however, not only the amount of protein present in the body that is important, but whether it is able to function normally. The body's proteins are in a dynamic state: they are continually being broken down to their constituent amino acids and resynthesized (Fig. 2). Although the rate of muscle protein synthesis is low, the total amount of muscle protein made per day is large because of the large amount of muscle in the body (37,45) (Figs. 1 and 3).

There are two major advantages to protein turnover. First, a dynamic protein turnover makes maximum use of a minimum amount of amino acids. The body has no spare amino acid stores per se as it has for carbohydrate (glycogen) and fat (adipose tissue). Second, protein turnover is a major means of metabolic regulation (18,45). The disadvantage of a dynamic protein turnover is that it has high energy costs.

For a terrestrial animal storage of any unnecessary products in quantity takes up space, increases body mass and energy needs, and therefore decreases mobility. It also increases the amount of time spent in gathering scarce resources. Amino acids are not widely distributed in nature; they are concentrated in other animals and plants. Animals are relatively scarce, but their protein quality is high; plants are more common, but the protein quality is poor because of their low essential amino acid content (Fig. 4). The more time that is spent foraging for food, the less time there is available for other activities and, more importantly, the greater the dependence on exogenous food. Therefore, there is a high premium on minimizing the dependence on exogenous resources.

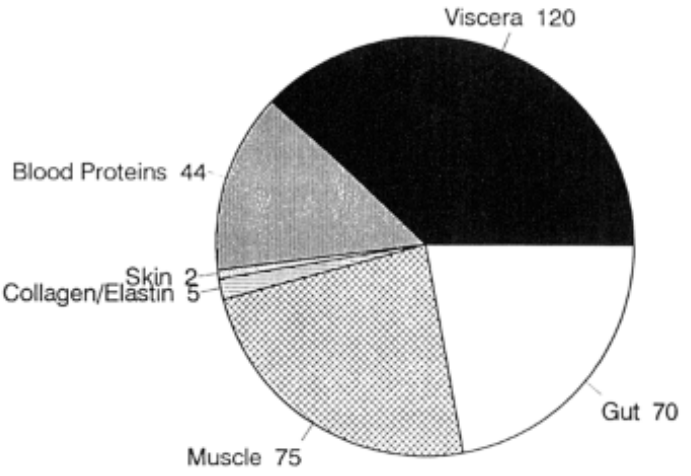

Figure 2 Amount of protein made per day by different tissues.

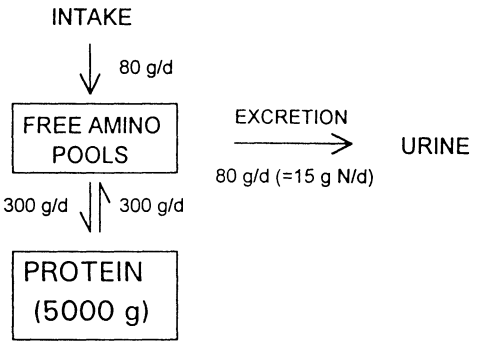

Figure 3 Relationship of protein intake to total protein turnover in a 70-kg man. The total protein pool is about 5000 g. About 300 g of new protein are made per day. Dietary intake provides only about 80 g of amino acids per day.

Three pathways for the conservation of nitrogen have been described in the literature. The first and most important is protein turnover: the reincorporation of catabolism-derived amino acids back into protein (4). The efficiency of this process is about 80%. Second, urea nitrogen recycling recycles about 15% of the daily nitrogen, which would otherwise be excreted (44). Third, and probably of marginal importance, is de novo synthesis by bacteria: death of the bacteria with the subsequent absorption of the bacterial amino acids into the body (24,39).

PROTEIN TURNOVER, A SUBSTRATE CYCLE

The more important a protein's role in the regulation of metabolism, the faster it turns over. Thus, enzymes, particularly those at the branch points of metabolic pathways, have very short half-lives, whereas structural proteins such as collagen hardly turn over at all (Table 1) (18). Other proteins with short half-lives are those involved in immunological

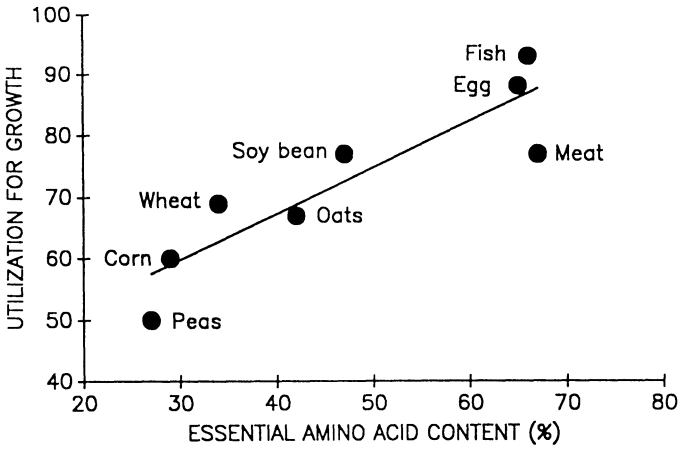

Figure 4 Relationship between essential amino acid content and protein quality as measured by the ability of the test protein to support growth in a rat.

Table 1 Some Representative Protein Turnover Rates[a]

Protein	Tissue	Approximate half-life
Ornithine decarboxylase	Liver	0.2 h
Tyrosine aminotransferase	Liver	2.0 h
Phosphoenolpyruvate	Liver	5.0 h
Glucokinase	Liver	12.0 h
Glucose-6-phosphate dehydrogenase	Liver	15.0 h
Fructose-bisphosphate aldolase	Muscle	120 h
Lactate dehydrogenase	Muscle	144 h
Cytochrome c	Muscle	144 h
Myosin	Muscle	Weeks
Elastin	Various	Months
Collagen	Various	Years

[a]Enzymes have the fastest protein turnover rates and structural proteins the slowest.

surveillance. For immune proteins there is a good correlation between plasma concentration and protein synthesis (Fig. 5) (25).

Protein turnover is an example of a substrate cycle. A substrate cycle exists when opposing, nonequilibrium reactions catalyzed by different enzymes are active simultaneously. Metabolically important cycles occur with all three macronutrients (47). For lipids there is the breakdown of stored fat (lipolysis) and the resynthesis (reesterification) of trigylcerides (triglyceride–fatty acid cycling). The major carbohydrate cycle is the conversion of glucose to glucose-6-phosphate and back to glucose (2,36,47,48). Unlike the carbohydrate and lipid cycles mentioned above, protein turnover involves many steps in both the forward and backward directions. Because many of the steps, especially in

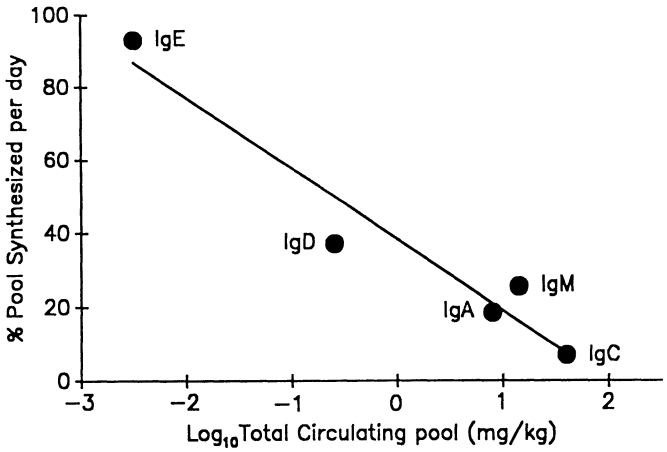

Figure 5 Relationship between the plasma concentration and synthesis rate for immunoglobulins. (From Ref. 25.)

protein synthesis, require ATP, protein turnover is the most energetically expensive of the macronutrient cycles (43).

The importance of protein turnover can be illustrated with an example (Table 2). Suppose that the liver has an acute need to double the rate of production of a particular protein. Three situations can be envisaged. Situation 1, with no cycle involved, would be to activate the necessary mRNA/protein synthesis machinery. Having to start from the beginning is not likely to result in a rapid response. Situations 2 and 3 assume the presence of an active substrate cycle. Assume that in the basal state the rate of protein synthesis is 10 mg/min and of protein breakdown is 9 mg/min. Net throughput (flux) is the same as without the cycle. If the rate of the forward reaction (protein synthesis) is increased by only 10%, the throughput doubles (situation 2). In situation 3, the back reaction (protein breakdown) rate is decreased by 10%, and again the net product flux is increased almost twofold. Without cycling, a 10% increase in the forward reaction rate leads to a 10% increase in product production. With substrate cycling a 10% increase in either synthesis or breakdown rates leads to doubling of the rate of protein accumulation.

Thus, small changes in hormones, activators, or other regulators can rapidly effect large changes in protein concentration. This ability to respond rapidly allows the body to maintain levels of many different proteins and to increase the concentration of any protein as needed. Protein turnover is also necessary because there is no space in the body to maintain optimal levels of all proteins at their optimal concentrations. Many proteins are needed at high concentrations only intermittently; for example, immunoglobulins and host defense proteins are needed to combat external threats, which can be infrequent and unpredictable.

Because there are no "reserve" amino acids, any loss of protein means that somewhere in the body there will be a shortfall of amino acids for making protein. Initially the deficit is met by skeletal muscle. Skeletal muscle is by far the largest metabolically active single protein pool in the body (Fig. 3). In spite of being about 50% of the total protein in the body, the contribution of collagen and elastin to the net protein loss is negligible (Table 1, Fig. 1). Collagen and elastin turn over extremely slowly, with half-lives measured in years. Collagen is a unique protein in another way: it contains few of the amino acids and therefore is a useless source of amino acids for protein synthesis.

Table 2 Importance of Protein Turnover (Substrate Cycling) in Regulating Tissue Protein Levels

	Enzyme activities		Throughput (net flux)	% Increase in flux
	Forward	Backward		
Situation 1 (no cycling)				
Basal	1	0	1.0	
10% increase in PSR	1.1	0	1.1	10
Situation 2 (with cycling)				
Basal	10	9.0	1.0	
19% increase in PSR	11	9.0	2.0	200
Situation 3 (with cycling)				
Basal	10	9.0	1.0	
10% decrease in PBR	10	8.1	1.9	190

PSR, protein-synthesis rate; PBR, protein-breakdown rate.

