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AUTHOR Allred, John B.
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ABSTRACT

Nutrition is well-recognized as a necessary component of educational programs for physicians. This is to be valued in that of all factors affecting health in the United States, none is more important than nutrition. This can be argued from various perspectives, including health promotion, disease prevention, and therapeutic management. In all cases, serious consideration of nutrition related issues in the practice is seen to be one means to achieve cost-effective medical care. These modules were developed to provide more practical knowledge for health care providers, and in particular primary care physicians. This module discusses the cyclic mechanisms involved in storage and mobilization of protein, fat, and carbohydrates. It is designed to illustrate the relevance of biochemistry in daily clinical practice as it relates to patient nutrition. Included are learning goals and objectives, a self-check of achievement with regard to goals, and references. Appendices include discussions of the regulation of glucose uptake by the liver, and the molecular mechanism of glucagon and insulin action on enzyme regulation. (CW)

The Nutrition in Primary Care Series Contains These Modules:

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2. Appraisal of Nutritional Status
3. Nutrient and Drug Interactions
4. Normal Diet: Age of Dependency
5. Normal Diet: Age of Parental Control
6. Normal Diet: Adolescence
7. Normal Diet: Pregnancy and Lactation
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9. Dietary Management in Obesity
10. Dietary Management in Diabetes Mellitus
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12. Dietary Management in Hyperlipidemia
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22. Exercise and Physical Activity
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24. Behaviorial and Neurological Disorders
25. Preventing Hospital and Home Malnutrition
26. Questions About Common Ailments

Faculty Guide (includes comprehensive index for Modules 1-26)

Department of Family Medicine
College of Medicine - The Ohio State University
456 Clinic Drive - Columbus, Ohio 43210

18 Nutrition in Health Promotion: Metabolic Principles

John B. Allred, Ph.D.
Professor
Department of Food Science and Nutrition
The Ohio State University
Columbus, Ohio

Project Editor
Lawrence L. Gabel, Ph.D.

Nutrition Content Editor
Charlette R. Gallagher-Allred, Ph.D., R.D.

Family Medicine Content Editor
Patrick J. Fahey, M.D.

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Bureau of Health Professions
Division of Medicine

Project Officer: Margaret A. Wilson, Ph.D.

Acknowledgments

Project Staff

Lawrence L. Gabel, Ph.D.-Project Director, Associate Professor and Director, Graduate Education and Research Section, Department of Family Medicine, The Ohio State University, Columbus, Ohio

Joan S. Rehner-Project Assistant, Secretary, Graduate Education and Research Section, Department of Family Medicine, The Ohio State University, Columbus, Ohio

Patrick J. Fahey, M.D.-Family Medicine Coordinator, Assistant Professor and Director, Predoctoral Education Section, Department of Family Medicine, The Ohio State University, Columbus, Ohio

Charlette R. Gallagher-Allred, Ph.D., R.D.-Nutrition Coordinator, Nutritionist, Riverside Methodist Hospital, Columbus, Ohio

John S. Monk, Ph.D.-Evaluation Coordinator, Assistant Professor and Coordinator, Research and Evaluation, Graduate Education and Research Section, Department of Family Medicine, The Ohio State University, Columbus, Ohio

Independent Study Package Consultant

Tennyson Williams, M.D., Professor and Chairman, Department of Family Medicine, The Ohio State University, Columbus, Ohio

Nutrition Consultant

Jil Feldhausen, M.S., R.D., Nutritionist, Department of Family & Community Medicine, University of Arizona, Tucson, Arizona

Editorial Consultant

Chester E. Ball, M.A., Assistant Professor Emeritus, The Ohio State University

Technical Assistants

Annette M. Battafarano, M.A., Graduate Research Associate, Graduate Education and Research Section, Department of Family Medicine, The Ohio State University, Columbus, Ohio

Richard E. Doty, M.S., Graduate Research Associate, Graduate Education and Research Section, Department of Family Medicine, The Ohio State University, Columbus, Ohio

Criteria/Assessment Committee

Mark T. Winders, M D., Resident, Department of Family Medicine, The Ohio State University, Columbus, Ohio

David R. Rudy, M.D., Director, Monsour Family Practice Residency Program, Monsour Medical Center, Jeannette, Pennsylvania.

Maria Steinbaugh, Ph.D., Associate Director, Nutrition Services, Ross Laboratories, Inc., Columbus, Ohio

Wilburn H Weddington, M.D., Family Physician, Columbus, Ohio

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Introduction

Every medical student has memorized the biochemical pathways several times, probably in first-year biology and again in first-year medical school, as well as countless times for numerous courses in between, perhaps without always understanding their relevance and interactions. Significant advances in our understanding of the interactions of these pathways and their regulation under various hormonal/dietary states have been made in the past few years, much of which has not made it into the standard textbooks. It is now more apparent than ever that those metabolic pathways which you memorized are real and must occur all of the time if our cells (and indeed we) are to survive. Not only must the biochemical pathways operate, they must be coordinated within each cell, as well as with all other cells. In order to operate, a continuous source of substrate and material to keep the machinery in repair must be provided—that is the purpose of nutrition. The purpose of this module is to review how dietary nutrients provide the substrates for these pathways and to consider how the pathways interact and how they are regulated.

Obviously, it is rare indeed for a patient to ask his physician about the regulation of glycolysis, the citric acid cycle, or fatty acid synthesis and mobilization. However, if you understand the interactions among these pathways, it is much easier to understand normal nutrition and weight control, as well as the relationship between nutrition and such metabolic diseases as diabetes mellitus and heart disease.

Nutrition is usually thought of in long-range terms. For example, patients are told, and rightly so, that excess body fat stores were deposited over a long period of time and that it is only reasonable that reduction of body weight also requires time. Although this analysis is essentially correct, it tends to conceal the fact that what happens over the long term is the summation of short-term regulatory processes. This module includes discussions of the cyclic mechanisms involved in storage and mobilization of protein, fat, and carbohydrates, which may happen as often as between meals.

As a physician, you are looking for clinical applications of biochemistry to patient care. Therefore, to illustrate the relevance of biochemistry to your daily practice, the following topics will be presented:

- Why we must eat
- Regulation of blood glucose and glucose utilization by various tissues
- Fat deposition and mobilization
- Protein and amino acid metabolism
- Role of insulin and glucagon in regulation of metabolism
- Lipid transport in blood — lipoproteins
- Brown adipose tissue and efficiency of calorie utilization
- Low-carbohydrate diets for weight control
- Diet aids for weight control
- Sucrose, fructose, and honey
- Non-nutritive diet constituents, including fiber, cholesterol, and caffeine

After reviewing the topics in this module, it is hoped that you will agree that there really is relevance of biochemistry to patient care.

Goal

The goal of this module is to provide a comprehensive foundation of nutrition concepts for the basic understanding needed to fully comprehend the role of nutrition in health promotion. It will lay the foundation to help resolve controversies regarding what nutrients will and will not do and how their action and control can be evaluated.

Objectives

Upon completion of this module, you will be able to:

1. *Describe the basic processes which govern carbohydrate, protein, and fat metabolism and the applications of these processes to the maintenance of health through nutrition.*
2. *Discuss the relationship of metabolic processes to weight control.*
3. *Identify the metabolic changes associated with various diets and discuss how such changes affect weight control.*
4. *Describe the physiologic role of dietary fiber, caffeine, and other non-nutrients in healthy people.*
5. *Use basic concepts relative to the digestive and metabolic processes to guide patients in understanding the controversies surrounding such things as sugar in the diet, artificial sweeteners, sugar substitutes, and weight-control pills.*

Note on Reading and Using This Module

The obvious danger in writing this module is telling you, the physician, more (or less) than you want to know. Therefore, the module is written at essentially three levels. The basic ideas and, where appropriate, applications to patient care are summarized in the highlights at the beginning of each section. Important details of the highlighted materials then follow. Finally, more basic biochemistry information is included in the Appendices for the reader interested in a more in-depth treatment.

Why We Must Eat

Food must be consumed to provide chemical energy in the form of ATP (adenosine triphosphate) to all cells of the body and to provide replacement for those chemicals lost through normal turnover and excretion.

If a patient were to ask, "Why must I eat?", you might suggest that the body must have a continuous source of chemical energy to carry on body functions; thus, calorie consumption is required. In addition, a continuous supply of certain chemicals which the body cannot make, such as vitamins, minerals, essential fatty acids, and essential amino acids, must be consumed in order to replace those lost through metabolism or elimination from the body.

A more detailed and more accurate answer, in biochemical terms, is that food must be eaten because each cell of the body must have nutrients to generate a constant supply of ATP for that cell to survive. This continuous need for ATP is to maintain the integrity of the cell which can be translated for the most part as ion pumping. That is, extracellular sodium ions have a tendency to leak into the cell, while intracellular potassium ions have a tendency to leak out. ATP supplies the chemical energy needed to maintain an appropriate concentration of these ions in the cell by the process of ion pumping, catalyzed by sodium-potassium ATPase. The expenditure of ATP for this ion pumping is not insignificant and, in fact, accounts for most of the energy expended for "basal metabolic rate." A marked rise in the sodium ion concentration and a loss of potassium ion concentration can cause cellular death because many enzymes are inhibited by sodium ions and/or activated by potassium ions. This is the reason anoxia is so rapidly destructive to cells in many tissues of the body, including brain, heart, and liver. Without sufficient oxygen, ATP can not be generated rapidly enough to maintain the appropriate ionic environment in these cells.

ATP, in common with other phosphorylated compounds, does not cross cellular membranes without a carrier. Thus, ATP does not circulate but rather must be synthesized in the cell in which it is to be used. Instead of ATP, nutrients to generate ATP are supplied in the blood.

Why the Body Needs Glucose

Although all tissues require a constant supply of nutrients, tissues vary in terms of which substrates can be utilized, ranging from the mature red blood cell and nervous tissue, which require glucose, to liver, which can utilize carbohydrate, fat, or protein as substrate.

Since carbohydrate and protein supply 4 kcal/gm and fat supplies 9 kcal/gm, why can we not simply eat and store fat as a calorie source? The reason is that tissues vary markedly in their ability to utilize different substrates for energy production. For example, since the mature red blood cell does not have mitochondria and therefore does not have the enzymes necessary for the production of ATP by oxidative processes, it must rely upon glucose metabolism through anaerobic glycolysis for the production of ATP. Thus, fatty acids or amino acids are not utilized as an energy source in this tissue. Brain and nervous tissue have the capacity for oxidative metabolism; but because of limited permeability to most substrates other than glucose, glucose oxidation is by far the most important pathway for the production of ATP. If brain cells are deprived of either glucose (as in insulin shock) or oxygen for even a few minutes, irreversible cellular damage occurs, resulting clinically in patient coma or stroke, depending upon the site of damage.

In contrast, the liver can utilize either carbohydrate, amino acids, or fatty acids to generate ATP. Adipose tissue also can utilize glucose or fatty acids as oxidizable substrates.

Skeletal muscle can be considered somewhere between these two extremes. This tissue also can utilize glucose, amino acids, or fatty acids if oxygen is available. During vigorous exercise, ATP is utilized rapidly for muscular activity. If there is insufficient oxygen to regenerate this ATP by oxidative processes, ATP is generated by glycolysis, and lactate is excreted by the muscle cell.

Heart muscle normally has an adequate supply of oxygen available and operates aerobically. Usually glucose is not a very important substrate for heart muscle; lactate and fatty acids are quantitatively much more important. This is not to say that heart muscle does not have the glycolytic pathway; it can utilize glucose and store glycogen for use under stress. During anoxia, the

only source of substrate for ATP generation is glycogenolysis and glycolysis. Unfortunately, this is usually not sufficient to keep cells alive in a section of the heart deprived of oxygen. If the shortage of ATP that develops is not corrected within a very few minutes, the patient is said to have suffered a myocardial infarction because those cells die and cannot be regenerated.

- The substrate requirement for the kidney depends upon the specific tissue in this organ. The kidney medulla has a very limited blood supply, and therefore oxygen supply, and must rely almost exclusively upon glycolysis to generate ATP. In contrast, the cortex has a very generous blood supply and can therefore generate ATP by oxidative processes, through the oxidation of lactate, fatty acids, and amino acids. A portion of the glucose that is produced in the cortex enters the blood stream so that the kidney can be said to be gluconeogenic and contribute to the total blood glucose available. However, the gluconeogenic capacity of the kidney is far less than that of the liver. Thus, in patients with liver disease, synthesis of glucose by the kidney is insufficient to compensate for the loss of liver gluconeogenic capacity, and blood glucose levels often fall to below normal.

Maintaining Blood Glucose Between Meals

The red blood cell and nerve tissue must have a continuous supply of glucose to produce chemical energy even though glucose is not continuously available from our diet. Glycogen is stored in the liver during the fed state and is mobilized during the post-absorptive state to supply blood glucose. In addition, the liver can synthesize glucose from lactate and amino acids. Glucose is also conserved when blood insulin is low because glucose entry into muscle and adipose tissue requires insulin.

In spite of the fact that tissues have a continuous demand for ATP and therefore for substrates to generate ATP, we do not eat continuously nor do we eat often enough to maintain a source of nutrients from digestive processes. Absorption of nutrients reaches a peak relatively soon (within 1 to 3 hours) after a meal is consumed and then declines. In order to provide a continuous supply of substrates to tissue, nutrients, including carbohydrate, fat, and protein, are stored during the fed state to be mobilized during the post-absorptive state (Figure 18-1). Assuming a normal eating pattern of three meals per day, this cyclical process of storage and mobilization of nutrients occurs three times each day. This cyclical storage and mobilization occurs because of marked changes in metabolism in several of the tissues of the body and is controlled primarily by insulin and glucagon.

Glycogen Storage and Degradation

When carbohydrate is present in the diet and insulin is secreted, glycogen is synthesized and stored in liver and other tissues. This is important because liver glycogen is the most direct source of blood glucose between meals. The clinical importance of this, as we have already seen, is that red blood cells and nerve tissue require a continuous source of glucose. However, there is a limit to the amount of glycogen that can be stored in any tissue, including liver. The limit is normally about 8% of the liver weight. Dramatically higher amounts of glycogen in the liver can result in cellular damage as is found in glycogen storage diseases. Glycogen is mobilized during the post-absorptive state to aid in the maintenance of blood glucose.