NORMAL PROTEIN REQUIREMENTS

It takes a calorie-to-nitrogen ratio of about 150:1 for the body to convert amino acids into protein. If energy is lacking, the amino acids are oxidized to supply energy and the nitrogen is excreted in the urine as urea. The classical method for determining protein requirements is the nitrogen balance method, which in spite of its limitations (21) is still the accepted standard (15,35). Although other methods—for example, determining the point at which isotopically labeled amino acids are oxidized rather than incorporated into protein—are currently under investigation, the results have not been generally accepted (14,51). The values tend to be much higher than those found by the nitrogen balance method (51,53). Part of the reason may be that the nitrogen balance method gives the value over an extended period of time, whereas isotope kinetic studies last only a few hours. Another method, which is really a variant of the nitrogen balance method, is to use urea synthesis versus urea excretion (14).

Over the years, many nitrogen balance studies have been done on normals and on sick and injured patients (see Chap. 19) The data on normals are collected and published by many countries as the Recommended Dietary Allowances (35). Stated briefly, the U.S. RDA for high-quality protein is 0.8 g protein/kg/day for an adult. To ensure that human variability is factored into the RDA, the requirements are purposely set 30–50% above actual needs. An exception is the requirement for energy, where excess intake is contraindicated. The latest compilation of the RDA for protein is shown in Table 3.

Protein requirements (Table 4) are actually restricted to the amino acids that the body is unable to synthesize—the "essential" amino acids (Table 5). During the course of evolution humans have lost the ability to synthesize about half of the amino acids. For the most part these amino acids' principal biochemical role is the incorporation into protein.

Many amino acids have important nonprotein metabolic functions (33,52). In some cases incorporation into protein accounts for only a small part of the daily production of amino acids, for example, alanine, glutamate, and aspartate. The carbon skeletons of these amino acids are key components in the Krebs cycle. Other amino acids where the nonprotein functions represent a significant proportion of the flux are glycine and serine, which serve as sources of one-carbon fragments for biosynethetic processes. Also in this category is glutamine, which is involved in the interorgan transport of nitrogen and as a

Table 3 RDA for Amino Acids

Amino acid	Infants 3–4 months	Children ~2 y	Children 10–12 y	Adults
Histidine	28	?	?	8–12
Isoleucine	70	31	28	10
Leucine	161	73	42	14
Lysine	103	64	44	12
Methionine + Cystine	58	27	22	113
Phenylalanine + Tyrosine	125	69	22	14
Threonine	87	37	28	7
Tryptophan	17	12.5	3.3	3.5
Valine	93	38	25	10
Total without histidine	714	352	214	84

Table 4 RDA for Dietary Protein

Category	Age (y)/ Condition	Weight	g/kg/day	g/day
Both sexes	0–0.5	6	2.2	13
	0.5–1	9	1.6	14
	1–3	13	1.2	16
	4–6	20	1.1	2.4
	7–10	28	1.0	28
Males				
	11–14	45	1.0	45
	15–18	66	0.9	59
	19–24	72	0.8	58
	25–50	79	0.8	63
	51+	77	0.8	63
Females				
	11–14	46	1.0	46
	15–18	55	0.8	44
	19–24	58	0.8	46
	25–50	63	0.8	50
	51+	65	0.8	50
Pregnancy				
	First trimester			+10
	Second trimester			+10
	Third trimester			+10
Lactation				
	First 6 months			+12
	Second 6 months			+12

preferred fuel for the gut and rapidly proliferating immune cells (4,36). Any shortfall in these amino acids would rapidly be lethal, so humans have retained the capacity to synthesize them.

PROTEIN REQUIREMENTS IN STRESSED STATES

In stressed states protein requirements are higher, but too much protein can cause complications, for example, hepatic and renal insufficiency. Thus most authors recommend only a conservatively increased intake. (For a review of protein requirements in stressed states, see Chap. 19.) Protein losses can be very high in stressed states, particularly in the immediate postinjury phase or in chronic stressed states such as sepsis and burns. There are two components to this protein loss: (1) the decreased intake that usually occurs after injury/trauma and (2) the systemic response to the injury.

Decreased Intake

The effect of decreased intake is similar in the stressed and the unstressed patient. If either energy or dietary protein is inadequate to meet needs, there is a progressive loss of muscle mass (37,46,52). Eventually a point is reached when other tissues start to lose amino acids as the body progressively restricts protein synthesis to the more essential functions.

Table 5 Nonprotein Functions of Essential and Nonessential Amino Acids

Amino acid	Minor pathways	Major pathways
Nonessential		
Glycine		1 C source/Glycine synthesis
Serine		1 C source/Serine synthesis
Alanine		TCA cycle, N transport
Glutamine		TCA cycle, N transport, fuel[a]
Glutamic		TCA intermediates
Aspartic		TCA intermediates
Arginine	Creatinine	Urea cycle, immune stimulant[a]
Proline		
Hydroxyproline		
Essential		
Methionine	CH_3, polyamines	
Phenylalanine	Catecholamines	
Tyrosine	Catecholamines, T_3,T_4	
Cysteine	Taurine	
Tryptophan	Serotonin	
Lysine	Carnitine	
Leucine		
Isoleucine		
Valine		
Threonine		
Marginal		
Histidine	Histamine	

A major pathway is defined as a pathway in which a substantial amount of the amino acid or its keto acid is needed. In some cases, e.g., nitrogen transport and TCA cycle activity, the amount used will far exceed the quantity needed for protein synthesis. A minor pathway is one in which the amount of amino acid needed is only a small fraction of the amount needed for protein synthesis.

[a]Probably stressed states only.

Eventually the low-priority protein pools can be depleted no further and the more important protein pools become depleted. Then, if the body is challenged by an infection, the normal response mechanisms such as mobilization of the immune system are compromised because the available resources are limited. By mobilizing the immune system, another protein pool becomes weakened and vulnerable, for example, the lungs (5,42). This is why the immediate cause of death from starvation is usually pneumonia. The difference between the stressed state and the unstressed state is that the process occurs much faster because the undernutrition response is superimposed on the injury-related protein loss.

The same result can occur with either an energy or a protein deficiency. With the former, it is the amino acids that have become limiting; with the latter, the energy is not available. The protein deficiency situation is more serious because the resources just are not there. With an energy deficiency the body can partially adapt by conserving energy, for example, by reducing the rate of protein turnover (43). But if mobilization is needed, it can still be effected.

The protein turnover theory explains why declining nutritional status results in a vicious cycle of continued depletion of lean body mass, weakening of host defenses, leading to more and more prolonged infections, leading to further weakening of the body. It is

important to emphasize that the deficiencies are primarily of macronutrients, protein, and energy and not of vitamins and minerals, so that assessment of a patient's nutritional status should focus on energy and protein metabolism.

Hypermetabolism and Protein Loss

The second component of the postinjury/stress-related protein loss is stress specific. The amount of protein lost after injury is greater than would be expected from the magnitude of the injury alone, indicating that a systemic rather than a local response was occurring (29). Protein loss increases with the severity and duration of the injury. The metabolic responses to infection, trauma, or presence of a tumor are manifestations of a common response pattern (the hypermetabolic response) involving lymphokines and other macrophage-originated factors (Fig. 6) (9,26,34). Thus a similar pattern of metabolic abnormalities in host intermediary metabolism found with infection, trauma, and sepsis occur with cancer cachexia (6,9,12,23,26,34,38,47). The hypermetabolic response serves to limit the extent of the injury/infection, initiate countermeasures such as wound repair, and restore normal metabolic homeostasis as rapidly as possible (16,30).

Characteristic features of the hypermetabolic response are increased protein turnover,

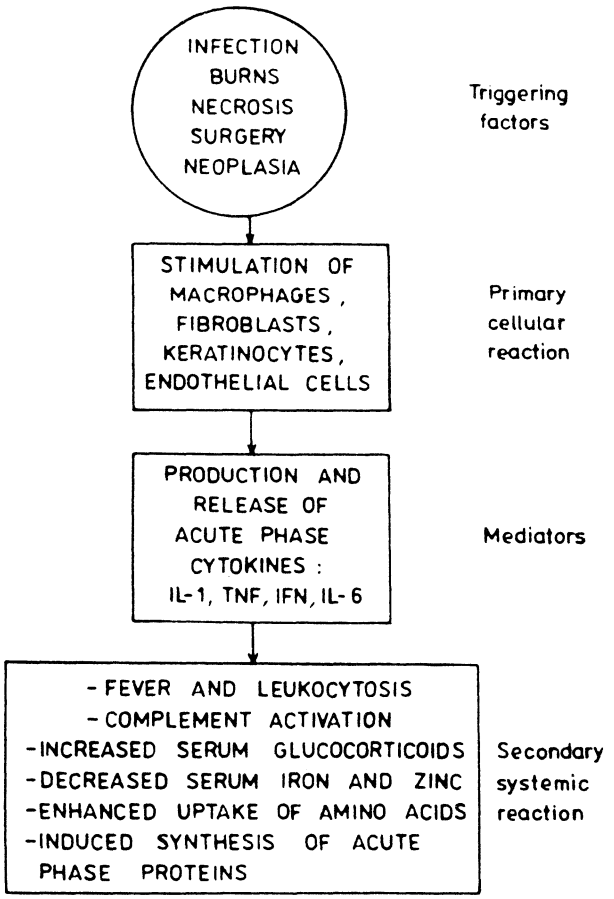

Figure 6 The cascade of events leading to the acute phase response. (From Ref. 30.)

acute phase protein synthesis, gluconeogenesis, lipolysis, increased substrate cycling, and loss of body protein (9,26,38,42,47). The energy component is provided for by the mobilization of endogenous nutrients from peripheral muscle and fat (9,26,36). A particularly interesting feature of the hypermetabolic response is that endogenous energy is still mobilized even when exogenous intake is apparently adequate (9,26,36). The purpose of this response is to restore metabolic homeostasis, facilitate the response to any infection, and promote wound repair. The hypermetabolic response is associated with the loss of body protein (16,30,40).

The hypermetabolic response involves three complementary changes in protein metabolism. The pathways are (1) increased synthesis of stress-related proteins and the two fuel-related responses; (2) shifting the body's energy metabolism toward a greater reliance on endogenous fat (Fig. 7); and (3) development of tissue-specific nutrition. The two fuel-related changes serve to minimize the need for exogenous nutrients, use available nutrients sparingly, and selectively target nutrients for those cells where great increases in activity are needed (36).

The hypermetabolic response involves the synthesis of substantial quantities of proteins already being made in small amounts (e.g., immune proteins) or increasing the rate of synthesis of proteins already present in appreciable amounts (e.g., acute phase proteins) and, if necessary, new proteins (e.g., wound repair proteins). This additional protein synthesis is outside the daily ebb and flow of proteins associated with metabolic fuel homeostasis. Which proteins are made in increased amounts will depend on the specific stress involved.

The questions of interest are (1) what determines which hypermetabolism stress-specific proteins are made; (2) how this process results in a net loss of body protein; and (3) how adequate nutrition is supplied to the cells involved (tissue-selective nutrition) at a time when the body is under pressure to conserve resources. For the immune system, the answer is known: the actual proteins made in quantity are determined by clonal selection. Clonal selection is a common cellular mechanism when there is the need to rapidly screen many possible proteins and select the few suitable for the particular situation. It now

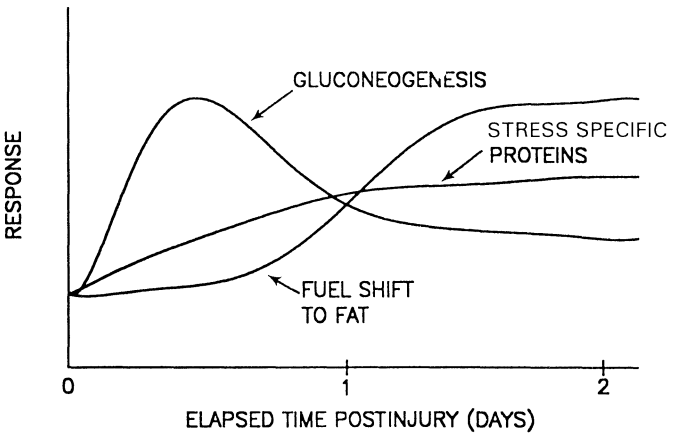

Figure 7 Schematic of the time course for the three major metabolic processes involved in the stress response.

seems likely on both theoretical and experimental grounds that the same clonal-selection mechanism also applies to the acute phase as well as to injury-specific proteins (32).

As a part of the stress response, the liver secretes a family of proteins that have been collectively termed acute phase proteins (40). Typical acute phase proteins are fibrinogen, alpha-macroglobulin, and the various antiproteases. In theory, each hepatocyte can make any number of acute phase proteins depending on the message activated. In fact, there appears to be one hepatocyte per acute phase protein (32). Thus in turpentine-treated mice, the number of hepatocytes making fibrinogen increases dramatically while the number making albumin goes down, and these changes in cell populations are reflected in the changed synthesis rates of the two proteins (Fig. 8). Probably only a limited increase can be obtained by increasing protein production by an individual cell. This need for increasing cell number may account for the time lag in acute phase protein synthesis after the actual injury (Fig. 8).

Given the multiplicity of liver-originated plasma proteins, what governs which hepatocytes proliferate and which ones decline? The selection process can be either Lamarckian or Darwinian (32). With Lamarckian selection, the type of proteins a cell makes depend on the external environment. Clonal selection is a Darwinian process, where cells making the right sort of protein multiply and those making the wrong sort die. There is a complex feedback loop, the fine details of which are still to be elucidated.

Tissue-Selective Nutrition

Following injury, energy expenditure and protein turnover are increased, while the opportunity to obtain food is severely restricted by immobility. The body normally has about a day's supply of carbohydrate in reserve (glycogen) and several weeks of lipid reserves. Minimizing the need for exogenous nutrients is accomplished by a switching over from glucose to lipid by the fed-starved cycle. During this brief adaptation period there is an increase in gluconeogenesis. By doing so scarce fuels such as glucose and its precursors (protein) are conserved. Glucose utilization is restricted to those tissues that

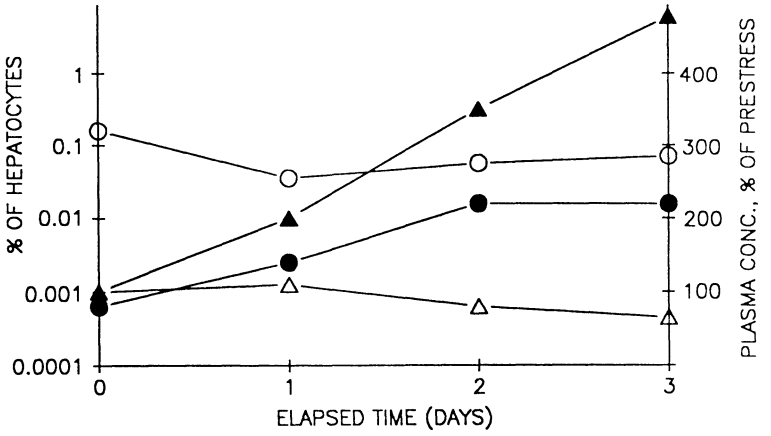

Figure 8 Relationship between hepatocyte type and plasma albumin and fibrinogen levels. (●) and (▲) are the % of hepatocytes staining positive for albumin or fibrinogen, respectively. (△) and (○) are the plasma concentrations of albumin and fibrinogen, respectively. (From Refs. 32,40.)

are obligate glucose users, e.g., brain and red blood cells. With time these tissues too will adapt to a predominantly lipid-based fuel source. Uptake of glucose by omnivorous tissues such as muscle is decreased by the development of insulin resistance (7). Activation of the fed-starved cycle is not unique to the stress response, but is a normal part of the regulation of intermediary metabolism. Nevertheless it is an integral part of the stress response, but is a normal part of the regulation of intermediary metabolism.

Some cells and tissues, for example, those involved in the immune system, wound repair, and acute phase protein synthesis, require additional nutrition because of their greatly increased activity. Rather than flood the plasma with the nonspecific fuel glucose or lipid or rely on hormonal means to meet the increased needs of specific cells or tissues, the body generates tissue- and cell-specific nutrients for the occasion. Examples of these nutrients are glutamine, the branched-chain amino acids, and arginine. Tissue-selective nutrition enables the body to rapidly and specifically supply additional scarce nutrients to those cell populations that critically need it while other tissues are restricted. It is a much more selective mechanism than altered blood flow, and, unlike the reprogramming of metabolism from carbohydrate to lipid, the provision of tissue-specific nutrients is stress specific.

Hypermetabolism and Protein Loss After Injury

The acute endogenous tissue-selective fuels usually are amino acids or are derived from amino acids; possible exceptions are the ketone bodies. Muscle is a source of amino acids (36,38). Since tissue-selective nutrients are needed for their carbon skeletons, the nitrogen component is redundant and is excreted in the urine as urea. The more tissue-selective nutrients needed, the greater the loss of nitrogen in the urine and the more negative the nitrogen balance. The result of tissue-selective nutrition by cells that would otherwise use glucose is to spare protein by decreasing the need for gluconeogenesis until adaptation to a lipid-based nutrient mix is accomplished.

Hypermetabolism and Amino Acid Supplementation

Much effort has been expended over the last 20 years to find specific nutrients (branched-chain amino acids (BCAAs), glutamine, keto acid analogs, etc.) that will attenuate postinjury protein loss. Each of these specific nutritional interventions is based on a sound biochemical rationale.

An example from the BCAA literature is given in Figure 9. The keto analogs of the BCAAs are predominantly oxidized by muscle. The posttrauma insulin resistance decreases glucose uptake, which forces muscle to oxidize the BCAA keto acids for energy. Since protein synthesis requires a full complement of amino acids, the remaining 17 amino acids are useless for protein synthesis, and the carbon skeletons are oxidized for energy and the nitrogen excreted in the urine as urea. There is also some evidence that leucine may stimulate muscle protein synthesis in vivo, in which case giving more leucine should decrease the loss of muscle protein due to the depressed muscle protein synthesis posttrama (37). Providing supplemental BCAAs does attenuate the negative posttrauma nitrogen balance, but only in the early phase; by day 4 the advantage has disappeared (Fig. 9).

Another example is the preference of the immune cells for glutamine. Glutamine provides both energy for protein synthesis and the building blocks for anabolic processes such as nucleotide synthesis (1,3,41). The initial need for glutamine is met mainly by the

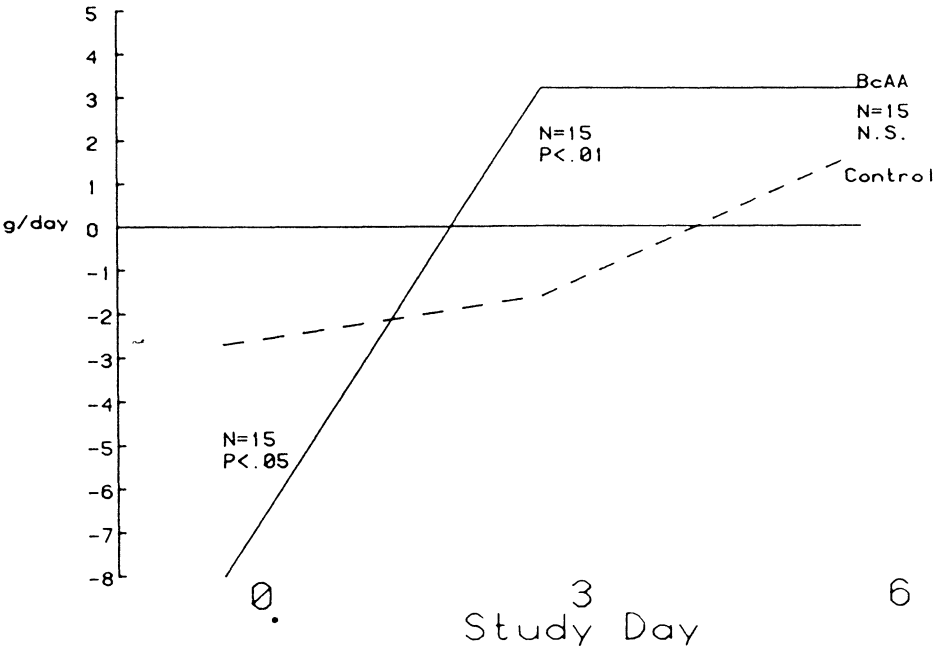

Figure 9 Nitrogen retention becomes positive earlier when a solution enriched with branched-chain amino acids is given to traumatized patients. (From Ref. 10.)

breakdown of skeletal muscle (20,36,50). The carbon skeletons of the other amino acids are converted into glutamine via a shift in the Krebs cycle away from oxidation toward anaplerosis. Even the branched-chain amino acids contribute to the increased glutamine synthesis (49).