It should be noted that glycogen stores in muscle as well as liver can be temporarily expanded by a process called "glycogen loading" which may be of benefit to athletes performing in long-endurance events (see Module 22, Exercise and Physical Activity). On the other hand, very low levels of liver glycogen occur in starvation, in uncontrolled diabetes mellitus, in inborn errors of metabolism which limit gluconeogenesis, and in response to stress such as severe exercise ("hitting the wall") or surgery.

Glucose Synthesis

In addition to glycogen mobilization, the liver has the capacity to synthesize glucose from amino acids, lactate, and glycerol. This process of gluconeogenesis occurs simultaneously with glycogenolysis during the post-absorptive state and becomes increasingly important as the length of the fast increases. The glycogen stores are limited and are effectively depleted after about 20 hours of fasting.

Glucose Conservation

When blood glucose concentration is low, it is conserved for those tissues which have an absolute require-

ment for it. Under these conditions, the utilization of glucose as an energy source and as a source of carbon for the synthesis of fat markedly declines in the liver. In addition, glucose entry into heart and skeletal muscle, as well as adipose tissue, requires insulin so that when blood glucose and insulin are low, these tissues remove less glucose from blood. Part of the reason for elevated blood glucose in the diabetic is that glucose is not removed by tissues which require insulin for glucose entry, either because of insufficient insulin as in the insulin-dependent diabetic or because of changes in cellular insulin receptors in the case of non-insulin-dependent diabetics.

In the post-absorptive state, when glucose entry into muscle and adipose tissue is decreased, these tissues use fatty acids as a source of oxidizable substrate for energy production. Thus, when insulin levels are reduced, mobilization of triglyceride occurs to provide these fatty acids. In addition, utilization of glucose in the liver decreases, and fatty acids as well as amino acids become an important substrate for the liver.

Conditions for Making and Storing Fat

Sources of Depot Lipids

Triglyceride synthesis in the liver is increased by insulin and decreased by glucagon. Thus, liver lipogenesis increases in response to feeding a diet sufficiently high in carbohydrate to elevate insulin and depress glucagon. Glucose, as well as carbon from other sources, including lactate, glycerol, other hexoses, and amino acids, can be used for liver lipogenesis. Triglyceride from liver synthesis or from dietary sources (containing fatty acids of 16 or more carbons) is transported in the blood as a particle with a protein coat called a lipoprotein.

Triglyceride storage can be considered a hedge against future food shortages. It has been argued that our evolutionary ancestors stored fat on their bodies during periods of abundant food supplies to allow them to survive the famine which was sure to follow. Less efficient individuals did not survive the famine and, therefore, did not live long enough to reproduce. By this argument, we are genetically programmed to store fat. However, for most of us the famine never comes. On a shorter-term basis, we store fat during the fed state to be utilized during the post-absorptive state. In man, the liver is the major site of *de novo* synthesis of fatty acids destined for storage.

A high-carbohydrate diet which increases blood glucose and insulin concentrations results in an increase in fatty acid biosynthesis in the liver at the same time and by the same biochemical mechanisms which result in resynthesis of glycogen stores. However, as noted above, there is a limit to the amount of glycogen that can be stored in the liver. If more glucose arrives at the liver than that required to replenish the glycogen stores, the excess is used for fatty acid biosynthesis. There appears to be no reasonable limit to fat storage capacity in adipose tissue.

Numerous studies have shown that insulin increases liver fatty acid biosynthesis. On the other hand, glucagon (which is increased during the post-absorptive state) decreases liver fatty acid biosynthesis. Although insulin increases hepatic fatty acid biosynthesis, glucose is not the only substrate that can be used as a carbon source. Other substrates that may be used include lactate, glycerol, other hexoses such as fructose or galactose, and amino acids, provided that sufficient glucose from digestive processes has been absorbed to elevate insulin and depress glucagon concentrations in the blood.

The initial product of the liver fatty acid synthesis system is palmitate (16 carbons, saturated), much of which undergoes elongation and/or desaturation before it is converted to triglyceride. Since triglycerides are not miscible with the aqueous blood system, the triglyceride is surrounded by specific proteins and exported as a lipoprotein.

Most of the triglycerides in our diet contain long-chain fatty acids; i.e., 16 or more carbons. These dietary triglycerides are emulsified by bile acids and digested by pancreatic lipase in the small intestine. Some glycerol is released in the digestive process and is absorbed into the mucosal cell and transported to the liver via the hepatic portal vein like other water-soluble compounds. Fatty acids and monoglyceride released during triglyceride digestion are absorbed into the intestinal mucosal cell by molecular diffusion where they are resynthesized into a triglyceride before they are released as a lipoprotein particle into the lymph and then into the blood stream.

Triglycerides containing short-chain and medium-chain fatty acids can be hydrolyzed in the lumen of the small intestine, or they may be absorbed into the

intestinal mucosal cell and hydrolyzed inside. These short- and medium-chain fatty acids are not resynthesized into triglycerides but rather, since they are water-soluble, are transported to the liver via the hepatic portal vein. In the liver they undergo beta-oxidation to form acetyl CoA which can be utilized in the citric acid cycle or for synthesis of palmitate (assuming that the insulin: glucagon ratio is elevated).

Fate of Blood Lipoproteins

Triglycerides synthesized in the liver are secreted into the blood as a particle called very-low-density lipoproteins (VLDL). The lipoprotein particle synthesized by the intestinal mucosal cell from dietary long-chain fatty acids is called a chylomicron. The triglycerides in both types of lipoprotein can be hydrolyzed by lipoprotein lipase. Low-density lipoprotein (LDL) is removed from the blood by a variety of tissues, including liver, after it interacts with specific LDL receptors. Chylomicron remnants are removed from the blood by the liver.

The triglyceride in both chylomicrons and VLDL can be hydrolyzed by lipoprotein lipase present in adipose tissue as well as heart and skeletal muscle. Adipose tissue lipoprotein lipase occurs on the outer surface of the fat cell membrane and is activated by insulin. Triglyceride hydrolysis yields glycerol (which goes back to the liver via blood) and free fatty acids. The fatty acids that are released diffuse into the fat cell and are reconverted to triglycerides before they are stored. Resynthesis of the triglyceride requires alpha-glycerol phosphate to provide the glycerol backbone which is only available from the glycolytic degradation of glucose. Glycerol is not utilized by adipose tissue because of low activity of glycerol kinase which would convert glycerol to alpha-glycerol phosphate. Since glucose entry into adipose tissue is very insulin-sensitive, resynthesis, and therefore deposition, of triglyceride would be minimal with low insulin levels.

Heart and skeletal muscles also have lipoprotein lipase activity on the cell surface. The activity is low but is constant; i.e., it is not activated by insulin. Thus, these tissues can utilize the triglyceride in VLDL and chylomicrons, regardless of the insulin levels. Therefore, when triglyceride which contains long-chain fatty acids is fed without a source of glucose, heart and skeletal muscles remove much more of the triglyceride from the blood than adipose tissue does. Under low-insulin conditions, glucose entry into these tissues is markedly reduced, and therefore fatty acids must become a more important source of substrate for ATP production.

When much of the triglyceride is removed from chylomicrons by the action of lipoprotein lipase, the remaining chylomicron remnants travel via the blood to the liver where the remaining triglyceride and cholesterol are removed. The triglyceride can be stored, utilized in the liver, or re-exported, this time as VLDL.

Removal of the triglyceride from VLDL by lipoprotein lipase results first in the formation of lipoproteins of intermediate density (IDL) and then low density (LDL). Since triglyceride has been removed but not protein or cholesterol, the relative concentration of the latter two compounds is increased in LDL compared to VLDL. In the blood, a portion of the LDL may "pinch off" and become one of the forms of high-density lipoproteins (HDL). Serum HDL-cholesterol can be measured clinically and LDL-cholesterol levels can be calculated from the basic lipid screen.

Normal Clearance of LDL and the Lack of Normal Clearance in the Diabetic

LDL is normally removed from the blood because it attaches to a very specific LDL receptor located on the plasma membrane of cells of a variety of tissue, including liver. The LDL is then internalized where the proteins are degraded to amino acids and the triglyceride and cholesterol are removed. In diabetics, the high concentration of glucose in the blood leads to a modification of the LDL proteins by a process called glycosylation. The modified LDL can no longer interact with the LDL receptors and therefore can not be removed from the blood. It is not clear whether the resulting elevated LDL causes or is a complicating factor in the high incidence of heart disease found in diabetics.

Low-density lipoproteins (LDL) are normally cleared from the blood by a variety of tissues, including liver, each of which has specific LDL receptors on the plasma membrane. After the LDL attaches to its receptor, the LDL is internalized; the protein is degraded to amino acids in lysosomes. Triglyceride can be hydrolyzed in the cell, and the resulting fatty acids are utilized as an energy source or resynthesized in the liver into triglyceride and re-exported as VLDL. Cholesterol can be utilized by the cell for membrane repair or converted to bile salts in the liver.

Thus, under normal conditions one can expect to see an elevated level of triglyceride in the blood in the form of VLDL following the consumption of a high-carbohydrate meal. The concentration of VLDL would then decline as the LDL concentration increases. Over time, the LDL concentration also would normally decrease. However, the high concentration of glucose, as might occur in the blood of a diabetic, can result in a modification of the LDL protein, by a process called protein glycosylation, so that it will not interact with the LDL receptor.

Protein glycosylation occurs when the aldehyde group of glucose reacts with free amino groups of proteins. Free amino groups of lysine residues in a protein are particularly susceptible to glucose addition. The reaction can happen in blood since it is non-enzymatic; therefore its rate depends on the concentration of blood glucose. Thus, diabetics not under tight glycemic control have an increased rate of glycosylation because of higher glucose concentration. Clinical advantage is taken of this fact by measuring glycosylation of hemoglobin to determine relatively long-term glycemic control. Such a modified protein does not allow dissociation of oxygen as readily as normal hemoglobin, which can result in a relative hypoxia, particularly in peripheral tissues of diabetics.

Other proteins, in addition to hemoglobin, can be modified by the addition of glucose, including the proteins associated with LDL. Such glycosylation prevents the normal interaction of the modified LDL with its receptors, and thus LDLs are not removed from the blood, resulting in a constant hyperlipoproteinemia. It is not clear whether this elevated LDL is causative or simply a complicating factor of the increased incidence of heart disease found in diabetics (see Module 19, Risk Factors and Disease Prevention).

Mobilizing Fat Stores

Triglyceride is mobilized from adipose tissue when glucose is no longer available from the digestive processes because glucagon causes the activation of the enzyme which regulates adipose tissue triglyceride hydrolysis. Insulin decreases the activity of this regulatory enzyme. Free fatty acids produced from triglyceride hydrolysis are carried in blood bound to albumin. Oxidative degradation of long-chain fatty acyl CoA is determined by the rate of entry into mitochondria via fatty acyl carnitine, the formation of which is inhibited by a product of fatty-acid biosynthesis. Thus, synthesis and oxidation of long-chain fatty acids do not occur at the same time.

When the concentration of glucose decreases in blood because it is no longer available from digestive processes, synthesis and deposition of triglyceride decrease. In response to lowered blood glucose and a concomitant reduction in blood insulin and increased glucagon, stored triglycerides are hydrolyzed to produce free fatty acids which can then be used as an oxidizable substrate in the liver and in tissues which require insulin for glucose entry.

The decrease in triglyceride deposition can be attributed to lowered insulin for the reasons described above. Triglyceride mobilization occurs because glucagon activates the enzyme which regulates the rate of hydrolysis of stored triglyceride, hormone-sensitive triglyceride lipase. Insulin decreases the activity of this regulatory enzyme. As the name hormone-sensitive triglyceride lipase implies, this enzyme can be regulated by a number of hormones, including activation by catecholamines which is increased during exercise. The hydrolytic products of hormone-sensitive triglyceride lipase are a free fatty acid and a diglyceride. The free fatty acids produced by hormone-sensitive triglyceride lipase, as well as the free fatty acids produced from the subsequent hydrolysis of the diglyceride, diffuse into the blood where they are carried by non-covalent attachment on albumin.

During the post-absorptive state, the concentration of albumin-bound fatty acids increases in the blood. When

this complex arrives at a liver or muscle cell, the fatty acids diffuse into the cell cytoplasm and are activated to their metabolically active form, fatty acyl CoA, but fatty acyl CoA is not permeable to the mitochondrial membrane. In order to be transported into the mitochondria, long-chain fatty acyl CoA must be converted to fatty acyl carnitine. After fatty acyl carnitine enters the mitochondria, carnitine is removed and replaced by coenzyme A which regenerates fatty acyl CoA inside the mitochondrion. The fatty acyl CoA then undergoes beta-oxidation. The enzyme which forms fatty acyl carnitine on the cytoplasmic side of the mitochondrial membrane is inhibited by malonyl CoA which is produced during fatty acid biosynthesis. This mechanism prevents the synthesis and oxidation of long-chain fatty acids from occurring at the same time in the liver. Some of the important clinical implications of triglyceride metabolism will be reviewed in the next section.

Changing Fat Stores

Dietary Alteration of Triglyceride Stores

To lose weight it is necessary to mobilize more triglyceride during the post-absorptive state than is stored during the fed state. To gain weight, one must store more triglyceride in the fed state than is mobilized in the post-absorptive state. The number of meals per day is not nearly as important as total caloric intake, but patients should be encouraged to be consistent with meal patterns.