It appears that at the biochemical level all of these mechanisms are operative and have for the most part been demonstrated successfully in rat models. In humans, similar biochemical results are found, but there is a critical difference in the desired endpoint. In the rodent it is usually the demonstration of an effect and an understanding of the mechanism involved; in humans the crucial endpoint is clinical outcome. Almost without exception, none of the amino acid manipulation strategies have been able to convincingly show improved clinical outcome as defined by hospital stay or survival. Any benefit is usually transient; the body adjusts to the change in nutrient intake and reestablishes homeostasis. A common finding is that using biochemical endpoints, e.g., protein synthesis and nitrogen balance, there is improvement, but the results are transient and apply only to the immediate postinjury phase.

The reason for the limited success with tissue-specific nutrients is that such a vital process as the response to injury is too important to be left to the vagaries of obtaining exogenous food. After injury, the ability to obtain protein is often compromised. Thus the resources for the initial stages of the response are already present in the body. Since the process has already been optimized and is so tightly controlled, it is relatively insensitive to exogenous manipulation by nutrition. The process is hormonally mediated with the various cytokines playing a critical role (Fig. 6). To date there is little evidence that cytokine activation is much affected by nutrition. This generalization appears to apply to the whole spectrum of the hypermetabolic response, from injury-specific nutrition to

attempts to manipulate the tumor-host relationship by feeding amino acid–deficient or –supplemented diets.

The stress-specific nutrients provide tissue-specific nutrients a little earlier than the body can, but once the new metabolic steady state required by the stress response has been attained, the effect of the specific nutrients disappears (Fig. 9). Once the new steady state is established, the system is capable of rapidly adjusting to either a deficit in key nutrients or disposing of an excess, which is what the stress-specific nutrients now become. At this point the need is for a diet sufficient in energy and protein that is balanced in amino acids. If this is provided, the negative nitrogen balance is greatly reduced and, provided that the hypermetabolic phase of the response to injury is self-limiting, of no clinical consequence.

Important possible exceptions occur if the hypermetabolic response is low grade but chronic, for example, in cancer and probably in AIDS patients. In these cases the protein loss continues, is relatively independent of exogenous nutrition, and protein wasting becomes a major factor leading to the patient's poor prognosis.

In summary, provided the basic energy and amino acid requirements are met, tissue-selective nutrition will only be effective in the gluconeogenic and fuel-adaptation phases, which occur early on and are usually transient and, for a normal person, not limiting. Once the adaptation is complete, exogenous tissue-specific nutrients are treated as any other dietary excess—they are either oxidized or stored. Where the hypermetabolism is ongoing, for example, in cancer and possible AIDS, other means are needed to end the hypermetabolism, such as by pharmacological intervention or, preferably, by treating the cause.

ACKNOWLEDGMENTS

This work was supported by NIH grant #DK-41927 and NASA contract #NAS-917276.

REFERENCES

1. Alverdy JC. Effects of glutamine-supplemented diets on immunology of the gut. JPEN 1990; 14(suppl):109S–113S.
2. Ardawi MS, and Newsholme EA. Essays Biochem 1985; 21:1–44.
3. Ardawi MS, Jamal YS, Ashy AA, Nasr H, Newsholme EA. Glucose and glutamine metabolism in the small intestine of septic rats. J Lab Clin Med 1990; 115:660–668.
4. Ardawi MS, Newsholme EA. Glutamine, the immune system, and the intestine (editorial comment). J Lab Clin Med 1990; 115:654–655.
5. Askenazi JA, Weissman C, Rosenbum SA, et al. Nutrition and the respiratory system. Crit Care Med 1982; 10:163–187.
6. Bennegard K, Lindmark L, Eden E, et al. Flux of amino acids across the leg in weight-losing cancer patients. Cancer Res 1984; 44:386–393.
7. Cahill GF Jr. Starvation in man. NEJM 1970; 282:668–675.
8. Black PR, Brooks DC, Bessey PQ, et al. Mechanisms of insulin resistance following injury. Ann Surg 1982; 196:420–435.
9. Cerra FB. Hypermetabolism, organ failure and metabolic support. Surgery 1987; 101:1–14.
10. Cerra FB, Upson D, Angelico R, et al. Branched chain amino acids support postoperative protein synthesis. Surgery 1982; 92:192–199.
11. Chandra S, Chandra RK. Nutrition, immune response and outcome. Prog Food Nutr Sci 1966; 10:1–65.

12. Clark ER, Lewis AM, Waterhouse C. Peripheral amino acid levels in patients with cancer. Cancer 1978; 42:2909–2913.
13. Cunningham-Rundles S. Effects of nutritional status on immunologic function. Am J Clin Sci Nutr 1982; 35:1202–1210.
14. Danielsen M, Jackson AA. Limits of adaptation to a diet low in protein in normal man. Clin 1992; 83:103–108.
15. FAO-WHO-UNU Expert Consultation. Energy and Protein Requirements. Geneva, Switzerland: World Health Authority, 1985. (WHO Tech. Rep. Ser. 724).
16. Gauldie J, Richards C, Baumann H. IL6 and the acute phase reaction. Res Immunol 1992; 143:755–759.
17. Gleason WA, Roodman ST. Reversible T cell depression in malnourished infants with pneumocystis pneumonia. J Pediatr 1977; 90:1023–1033.
18. Goldberg AL, Dice JF. Intracellular protein degradation in mammalian and bacterial cells. Ann Rev Biochem 1974; 43:835–869.
19. Grunfeld C, Feingold KR. Metabolic disturbance and wasting in the acquired immunodeficiency syndrome. N Eng J Med 1992; 327:337.
20. Hammarqvist F, Wernerman J, Von der Decken A, Vinnars E. Alanyl-glutamine counteracts the depletion of free glutamine and the postoperative decline in protein synthesis is skeletal muscle. Ann Surg 1990; 212:637–644.
21. Hegsted DM. Assessment of nitrogen requirements. Am J Clin Nutr 1978; 31:1669–1677.
22. Hughes WT, Price RA, Sisko F, et al. Protein calorie malnutrition: A host determination for pneumocystis carinii infection. Am J Dis Child 1988; 128:44.
23. Inculet RI, Stein TP, Peacock JL, Leskiw, MJ, Maher M, Gorschboth CM, Norton JA. Altered leucine metabolism in non-cachectic sarcoma patients. Cancer Res 1977; 47:4746–4749.
24. Jackson AA. Amino acids: essential and non-essential. Lancet 1983 1:1034–1037.
25. Iio A, Warren S, Broder S, et al. The metabolism of IgE in patients with immunodeficiency states and neoplastic conditions. J Clin Invest 1977; 59:743–757.
26. Kern KA, Norton JA. Cancer cachexia. Parenter Ent Nutr 1988; 12:286–298.
27. Keusch GT, Farthing MJG. Nutritional aspects of AIDS. Ann Rev Nutr 1990; 10:475–501.
28. Keys A, Brozek J, Henschel A, et al. The Biology of Human Starvation. Minneapolis: University of Minnesota Press, 1950.
29. Kinney JM, Elwyn DE. Protein metabolism and injury. Ann Rev Nutr 1983; 3:433–466.
30. Koj A. The role of interleukin-6 as the hepatocyte stimulating factor in the network of inflammatory cytokines. Ann NY Acad Sci 1989; 557:1–8.
31. Lundholm K, Edstrom S, Karlberg I, et al. Glucose turnover, gluconeogenesis from glycerol, and estimation of net glucose cycling in cancer patients. Cancer 1983; 50:1142–50.
32. Michaelson J. The significance of cell death. In: Apopstosis: The Molecular Basis of Cell Death. 1991:31–44.
33. Millward DJ, JWP Rivers. The nutritional role of the indispensable amino acids and the metabolic basis for their requirement. Eur J Clin Nutr 1988; 42:367–393.
34. Moldawer LL, Georgieff M, Lundholm K. Interleukin 1, tumour necrosis factor-alpha (cachectin) and the pathogenesis of cancer cachexia. Clin Physiol 1987; 7:263–274.
35. National Research Council. Proteins and amino acids. In: Recommended Dietary Allowances. 10th ed. Washington DC: National Academy of Sciences–National Research Council, 1989.
36. Newsholme EA, Newsholme P, Curi R, et al. A role for muscle in the immune system and its importance in surgery, trauma, sepsis and burns. Nutrition 1988; 4:261–268.
37. Rennie MJ. Muscle protein turnover and the wasting due to injury and disease. Br Med Bull 1985; 41:257–264.
38. Rennie MJ, Maclennan PA, Hunal PS, et al. Skeletal muscle glutamine transport, intramuscular glutamine concentration and muscle protein turnover. Metabolism 1989; 38(suppl 1):47–51
39. Richards P. Nutritional potential of nitrogen recycling in man. Am J Clin Nutr 1972; 25:615–25

40. Schreiber G, Tyskin A, Aldred AR, et al. The acute phase response in the rodent. Ann NY Acad Sci 1989; 557:61–86.
41. Smith RJ, Wilmore DW. Glutamine nutrition and requirements. JPEN 1990; 14(suppl):94S–99S.
42. Stein TP, Leskiw MJ, Oram-Smith JC, Wallace HW. Changes in protein synthesis after trauma: importance of nutrition. Am J Physiol 1977; 233:348–355.
43. Stein TP, Rumpler WV, Leskiw MJ, et al. Effect of reduced calorie intake on protein turnover and glucose cycling in man. Metabolism 1991; 40:478–453.
44. Walser M, Bodenlos LJ. Urea metabolism in man. J Clin Invest 1959; 38:1617–1626.
45. Waterlow JC, Garlick PJ, Millward DJ. In: Protein Turnover in Mammalian Tissues and in the Whole Body. Amsterdam: North-Holland Publishing Co. 1978:443–766.
46. Waterlow JC. Metabolic adaptation to low intakes of protein and energy. Ann Rev Nutr 1986; 6:495–526.
47. Wolfe RR, Herndon DL, Jahoor F, Miyoshi H, Wolfe M. Effect of severe burn injury on substrate cycling by Glucose and Fatty Acids. NEJM 1987; 317:403–407.
48. Wolfe RR. Radioactive and stable isotope tracers in biomedicine. In: Principles and Practice of Kinetic Analysis. New York: Wiley-Liss, 1992:377–382.
49. Yoshida S, Lanza-Jacoby S, Stein TP. Leucine and glutamine metabolism in septic rats. Biochem J 1991; 276:405–409.
50. Yoshida S, Leskiw MJ, Schluter MD, et al., Effect of total parenteral nutrition, systemic sepsis and glutamine on gut mucosa in rats. Am J Physiol 1992; 263:E368–E373.
51. Young VR, Bier DM, Pellet PL. A theoretical basis for increasing current estimates of the amino acid requirements in adult man, with experimental support. Am J Clin Nutr 1989; 50:80–92.
52. Young VR, Marchini S. Mechanisms and nutritional significance of metabolic responses to altered intake to protein and amino acids with reference to nutritional adaptation in humans. Am J Clin Nutr 1990; 511:270–289.
53. Zello GA, Pencharz PB, Ball RO. Dietary lysine requirement of young adult males determined by oxidation of L-[1-^{13}C] phenylalanine. Am J Physiol 1993; 264:E677–E685.