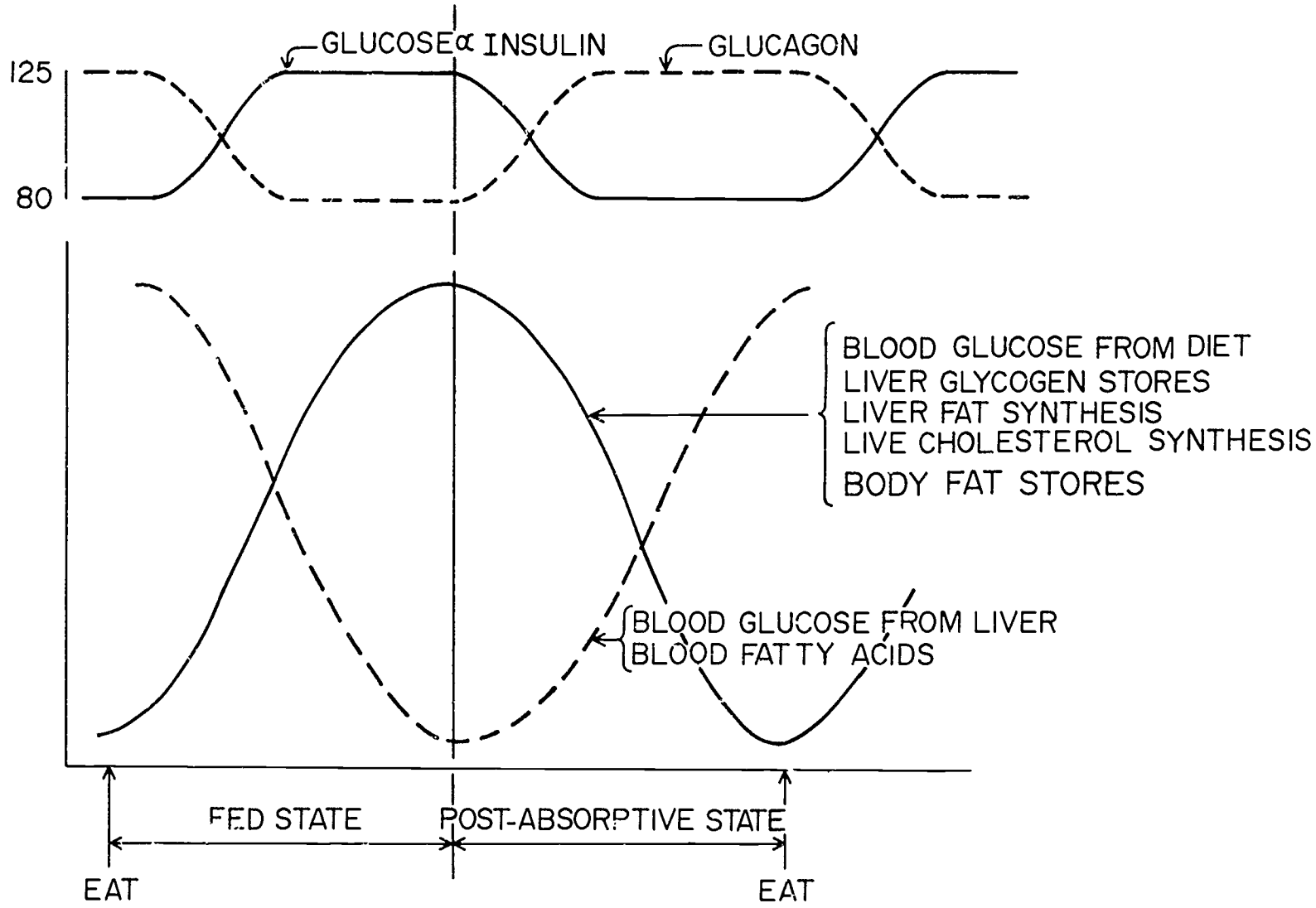
Triglyceride is stored during the fed state when insulin is elevated and is mobilized during the post-absorptive state when insulin is reduced and glucagon is increased. It is clear from Figure 18-1 that the secret of control of body fat stores is simple; to lose lipid stores, it is necessary to mobilize more triglyceride during the post-absorptive state than is stored during the fed state. Weight gain occurs when the amount stored during the fed state exceeds that mobilized during the post-absorptive state. Unfortunately for those who want to alter body fat stores, either up or down, the body has a very effective mechanism to balance appetite control, efficiency of energy utilization, and body fat stores so that altering the system is extremely difficult.

The question is often asked, "Is it more fattening to eat one large meal per day than three small meals?" Generally, clinical studies indicate that the total number of calories consumed is much more of a factor than the number of meals per day. However, animal studies have shown that refeeding a high-carbohydrate diet after a fast of sufficient duration to deplete liver glycogen stores (i.e., 20 hours or longer) will result in an "overshoot" in hepatic synthesis of both glycogen and fat. Thus, in practice, patients attempting to reduce body fat stores should be encouraged to be consistent in meal patterns. The practice of restricting caloric intake during the five-day work week and not restricting caloric intake on the weekend should specifically be discouraged as self-defeating. Animal studies indicate that readjustment to a new meal pattern requires five to seven days.

Another frequent question is, "Are the calories I eat just before I go to bed more fattening than those consumed during the earlier part of the day?" The answer to this question from clinical studies is much less clear-cut, although it is likely that the total caloric intake per day is much more of a factor than when the calories are consumed. It is also clear that dietary or medical practices which result in an increased insulin:glucagon ratio will cause increased hepatic triglyceride synthesis, increased blood triglyceride, increased triglyceride deposition in adipose tissue, and decreased triglyceride mobilization. The elevation of the insulin:glucagon ratio can obviously occur when carbohydrate is consumed, regardless of whether it is a snack in the morning, afternoon, or at bedtime. Peritoneal dialysis of kidney patients with a glucose solution will also elevate the insulin:glucagon ratio, with the consequences on fat metabolism described above.

A related question that patients may ask is, "How soon after the consumption of excessive calories will I see an increase in fat deposits?" Assuming that the extra calories were consumed as a part of a mixed meal which contained adequate carbohydrate to elevate blood glucose, additional fat will be deposited almost immediately, certainly within the next few hours. The efficiency with which fat is deposited will depend upon the composition of the meal and the dietary history of the patient over the past few weeks.

Figure 18-1. Changes in Nutrient Storage and Mobilization as a Function of Dietary State



Low Carbohydrate Diets — Effectiveness

Since insulin is required for fat synthesis and deposition and since glucagon inhibits fat synthesis and increases mobilization, restriction of both caloric and carbohydrate intake is apparently more effective for weight reduction than simple restriction of caloric intake. Excessive ketogenesis, which results in ketosis, suppresses appetite.

Over the years, there have been a number of "fast-weight-loss," low-carbohydrate diets most of which are based upon a low-carbohydrate, "diabetic" diet first published in *Harper's Magazine* about 1868. Every few years an enterprising author writes a new book based on the same principle which immediately becomes among the top books on the non-fiction (?) best-seller list. Two questions are relevant: (a) are low-carbohydrate diets effective for weight control? and (b) should such diets be used; i.e., are they safe?

Since insulin is required for the synthesis of triglyceride in the liver and its deposition in adipose tissue, it follows that a diet that maintains a lower blood glucose and insulin concentration, as well as maintains a higher glucagon concentration, should increase mobilization and decrease triglyceride storage. This conclusion must be tempered by the fact that amino acids can stimulate insulin release synergistic with glucose so that insulin may not drop as low as it would in response to fasting. Secondly, our cells have a remarkable ability to adapt to differences in insulin level by a process called down- or up-regulation. Down-regulation occurs when cells treated with a high level of insulin "swallow" insulin receptors. The insulin receptors are internalized and therefore disappear from the cellular membrane surface, thereby reducing insulin sensitivity. This process is thought to be a major factor in the development of adult-onset diabetes (see Module 19, Risk Factors and Disease Prevention). Up-regulation also occurs; i.e., when cells are exposed to low insulin levels for a period of time, there is an increase in insulin receptors on the surface of the cell so that there is an increase in insulin sensitivity. Thus, a low-carbohydrate diet may lower blood insulin levels, but this reduction may be less effective than expected because such conditions would lead to greater insulin sensitivity.

Experimental evidence indicates that when caloric intake is reduced to a level below that required to maintain body weight, a low-carbohydrate diet is more effective than the same number of calories from a mixed diet, especially over a short term. During the first few days of dieting, however, most of this weight loss is due to a decrease in glycogen and protein stores and the water stored with them. Insulin favors storage and glucagon favors mobilization of both of these forms of nutrients so that the time-averaged decrease in the insulin:glucagon ratio resulting from reduced carbohydrate intake could account for a more rapid initial weight loss.

Weight lost initially, representing mostly protein, glycogen, and water, is regained just as rapidly when sufficient quantities of a mixed diet are consumed. Some triglyceride stores are also lost during this same period, but significant reduction in body fat occurs much more slowly. Evidence from well-controlled, long-term studies indicates that when caloric intake is maintained at a level far below that needed to maintain body weight, diets become increasingly effective in reducing actual fat stores as the carbohydrate content is reduced. The greater negative energy balance that occurred in response to reducing carbohydrate intake could not be attributed solely to greater excretion of oxidizable substrate such as ketone bodies; therefore, it must represent a greater heat output, most likely by diet-induced thermogenesis from brown adipose tissue (see section on Brown Adipose Tissue).

The effectiveness of low-carbohydrate diets on reducing fat stores has been shown when caloric intake was restricted. It is far less certain that unrestricted caloric intake, even from low-carbohydrate diets, would be nearly as effective as some diet books suggest. However, since such diets are ketogenic and ketone bodies inhibit appetite, there may well be a voluntary reduction in caloric intake with such diets.

Low-Carbohydrate Diets — Safety

Low-carbohydrate diets lead to increased urinary excretion of cations as well as urea, which requires adequate intake of sodium and potassium ions along with water to replace losses from the body. Life-threatening hypokalemia can occur if large quantities of carbohydrate are ingested after long-term consumption of a low-carbohydrate diet, especially when there is also a severe restriction of caloric intake as occurs with liquid

protein diets. Consumption of excess potassium ions during the period of low-carbohydrate and low-calorie intake does not protect against this potential hazard.

Several factors must be considered relative to the safety of low-carbohydrate diets for weight reduction, one of which is that such diets are ketogenic. Ketone bodies are produced continuously in the liver and become excessive when fatty acids become the major source of oxidizable substrate in this tissue as they do in uncontrolled (or poorly controlled) diabetics, during fasting, or during the feeding of a low-carbohydrate diet. The major ketone bodies are acetoacetic and beta-hydroxy butyric acids, both of which are excreted in the urine in their ionized form, which means that they remove cations, especially sodium and potassium, from the body. Urinary loss of these cations requires an increased intake in order to maintain appropriate sodium and potassium ion concentrations in blood and tissue. If you have patients on a low-carbohydrate diet, blood levels of these as well as other cations should be monitored frequently.

Excessive ketogenesis may lead to another problem in some patients in that it may precipitate gout. Gout occurs when the uric acid content of blood increases, which can occur during excessive ketogenesis because the excretion site in the kidney is the same for uric acid and beta-hydroxy butyrate. For those patients prone to gout, this competition for the excretion site can cause a subclinical problem to become overt gout. Dietary purines, but not protein, are precursors of uric acid and can therefore exacerbate the problem.

The same dietary/hormonal conditions which lead to excessive ketogenesis lead to increased excretion of nitrogenous waste products in the urine because under such conditions there is a marked increase in gluconeogenesis in the liver, especially from amino acids. The amino group of these amino acids is incorporated into urea and excreted, which results in a larger urinary volume. Thus, patients must be careful to drink adequate water when consuming a low-carbohydrate diet to prevent dehydration. Further, this increase in urinary nitrogen excretion could cause difficulties for those patients who have an existing kidney problem.

Ironically, the greatest potential hazard of low-carbohydrate diets occurs immediately after the cessation of such a dietary regimen. This is especially true for low-carbohydrate diets in which caloric restriction is severely limited, as with the commercially available liquid protein diets. If such diets are effective, it is because there has been a reduction in blood insulin level for a long period of time. This low insulin level leads to up-regulation of insulin receptors; i.e., cells become more sensitive to insulin. If a patient goes on a binge after a long period on such a dietary regimen and consumes a large quantity of carbohydrate, the result is an insulin surge. Since cells have a greater than normal number of receptors because of the extended period of low insulin level, insulin has a greater than normal effect. Insulin is not only required for the entry of glucose and amino acids into certain tissue, it also increases potassium ion uptake. An insulin surge, coupled with increased cellular sensitivity to insulin, can result in a rapid uptake of potassium ions, much of which goes into skeletal muscle. The resulting marked, transient hypokalemia can produce a temporary deficiency of potassium in heart muscle which could lead to disruption of normal metabolism in the heart. This mechanism probably accounts for a number of the deaths that have been attributed to the use of liquid protein diets. The problem cannot be overcome by the consumption of larger quantities of potassium ion during the intake of a low-carbohydrate diet because the excessive potassium ion consumed is excreted, not stored. Rather, patients consuming low-carbohydrate diets should be warned to reintroduce carbohydrate into their diets slowly and never binge as a reward for staying with the diet long enough to achieve considerable weight loss.

Increasing Caloric Expenditure — The Exercise Factor

Weight control is a matter of balancing caloric intake with caloric expenditure. Vigorous exercise will increase the concentration of blood epinephrine, which in turn will increase the release of glucagon from the pancreas and decrease insulin release. These hormonal changes will increase heart and respiration rate, gluconeogenesis in liver, and, most importantly for weight loss, mobilization of triglyceride from adipose tissue.

It is axiomatic in the field of nutrition that weight control is simply a matter of caloric balance. If more calories are expended than are consumed, the extra calories must come from those stored in the body. Thus, exercise can be used by a patient desiring to lose weight as a mechanism to increase caloric expenditure. Unfortunately, strenuous exercise often increases the appetite which makes restriction of caloric intake an even greater problem. Even so, an exercise program, along with the reduction of calories consumed, will likely have a greater chance of success than dieting alone.

The biochemical mechanism involved in triglyceride mobilization is similar to that observed during the post-absorptive state described above. During "aerobic" exercise, there is an increased concentration of epinephrine in the blood. Whenever there is an epinephrine response, there is also an increase in release of glucagon from the pancreas. Since there is a feed-back mechanism operating in the pancreas between glucagon and insulin release, there is a reduction in the release of insulin. It is interesting that even though there is a decrease in insulin concentration in the blood, there is an increase in glucose uptake by skeletal muscle during exercise because more insulin receptors come to the cell surface of an exercising muscle. Thus, during exercise, muscle glucose uptake is enhanced not because of increased insulin but rather because the muscle cell becomes more sensitive to insulin. This is the reason that exercise can cause an insulin-dependent diabetic to experience insulin shock.

Epinephrine increases glycogen degradation in muscle which provides more glucose-6-phosphate, much of which is converted to lactate via the glycolytic pathway. The remainder is converted to pyruvate which can be oxidized by the citric acid cycle. Epinephrine increases heart and respiration rate which makes more oxygen available to the muscle to support the production of ATP by oxidative processes. The lactate produced by skeletal muscle can be utilized in the liver for the synthesis of glucose which can return to muscle to be utilized again via glycolysis. Epinephrine and glucagon stimulate the gluconeogenic process, as well as glycogen degradation in liver, as described above for the post-absorptive state.

Epinephrine and glucagon also increase triglyceride mobilization in adipose tissue by activating hormone-sensitive triglyceride lipase. The free fatty acids released from adipose tissue are transported in blood and then bound to albumin, to liver, and to skeletal muscle. Thus, during aerobic exercise, fatty acids are an important substrate for muscle metabolism.

Patients should be told that to be of the most value, exercise should be sufficiently vigorous to elevate epinephrine so that the muscles are "burning" fat. The patient can tell when epinephrine is elevated because there will be an increase in heart and respiration rate.

Brown Adipose Tissue — The Efficiency Factor

Brown adipose tissue is a specialized type of fat cell containing more mitochondria than normal adipose tissue and having the capability of oxidizing substrates to produce heat instead of ATP. Cold, overeating, epinephrine, and smoking all increase heat production, while the beta blocker, propranolol, and probably restriction of caloric intake reduce heat production. The amount of heat produced is a major factor in efficiency of metabolism which determines how much food we can eat without experiencing a body weight change.

When we consume a nutrient that contains a calorie, three things can happen to the calorie: (a) it can be used as a substrate immediately for the production of ATP, (b) it can be stored, or (c) it can be converted to heat. We have a specialized tissue, brown adipose tissue, that can specifically produce heat from oxidation of nutrients. All of us are born with brown adipose tissue ("baby fat") which has the important function of providing heat to maintain body temperature. It was assumed for some time that as we developed we lost this brown fat, but it turns out that this is not the case. Brown fat becomes proportionately less important as we grow because we increase our white adipose tissue. Adults still have it, localized intrascapular as well as on the neck and face.

Brown adipose tissue is brown because of a high concentration of mitochondria, the metabolism of which is somewhat different than mitochondria of other tissue. Normally mitochondria generate ATP during phosphorylation because of a charge distribution across the mitochondrial membrane which develops as we produce reducing equivalents by the oxidation of substrate through the citric acid cycle. The reducing equivalents move through the electron transport chain located in the mitochondrial membrane which creates the charge across

that membrane. This charge is then used to drive the reaction which synthesizes ATP from ADP and inorganic phosphate. Brown adipose tissue has a protein in the mitochondrial membrane, called GDP-binding protein, which can carry a charge across the membrane, thus neutralizing the charge without generating ATP. The energy that would normally go into ATP production is lost as heat. The net effect is that the oxidation of substrate, either from food or our nutrient stores, produces heat instead of chemical energy. The more brown adipose tissue one has and the more active it is, the more of the calories consumed are used for heat production instead of storage.

Brown adipose tissue can be stimulated to be more active by several mechanisms. Cold stimulates it, presumably to increase heat production and thus maintain body temperature (called non-shivering thermogenesis). More recent work indicates that it also can be stimulated by overfeeding, a process that has been called diet-induced thermogenesis. This observation coincides with the idea that we are pre-programmed, presumably genetically, to store a certain amount of fat in our body (adipose-set-point theory). If we try to reduce our fat stores below this set point, we become more efficient (i.e., produce less heat); and if we try to go above the set point, we become less efficient (i.e., produce more heat). Thus, it is difficult to change our fat stores and the further away from the set point we get, the more difficult it is. If you are 80 pounds overweight, it is much easier to lose the first 20 pounds than it is to lose the last 20 pounds. You should not be surprised to find patients who are no longer losing weight with a caloric intake that had previously resulted in a slow but consistent weight loss. It simply means that the body has become more efficient. As discussed above, exercise can be an important part of a weight-control program. It not only increases caloric expenditure, but may counteract the usual decrease in basal metabolic rate observed when weight has been reduced.

Little is known about the mechanism of establishing the set point, although it likely involves the hypothalamus which regulates appetite and perhaps the activity of brown adipose tissue. It does seem clear, however, that genetics plays a major role in the regulation of body weight. It appears that the best way to avoid a weight problem is to choose your parents wisely!

Epinephrine and its analogs have been shown to stimulate heat production by brown adipose tissue. Propranolol, a beta blocker, has the opposite effect, which suggests that epinephrine works through the beta receptors. More importantly, you can probably expect your patients who are taking propranolol to have more difficulty controlling their weight. Smoking, presumably because of nicotine, increases brown adipose tissue heat production so that a patient may gain weight when they quit smoking, even if they do not change caloric intake.

Protein and Amino Acids

Protein synthesis, stimulated by insulin, and protein degradation, stimulated by glucagon, follow the same cyclical pattern as lipid and carbohydrate. Restriction of caloric intake, especially from carbohydrate, results in a rapid degradation of protein and glycogen stores, each of which is stored with about three times its weight of water. The result is a very rapid weight loss for the first few days associated with any diet which restricts caloric intake.

Control of Synthesis and Degradation of Proteins

Regulatory mechanisms involved in protein and amino acid metabolism are considerably more complicated than those of carbohydrate and lipid, and the details are therefore much less understood. It is clear, however, that protein synthesis is increased by insulin, both because of increased amino acid uptake by tissue and by an insulin-mediated activation of protein biosynthesis. A rise in glucagon is associated with increased protein degradation which provides amino acids to furnish the carbon source for gluconeogenesis. At the same time, urea production in the liver is activated. Thus, like carbohydrate and triglyceride, protein is stored during the fed state, only to be degraded as an energy and carbon source during the post-absorptive state.

Protein Utilization with Weight Loss

Mobilization of stored protein has particular significance to individuals who are attempting to reduce body fat stores. Restriction of caloric intake, and especially carbohydrate intake, will result in a rapid net mobilization of protein as well as glycogen stores. Since each gram of protein and glycogen is stored with about three grams

of water, the dieter will experience a very rapid weight loss for the first few days until the "labile" protein and glycogen stores are depleted. This rapid weight loss can amount to as much as 3 to 5% of body weight. The loss of labile protein stores does not appear to be a health hazard, but it can affect the morale of the dieter because the rapid weight loss is followed by a much slower rate of weight reduction which represents actual fat mobilization. If the dieter is not made aware that this will happen, the cessation of the rapid weight loss will likely make him conclude that "the diet isn't working any more" and abandon the effort. Upon resumption of normal caloric intake, weight lost due to loss of protein, glycogen, and water stores will be rapidly regained. Thus, it is common for intermittent dieters to experience a "yo-yo" effect of body weight.

The practice of providing protein in low-carbohydrate diets, discussed above, is predictably not very effective in decreasing mobilization of the labile protein stores. The regulation of protein synthesis and degradation has much more to do with circulating insulin and glucagon levels than with dietary protein, provided that amino acid requirements are met. That is, protein accretion, or even maintaining nitrogen balance, requires the consumption of both sufficient protein (including sufficient essential amino acids) and sufficient calories, especially from carbohydrate.

Summary of Metabolic Effects of Dietary Carbohydrate

In the fed state, when blood glucose level is elevated, the liver removes glucose from the blood to replenish glycogen stores, to use as a substrate for ATP production, and to synthesize triglyceride. In the post-absorptive state, the liver produces glucose from glycogen mobilization and gluconeogenesis. Amino acids from protein degradation, as well as glycerol from triglyceride degradation, and lactate serve as carbon sources for glucose synthesis. In the post-absorptive state, fatty acids, mobilized from adipose tissue, serve as the major oxidizable substrate in liver instead of glucose.

The liver is the organ with the major responsibility for glucose homeostasis. Glucose, as well as all other water-soluble constituents of our diet, is absorbed into the intestinal mucosal cells and transported to the liver via the hepatic portal vein. During the fed state, the concentration of glucose in the hepatic portal vein may reach 250 to 300 mg/dl, while the concentration of glucose on the venous side of the liver is maintained at about 125 mg/dl. Thus, under these conditions, the liver successfully removes glucose from the blood as it traverses the liver. The glucose that is removed is used as a substrate to generate ATP via glycolysis and the citric acid cycle, to regenerate glycogen stores, and to synthesize fatty acids, and subsequently triglyceride, exported from the liver as VLDL (Figure 18-2). Note that insulin also increases cholesterol biosynthesis.

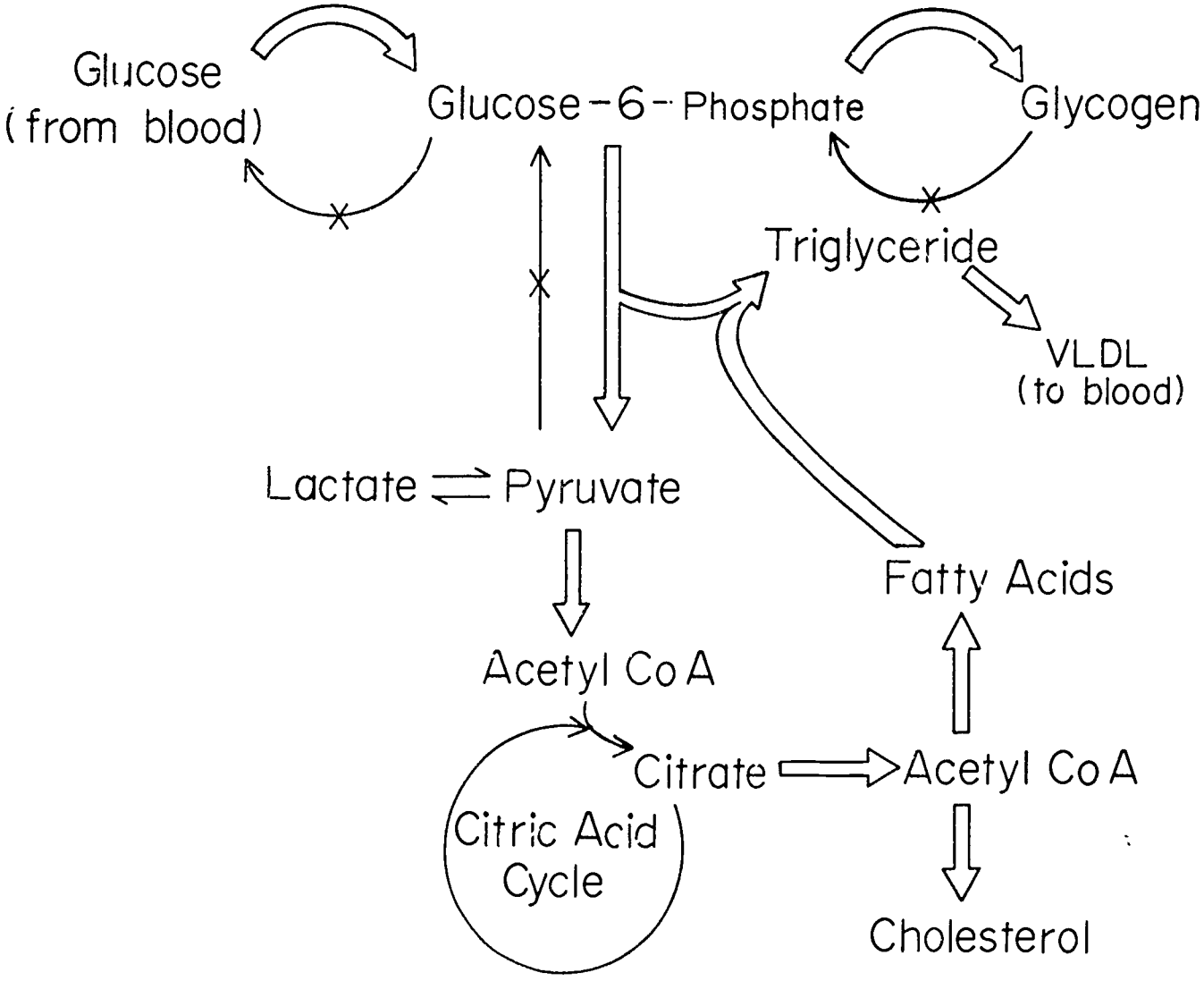
In the post-absorptive state, the liver becomes a glucose producer instead of a glucose user. When blood glucose, and consequently blood insulin, is low, the glucose concentration increases as the blood traverses the liver because of mobilization of glycogen as well as increased gluconeogenesis (Figure 18-3). At the same time, utilization of glucose via the glycolytic pathway is markedly reduced, while fatty acids become the major oxidizable substrate to maintain adequate ATP levels in the liver cell as well as provide ATP needed for gluconeogenesis. Lactate, amino acids, and glycerol all serve as carbon sources for glucose synthesis. The excretion of urea, synthesized from the amino groups of amino acids, is increased in the post-absorptive state.

In addition to glucose homeostasis, the concentration in blood of most of the other nutrients is also under tight control. Triglyceride, for example, from diet or the liver is removed from the blood, primarily by adipose tissue, during the fed state to be replaced by free fatty acids, carried on albumin, during the post-absorptive state. During the fed state, amino acid uptake by the liver as well as extra-hepatic tissue increases as does protein synthesis. The post-absorptive state is characterized by a decrease in amino acid uptake by extra-hepatic tissue, accompanied by a decrease in protein synthesis and an increase in proteolysis. The amino acids available from protein breakdown can be used as oxidizable substrates as well as a source of carbon for glucose synthesis in the liver.