3

Lipid Metabolism

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INTRODUCTION

Until the 1930s biologists viewed adipose as a metabolically inert tissue. In the following 10–20 years evidence accumulated suggesting that adipose was metabolically active and played an important role in caloric homeostasis. Wertheimer and Shapiro presented this evidence in a classic review in 1948 (1), which largely shaped our present view of adipose as a highly active tissue with very important functions in storage, synthesis, and mobilization of lipids for provision of energy.

Similarly, our view of lipids and their derivatives continues to evolve. The classic description of lipid function is fourfold: (1) they serve as an efficient energy storage depot; (2) they are integral elements of cell membranes; (3) they are precursors of many hormones and vitamins; and (4) they emulsify and transport other lipids. As we will see, this description of lipid function, though accurate, does not reflect the innumerable complex functions that lipids and their derivatives perform in biological systems.

Fatty acids, acylglycerides, phospholipids, and sterols make up the majority of plasma lipids. Additionally, several lipid derivatives play major roles in normal metabolism. These include lipoproteins, which transport various lipids through the circulation, and eicosanoids, which are important autocoid regulatory compounds.

PLASMA LIPIDS

Fatty Acids

The general structural formula $CH_3(CH_2)_nCOOH$ represents all fatty acids. The single carboxyl group makes them weak acids, and most natural fatty acids contain an even number of carbon atoms. Saturated fatty acids contain no carbon-carbon double bonds,

while monounsaturated, or monoenoic, fatty acids contain one carbon-carbon double bond in the aliphatic chain. Polyunsaturated fatty acids contain more than one double bond.

Palmitic acid (C16) and stearic acid (C18) are the two most abundant saturated fatty acids, while oleic acid (C18) is the most common monounsaturated fatty acid in mammals. Linoleic acid and linolenic acid are unsaturated fatty acids important for normal metabolism, but they are not synthesized by mammals. Therefore, linoleic and linolenic acids are a dietary requirement and are termed essential fatty acids.

Fatty acids are commonly abbreviated as shown in Table 1. The number to the left of the colon indicates the number of carbon atoms, and the number to the right indicates the number of double bonds in each compound. The position of the double bond is preceded by the superscript Δ followed by the number of carbon atoms between the double bond and the carboxyl group. In this case numbering begins at the carboxyl group. Often, however, numbering of unsaturated fatty acids proceeds from the terminal methyl group. In such cases, the numbering is preceded by a lowercase omega (ω). Therefore, linoleic acid (18:2,$^{\Delta 9,12}$) can be called Δ9,12-octadecadienoic acid or ω-6,9-octadecadienoic acid. Additionally, unsaturated fatty acids may be classified by the nomenclature (n–), which designates the position of the first double bond counting from the terminal methyl group. Using this convention, linoleic acid would be 18:2(n-6). This nomenclature is useful for quickly identifying fatty acids derived from the same precursors, such as arachidonic acid [20:4(n-6)], which is synthesized from linoleic acid [18:2(n-6)].

The physical form of a fatty acid at room temperature depends on the number of carbon atoms and the number of double bonds. If it contains 8 or fewer carbons, the fatty acid is a liquid; if it has 10 or more carbons, the fatty acid is a solid. An unsaturated fatty acid will have a lower melting point than a saturated fatty acid with the same number of carbon atoms. Because the double bonds in virtually all naturally occurring fatty acids are *cis*, the aliphatic chains are shorter and curved relative to their saturated counterparts. This curved shape interferes with the tight packing in membranes that occurs with saturated fatty acids.

Triglycerides

Acylglycerides result from the binding of fatty acids to a glycerol backbone via esterification of the hydroxyl groups. If each of the three hydroxyl groups of glycerol binds a fatty acid, triglycerides result (Fig. 1). If only one or two of the hydroxyl groups of glycerol are esterified, the compounds are call mono and diglycerides, respectively. It is by incorporation into triglycerides that fatty acids are stored as an energy reserve. Binding of the carboxyl groups of the fatty acids within the ester linkages renders the acylglycerides neutral in charge.

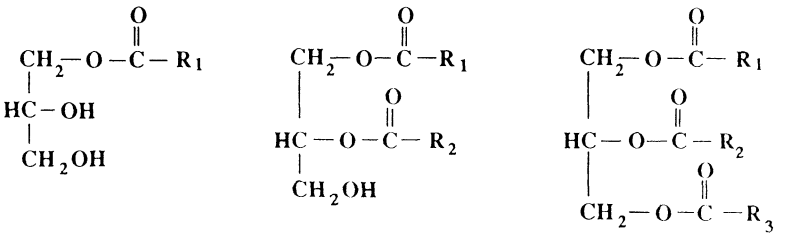
Adipocytes, the primary cells that make up adipose tissue (fat), are the storage depots for triacylglycerol. The nucleus and cytoplasm of the adipocyte occupy a narrow band surrounding a central lipid vacuole, which in the fed state fills most of the cell. This lipid vacuole is the distinguishing feature of the adipocyte and is made up almost exclusively of triglycerides.

Phosphoglycerides

Phosphoglycerides are quantitatively the most important class of phospholipids. They are the major structural lipids of biological membranes, as well as an important component of lipoproteins and bile. Phosphoglycerides have a glycerol-3-phosphate backbone and

Table 1 Common Fatty Acids

Common name	Systemic name	Structure	Abbreviation
Saturated fatty acids			
Palmitic acid	*n*-Hexadecanoic acid	$CH_3(CH_2)_{12}CH_2CH_2COOH$	16:0
Stearic acid	*n*-Octadecanoic acid	$CH_3(CH_2)_{12}CH_2CH_2CH_2CH_2COOH$	18:0
Arachidic acid	*n*-Eicosanoic acid	$CH_3(CH_2)_{12}CH_2CH_2CH_2CH_2CH_2CH_2COOH$	20:0
Unsaturated fatty acids			
Palmitoleic acid	*cis*-9-Hexadecenoic acid	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$	$16{:}1^{\Delta 9}$ or 16:1(n-7)
Oleic acid	*cis*-9-Octadecenoic	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	$18{:}2^{\Delta 9}$ or 18:1(n-9)
Linoleic acid	*cis*,*cis*-9,12-Octadeca-dienoic aicd	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	$18{:}2^{\Delta 9,12}$ or 18:2(n-6)
Linolenic acid	All-*cis*-9,12,15-Octa-decatrienoic acid	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	$18{:}3^{\Delta 9,12,15}$ or 18:3(n-3)
Arachidonic acid	All-*cis*-5,8,11,14-Eicosatetraenoic acid	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$	$20{:}4^{\Delta 5,8,11,14}$or 20:4(n-6)



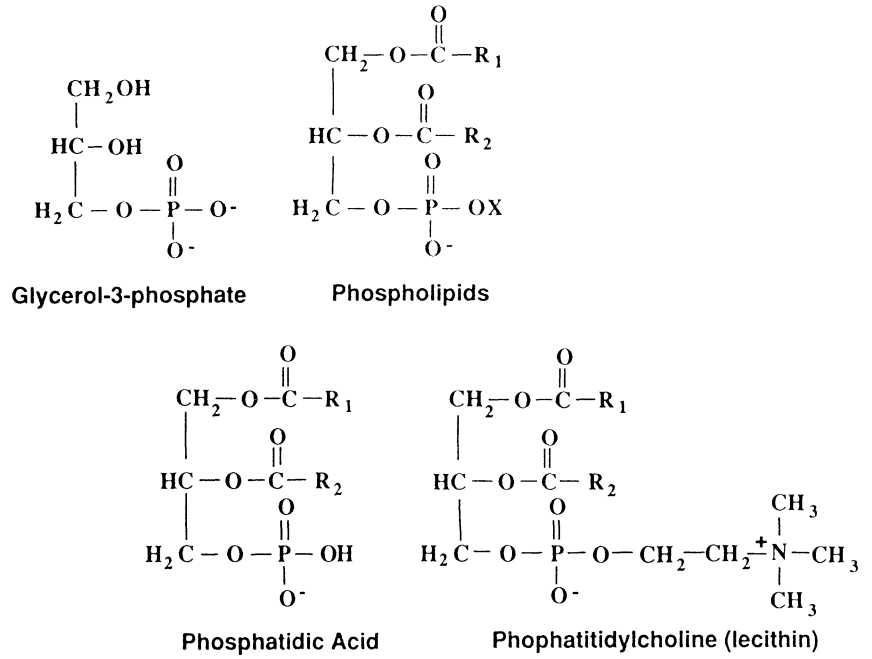
Monoglyceride Diglyceride Triglyceride

Figure 1 Acylglycerides.

are phosphate esters of diglycerides. Carbons 1 and 2 are usually esterified with fatty acids to produce the phosphatidic acids, which are intermediates in the synthesis of triacylglycerols and various phospholipids. Phosphoglycerides are named according to the substituent (X) on the phosphate group (Fig. 2).