Body Detection and Response to Changes in Dietary Carbohydrate

It is apparent from the above discussion that an alteration in the nutrient supply from digestion has a

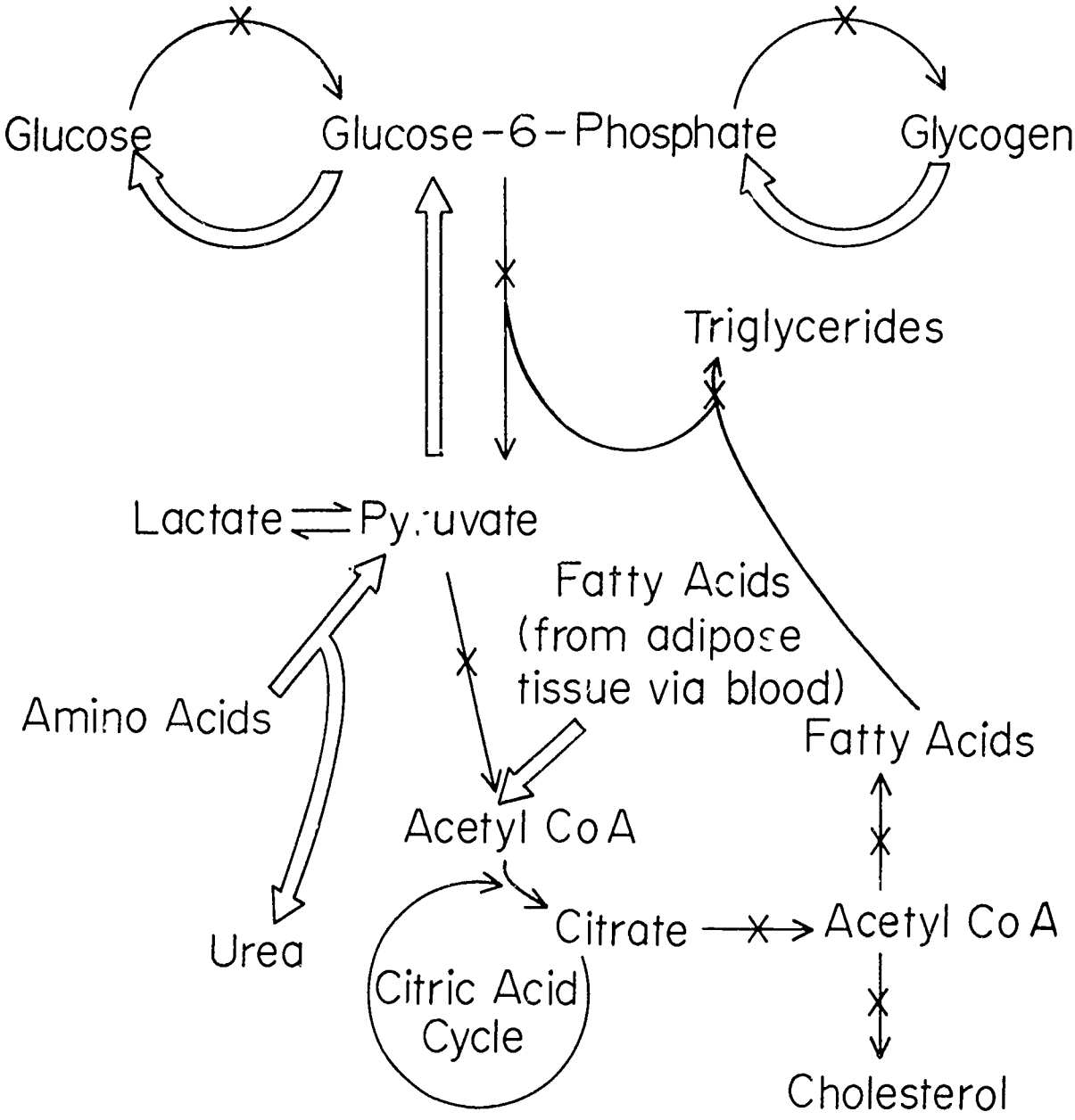
Figure 18-2. Liver Metabolism — Fed State



⟹ Increased by increased insulin and glucose

⟶✕⟶ Decreased by increased insulin

Figure 18-3. Liver Metabolism — Post Absorptive State



very rapid effect on metabolism of several tissues and especially the liver. In this section, the "message system" (i.e., the regulatory signals for alteration of metabolism) will be discussed.

Regulation of Glucose Uptake in the Liver

Glucose is freely permeable to the liver cell; i.e., it does not require insulin for entry. As the concentration of glucose increases in the hepatic portal vein during glucose absorption, the concentration increases in the liver cell which increases the rate of its conversion to glucose-6-phosphate. Since phosphorylated compounds do not cross cellular membranes, glucose is trapped in the cell as the phosphorylated derivative. Thus, the concentration of glucose is lower in blood coming from the liver than that in blood going to the liver. The rate at which glucose is released by the liver is regulated by insulin and glucagon.

The mechanism by which the liver is able to remove glucose from the blood during the fed state turns out to be very simple. Since glucose entry into the liver cell is regulated by diffusion and does not require insulin, the concentration of glucose inside the liver cell is essentially the same as the concentration outside the cell. Glucose that enters can be trapped in the liver cell by converting it to the phosphorylated derivative, glucose-6-phosphate. Once phosphorylated, it cannot leave the cell because phosphorylated derivatives do not cross the cellular membrane. Thus, the rate of removal of glucose from the blood as it traverses the liver is regulated by the rate of its phosphorylation.

Once glucose is phosphorylated in the liver cell, it can be reconverted to glucose or it can be further metabolized, either for glycogen synthesis or through the glycolytic pathway (Figure 18-2). The dietary/hormonal state that leads to increased glucose-6-phosphate production increases the rate of its utilization through glycolysis and glycogen synthesis which effectively reduces the rate of reconversion to free glucose. Thus, the rate of glucose-6-phosphate utilization in liver is regulated primarily by insulin and glucagon. Refer to Appendix A for further information about the mechanism regulating glucose uptake and production by the liver.

Insulin and Glucagon Release

The interplay of insulin, glucagon, and glucose is responsible for the rapid metabolic changes occurring in many tissues in response to food intake. Insulin is released from the pancreatic beta cells in response to glucose by a process that can be further stimulated by one of the gut hormones, gastric inhibitory peptide, and by amino acids. Glucagon release from the pancreatic alpha cells increases as blood glucose decreases.

When a diet is consumed containing glucose or a glucose precursor such as starch, glucose is absorbed from the intestinal mucosal cells and blood glucose rises. As blood glucose increases, the release of insulin increases from the pancreatic beta cells and the release of glucagon from the pancreatic alpha cells decreases. It is the interplay of these three compounds (glucose, insulin, and glucagon) that is responsible for the rapid metabolic changes which occur in our tissues in response to eating.

Although the role of glucose in the release of insulin from the pancreas has long been known, the mechanism of the process is still far from being resolved. It has been established, however, that the presence of glucose in the intestinal mucosal cells causes the release of one of the many gut hormones, gastric inhibitory peptide (GIP). GIP was first discovered as a gut hormone that inhibited gastric motility, but its more likely physiological role is to work synergistically with glucose to cause insulin release; i.e., the quantity of insulin released at a given glucose concentration is increased by GIP. Thus, GIP can be considered as an early warning that glucose is on its way. It can increase the release of insulin after carbohydrate is consumed even before blood glucose has increased. This is the reason that oral glucose results in a greater increase in blood insulin level than an equal amount of glucose given intravenously. The insulin is secreted into the hepatic portal vein which ends in the liver. A portion of this insulin traverses the liver and enters general circulation. Abnormalities in the response of pancreatic beta cells to GIP have been noted in obese and non-insulin-dependent diabetics, characterized by an

elevated secretion of GIP but a lowered output of insulin at the same time.

In addition to GIP, amino acids can also increase insulin output, not by themselves but only by acting synergistically with glucose. Further, there is evidence that insulin release is also under neural control.

Glucagon secretion from the alpha cells of the pancreas increases as blood glucose level decreases. Amino acids will also trigger glucagon release, although glucose will inhibit the amino acid stimulation of glucagon secretion. In addition to pancreatic glucagon, there is also gut glucagon which has some, but not all, of the properties of the pancreatic hormone.

A question that may be of concern to a diabetic is, "How fast and how high does blood glucose rise after the consumption of a high-carbohydrate food?" The answer is not simple because the composition of the food consumed has a major effect on the glycemic response. The variation in the glycemic response to foods can, to a large extent, be attributed to the rate of digestion and absorption, which in turn is due to the effects of different nutrients on stomach emptying time. Fat and slowly solubilized protein will reduce the rate of stomach emptying, whereas soluble carbohydrate and protein will leave the stomach rapidly. Thus, the observation that cooked potatoes and ice cream have similar glycemic responses can be attributed, at least in part, to the slower rate of stomach emptying with ice cream because of its fat content. The practical effect of this observation is that diabetics may be able to incorporate small amounts (30-60 gm/day) of sucrose in their diets without adversely affecting glycemic control, provided the sucrose is consumed as a part of a mixed meal containing fat and insoluble protein. Thus, ice cream for dessert immediately after a regular meal will not likely cause a problem of elevated blood glucose, but the same amount of sucrose in the form of candy in the middle of the afternoon could cause a problem.

Insulin and Glucagon—Regulation of Metabolism

Storage and mobilization of nutrients are clearly coordinated. Insulin and glucagon control these processes by altering the structure and therefore the activity of regulatory enzymes. The structural change, called covalent modification, results in the attachment or removal of phosphate to control enzymes. Coordination is achieved because this same basic mechanism regulates the activities of control enzymes in glycolysis, pyruvate oxidation, fatty acid biosynthesis, triglyceride mobilization, and protein synthesis and degradation.

It is clear from the foregoing discussion that rapid, coordinated changes occur in several metabolic processes in response to an alteration of substrates available from digestion. The fed state, in which blood glucose and insulin are elevated simultaneously, increases glycogen synthesis, glycolysis, and fatty acid biosynthesis in the liver (Figure 18-2) and triglyceride deposition in adipose tissue. The post-absorptive state, in which blood glucose is reduced and glucagon is elevated, results in decreased glycolysis, glycogen synthesis and fatty acid biosynthesis, and increased glycogen mobilization in the liver (Figure 18-3). At the same time, triglyceride stored in adipose tissue in the fed state is mobilized. Thus, substrate is continuously available to all tissues.

Coordination of the metabolic processes is achieved by the action of insulin and glucagon by a remarkably simple mechanism called covalent modification. The mechanism depends upon the attachment or removal of phosphate from enzymes which control these processes. The presence of the phosphate group alters the activity of these regulatory enzymes. In general, enzyme phosphorylation results in the activation of those enzymes involved in mobilization of stored nutrients and inactivates those enzymes involved in fuel storage. Removal of phosphate has the opposite effect.

Physiological Mechanism of Glucagon Action

The only known biochemical mechanism of action of glucagon is initiated when the hormone interacts with its receptors located on the plasma membrane of liver and adipose tissue cells. When the glucagon receptor is occupied, an enzyme (adenylate cyclase) also located in the plasma membrane is activated. This activated enzyme catalyzes the production of cyclic-adenosine monophosphate (cyclic AMP) from ATP. Thus, glucagon interaction with either liver or adipose cells results in an increase in the concentration of cyclic-AMP.

The only known function of cyclic-AMP is to bind to a protein in the cell and to cause the release of an active enzyme called cyclic-AMP-dependent protein kinase. This protein kinase catalyzes the addition of phosphate from ATP to several enzymes in the cell cytoplasm which

regulates the activity of those enzymes. Cyclic-AMP-dependent protein kinase is not specific for particular proteins but rather for a certain amino acid sequence within proteins (see Appendix B). Table 18-1 lists several processes which are regulated by phosphorylation catalyzed by cyclic-AMP-dependent protein kinase Note that, in general, enzymes involved in fuel storage have decreased activity when phosphorylated, while enzymes involved in fuel mobilization have increased activity when phosphorylated. Note also that this mechanism automatically coordinates the listed metabolic processes because glucagon regulates each of them by activating a single enzyme, cyclic-AMP-dependent protein kinase.

Although the only known function of cyclic-AMP is to activate protein kinases, glucagon is not the only hormone which will increase the cyclic-AMP concentration in cells. Catecholamines, as well as variety of other hormones, utilize cyclic-AMP as a second messenger to activate protein kinases in several tissues and thereby regulate numerous cellular processes. Some of the varied effects of cyclic-AMP are discussed in Appendix B.

Physiological Mechanism of Action of Insulin

Unlike glucagon, insulin has more than one mechanism of action. The most widely known effect of insulin is that it is required for glucose (and other metabolites including amino acid and monovalent cation) entry into cells of skeletal muscle, heart muscle, and adipose tissue. It is not required for glucose entry into liver, kidney, mucosal cells, mature red blood cells, or the central nervous system. Glucagon is not antagonistic to insulin-mediated entry of glucose into tissue.

Even though insulin is not required for glucose uptake by liver cells, it does have profound metabolic effects in liver and other tissues. Most of the metabolic effects of insulin can be attributed to insulin causing dephosphorylation of regulatory enzymes. The mechanism by

Table 18-1. Processes and Enzymes Regulated by Glucagon via Activation of Cyclic-AMP-Dependent Protein Kinase

Process	Regulatory Enzyme Phosphorylated	Effect on Enzyme Activity
Liver		
Glycogen synthesis	Glycogen synthetase	Decreased
Glycolysis	Phosphofructokinase*	Decreased
Glycolysis	Pyruvate kinase	Decreased
Fatty acid synthesis	Acetyl CoA carboxylase	Decreased
Fatty acid synthesis	ATP citrate lyase	Decreased
Cholesterol synthesis	Beta-hydroxy beta-methyl glutaryl CoA reductase	Decreased
Glycogen degradation	Phosphorylase	Increased
Gluconeogenesis	Phosphoenolpyruvate carboxykinase*	Increased
Gluconeogenesis	Fructose diphosphatase*	Increased
Beta-oxidation of fatty acids	Fatty acyl CoA carnitine acyl transferase I*	Increased
Adipose Tissue		
Triglyceride mobilization	Hormone sensitive triglyceride lipase	Increased

*Indirect effect; i.e., other enzymes are phosphorylated which in turn regulates the enzyme listed.

which insulin results in enzyme dephosphorylation is still under investigation, but there is considerable evidence that the effect of insulin is the activation of a protein phosphatase which catalyzes the hydrolytic removal of regulatory phosphates which had been attached to enzymes by cyclic-AMP-dependent protein kinase (Table 18-2). The action of this insulin-activated protein phosphatase therefore accounts for the fact that insulin and glucagon are often antagonistic to each other. Other proteins, such as pyruvate dehydrogenase, are activated by insulin via a dephosphorylation mechanism, but the phosphate is not attached by cyclic-AMP-dependent protein kinase. Rather, pyruvate dehydrogenase is phosphorylated and inactivated by a specific mitochondrial protein kinase which is active when insulin concentration is low. Other effects of insulin on enzyme activities, such as activation of adipose tissue lipoprotein lipase, are not counteracted by glucagon.

Automatic Coordination of Control by Insulin and Glucagon

It should be emphasized that in order for glucagon to cause mobilization of glycogen and triglyceride and to decrease fat synthesis and deposition, it is required only to activate one enzyme, cyclic-AMP-dependent protein kinase, which adds a phosphate to regulatory proteins. On the other hand, in order for insulin to increase glycogen and triglyceride synthesis in liver and to decrease triglyceride mobilization from adipose tissue, it is required only to activate one enzyme in each of these tissues, a protein phosphatase which removes the added phosphate from the regulatory enzymes. Thus, regulation of these processes cannot occur uncoordinated.

Table 18-2. Processes and Enzymes Regulated by Insulin via Activation of Protein Phosphatase

Process	Regulatory Enzyme Dephosphorylated[1]	Effect on Enzyme Activity
Liver		
Glycogen synthesis	Glycogen synthetase	Increased
Glycolysis	Phosphofructokinase[2]	Increased
Glycolysis	Pyruvate kinase	Increased
Fatty acid synthesis	Acetyl CoA carboxylase	Increased
Cholesterol synthesis	HMG CoA reductase	Increased
Pyruvate oxidation	Pyruvate dehydrogenase[3]	Increased
Glycogen degradation	Phosphorylase	Decreased
Gluconeogenesis	Fructose-diphosphatase[2]	Decreased
Beta-oxidation of fatty acids	Fatty acyl CoA-carnitine acyl transferase[2]	Decreased
Adipose Tissue		
Triglyceride mobilization	Hormone sensitive triglyceride lipase	Decreased
Triglyceride deposition	Lipoprotein lipase[4]	Increased

1. Except in the few cases noted, the phosphate removed is a phosphate attached by cyclic-AMP-dependent protein kinase (compare Table 18-1).
2. Indirect effect (see Table 18-1).
3. Phosphorylation is not catalyzed by cyclic-AMP-dependent protein kinase.
4. Activation of lipoprotein lipase may not involve dephosphorylation.

Non-Nutritive Constituents of Our Diet

Most of the chemicals in our food supply, other than essential nutrients, are not absorbed. A few compounds that are consumed, including deliberately administered drugs or non-nutritive constituents of our food such as cholesterol and caffeine, are absorbed and can have physiological effects on metabolism. Some dietary constituents such as fiber can have physiological effects even though they are not absorbed.

As a practicing physician, you will surely be asked about "all the chemicals that are added to our food during processing." What most people do not realize is that there are literally thousands of "chemicals" in our food supply, most of which are there not because they have been added but because they are natural constituents of the foods that we consume. These chemicals are important because they give food distinctive properties, including its characteristic odor, flavor, and color. Another thing that your patients may not realize is that just because one swallows something, it does not mean that it is in the body. The gastrointestinal tract can best be considered a tube running through the body, the contents of which are not really "in the body" unless the chemicals are absorbed across the membrane of the mucosal cells which line the gastrointestinal tract. Since the absorption mechanisms are rather selective, only a few classes of compounds, including required nutrients, actually enter the body so that most of the chemicals consumed are eliminated via the fecal route.

A few chemical constituents of our diet have physiological effects even though, as in the case of fiber, they are not absorbed. Other dietary constituenrs, such as cholesterol and caffeine, are absorbed and have physiological effects but do not serve as "nutrients."

Fiber

Dietary fiber has an important function in our diet for proper gastrointestinal function. Chemically, fiber is a complex mixture of compounds, some of which carry an ionic charge at physiological pH and can therefore act as ion-exchange resins to remove charged compounds, such as bile acids, from the GI tract.

The most abundant fiber compound in nature is cellulose, which does not carry a charge.

Dietary fiber, by definition, may almost be considered a non-nutrient because it is not absorbed. On the other hand it has long been known that fiber is an important constituent of our diet for proper gastrointestinal function. That is, it increases the rate of food passage, decreases the incidence of diverticular disease, and softens the stool by absorbing water. In addition, dietary fiber can be of value in the control of food intake in that it reduces the caloric density of the diet. However, the commercially available products such as methylcellulose or glucomannan, touted as weight control pills, are of doubtful benefit for such purposes. It also should be noted that some types of dietary fiber, as well as other dietary constituents that are poorly digested and absorbed in the small intestine, can be metabolized by the bacteria inhabiting the large intestine. Some of the metabolic products produced by the bacteria, such as short-chain, volatile fatty acids, may be absorbed and therefore contribute to total caloric intake. Metabolism by these bacteria can produce an undesirable side effect, flatulence.

Chemically, fiber is a complex mixture of compounds, some of which carry a net ionic charge at physiological pH. These charged compounds can act as ion exchange resins which can reduce the absorption of charged compounds. It has been suggested, though not established, that the combination of decreasing residence time and the ion-exchange effect of some forms of fiber might reduce intestinal cancer by removing potential carcinogens. Although the loss of nutrients appears to be too insignificant to be of concern, fiber with an ionic charge can reduce the reabsorption of bile acids and thus lower blood cholesterol. Some types of fiber have been reported to improve glucose tolerance test results in some diabetics, perhaps by altering gut hormone production, although the significance or mechanism has not been shown.

Many of the beneficial effects of fiber appear to be due to the ion exchange capability; thus, it is important to note that all types of fiber are not equal. The most abundant type of fiber in nature is cellulose. Since cellulose does not have a charge, it does not remove bile acids and therefore does not lower blood cholesterol. Cellulose does, however, have most of the other beneficial effects of fiber.

Cholesterol Metabolism

The synthesis of cholesterol is increased by insulin and decreased by glucagon, following the pattern of triglyceride metabolism. In addition, a feedback control system limits cholesterol production if it is supplied in the diet.

Like dietary triglyceride, there are two important sources of cholesterol in the body, diet and liver synthesis, although other tissues have a limited synthetic capacity. Regulation of the synthesis of cholesterol in the liver is remarkably similar to the regulation of the synthesis of fatty acids. The rate-limiting enzyme, beta-hydroxy-beta-methyl glutaryl CoA reductase, is inactivated by phosphorylation, a process stimulated by glucagon through cyclic-AMP. The enzyme is reactivated by dephosphorylation, favored by insulin. In addition to hormonal control, cholesterol and its degradation product, bile acids, decrease the activity of this regulatory enzyme so that cholesterol limits its own synthesis.

The normal adult excretes about one gram of cholesterol per day either directly or after its conversion to bile acids. For most people, the feedback control system works so that if cholesterol is consumed (up to 1 gm/day), there is an equivalent reduction in liver cholesterol synthesis. Since it is difficult to conceive of a reasonable diet which would contain more than one gram of cholesterol, it is unlikely that dietary cholesterol *per se* has any significant effect on the body cholesterol pool.

Cholesterol occurs in blood as a component of lipoprotein so that blood cholesterol concentration has more to do with lipoprotein and chylomicron metabolism than it has to do with cholesterol metabolism. It has been shown that polyunsaturated fatty acids in the diet will result in a lowering of blood cholesterol by up to 15%, but it remains a controversial question as to whether this reduction is advantageous in the prevention of heart disease. (See Module 19, Risk Factors and Disease Prevention.)

Function of Caffeine

Methyl xanthines are absorbed because they are analogs of purines. The physiological effect of caffeine and other methyl xanthines is to inhibit the enzyme which degrades cyclic-AMP and thus exaggerates any cyclic-AMP-dependent mechanism. These include not only the regulation of nutrient storage but also brain activity, heart rate, and several other processes.

Purine and pyrimidine bases, although not required in our diet, are absorbed and utilized for nucleic acid synthesis. Analogs of purines, the methyl xanthines, are therefore also absorbed and can cause physiological problems for some patients, especially if consumed in large amounts.

Caffeine and other methyl xanthines (theophylline and theobromine) function physiologically by inhibiting the activity of cyclic-AMP phosphodiesterase (the enzyme responsible for cyclic-AMP breakdown) and thus maintain the concentration of cyclic-AMP higher than it would be if these inhibitors were not present. A higher level of cyclic-AMP is translated into an increased activity of cyclic-AMP-dependent protein kinase as discussed above. Since caffeine only inhibits the degradation of cyclic-AMP and does not stimulate its formation, the effect of caffeine is always secondary to some stimulus which increases cyclic-AMP in the first place.

With this in mind, it is not surprising that caffeine will elevate blood glucose when it is low. Glucagon provides the stimulus for the production of cyclic-AMP, and caffeine inhibits its degradation. In contrast, when blood glucose is high, caffeine lowers it. The apparent reason for this is that the release of insulin from the pancreas is a cyclic-AMP-dependent mechanism. Thus, by maintaining a higher concentration of cyclic-AMP in the pancreatic beta cell, a greater quantity of insulin is secreted than would have occurred without the caffeine.

Since caffeine inhibits the degradation of cyclic-AMP, it will affect any cyclic-AMP-dependent reaction—and there are many of them—in addition to regulating nutrient utilization, as previously discussed (see Appendix B). For example, a number of brain neurotransmitters utilize cyclic-AMP as a second messenger, which results in increased brain activity. Thus, a stimulus which results in the elevation of cyclic-AMP in the brain will be exaggerated by caffeine, but caffeine would not have any effect in the absence of some stimulus. Caffeine may or may not keep one awake, depending upon what

else is happening to activate cyclic-AMP production. Other cyclic-AMP-dependent processes are listed in Table 18-3, all of which may be exaggerated by caffeine. The list is not exhaustive but does account for most of the physiological effects of excessive methyl xanthine consumption. It should be noted that epinephrine, working through the beta-adrenergic system, has its physiological effect by increasing cyclic-AMP production. Since the beta blocker propranolol inhibits cyclic-AMP synthesis, caffeine and propranolol have opposing effects. Thus, when patients are treated with propranolol, the intake of methyl xanthines should be restricted.

The various physiological effects of caffeine shown in Table 18-3 are related to symptoms of a variety of medical problems which patients might experience. If patients have such symptoms, obviously the intake of methyl xanthines would need to be restricted. For example, a patient with cardiac arrhythmia, hypertension, stroke, peptic ulcer disease, or diarrhea should be discouraged from consuming caffeine. On the other hand, theophylline, along with analogs of epinephrine, is included in throat sprays used for the treatment of lung congestion because dilation of pulmonary capillaries is cyclic-AMP-dependent. In the absence of any direct medical problem, the consumption of methyl xanthines in moderation is likely not harmful.

Table 18-3	Effects of Caffeine in Addition to Those Listed in Table 18-1.
	Increases brain activity
	Increases heart rate
	Increases HCl secretion in stomach
	Decreases water reabsorption in large intestine
	Increases constriction of blood vessels except pulmonary
	Increases dilation of pulmonary blood vessels

Although there has been a suggestion that fibrocystic breast disease might be treated by restriction of methyl xanthine intake, no clearcut evidence for this has been reported, and carefully controlled studies have not been done. On the other hand, there are reports of epidemiological studies involving large numbers of subjects which indicate that the consumption of methyl xanthines from coffee, tea, or chocolate are not correlated with the incidence of fibrocystic breast disease or breast cancer.

Caffeine is present in a variety of foods and beverages (Table 18-4), including both tea and coffee. The question is often asked as to which of these two beverages contains more methyl xanthine. Tea leaves contain more caffeine than coffee beans, but because of the way we prepare the beverages, more is present in prepared coffee than in tea. Chocolate contains a chemically related compound, theobromine, that has the same biochemical effect as caffeine. Thus, for patients whose intake of caffeine should be restricted, the intake of chocolate should also be reduced.

Controversial Issues

Sugar—Is It Bad for You?

Sucrose and honey have essentially the same composition with respect to glucose and fructose, neither of which, in reasonable amounts, is especially good or bad in terms of health. Sucrose, as such, does not enter the body but rather is converted to glucose and fructose during absorption. The glucose produced is utilized like glucose from any other source. Fructose is utilized by the liver and does not pass into general circulation in significant amounts. It is converted to triose phosphate in the liver and can then be converted to pyruvate or to glucose, depending upon the hormonal conditions occurring during its consumption.

Everyone seems to have a desire for food that has a sweet taste, and the most common substance in our diet that provides such a taste is sucrose. It is therefore unfortunate that there are probably more myths believed by the general public about sucrose than any other single food, with the possible exception of honey. The problem is that sucrose is supposed to be bad for you and honey is supposed to be good even though they have essentially the same composition. Sucrose is composed of equimolar amounts of fructose and glucose. By far the major solids in honey are the same two hexoses, fructose and glucose, each in about equal amounts, with a small amount of other sugars, none of which is required in our diet.