Phosphatidylcholine (lecithin) is the predominant phospholipid found on the surface of lipoproteins. Its interaction with lecithin-cholesterol acyltransferase (LCAT) results in esterification of free cholesterol for transport in plasma lipoproteins.

The phosphate group and X-substituent of the phosphoglycerides form a polar region of the molecule that is hydrophilic, while the acyl substituents form a nonpolar, hydrophobic region. Thus the phospholipids as a group are considered amphipathic and



Glycerol-3-phosphate Phospholipids

Phosphatidic Acid Phophatitidylcholine (lecithin)

Figure 2 Phospholipids.

are able to form an interface between aqueous and nonaqueous microenvironments. This property makes phospholipids ideal emulsifying agents for the more nonpolar triglycerides and cholesterol esters. It also allows the phospholipids to spontaneously form bilayers when in an aqueous environment, a property vitally important to all biological membranes.

Sterols

Cholesterol is the most famous (or infamous) member of the sterol family. Biological membranes incorporate cholesterol, and cholesterol serves as the precursor for steroid and bile acid synthesis. The essential "steroid nucleus" of it and all sterols consists of three fused cyclohexane rings (Fig. 3, A–C) joined to a cyclopentane ring (Fig. 3, D). The carbons are numbered as shown. In addition to the steroid nucleus, cholesterol contains an hydroxyl group at C-3, an aliphatic chain at C-17, methyl groups at C-10 and C-13, and a Δ5 double bond (Fig. 3).

Cholesterol synthesized from acetate by the liver and injested from the diet is widely distributed to other tissues, transported predominantly in esterified form within the core of plasma lipoproteins. Lipoprotein particles harbor unesterified (free) cholesterol on their surface, which diffuses passively between tissues and lipoprotein particles. Adult humans excrete approximately 1100 mg of this sterol every day, hepatic biosynthesis replaces 850 mg, and absorption of dietary cholesterol accounts for another 250 mg daily.

Bile acids are dihydroxylated and trihydroxylated steroids with 24 carbons, which are degradation products of cholesterol. All hydroxyl groups are in the alpha orientation, whereas the two methyl groups are in the beta orientation. This arrangement results in a polar face and a nonpolar face for the bile acids. Bile acids exist in bile primarily as amide conjugates of taurine or glycine and when conjugated in this way are referred to as bile salts.

The amphipathic properties of bile salts make them ideally suited to their task of solubilizing dietary lipids to make them more readily degraded by intestinal lipases. The hydrophilic polar groups all lie on the alpha face of the steroid nucleus, and the nonpolar, beta face interacts with the hydrophobic lipids. The proximal jejunum absorbs digested

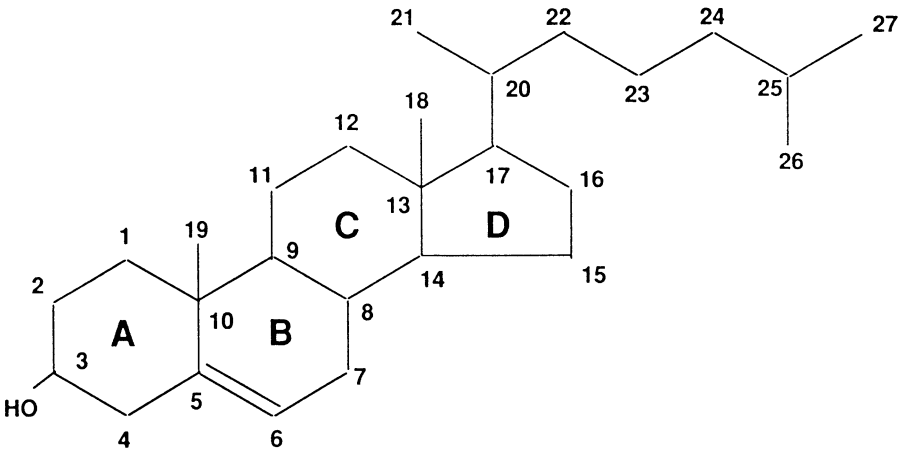


Figure 3 Cholesterol.

lipids and the ileum absorbs the bile acids, which recycle through the liver via the enterohepatic circulation.

Other Lipids

The sphingolipids are fatty acid–containing compounds, which are abundant in the nervous system as components of myelin and other structural lipids. Terpenes are a class of isoprene derivatives that are mainly found in plants. In humans, the cholesterol precursors squalene, geraniol, and farnesol are terpine derivatives. Additionally, beta-carotene and retinol are derived from terpines as well. Finally, the fat-soluble vitamins A, E, K, and D are essential factors that cannot be synthesized in sufficient amounts by humans.

LIPID CATABOLISM

Adipose Tissue, Fatty Acid Absorption, and Chylomicrons

Adipose tissue synthesizes and stores lipids during the fed state. When glycogen reserves are insufficient to meet the body's energy demands, the fatty acyl components of the stored triglycerides are mobilized and transported to other tissues to meet those demands. Also, by surrounding internal organs such as the heart and kidneys, adipose tissue protects the organs from mechanical trauma, and subcutaneous adipose tissue insulates against heat loss.

Two properties of fat make it more than ninefold more efficient than carbohydrate as an energy store. First, oxidation of 1 g of fat releases more energy (9.3 kcal) than the oxidation of 1 g of carbohydrate (3.7 kcal). The more reduced state of fat relative to the partially oxidized state of carbohydrate accounts for this difference in oxidative energy yield. Also, the adipose tissue stores the hydrophobic fats in an anhydrous state, which produces a tight, concentrated energy storage pool.

Dietary triglycerides supply the major source of fatty acids, although the liver synthesizes them from carbohydrates and, to a lesser extent, from amino acids. The fatty acid components of ingested complex lipids (triglycerides and phospholipids) provide 30–40% of the daily caloric intake in the human diet.

In the duodenum, pancreatic lipase and phospholipase hydrolyze the triglycerides, resulting mostly in free fatty acids (FFA) and monoglycerides. The enterocytes of the intestinal wall absorb the FFA and monoglycerides via passive diffusion, then resynthesize the triglyceride by direct esterification of the monoglyceride with fatty acyl-CoA (Fig. 4). Long-chain fatty acids (C10 or longer) tend to be esterified in this way, while the more soluble shorter ones may escape esterification and directly enter the portal blood where they combine with albumin for transport to the liver (2).

The liver could then oxidize these FFA or use them in the synthesis of triglyceride or phospholipid. In the fed state, these FFA would be esterified, but because the liver has limited triglyceride storage capacity, the hepatocytes secrete most of the triglycerides into the plasma in the form of very low-density lipoproteins.

The resynthesized triglycerides collect within the endoplasmic reticulum, where enterocytes incorporate them into chylomicrons, the largest of the lipoproteins. Triglycerides comprise >90% of the total mass of lymph chylomicrons. Chylomicrons exit the enterocytes via secretion into the mesenteric lymph, which enters the circulation through

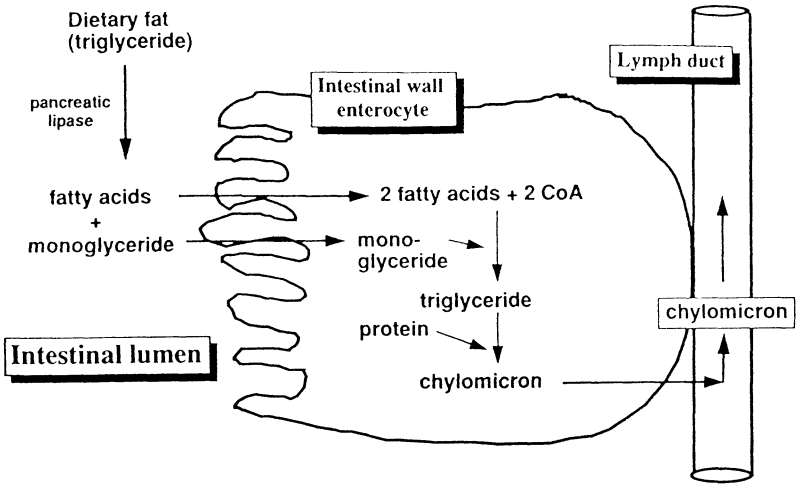


Figure 4 Duodenyl enzymes hydrolyze dietary fats to fatty acids and monoglycerides, which diffuse into the enterocytes. The enterocytes resynthesize the triglycerides and incorporate them into chylomicrons that are secreted into the mesenteric lymph and enter the circulation via the thoracic duct.

the thoracic duct, Liver and extrahepatic tissues rapidly clear the chylomicrons from the plasma, the half-life being 10–15 min.

Chylomicron and VLDL triglyceride hydrolysis requires the enzyme lipoprotein lipase, which is synthesized by adipose, muscle, and several other tissues. After synthesis, the parenchymal cells transport the enzyme to the luminal surface of the capillary endothelial cells of these tissues, where it binds to heparan sulfate proteoglycans. Here lipoprotein lipase binds rapidly and avidly to the phospholipid surface of circulating lipoproteins and catalyzes the hydrolysis of the triglycerides contained therein, producing locally high FFA and monoglyceride concentrations (Fig. 5). Most of the monoglycerides and a portion of the FFA diffuse into the adjacent tissues, where they can be esterified or oxidized for energy production. Albumin binds the remainder of the FFA and transports them through the circulation.

Nutritional and hormonal signals control the synthesis, release, and activity of lipoprotein lipase. The response to these signals varies among the responsive tissues. For example, starvation decreases lipoprotein lipase activity in adipose and increases it in muscle, while during the fed state, insulin induces the opposite response. Free fatty acids that are not immediately absorbed by adjacent tissues exert an inhibitory effect on lipoprotein lipase and appear also to cause dissociation of lipoprotein lipase from its binding to endothelial heparan sulfate.