In considering the metabolism of sucrose, it is important to remember that sucrose does not enter the body since the contents of the gastrointestinal tract can be considered as a tube that runs through the body. That

Table 18-4 Caffeine and Theobromine Content of Selected Foods and Drugs

	Caffeine mg	*Theobromine* mg
Coffee Beverage		
Drip, automatic—5 fl oz	110-164	
Drip, non-automatic—5 fl oz	106-145	
Instant—5 fl oz	47-68	
Instant, decaffeinated—5 fl oz	2-5	
Percolated, automatic—5 fl oz	99-134	
Percolated, nonautomatic—5 fl oz	93-130	
Coffee, flavored from instant mixes—6 fl oz	30-60	
Coffee, Instant Dry Powder		
Regular—1 tsp	50-65	
Freeze dried—1 tsp	50-65	
Decaffeinated—1 tsp	3	
Tea Beverage		
Am black, 1 min brew—5 fl oz	21-33	
Am black, 3 min brew—5 fl oz	35-46	2
Am black, 5 min brew—5 fl oz	39-50	
Black, imported, 5 min brew—6 fl oz	63-67	
Decaffeinated, 5 min brew—6 fl oz	1	
Green, 1 min brew—5 fl oz	9-19	
Green, 3 min brew—5 fl oz	20-33	
Green, 5 min brew—5 fl oz	26-36	
Instant—6 fl oz	32-35	2
Flavored (spice, orange, mint)—6 fl oz	30-60	2
Oolong—1 min brew	13	
Oolong—3 min brew	30	
Oolong—5 min brew	40	
Tea, Instant Dry Powder		
Regular—1 tsp	32	
Lemon flavored—1 tsp	38	
Soft Drinks		
Big Red (regular and diet)—12 fl oz	38	
Coca-Cola—12 fl oz	45	
Cola soda, decaffeinated, diet—12 fl oz	trace	
Diet Coke—12 fl oz	45	
Dr. Pepper (regular and diet)—12 fl oz	40	
Mountain Dew—12 fl oz	54	
Mr. Pibb—12 fl oz	41	
Mr. Pibb, diet—12 fl oz	57	
Pepsi Cola (regular, diet, light)—12 fl oz	36	
Royal Crown—12 fl oz	36	
Shasta (regular and diet)—12 fl oz	44	
Tab—12 fl oz	45	

Table 18-4 (cont) Caffeine and Theobromine Content of Selected Foods and Drugs

	Caffeine	*Theobromine*
Chocolate	*mg*	*mg*
Baking chocolate—1 oz	35	55
Chocolate candy—1 oz	1-15	40-60
Chocolate cake—1/16 of 9″ cake	14	
Chocolate ice cream—2/3 cup	5	
Chocolate milk—8 oz.	2-7	60
Chocolate pudding—1/2 cup	6	
Chocolate powder—instant Quik, 2 tsp	7	88
Cocoa, dry powder—1 Tbsp	4-19	102
Cocoa, dry—1 oz	70	409
Cocoa mix, 1 oz—1 pkt	5	67
Prescription Drugs	*mg/tablet or capsule*	
Apectol tablets (sedative/analgesic)	40	
Cafergot capsules (migraine headaches)	100	
Darvon (pain reliever)	32	
Migrol (headaches)	50	
Migralam capsules (migraine headaches)	100	
Soma Compound (pain reliever/muscle relaxant)	32	
Non-Prescription Drugs		
Anacin	32	
Bromoquinone (for colds)	15	
Cenegistic (for cold/allergy)	15	
Cope (for pain)	32	
Coryban-D (for colds)	30	
Dexatrim (for weight control)	200	
Dietac (for weight control)	200	
Dristan (decongestant)	16	
Excedrin (for pain)	65	
Midol (for pain/diuretic)	32	
No Doz (stimulant)	100	
Neo-synephrine (for cold/allergy)	15	
Prolamine (for weight control)	140	
Triaminicin (for colds)	30	
Vanquish (for pain)	33	
Vivarin (stimulant)	200	

Adapted from Pennington, J.A.T., and Church, H.N.: *Bowes & Church's Food Value of Portions Commonly Used*, 14th ed. Philadelphia: J. B. Lippincott, 1985.

is, before it is absorbed into the mucosal cell of the small intestine, sucrose is hydrolyzed by sucrase to the two hexoses, glucose and fructose. The consumption of honey provides these same two sugars without the need for the action of sucrase. The metabolism of glucose occurs the same as it does with glucose from any other source. Thus, the special metabolic considerations of sucrose and honey actually involve the metabolism of fructose.

Fructose, like all other water-soluble materials absorbed into the intestinal mucosal cell, is transported to the liver via the hepatic portal vein. There it readily diffuses into the liver cell and is immediately phosphorylated by fructokinase. The fructose-1-phosphate formed is converted by a series of reactions to triose phosphate, which can be further metabolized via glycolysis (Figure 18-2) or converted to glucose by gluconeogenesis (Figure 18-3). The direction that it goes is controlled by the relative activities of the glycolytic and gluconeogenic enzymes, which in turn are controlled by the hormonal state, as described in previous sections. Fructose consumed in any reasonable amount does not get past the liver into general circulation.

There appears to be no biochemical reason that the consumption of reasonable amounts of sucrose or, for that matter, honey would cause a problem. It is true that sucrose does not contain other nutrients, but if consumed as a part of an otherwise balanced diet, obtaining necessary nutrients from the other foods should not be difficult. If you have a patient that is on a weight-reduction diet, sucrose is no more fattening than the same amount of calories in any other food so that some sucrose is not unreasonable. Even diabetics can safely consume small amounts of sucrose, particularly with a meal, since other constituents in the diet, especially fat, will slow down stomach emptying time and not cause a blood glucose spike that free sucrose or glucose might give. The problem is that some patients, diabetic or overweight, may not be very effective judges about how much sugar is a "small amount."

It has long been known that sucrose can increase dental caries, but even that argument is not absolute. It is true that sucrose is a good substrate for the anaerobic bacteria that inhabit the mouth. They utilize glucose and fructose from it via the same glycolytic pathway present in our tissues and produce lactic acid. The lactic acid will lower the pH sufficiently to cause solubilization of the calcium hydroxyapatite of teeth. Soluble sucrose, especially if the mouth is rinsed with water after sucrose consumption, is not cariogenic; but sucrose in a form that sticks to the teeth, or soluble sucrose that remains in the mouth for a significant length of time, will result in caries. Note, however, that any sticky food that provides a substrate for these organisms will result in dental caries.

Fructose and Sorbitol

Fructose is sweeter than sugar when it is in cold solution at acid pH, and therefore less fructose needs to be used under these conditions to provide the same level of sweetness in food as sucrose. Fructose, as well as dietary sorbitol which is converted to fructose in the liver, is metabolized like the fructose from sucrose. Sorbitol is less sweet and less cariogenic than sucrose but contains 4 kcal/gm like fructose, glucose, or any other carbohydrate. Sorbitol is synthesized from glucose in the lens of the eye and can be made in excessive amounts in the poorly controlled diabetic, leading to an increase in osmotic pressure in the lens and to diabetic cataracts.

Fructose and sorbitol, the sugar alcohol of both fructose and glucose, are often used as sweeteners. Fructose in cold solutions and at acid pH is sweeter than sucrose and therefore is required in smaller quantities for the same level of sweetness. It is metabolized the same as the fructose produced from sucrose digestion. There has been a great amount of confusion about the metabolic effects of frutose, particularly in the diabetic. It is true that fructose can be readily metabolized by muscle of diabetics because, unlike glucose, insulin is not required for fructose entry into muscle cells. Once inside, it is phosphorylated by hexokinase—forming fructose-6-phosphate which is metabolized identically to the metabolism of the same compound produced from glucose-6-phosphate. However, orally administered fructose never gets to the muscle because it is utilized or, in the case of the diabetic, is converted to glucose in the liver. Thus, dietary fructose contributes to blood glucose in the diabetic just like any other carbohydrate.

Sorbitol is not nearly as sweet as sucrose but has the same caloric content as any other carbohydrate, 4 kcal/gm. Except for the fact that sorbitol is not metabolized as well by the oral bacteria and can therefore

be expected to cause less of a dental problem, it offers no particular advantages over fructose. In fact, sorbitol is absorbed by passive diffusion (large amounts are not completely absorbed and can cause osmotic diarrhea) into the mucosal cell and transported to the liver via the hepatic portal vein. In the liver, it is rapidly converted to fructose, which is then metabolized as described above.

Sorbitol is produced by the reduction of glucose in two tissues of the body, one of which is the lens of the eye. Since this reaction is concentration-dependent, elevated blood glucose that would occur in the poorly controlled diabetic will increase the synthesis of sorbitol in the lens, which results in an increase in the osmotic pressure and leads to diabetic cataracts. Dietary sorbitol does not contribute to this problem because orally administered sorbitol, like fructose, does not get past the liver. Sorbitol is also produced in the seminal vesicles as an intermediate in the conversion of glucose to fructose. Fructose that is produced is then secreted in semen as an energy source for sperm.

Non-nutritive Sweeteners

Non-nutritive sweeteners provide a source of sweet taste for food without providing carbohydrate or calories, thus are advantageous for diabetics and patients who are attempting to lose excessive fat stores. Evidence that they cause cancer with reasonable intake is questionable.

The desire for food that tastes sweet is just as strong in the diabetic or the person who has a problem controlling weight as in the rest of us. Non-nutritive sweeteners were designed to satisfy such a desire without adding to the glucose or caloric load. There are, or have been, three such compounds in widespread use: saccharin, cyclamate, and aspartame. They are called non-nutritive because saccharin and cyclamate are excreted as such and therefore do not contribute calories. Aspartame is a dipeptide consisting of aspartic acid and phenylalanine methyl ester and is metabolized, but since it is 200 times sweeter than sucrose, the quantity needed to provide sweetness is insignificant as a calorie source.

Saccharin is the oldest of the compounds used as non-nutritive sweeteners, but the possibility that it may be carcinogenic has led to consideration of discontinuing its use. The evidence of carcinogenicity came from a study in which large amounts, 7.5% of the diet (equivalent to 800 diet colas per day for an adult), were fed to rats for successive generations. Male (but not female) rats developed more bladder cancers than control rats, but only after saccharin was fed for three generations. The risk of cancer from saccharin must be weighed against the problems that could occur if it or some similar compound were not available to diabetic or obese patients.

Cyclamate was banned by the Food and Drug Administration (FDA) in 1969 because of reports that it was carcinogenic in rats. The experiments used as a basis of the ban are currently under review by the FDA, so cyclamate may again be available.

The newest of the non-nutritive sweeteners, aspartame, contains one ester bond and one peptide bond and therefore can be hydrolyzed in aqueous media, in which case it loses its sweet taste. Thus, colas that use aspartame have a finite shelf life. There has been some concern that such hydrolysis would lead to the production of methanol which could then be oxidized to formaldehyde. However, the quantity of methanol produced would be extremely small, less than one would find in orange juice or wine. Perhaps of more concern would be the consumption of aspartame by phenylketonuria patients, but again the quantity would be very low compared to the phenylalanine found in dietary protein.

Diet Aids—The Drug Route to Weight Control

Several non-prescription drugs available for weight control appear to be equally non-effective. Appetite suppressors, such as phenylpropanolamine, may reduce appetite for a short time but not long enough to be effective for significant weight loss. Others, including those to "fill up the stomach" or "block starch digestion," are even less effective.

Altering fat stores from the level pre-programmed genetically is a difficult task. The cure rate for obesity, defined as reducing fat stores and keeping them reduced for five years, is less than 3%. The difficulty probably accounts for the numerous products, books, and magazine articles available to consumers that promise to solve their weight problems.

The type of non-prescription diet pill most widely advertised contains phenylpropanolamine (an analog of epinephrine as well as amphetamine), often with caffeine. The theory is that phenylpropanolamine will work on the hypothalamus and reduce appetite; in fact, there is evidence that it does reduce food intake in animals—but only for the first few days of treatment. Unfortunately, a widely publicized committee report from the FDA stated that phenylpropanolamine appears to be effective in reducing food intake, but the fact was not publicized that the effect is temporary at best nor did the report cite the evidence used to arrive at that conclusion.

Other non-prescription drugs used to reduce food intake include local anesthetics, such benzocaine, which presumably reduce the sense of taste and therefore appetite. The control of food intake is obviously more complicated than taste. Another approach to reduce food intake is to "fill up the stomach" with non-digestible material such as cellulose, methyl cellulose, or, the latest entry, glucomannan. All of these materials will expand when they take up water so that a relatively small pill is supposed to take up a significant amount of stomach space, which it obviously cannot do. Further, material in the stomach may affect very short-term but not long-term appetite.

Still another approach has been "starch blockers." This approach is to use a protein that inhibits the activity of alpha amylase and thus reduces starch digestion. It has not been explained how this protein escapes the same digestion in the stomach as any other protein nor how much the amylase activity would have to be reduced to have a significant effect. If starch digestion were in fact inhibited significantly, the result would be the provision of large amounts of highly digestible material for the bacteria in the large intestine. The effect would be the same as it is in lactose intolerance, flatulence, diarrhea, and bloating. Further, if the starch were not digested, the appetite would not be satisfied and the patient would be just as hungry as if he had not eaten. Although "starch blockers" were advertised as a food supplement and not a drug, federal courts have ruled otherwise. Therefore, the legal manufacture and sale of "starch blockers" must have the approval of the FDA.

Evaluation

By calling upon one's knowledge of metabolism, many questions concerning nutrition and health promotion can be answered in a logical fashion. This evaluation asks you to apply metabolic principles to some relatively common questions asked and beliefs held by patients. How would you respond to the following statements or questions? The answers for these questions may be found by reviewing the module and should be discussed with fellow residents, faculty, and available nutrition specialists.

1. When I diet, I seem to lose the first 20 lb fast, then I just can't seem to lose that extra 20 which would bring me down to weight. Why is this?
2. I want to try one of these high-protein diets, but I read that they can kill you. Is that so? Why?
3. Oh—I don't eat sugar, I only eat honey.
4. You say I'm a diabetic. What does that really mean? Why must I watch my diet?
5. I want to increase my fiber intake. Is that a good idea? What type of fiber should I use? Why?
6. I read about carbohydrate cravers the other day. I think I probably am a carbohydrate craver and that is why I'm fat. What can I do?
7. What is really happening when I put on weight?

Bibliography

Books

Harper, H.A., Rodwell, V.W., and Mayes, P.A.: *Review of Physiological Chemistry* (17th Edition). Los Altos, California: Lange Medical Publications, 1979.

Horecker, B.L., and Stadtman, E.R. (Eds.): *Current Topics in Cellular Regulation.* Volume 18. New York: Academic Press, 1979.

Klachko, D.M., Anderson, R.A., and Heimberg, M.: "Hormones and Energy Metabolism." *Advances in Experimental Medicine and Biology,* Volume III, 1979.

Reaven, G.M., and Steiner, G. (Eds.): "Conference on Diabetes and Atherosclerosis." *Diabetes,* Volume 30, Supplement 2, 1981.

Peterson, C.M. (Ed.): "Conference of Nonenzymatic Glycosylation and Browning Reactions: Their Relevance to Diabetes Mellitus." *Diabetes,* Volume 31, Supplement 3, 1982.

Cohen, P. (ed.): *Recently Discovered Systems of Enzyme Regulation by Reversible Phosphorylation. Molecular Aspects of Cellular Regulation,* Volume 1. New York: Elsevier, 1980.

Lefebvre, P.J., and Unger, R.H.: *Glucagon.* New York: Pergamon Press, 1972.

Brownlee, M. (Ed.): *Diabetes Mellitus.* Volumes 1 through 5. New York: Garland STPM Press, 1981.

Review Articles.

Nicholls, D.G.: "The Thermogenic Mechanism of Brown Adipose Tissue—Review." *Bioscience Reports,* 3:431, 1983.

Hers, H.G., and Van Schaftingen, E.: "Fructose-2,6-BisPhosphate—Two Years After Its Discovery." *Biochemical Journal,* 206:1, 1982.

Volpe, J.J., and Vagelos, P.R.: "Mechanisms and Regulation of Biosynthesis of Saturated Fatty Acids." *Physiological Reviews,* 56:339, 1976.

Wakil, S.J., Stoops, J.K., and Joshi, V.C.: "Fatty Acid Synthesis and Its Regulation." *Annual Reviews of Biochemistry,* 52:537, 1983.

Appendix A

Mechanism Regulating Glucose Uptake and Production by the Liver

The process by which diet rapidly affects metabolism was briefly reviewed in the early part of this module. Additional details are given here for those who would like a more in-depth treatment.

Metabolic processes in the liver, perhaps more than any other tissue, are profoundly affected by nutritional status. In the fed state, the liver is responsible for removing excess glucose from blood. The glucose removed is used for ATP production in the liver, restoration of glycogen stores, and the synthesis of triglyceride. The concentration of glucose is much lower in the blood coming from the liver in the fed state than in the blood supply to the liver because glucose is converted in the liver to glucose-6-phosphate at a higher rate when the liver glucose concentration is elevated. Once glucose is phosphorylated, it cannot leave the liver cell as glucose unless the phosphate is removed. The net rate of glucose uptake by the liver depends upon the relative rate of formation of glucose-6-phosphate versus the rate of the hydrolysis of glucose-6-phosphate.

There are two enzymes in the liver which can catalyze the formation of glucose-6-phosphate, hexokinase, and glucokinase:

$$\text{Glucose} + \text{ATP} \longrightarrow \text{Glucose-6-P} + \text{ADP}$$

Although hexokinase occurs in all of our tissues, glucokinase occurs only in the liver. One difference between the two enzymes is the "tightness" by which they bind glucose. The binding constant of hexokinase for glucose (remember the Michaelis constant, Km) is extremely low, corresponding to a blood glucose level of about 0.2 mg/dl. Thus, hexokinase in the liver is always saturated with glucose, and changing the blood glucose level does not alter the rate of phosphorylation catalyzed by hexokinase. In contrast, the binding constant of glucokinase for glucose is much higher and is not saturated by glucose levels of well above 200 mg/dl. What this means in practical terms is that as the glucose concentration in the liver increases because of increased absorption, more of it gets phosphorylated by glucokinase. In addition, there is recent evidence that insulin, which increases in the fed state, rapidly turns on the synthesis of glucokinase. Thus, the fed state results in increased quantity of enzyme, as well as increasing its "busyness." As the blood glucose goes down in the post-absorptive state, presumably the synthesis of glucokinase would decrease and its destruction increase, resulting in a lower quantity of enzyme. At the same time, the decrease in the glucose concentration automatically decreases its rate of phosphorylation.

The hydrolysis of the phosphate from glucose-6-phophate is catalyzed by an enzyme (glucose-6-phosphatase) occurring exclusively in the liver. Ordinarily, the rate of phosphate removal from glucose-6-phosphate by glucose-6-phosphatase is low during the fed state because it obviously would not be advantageous to the cell to use ATP to form glucose-6-phosphate and then remove the phosphate. The net effect of such a sequence would be to generate heat from the hydrolysis of ATP by a futile cycle. It turns out that the rate of removal of the phosphate from glucose-6-phosphate by glucose-6-phosphatase is dependent upon the glucose-6-phosphate concentration in the same way and for the same reasons that the glucose concentration controls the rate of glucose-6-phosphate formation by glucokinase. That is, as the concentration of glucose-6-phosphate increases, the more it is hydrolyzed. In the fed state, the concentration of glucose-6-phosphate is maintained low because its utilization for glycolysis and glycogen synthesis is increased as a result of the action of insulin. Therefore, the rate of hydrolysis is low. In the post-absorptive state, glucose-6-phosphate is produced by glycogenolysis and gluconeogenesis. This increases the concentration of glucose-6-phosphate which allows a more rapid conversion to free glucose, catalyzed by glucose-6-phosphatase.

Appendix B

Molecular Mechanism of Glucagon and Insulin Action on Enzyme Regulation

Covalent modification (i.e., phosphorylation-dephosphorylation) mechanism is a recurrent theme in the regulation of nutrient storage and utilization. In addition to enzymes involved in glycogen synthesis and degradation, regulatory enzymes of other metabolic pathways, including glycolysis, pyruvate oxidation, triglyceride synthesis and mobilization, and protein synthesis and degradation, are subject to the same type of regulation.

The mechanism by which glucagon stimulates phosphorylation of enzymes is shown in Figure 18-4. Glucagon interacts with a receptor on the surface of the cell which results in the activation of an enzyme located within the cell membrane, adenylate cyclase. This enzyme catalyzes the formation from ATP of cyclic-AMP which has been called the "second messenger" of hormone action. Cyclic-AMP then interacts with a precursor to produce an active enzyme, cyclic-AMP-dependent protein kinase. The protein kinase then catalyzes the phosphorylation of various proteins in the cytoplasm of the cell. It is significant that the protein kinase is not specific for particular proteins but rather is specific for a serine residue one or two amino acid removed from an arginine residue. Obviously there may be many proteins in the cell with this amino acid sequence which therefore may be phosphorylated, whether they are regulatory or not. Further, regulatory proteins may be phosphorylated at more than one site, but only phosphorylation of a serine residue which can interact with the active site of the enzyme will affect activity. Since the protein kinase will catalyze the phosphorylation of a large number of regulatory proteins, it can and does affect a number of metabolic pathways at the same time. A partial list of regulatory enzymes regulated by phosphorylation-dephosphorylation is shown in Tables 18-1 and 18-2.

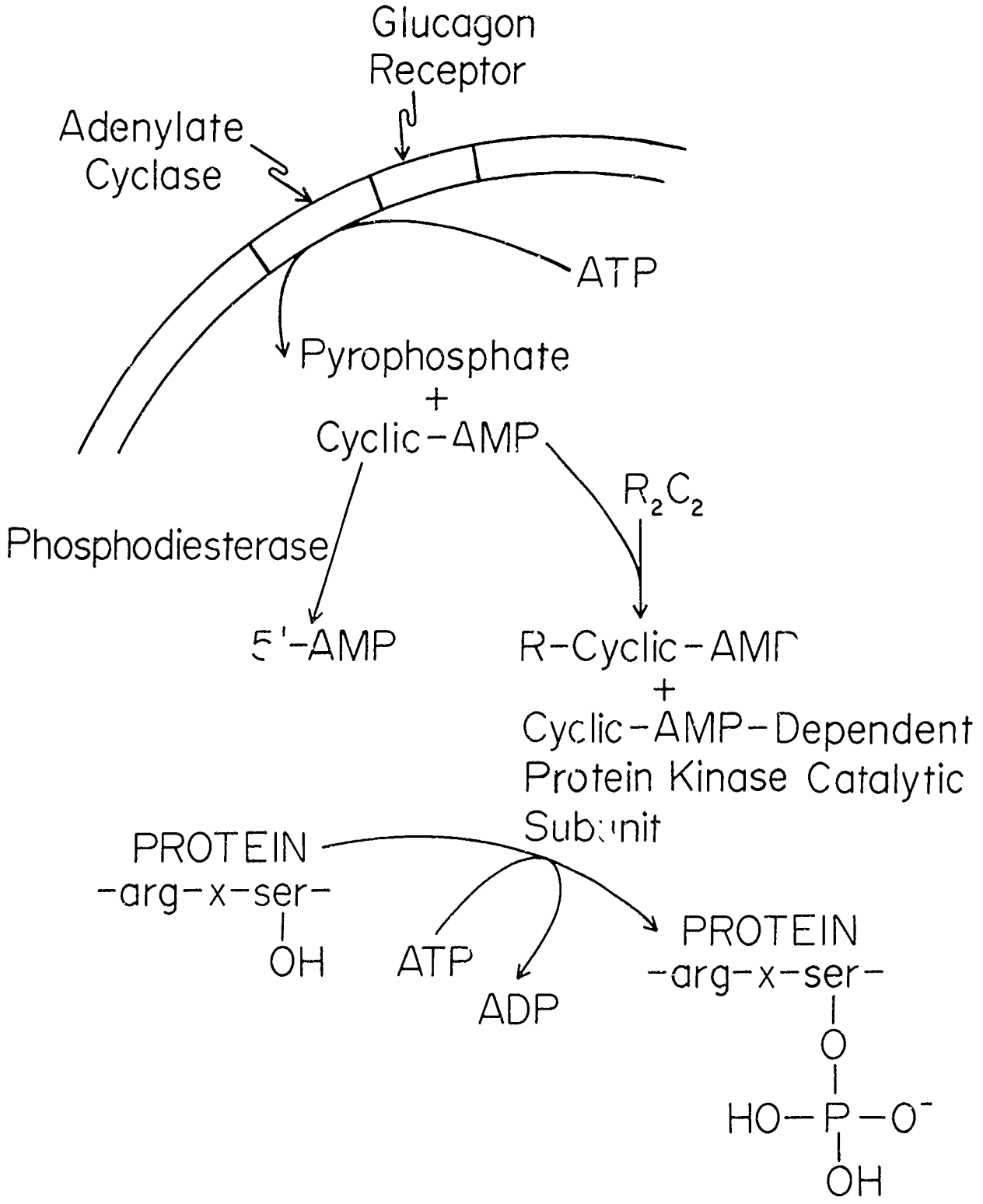
In the post-absorptive state when glycogen is being degraded to provide blood glucose, it is clearly advantageous to decrease the rate of glucose-6-phosphate utilization via glycolysis in the liver. At the same time that cyclic-AMP-dependent protein kinase results in the phosphorylation of phosphorylase (activating it) and glycogen synthetase (deactivating it), this same protein kinase results in the inactivation of both phosphofructokinase and pyruvate kinase, the two regulatory enzymes of glycolysis. In addition, the regulatory enzyme of fatty acid biosynthesis, acetyl CoA carboxylase, is phosphorylated and inactivated by the same protein kinase. It is no wonder that all of these pathways are coordinated because it is the same enzyme, cyclic-AMP-dependent protein kinase, activated by glucagon, which catalyzes the phosphorylation of the regulatory enzymes in all of them. In the fed state, insulin results in the dephosphorylation of all of the same regulatory enzymes, probably by activating a protein phosphatase.

The mechanism involved in the regulation of pyruvate oxidation is basically the same but differs in one significant detail. The rate of pyruvate oxidation is controlled by the activity of pyruvate dehydrogenase. This enzyme, like those of fatty acid beta-oxidation and the citric acid cycle, is located inside the mitochondrion. Cyclic-AMP-dependent protein kinase only catalyzes the phosphorylation of enzymes in the cell cytoplasm and therefore has no effect on pyruvate dehydrogenase. Pyruvate dehydrogenase is regulated by phosphorylation-dephosphorylation, but the addition of phosphate is catalyzed by a specific enzyme, pyruvate dehydrogenase kinase. The removal of the phosphate is catalyzed by a specific pyruvate dehydrogenase phosphatase. Phosphorylation, which inactivates the enzyme, occurs when insulin is low, and dephosphorylation, which activates the enzyme, occurs when insulin is high. Thus, even though the mechanism is a variation of the cytoplasmic scheme, the net effect is the same, a reduction in the use of glucose-derived substrate during periods when glucose is in short supply.

At the same time that cyclic-AMP-dependent protein kinase causes a decrease in the activity of the regulatory enzymes in glycolysis, there is an increase in the activity of the regulatory enzymes required for gluconeogenesis (Figure 18-3). There is evidence that two of the regulatory enzymes, glucose-6-phosphatase and fructose diphosphatase, may be regulated directly by the same type of covalent modification, but the control of the other two enzymes appears to be more indirect. In any event, an elevated glucagon:insulin ratio results in increased activity of the gluconeogenic pathway.

Appendix B (cont)

Mechanism by Which Hormones Control Cellular Cyclic-AMP Concentration



The rise in cellular cyclic-AMP concentration during the post-absorptive state occurs in response to glucagon stimulation of adenylate cyclase. It is obviously important that both cyclic-AMP and the activity of cyclic-AMP-dependent protein kinase return to a lowered state as soon as the stimulus to their increase is no longer present, which is when insulin increases and glucagon decreases in response to carbohydrate intake. The protein kinase is rapidly degraded by proteolysis. The cyclic-AMP is hydrolyzed to AMP by cyclic-AMP phosphodiesterase (Figure 18-4). The hydrolysis of cyclic-AMP is the reaction inhibited by methyl xanthines, including caffeine.

As noted previously, activation of adenylate cyclase, which produces cyclic-AMP, can occur as a result of the action of several hormones in various tissues. Table 18-1 shows a partial list of the metabolic processes which are regulated by cyclic-AMP via activation of cyclic-AMP-dependent protein kinase. Table 18-5 lists several hormones whose physiological action or release from endocrine glands involves cyclic-AMP. Each of the effects, as far as is known, is attributable to activation of cyclic-AMP-dependent kinases.

Table 18-5	Hormones Whose Physiological Action and/or Release from Endocrine Glands Involves Cyclic-AMP
	Adrenocorticotropic hormone
	Catecholamines
	Glucagon
	Growth hormone
	Insulin
	Leutenizing hormone
	Parathyroid hormone
	Thyroid stimulating hormone
	Thyroid hormones (T_3 and T_4)
	Steroids
	Vasopressin

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Some Abbreviations Used in the Nutrition in Primary Care Series

ATP	adenosine triphosphate
c	cup
cc	cubic centimeter
CNS	central nervous system
FDA	Food and Drug Administration
gm	gram
IBW	ideal body weight
IU	International Units
kcal	kilocalorie
kg	kilogram
lb	pound
lg	large
MCV	mean corpuscular volume
MDR	minimum daily requirement
med	medium
μg	microgram
mEq	milliequivalent
mg	milligram
MJ	megajoule
ml	milliliter
oz	ounce
RDA	Recommended Dietary Allowances
RE	retinol equivalents
sl	slice
sm	small
Tbsp	Tablespoon
TPN	total parenteral nutrition
tsp	teaspoon
USDA	United States Department of Agriculture