Fatty Acid Catabolism

Mobilization of Fatty Acids from Adipose

When dietary energy supplies become limited, the animal responds with hormonal signals leading to mobilization and release of FFA from adipose tissue to meet energy demands in other tissues such as heart and skeletal muscle. Through a cAMP-mediated response, epinephrine, norepinephrine, ACTH, thyroid hormone, growth hormone, and

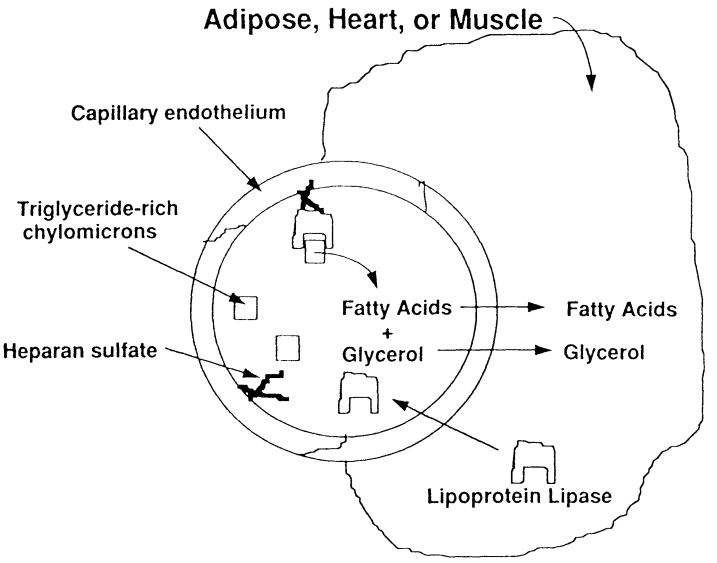


Figure 5 Parenchymal cells synthesize lipoprotein lipase and secrete it into capillaries where it binds to heparan sulfate on the endothelial surface. This enzyme catalyzes the hydrolysis of triglyceride and glycerol from chylomicrons and LDL.

glucagon stimulate activity of triglyceride (hormone-sensitive) lipase. Insulin inhibits triglyceride lipase. Triglyceride lipase hydrolyzes triglyceride to diglyceride with the release of a fatty acid. The hydrolysis of the remaining di- and monoglycerides to glycerol and FFA proceeds more rapidly, suggesting that the first hydrolysis of triglyceride is rate limiting. The FFA mobilized in this way move through the plasma membrane by passive diffusion and bind to serum albumin, which carries them to the energy-deficient tissues (Fig. 6).

In the well-fed state, adequate carbohydrate supplies and the high plasma insulin concentration inhibit lipolysis and favor triglyceride synthesis. Insulin stimulates adipose lipoprotein lipase activity, which increases the local extracellular FFA concentration. Insulin also increases glucose uptake and synthesis of glycerol-3-phosphate, which favors triglyceride synthesis as well.

The fate of the glycerol released from triglyceride hydrolysis depends upon the availability of the enzyme glycerokinase, which converts glycerol to glycerol-3-phosphate. Liver and kidney contain large amounts of this enzyme; muscle and adipose have little, if any. Glycerol-3-phosphate can be esterified with fatty acids to form triglycerides (as described above), can be oxidized to CO_2 and water, or can be used as a gluconeogenic precursor in the liver and kidney.

Oxidation of Fatty Acids

Cells that have absorbed FFA for energy needs activate them by a reaction with coenzyme A and ATP to form fatty acyl-CoA. Oxidation of fatty acyl-CoA occurs within the mitochondria, and since fatty acyl-CoA cannot cross the inner mitochondrial membrane, the acyl-CoA reacts with carnitine to form an acyl carnitine derivative. Carnitine acyltransferase I catalyzes this reaction in the cytoplasm. A carrier protein within the inner mitochondrial membrane carries this derivative to the inside of the mitochondria.

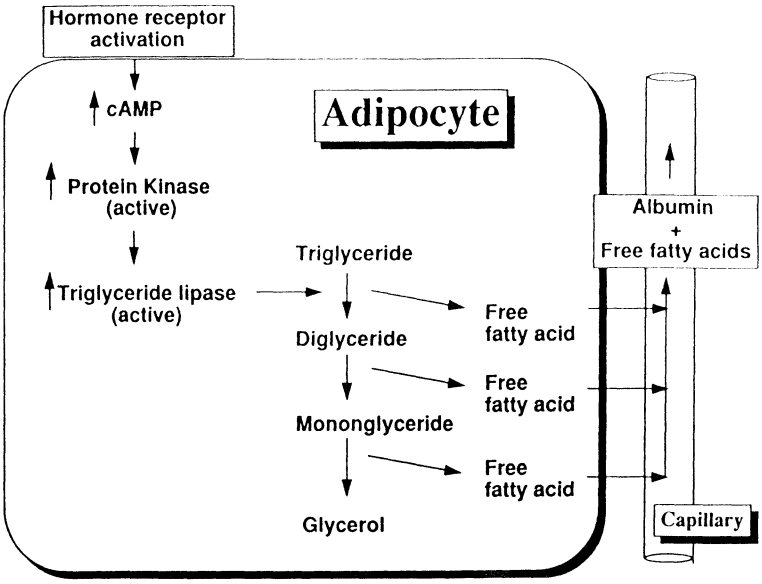


Figure 6 Hormonal signals activate triglyceride (hormone-sensitive) lipase, which hydrolyzes triglycerides to free fatty acids and glycerol. Insulin inhibits triglyceride lipase.

Once inside, carnitine acyltransferase II catalyzes decoupling of the carnitine derivative to liberate the fatty acyl-CoA, which now is poised for oxidation (Fig. 7).

Medium-chain fatty acids, which are relatively water soluble compared to long-chain fatty acids, do not require carnitine coupling to enter the mitochondria (3). This may explain why medium-chain fatty acids are oxidized more rapidly than long-chain fatty acids (4,5).

With each pass through the cycle of β oxidation, a series of reactions oxidizes fatty acyl-CoA to acetyl-CoA and a fatty acyl-CoA with two fewer carbons and produces 1 mole of $FADH_2$ and 1 mole of NADH. This yields 5 moles of ATP after reoxidation to FAD and NAD+ in the electron transport chain. The reactions are summarized in Figure 8.

The acetyl-CoA units produced may then enter the tricarboxylic acid (TCA) cycle for complete oxidation to carbon dioxide and water, which yields 12 moles of ATP for each acetyl-CoA oxidized. If the TCA cycle cannot accept all the acetyl-CoA produced, it may be diverted to ketone body synthesis in the liver or transferred to the cytosol as short-chain carnitine esters (6).

The complete oxidation of palmitoyl-CoA (C16) requires seven passes through the cycle to yield 8 moles of acetyl-CoA, 7 moles of $FADH_2$, and 7 moles of NADH. The electron transport chain utilizes 7 moles of O_2 to oxidize these $FADH_2$ and NADH to yield 35 moles of ATP. If the TCA cycle then oxidizes all 8 moles of acetyl-CoA to 16 moles of CO_2, then 8 moles of GTP, 8 moles of $FADH_2$, and 24 moles of NADH are generated. Oxidation of these $FADH_2$ and NADH requires 16 moles of O_2 generates 96 moles of ATP. These reactions are summarized as follows:

$$CH_3(CH_2)_{14}CO\text{-}CoA + 16\ O_2 + 131\ Pi + 96\ ADP \rightarrow$$
$$131\ ATP + 16\ CO_2 + 146\ H_2O + CoA$$

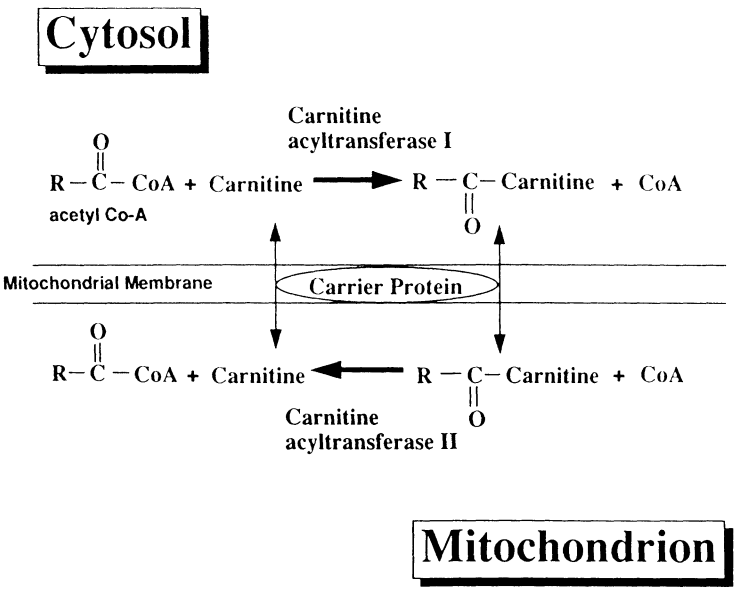


Figure 7 Carnitine acyltransferase I catalyzes the formation of the acylcarnitine derivative of acyl-CoA, which, unlike acyl-CoA, can cross the mitochondrial membrane. Within the mitochondria, acyltransferase II catalyzes the reverse reaction to yield the acyl-CoA ready for β oxidation.

Compared to the oxidation of 2.66 moles of glucose (16 carbons), which yields 96 moles of ATP, complete oxidation of 1 mole of palmitic acid (C16) to CO_2 and water produces 33 more moles of ATP. (The net ATP yield for complete oxidation of palmitic acid is 129, since two ATP equivalents are used to form palmitoyl-CoA from palmitic acid.)

The respiratory quotient, or RQ (ratio of CO_2 produced to O_2 consumed), indicates the primary metabolic fuel used. The RQ for palmitic acid is:

$$RQ = 16\ CO_2 \text{ produced} \div 23\ CO_2 \text{ consumed} = 0.70$$

Since oxidation of glucose produces 6 moles of CO_2 and consumes 6 moles of O_2, the RQ of glucose is 1.0. An RQ near 1 indicates a reliance on carbohydrate oxidation, while an RQ near 0.70 indicates a greater reliance on fatty acid oxidation.

Ketone Body Synthesis and Ketosis

When the rate of acetyl-CoA formation exceeds that of acetyl-CoA utilization in the TCA cycle, hepatic mitochondria synthesize ketone bodies from the "excess" acetyl-CoA (Fig. 9). Increased lypolysis and rare glucose availability lead to increased diversion of acetyl-CoA from the TCA cycle to ketone synthesis. During starvation, 80% of hepatic fatty acid catabolism yields ketone bodies (7). The liver releases acetoacetic acid and β-hydroxybutyric acid into the circulation, and extrahepatic tissues such as muscle, heart, and brain take them up and convert the ketones back into acetyl-CoA for oxidation in the TCA cycle. The liver does not possess the necessary converting enzyme and so does not use ketone bodies as extrahepatic tissues do. During prolonged starvation, the brain uses ketone bodies as an important energy source.

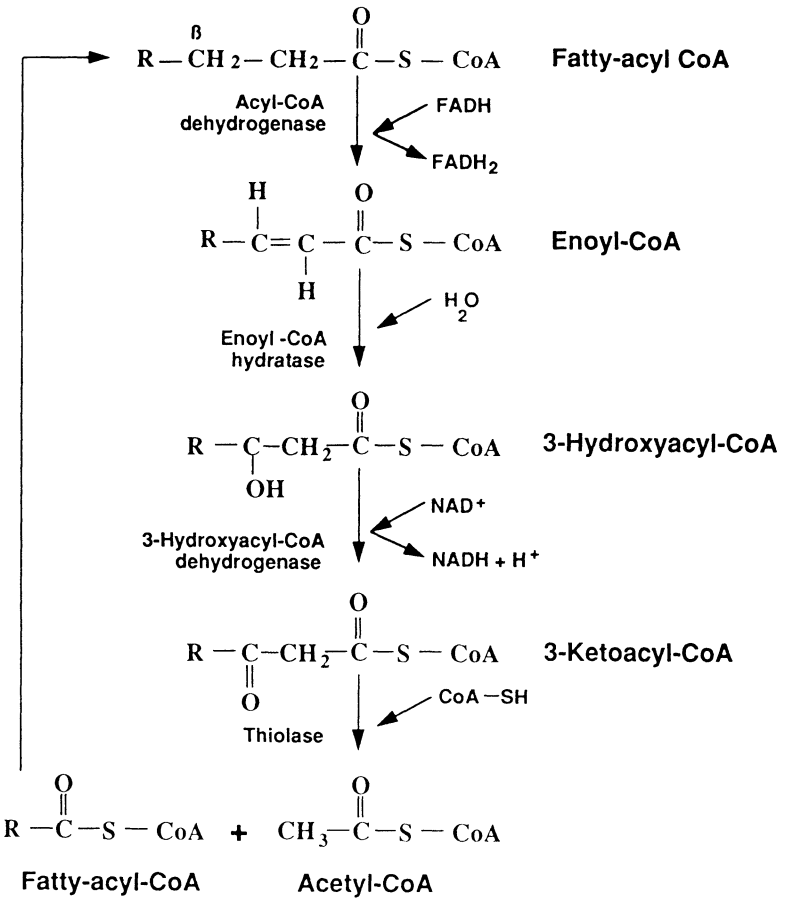


Figure 8 Beta oxidation of fatty acids.

Starvation ketosis and alcoholic and diabetic ketoacidosis occur if the rate of hepatic ketone production exceeds the rate of extrahepatic ketone utilization. Severe carbohydrate deficiency causes ketosis in at least two ways. First, it depletes TCA cycle intermediates, which slows the entry of acetyl-CoA into this cycle. Second, the absence of citrate inhibits the rate-limiting enzyme of fatty acid synthesis, acetyl-CoA carboxylase, thereby blocking another route of fatty acid metabolism.

Fatty Acid Synthesis and Regulation of Fat Metabolism

Biosynthesis of fatty acids takes place mainly in the liver to meet the body's demands for lipid membrane components, or if energy is in abundant supply the liver synthesizes fatty acids for storage as triglycerides to meet future energy demands. Like β oxidation, fatty acid synthesis proceeds by two-carbon units. In contrast to β oxidation, which takes place in the mitochondria and uses $FADH_2$ and NADH as electron carriers, fatty acid synthesis takes place in the cytosol, is powered by NADPH, and uses none of the same

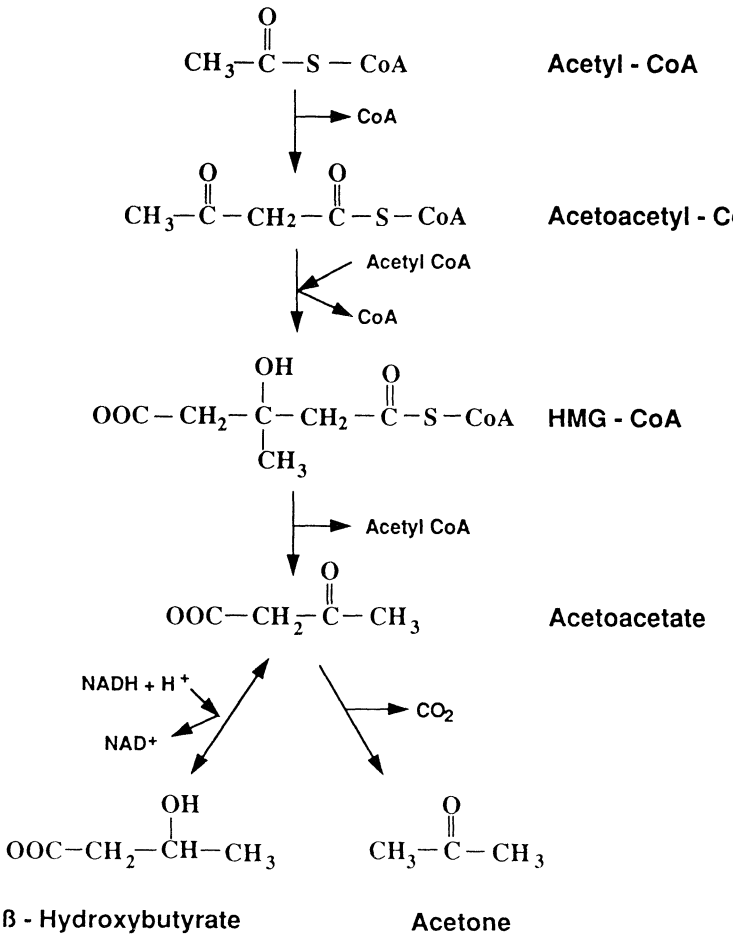


Figure 9 Ketone synthesis.

enzymes. Acyl carrier protein (ACP) carries the elongating fatty acid chain during synthesis.

The main substrates for fatty acid synthesis, acetyl-CoA and NADPH, are products of glycolysis and the TCA cycle. The NADPH for fatty acid synthesis is supplied chiefly by the pentose phosphate shunt, and glycolysis produces pyruvate, which in the mitochondria is converted to acetyl-CoA.

The first step in fatty acid synthesis is the carboxylation of acetyl-CoA by the allosteric enzyme acetyl-CoA carboxylase with biotin as a cofactor to form malonyl-CoA (Fig. 10). Citrate activates acetyl carboxylase by polymerization, while palmitoyl-CoA inhibits the enzyme. This relationship is an important point of control of fatty acid synthesis. When the energy needs of the cell are well met, high citrate concentrations activate fatty acid synthesis. On the other hand, an abundance of palmitoyl-CoA, the usual end product of fatty acid synthesis, not only inhibits acetyl-CoA carboxylase, but inhibits glucose-6-phosphate degradation by the pentose phosphate pathway, thereby turning off the major supply of NADPH.

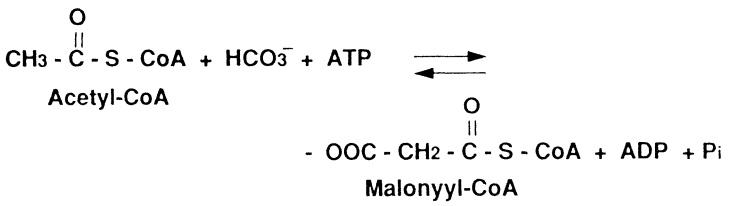


Figure 10 The first step in fatty acid biosynthesis, formation of malonyl-CoA from acetyl-CoA, is an important control point in the process.

As we saw above, the acetyl-CoA formed by β oxidation cannot cross the mitochondrial membrane, and so the citrate shuttle is necessary to make acetyl-CoA available in the cytoplasm for synthesis of malonyl-CoA and fatty acids. Within the mitochondria, citrate synthase converts acetyl-CoA and oxaloacetate (OAA) to citrate, which can diffuse into the cytosol where ATP-citrate lyase converts it back to into acetyl-CoA and OAA. In this way, the mitochondrial acetyl-CoA generated by glycolysis and pyruvate dehydrogenase becomes available for fatty acid synthesis.

After the formation of malonyl-CoA, the remaining steps in fatty acid synthesis all take place on the fatty acid synthase multienzyme complex. One full round of reactions on this complex employs seven distinct enzyme activities and produces butyryl-ACP. The reaction usually turns through six cycles to produce palmitoyl-ACP, which is released from the enzyme through the action of a thioesterase to yield palmitate (16:0). Fatty acids with chains longer than 16 carbons are synthesized by elongation of palmitic acid by two-carbon increments by the addition of malonyl-CoA in the microsomes on the endoplasmic reticulum.

Monounsaturation can occur after the long-chain 16:0 or 18:0 fatty acid has been synthesized. This requires the action of an enzyme complex on the endoplasmic reticulum consisting of NADH-cytochrome b_5 reductase, cytochrome b_5, and desaturase and results in the desaturation of stearoyl-CoA (18:0) to oleoyl-CoA ($18:1^{\Delta 9}$).

Animals lack $\Delta 12$ and $\Delta 15$ desaturases, so they cannot synthesize linoleic acid ($18:2^{\Delta 9,12}$) or linolenic acid ($18:3^{\Delta 9,12,15}$). However, both of these polyunsaturated fatty acids (PUFA) are absolutely required for normal health and must therefore be obtained in the diet from plant foods (i.e., they are essential). Other PUFAs are also obtained from the diet or are synthesized from linoleic or linolenic acid by a series of elongation and desaturation reactions.

LIPOPROTEINS AND LIPID TRANSPORT

General

With the exception of free fatty acids, whose carrier is albumin, the transport of the hydrophobic plasma lipids (triglyceride and cholesteryl esters) through the plasma circulation depends upon the formation of lipoprotein particles. These particles consist of an emulsifying, hydrophilic surface coat made of phospholipids, free cholesterol, and specific lipid-binding proteins (apoproteins). The surface coat surrounds the hydrophobic lipids, stabilizing them at the core of the particle.

Though the lipoproteins form a continuum of sizes and functions, ultracentrifugation flotation and electrophoretic mobility divide lipoproteins into four main subclasses: