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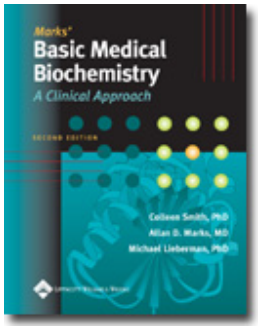

Marks' Basic Medical Biochemistry: A Clinical Approach, 2nd Edition

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Now in its second edition, *Basic Medical Biochemistry* continues to provide a unique clinically based approach to the subject that is perfect for medical students. The authors use patient vignettes throughout the book to emphasize the importance of biochemistry to medicine, delivering a text that is specifically oriented toward clinical application and understanding. **More >><< Less**

Patients have unique and humorous names that serve as mnemonics to help students remember the vignettes. Facts and pathways are also emphasized, showing how the underlying biochemistry is related to the body's overall physiologic functions. The result is a clear, comprehensive, and easy-to-read text that helps medical students understand the all-important role the patient plays in the study of biochemistry.

Other features and highlights include:

- A new back-of-book CD offers 9 animations on biochemical topics (oxidative phosphorylation, DNA replication, DNA mutation, protein synthesis, PCR, TCA cycle) as well as patient "files," disease links, and over 200 additional review questions not found in the book.
- A well-organized icon system quickly guides you to the information you need.
- Marginal notes provide brief clinical correlations, short questions and answers, and interesting asides.
- Each chapter ends with "Biochemical Comments" and "Clinical Comments"; both sections summarize the key biochemical and clinical concepts presented in the chapter.
- USMLE-style questions at the end of each chapter help students review for course or board exams.
- Two-color art program includes illustrations of chemical structures and biochemical pathways as well as conceptual diagrams.
- A new section on tissue metabolism has been added that summarizes common clinical problems such as liver disease and alcoholism.

To learn biochemistry in the context of clinical problems, you won't find a better resource than *Basic Medical Biochemistry*.

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Section Eight: Tissue Metabolism

Fuel Metabolism

In order to survive, humans must meet two basic metabolic requirements: we must be able to synthesize everything our cells need that is not supplied by our diet, and we must be able to protect our internal environment from toxins and changing conditions in our external environment. In order to meet these requirements, we metabolize our dietary components through four basic types of pathways: fuel oxidative pathways, fuel storage and mobilization pathways, biosynthetic pathways, and detoxification or waste disposal pathways. Cooperation between tissues and responses to changes in our external environment are communicated though transport pathways and intercellular signaling pathways (Fig. I.1).

The foods in our diet are the fuels that supply us with energy in the form of calories. This energy is used for carrying out diverse functions such as moving, thinking, and reproducing. Thus, a number of our metabolic pathways are *fuel oxidative pathways* that convert fuels into energy that can be used for biosynthetic and mechanical work. But what is the source of energy when we are not eating—between meals, and while we sleep? How does the hunger striker in the morning headlines survive so long? We have other metabolic pathways that are *fuel storage pathways*. The fuels that we store can be molibized during periods when we are not eating or when we need increased energy for exercise.

Our diet also must contain the compounds we cannot synthesize, as well as all the basic building blocks for compounds we do synthesize in our *biosynthetic pathways*. For example we have dietary requirements for some amino acids, but we can synthesize other amino acids from our fuels and a dietary nitrogen precursor. The compounds required in our diet for biosynthetic pathways include certain amino acids, vitamins, and essential fatty acids.

Detoxification pathways and *waste disposal pathways* are metabolic pathways devoted to removing toxins that can be present in our diets or in the air we breathe, introduced into our bodies as drugs, or generated internally from the metabolism of dietary components. Dietary components that have no value to the body, and must be disposed of, are called xenobiotics.

In general, biosynthetic pathways (including fuel storage) are referred to as *anabolic pathways,* that is, pathways that synthesize larger molecules from smaller components. The synthesis of proteins from amino acids is an example of an anabolic pathway. *Catabolic* pathways are those pathways that break down larger molecules into smaller components. Fuel oxidative pathways are examples of catabolic pathways.

In the human, the need for different cells to carry out different functions has resulted in cell and tissue specialization in metabolism. For example, our adipose tissue is a specialized site for the storage of fat and contains the metabolic pathways that allow it to carry out this function. However, adipose tissue is lacking many of the pathways that synthesize required compounds from dietary precursors. To enable our cells to cooperate in meeting our metabolic needs during changing conditions of diet, sleep, activity, and health, we need *transport pathways* into the blood and between tissues and *intercellular signaling pathways*. One means of communication is for *hormones* to carry signals to tissues about our dietary state. For example, a message that we have just had a meal, carried by the hormone insulin, signals adipose tissue to store fat.

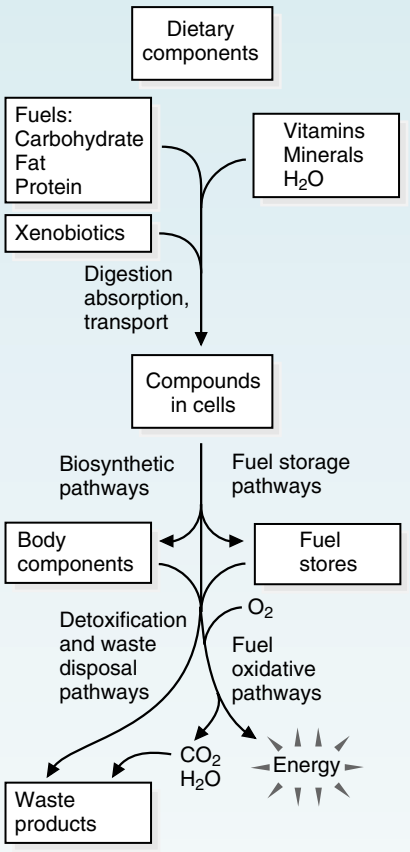

Fig. I.1. General metabolic routes for dietary components in the body. The types of Pathways are named in blue.

In the following section, we will provide an overview of various types of dietary components and examples of the pathways involved in utilizing these components. We will describe the fuels in our diet, the compounds produced by their digestion, and the basic patterns of fuel metabolism in the tissues of our bodies. We will describe how these patterns change when we eat, when we fast for a short time, and when we starve for prolonged periods. Patients with medical problems that involve an inability to deal normally with fuels will be introduced. These patients will appear repeatedly throughout the book and will be joined by other patients as we delve deeper into biochemistry.

1 Metabolic Fuels and Dietary Components

Fuel Metabolism. *We obtain our fuel primarily from* ***carbohydrates, fats****, and* ***proteins*** *in our diet. As we eat, our foodstuffs are* ***digested*** *and* ***absorbed****. The products of digestion circulate in the blood, enter various tissues, and are eventually taken up by cells and* ***oxidized*** *to produce* ***energy****. To completely convert our fuels to carbon dioxide (CO_2) and water (H_2O), molecular* ***oxygen*** *(O_2) is required. We breathe to obtain this oxygen and to eliminate the* ***carbon dioxide*** *(CO_2) that is produced by the oxidation of our foodstuffs.*

Fuel Stores. *Any dietary fuel that exceeds the body's immediate energy needs is stored, mainly as* ***triacylglycerol*** *(fat) in adipose tissue, as* ***glycogen*** *(a carbohydrate) in muscle, liver, and other cells, and, to some extent, as* ***protein*** *in muscle. When we are fasting, between meals and overnight while we sleep, fuel is drawn from these stores and is oxidized to provide energy (Fig. 1.1).*

Fuel Requirements. *We require enough energy each day to drive the* ***basic functions*** *of our bodies and to support our* ***physical activity****. If we do not consume enough food each day to supply that much energy, the body's fuel stores supply the remainder, and we lose weight. Conversely, if we consume more food than required for the energy we expend, our body's fuel stores enlarge, and we gain weight.*

Other Dietary Requirements. *In addition to providing energy, the diet provides* ***precursors*** *for the* ***biosynthesis*** *of compounds necessary for cellular and tissue structure, function, and survival. Among these precursors are the* ***essential fatty acids*** *and essential* ***amino acids*** *(those that the body needs but cannot synthesize). The diet must also supply* ***vitamins****,* ***minerals****, and* ***water****.*

Waste Disposal. *Dietary components that we can utilize are referred to as nutrients. However, both the diet and the air we breathe contain* ***xenobiotic compounds****, compounds that have no use or value in the human body and may be toxic. These compounds are excreted in the urine and feces together with metabolic waste products.*

Essential Nutrients
- Fuels
  - Carbohydrates
  - Fats
  - Proteins
- Required Components
  - Essential amino acids
  - Essential fatty acids
  - Vitamins
  - Minerals
  - Water

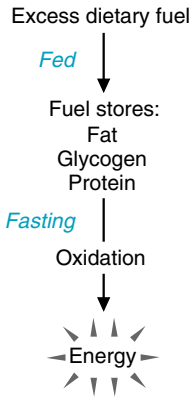

Fig. 1.1. Fate of excess dietary fuel in fed and fasting states.

THE WAITING ROOM

Percy Veere is a 59-year-old school teacher who was in good health until his wife died suddenly. Since that time, he has experienced an increasing degree of fatigue and has lost interest in many of the activities he previously enjoyed. Shortly after his wife's death, one of his married children moved far from home. Since then, Mr. Veere has had little appetite for food. When a

Percy Veere has a strong will. He is enduring a severe reactive depression after the loss of his wife. In addition, he must put up with the sometimes life-threatening antics of his hyperactive grandson, Dennis (the Menace) Veere. Yet through all of this, he will "persevere."

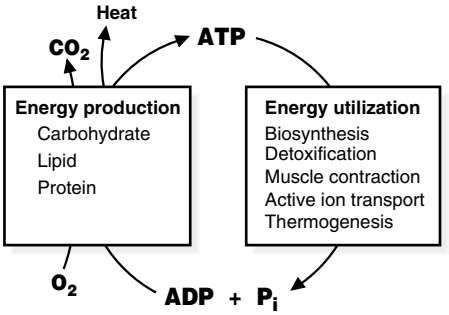

Fig. 1.2. The ATP–ADP cycle.

Oxidative pathways are catabolic; that is, they break molecules down. In contrast, anabolic pathways build molecules up from component pieces.

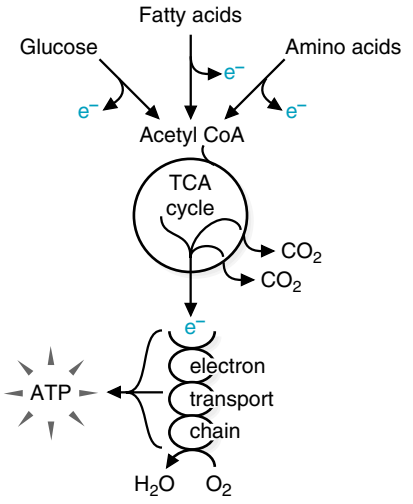

Fig. 1.3. Generation of ATP from fuel components during respiration. Glucose, fatty acids, and amino acids are oxidized to acetyl CoA, a substrate for the TCA cycle. In the TCA cycle, they are completely oxidized to CO_2. As fuels are oxidized, electrons (e^-) are transferred to O_2 by the electron transport chain, and the energy is used to generate ATP.

neighbor found Mr. Veere sleeping in his clothes, unkempt, and somewhat confused, she called an ambulance. Mr. Veere was admitted to the hospital psychiatry unit with a diagnosis of mental depression associated with dehydration and malnutrition.

Otto Shape is a 25-year-old medical student who was very athletic during high school and college, and is now "out-of-shape." Since he started medical school, he has been gaining weight (at 5 feet 10 inches tall, he currently weighs 187 lb). He has decided to consult a physician at the student health service before the problem gets worse.

Ivan Applebod is a 56-year-old accountant who has been morbidly obese for a number of years. He exhibits a pattern of central obesity, called an "apple shape," which is caused by excess adipose tissue deposited in the abdominal area. His major recreational activities are watching TV while drinking scotch and soda and doing occasional gardening. At a company picnic, he became very "winded" while playing baseball and decided it was time for a general physical examination. At the examination, he weighed 264 lb at 5 feet 10 inches tall. His blood pressure was slightly elevated, 155 mm Hg systolic (normal = 140 mm Hg or less) and 95 mm Hg diastolic (normal = 90 mm Hg or less).

Ann O'Rexia is a 23-year-old buyer for a woman's clothing store. Despite the fact that she is 5 feet 7 inches tall and weighs 99 lb, she is convinced she is overweight. Two months ago, she started a daily exercise program that consists of 1 hour of jogging every morning and 1 hour of walking every evening. She also decided to consult a physician about a weight reduction diet.

I. DIETARY FUELS

The major fuels we obtain from our diet are carbohydrates, proteins, and fats. When these fuels are oxidized to CO_2 and H_2O in our cells, energy is released by the transfer of electrons to O_2. The energy from this oxidation process generates heat and adenosine triphosphate (ATP) (Fig 1.2). Carbon dioxide travels in the blood to the lungs, where it is expired, and water is excreted in urine, sweat, and other secretions. Although the heat that is generated by fuel oxidation is used to maintain body temperature, the main purpose of fuel oxidation is to generate ATP. ATP provides the energy that drives most of the energy-consuming processes in the cell, including biosynthetic reactions, muscle contraction, and active transport across membranes. As these processes use energy, ATP is converted back to adenosine diphosphate (ADP) and inorganic phosphate (P_i). The generation and utilization of ATP is referred to as the ATP–ADP cycle.

The oxidation of fuels to generate ATP is called respiration (Fig. 1.3). Before oxidation, carbohydrates are converted principally to glucose, fat to fatty acids, and protein to amino acids. The pathways for oxidizing glucose, fatty acids, and amino acids have many features in common. They first oxidize the fuels to acetyl CoA, a precursor of the tricarboxylic acid (TCA) cycle. The TCA cycle is a series of reactions that completes the oxidation of fuels to CO_2 (see Chapter 19). Electrons lost from the fuels during oxidative reactions are transferred to O_2 by a series of proteins in the electron transport chain (see Chapter 20). The energy of electron transfer is used to convert ADP and P_i to ATP by a process known as oxidative phosphorylation.

In discussions of metabolism and nutrition, energy is often expressed in units of calories. "Calorie" in this context really means kilocalorie (kcal). Energy is also expressed in joules. One kilocalorie equals 4.18 kilojoules (kJ). Physicians tend to use units of calories, in part because that is what their patients use and understand.

The food "calories" used in everyday speech are really "Calories," which = kilocalories. "Calorie," meaning kilocalorie, was originally spelled with a capital C, but the capitalization was dropped as the term became popular. Thus, a 1-calorie soft drink actually has 1 Cal (1 kcal) of energy.

A. Carbohydrates

The major carbohydrates in the human diet are starch, sucrose, lactose, fructose, and glucose. The polysaccharide starch is the storage form of carbohydrates in plants. Sucrose (table sugar) and lactose (milk sugar) are disaccharides, and fructose and glucose are monosaccharides. Digestion converts the larger carbohydrates to monosaccharides, which can be absorbed into the bloodstream. Glucose, a monosaccharide, is the predominant sugar in human blood (Fig. 1.4).

Oxidation of carbohydrates to CO_2 and H_2O in the body produces approximately 4 kcal/g (Table 1.1). In other words, every gram of carbohydrate we eat yields approximately 4 kcal of energy. Note that carbohydrate molecules contain a significant amount of oxygen and are already partially oxidized before they enter our bodies (see Fig. 1.4).

Table 1.1. Caloric Content of Fuels

	kcal/g
Carbohydrate	4
Fat	9
Protein	4
Alcohol	7

B. Proteins

Proteins are composed of amino acids that are joined to form linear chains (Fig. 1.5). In addition to carbon, hydrogen, and oxygen, proteins contain approximately 16% nitrogen by weight. The digestive process breaks down proteins to their constituent amino acids, which enter the blood. The complete oxidation of proteins to CO_2, H_2O, and NH_4^+ in the body yields approximately 4 kcal/g.

C. Fats

Fats are lipids composed of triacylglycerols (also called triglycerides). A triacylglycerol molecule contains 3 fatty acids esterified to one glycerol moiety (Fig. 1.6).

Fats contain much less oxygen than is contained in carbohydrates or proteins. Therefore, fats are more reduced and yield more energy when oxidized. The complete oxidation of triacylglycerols to CO_2 and H_2O in the body releases approximately 9 kcal/g, more than twice the energy yield from an equivalent amount of carbohydrate or protein.

An analysis of **Ann O'Rexia's** diet showed she ate 100 g carbohydrate, 20 g protein, and 15 g fat each day. Approximately how many calories did she consume per day?

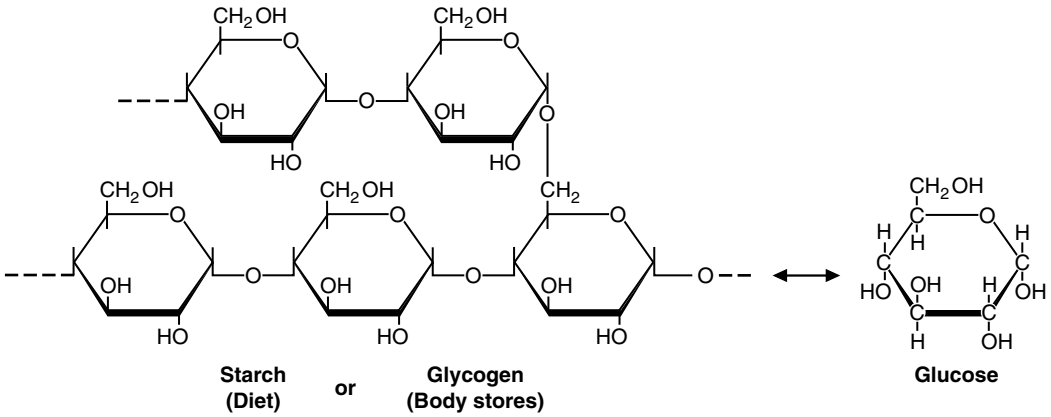

Fig. 1.4. Structure of starch and glycogen. Starch, our major dietary carbohydrate, and glycogen, the body's storage form of glucose, have similar structures. They are polysaccharides (many sugar units) composed of glucose, which is a monosaccharide (one sugar unit). Dietary disaccharides are composed of two sugar units.

A: **Miss O'Rexia** consumed
$100 \times 4 = 400$ kcal as carbohydrate
$20 \times 4 = 80$ kcal as protein
$15 \times 9 = 135$ kcal as fat

for a total of 615 kcal/day.

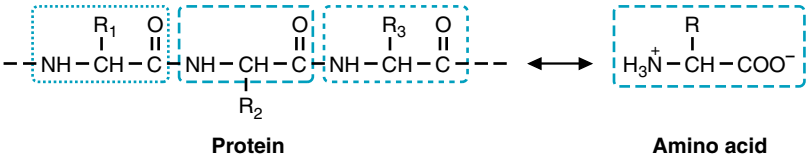

Fig. 1.5. General structure of proteins and amino acids. R = side chain. Different amino acids have different side chains. For example, R_1 might be $-CH_3$; R_2, ⬡; R_3, $-CH_2-COO^-$.

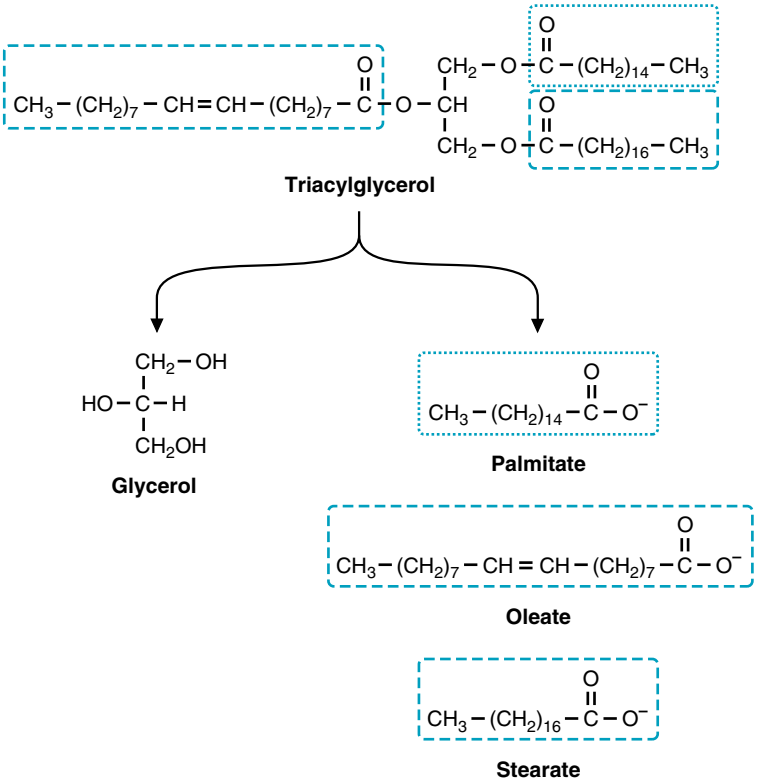

Fig. 1.6. Structure of a triacylglycerol. Palmitate and stearate are saturated fatty acids, i.e., they have no double bonds. Oleate is monounsaturated (one double bond). Polyunsaturated fatty acids have more than one double bond.

Q: **Ivan Applebod** ate 585 g carbohydrate, 150 g protein, and 95 g fat each day. In addition, he drank 45 g alcohol. How many calories did he consume per day?

D. Alcohol

Many people used to believe that alcohol (ethanol, in the context of the diet) has no caloric content. In fact, ethanol (CH_3CH_2OH) is oxidized to CO_2 and H_2O in the body and yields approximately 7 kcal/g—that is, more than carbohydrate but less than fat.

II. BODY FUEL STORES

It is not surprising that our body fuel stores consist of the same kinds of compounds found in our diet, because the plants and animals we eat also store fuels in the form of starch or glycogen, triacylglycerols, and proteins.

Although some of us may try, it is virtually impossible to eat constantly. Fortunately, we carry supplies of fuel within our bodies (Fig. 1.7). These fuel stores are light in weight, large in quantity, and readily converted into oxidizable substances. Most of us are familiar with fat, our major fuel store, which is located in adipose tissue. Although fat is distributed throughout our bodies, it tends to increase in quantity in our hips and thighs and in our abdomens as we advance into middle age. In addition to our fat stores, we also have important, although much smaller, stores of carbohydrate in the form of glycogen located primarily in our liver and muscles. Glycogen

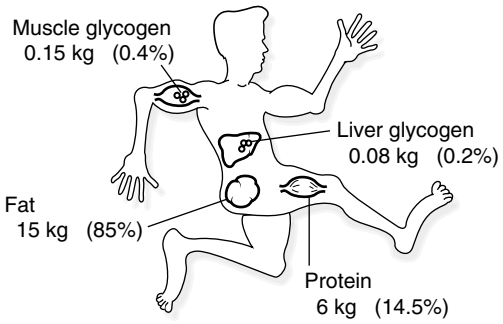

Fig. 1.7. Fuel composition of the average 70-kg man after an overnight fast (in kilograms and as percentage of total stored calories).

consists of glucose residues joined together to form a large, branched polysaccharide (see Fig. 1.4). Body protein, particularly the protein of our large muscle masses, also serves to some extent as a fuel store, and we draw on it for energy when we fast.

A. Fat

Our major fuel store is adipose triacylglycerol (triglyceride), a lipid more commonly known as fat. The average 70-kg man has approximately 15 kg stored triacylglycerol, which accounts for approximately 85% of his total stored calories (see Fig. 1.7).

Two characteristics make adipose triacylglycerol a very efficient fuel store: the fact that triacylglycerol contains more calories per gram than carbohydrate or protein (9 kcal/g versus 4 kcal/g) and the fact that adipose tissue does not contain much water. Adipose tissue contains only about 15% water, compared to tissues such as muscle that contain about 80%. Thus, the 70-kg man with 15 kg stored triacylglycerol has only about 18 kg adipose tissue.

B. Glycogen

Our stores of glycogen in liver, muscle, and other cells are relatively small in quantity but are nevertheless important. Liver glycogen is used to maintain blood glucose levels between meals. Thus, the size of this glycogen store fluctuates during the day; an average 70-kg man might have 200 g or more of liver glycogen after a meal but only 80 g after an overnight fast. Muscle glycogen supplies energy for muscle contraction during exercise. At rest, the 70-kg man has approximately 150 g of muscle glycogen. Almost all cells, including neurons, maintain a small emergency supply of glucose as glycogen.

C. Protein

Protein serves many important roles in the body; unlike fat and glycogen, it is not solely a fuel store. Muscle protein is essential for body movement. Other proteins serve as enzymes (catalysts of biochemical reactions) or as structural components of cells and tissues. Only a limited amount of body protein can be degraded, approximately 6 kg in the average 70-kg man, before our body functions are compromised.

III. DAILY ENERGY EXPENDITURE

If we want to stay in energy balance, neither gaining nor losing weight, we must, on average, consume an amount of food equal to our daily energy expenditure. The daily energy expenditure (DEE) includes the energy to support our basal metabolism (basal metabolic rate or resting metabolic rate) and our physical activity, plus the energy required to process the food we eat (diet-induced thermogenesis).

A: **Mr. Applebod** consumed
585 × 4 = 2,340 kcal as carbohydrate
150 × 4 = 600 kcal as protein
95 × 9 = 855 kcal as fat
45 × 7 = 315 kcal as alcohol
for a total of 4,110 kcal/day.

In biochemistry and nutrition, the standard reference is often the 70-kg (154-lb) man. This standard probably was chosen because in the first half of the 20th century, when many nutritional studies were performed, young healthy medical and graduate students (who were mostly men) volunteered to serve as subjects for these experiments.

What would happen to a 70-kg man if the 135,000 kcal stored as triacylglycerols in his 18 kg of adipose tissue were stored instead as skeletal muscle glycogen? It would take approximately 34 kg glycogen to store as many calories. Glycogen, because it is a polar molecule with –OH groups, binds approximately 4 times its weight in water, or 136 kg. Thus, his fuel stores would weigh 170 kg.

Daily energy expenditure = RMR + Physical Activity + DIT
where RMR is the resting metabolic rate and DIT is diet-induced thermogenesis. BMR (basal metabolic rate) is used interchangeably with RMR in this equation.

A. Resting Metabolic Rate

The resting metabolic rate (RMR) is a measure of the energy required to maintain life: the functioning of the lungs, kidneys and brain, the pumping of the heart, the maintenance of ionic gradients across membranes, the reactions of biochemical pathways, and so forth. Another term used to describe basal metabolism is the basal metabolic rate (BMR). The BMR was originally defined as the energy expenditure of a person mentally and bodily at rest in a thermoneutral environment 12 to18 hours after a meal. However, when a person is awakened and their heat production or oxygen consumption is measured, they are no longer sleeping or totally at mental rest, and their metabolic rate is called the resting metabolic rate (RMR). It is also sometimes called the resting energy expenditure (REE). The RMR and BMR differ very little in value.

The BMR, which is usually expressed in kcal/day, is affected by body size, age, sex, and other factors (Table 1.2). It is proportional to the amount of metabolically active tissue (including the major organs) and to the lean (or fat-free) body mass. Obviously, the amount of energy required for basal functions in a large person is greater than the amount required in a small person. However, the BMR is usually lower for women than for men of the same weight because women usually have more metabolically inactive adipose tissue. Body temperature also affects the BMR, which increases by 12% with each degree centigrade increase in body temperature (i.e., "feed a fever; starve a cold"). The ambient temperature affects the BMR, which increases slightly in colder climates as thermogenesis is activated. Excessive secretion of thyroid hormone (hyperthyroidism) causes the BMR to increase, whereas diminished secretion (hypothyroidism) causes it to decrease. The BMR increases during pregnancy and lactation. Growing children have a higher BMR per kilogram body weight than adults, because a greater proportion of their bodies is composed of brain, muscle, and other more metabolically active tissues. The BMR declines in aging individuals because their metabolically active tissue is shrinking and body fat is increasing. In addition, large variations exist in BMR from one adult to another, determined by genetic factors.

A rough estimate of the BMR may be obtained by assuming it is 24 kcal/day/kg body weight and multiplying by the body weight. An easy way to remember this is 1 kcal/kg/hr. This estimate works best for young individuals who are near their ideal weight. More accurate methods for calculating the BMR use empirically derived equations for different gender and age groups (Table 1.3). Even these calculations do not take into account variation among individuals.

Table 1.2. Factors Affecting BMR Expressed per kg Body Weight

Gender (males higher than females)
Body temperature (increased with fever)
Environmental temperature (increased in cold)
Thyroid status (increased in hyperthyroidism)
Pregnancy and lactation (increased)
Age (decreases with age)

What are **Ivan Applebod's** and **Ann O'Rexia's** RMR? (Compare the method for a rough estimate to values obtained with equations in Table 1.3.)

Registered dieticians use extensive tables for calculating energy requirements, based on height, weight, age, and activity level. A more accurate calculation is based on the fat-free mass (FFM), which is equal to the total body mass minus the mass of the person's adipose tissue. With FFM, the BMR is calculated using the equation BMR = 186 + FFM × 23.6 kcal/kg per day. This formula eliminates differences between sexes and between aged versus young individuals that are attributable to differences in relative adiposity. However, determining FFM is relatively cumbersome—it requires weighing the patient underwater and measuring the residual lung volume.

Indirect calorimetry, a technique that measures O_2 consumption and CO_2 production, can be used when more accurate determinations are required for hospitalized patients. A portable indirect calorimeter is used to measure oxygen consumption and the respiratory quotient (RQ), which is the ratio of O_2 consumed to CO_2 produced. The RQ is 1.00 for individuals oxidizing carbohydrates, 0.83 for protein, and 0.71 for fat. From these values, the daily energy expenditure (DEE) can be determined.

B. Physical Activity

In addition to the RMR, the energy required for physical activity contributes to the DEE. The difference in physical activity between a student and a lumberjack is enormous, and a student who is relatively sedentary during the week may be much

Table 1.3. Equation for Predicting BMR from Body Weight (W) in kg

Males		Females	
Age Range (years)	**BMR kcal/day**	**Age Range (years)**	**BMR kcal/day**
0–3	60.9W − 54	0–3	61.0W − 51
3–10	22.7W + 495	3–10	22.5W + 499
10–18	17.5W + 651	10–18	12.2W + 746
18–30	15.3W + 679	18–30	14.7W + 496
30–60	11.6W + 879	30–60	8.7W + 829
>60	13.5W + 487	>60	10.5W + 596

From Energy and protein requirements: report of a Joint FAO/WHO/UNU Expert Consultation. Technical report series no. 724. Geneva World Health Organization, 1987:71. See also Schofield et al. Hum Nutr Clin Nutr 1985;39 (suppl).

Table 1.4. Typical Activities with Corresponding Hourly Activity Factors

ACTIVITY CATEGORY	Hourly Activity Factor (for Time in Activity)
Resting: sleeping, reclining	1.0
Very light: seated and standing activities, driving, laboratory work, typing, sewing, ironing, cooking, playing cards, playing a musical instrument	1.5
Light: walking on a level surface at 2.5–3 mph, garage work, electrical trades, carpentry, restaurant trades, house cleaning, golf, sailing, table tennis	2.5
Moderate: walking 3.5–4 mph, weeding and hoeing, carrying loads, cycling, skiing, tennis, dancing	5.0
Heavy: walking uphill with a load, tree felling, heavy manual digging, mountain climbing, basketball, football, soccer	7.0

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The hourly activity factor is multiplied by the BMR (RMR) per hour times the number of hours engaged in the activity to give the caloric expenditure for that activity. If this is done for all of the hours in a day, the sum over 24 hours will approximately equal the daily energy expenditure.

Mr. **Applebod** weighs 264 lb or 120 kg (264 lb divided by 2.2 lb/kg). His estimated RMR = 24 kcal/kg/day × 120 = 2,880 kcal/day. His RMR calculated from Table 1.3 is only 2,271 kcal (11.6 W + 879 = (11.6 × 120) + 879). **Miss O'Rexia** weighs 99 lb or 45 kg (99/2.2 lb/kg). Her estimated RMR = (24 kcal/kg/day) × (45 kg) = 1,080 kcal/day. Her RMR from Table 1.3 is very close to this value (14.7 W + 496 = 1,157 kcal/day). Thus, the rough estimate does not work well for obese patients because a disproportionately larger proportion of their body weight is metabolically inactive adipose tissue.

more active during the weekend. Table 1.4 gives factors for calculating the approximate energy expenditures associated with typical activities.

A rough estimate of the energy required per day for physical activity can be made by using a value of 30% of the RMR (per day) for a very sedentary person (such as a medical student who does little but study) and a value of 60 to 70% of the RMR (per day) for a person who engages in about 2 hours of moderate exercise per day (see Table 1.4). A value of 100% or more of the RMR is used for a person who does several hours of heavy exercise per day.

Based on the activities listed in Table 1.4, the average U.S. citizen is rather sedentary. Sedentary habits correlate strongly with risk for cardiovascular disease, so it is not surprising that cardiovascular disease is the major cause of death in this country.

C. Diet-Induced Thermogenesis

Our DEE includes a component related to the intake of food known as diet-induced thermogenesis (DIT) or the thermic effect of food (TEF). DIT was formerly called the specific dynamic action (SDA). After the ingestion of food, our metabolic rate increases because energy is required to digest, absorb, distribute, and store nutrients.

The energy required to process the types and quantities of food in the typical American diet is probably equal to approximately 10% of the kilocalories ingested. This amount is roughly equivalent to the error involved in rounding off the caloric content of carbohydrate, fat, and protein to 4, 9, and 4, respectively. Therefore, DIT is often ignored and calculations are based simply on the RMR and the energy required for physical activity.

D. Calculations of Daily Energy Expenditure

The total daily energy expenditure is usually calculated as the sum of the RMR (in kcal/day) plus the energy required for the amount of time spent in each of the various types of physical activity (see Table 1.4). An approximate value for the daily energy expenditure can be determined from the RMR and the appropriate percentage of the RMR required for physical activity (given above). For example, a very sedentary medical student would have a DEE equal to the RMR plus 30% of the RMR (or 1.3 × RMR) and an active person's daily expenditure could be 2 times the RMR.

What are reasonable estimates for **Ivan Applebod's** and **Ann O'Rexia's** daily energy expenditure?

E. Healthy Body Weight

Ideally, we should strive to maintain a weight consistent with good health. Overweight people are frequently defined as more than 20% above their ideal weight. But what is the ideal weight? The body mass index (BMI), calculated as

BMI equals:

$$\text{Weight/height}^2\ (\text{kg/m}^2)$$

or

$$\frac{\text{Weight (lbs)} \times 704}{\text{height}^2\ (\text{in}^2)}$$

Where the height is measured without shoes and the weight is measured with minimal clothing.
BMI values of:

18.5 – 24.9 = desirable
<18.5 = underweight
25 – 29.9 = overweight
≥30 = obese

Q: Are **Ivan Applebod** and **Ann O'Rexia** in a healthy weight range?

A: **Mr. Applebod's** BMR is 2,271 kcal/day. He is sedentary, so he only requires approximately 30% more calories for his physical activity. Therefore, his daily expenditure is approximately 2,271 + (0.3 × 2,271) or 1.3 × 2,271 or 2,952 kcal/day. **Miss O'Rexia's** BMR is 1,157 kcal/day. She performs 2 hours of moderate exercise per day (jogging and walking), so she requires approximately 65% more calories for her physical activity. Therefore, her daily expenditure is approximately 1,157 + (0.65 × 1157) or 1.65 × 1,157 or 1,909 kcal/day.

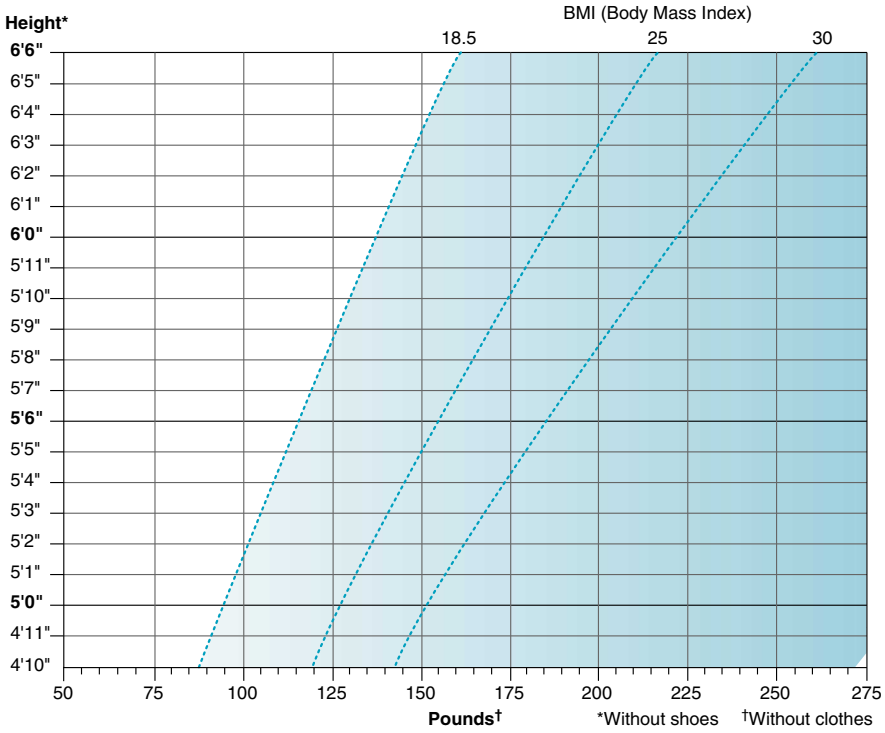
weight/height^2 (kg/m^2), is currently the preferred method for determining whether a person's weight is in the healthy range.

In general, adults with BMI values below 18.5 are considered underweight. Those with BMIs between 18.5 and 24.9 are considered to be in the healthy weight range, between 25 and 29.9 are in the overweight or preobese range, and above 30 are in the obese range.

F. Weight Gain and Loss

To maintain our body weight, we must stay in caloric balance. We are in caloric balance if the kilocalories in the food we eat equal our DEE. If we eat less food than we require for our DEE, our body fuel stores supply the additional calories,

To evaluate a patient's weight, physicians need standards of obesity applicable in a genetically heterogeneous population. Life insurance industry statistics have been used to develop tables giving the weight ranges, based on gender, height, and body frame size, that are associated with the greatest longevity, such as the Metropolitan Height and Weight Tables. However, these tables are considered inadequate for a number of reasons (e.g., they reflect data from upper-middle-class white groups). The BMI is the classification that is currently used clinically. It is based on two simple measurements, height without shoes and weight with minimal clothing. Patients can be shown their BMI in a nomogram and need not use calculations. The healthy weight range coincides with the mortality data derived from life insurance tables. The BMI also shows a good correlation with independent measures of body fat. The major weakness of the use of the BMI is that some very muscular individuals may be classified as obese when they are not. Other measurements to estimate body fat and other body compartments, such as weighing individuals underwater, are more difficult, expensive, and time consuming and have generally been confined to research purposes.



If patients are above or below ideal weight (such as **Ivan Applebod** or **Ann O'Rexia**), the physician, often in consultation with a registered dietician, prescribes a diet designed to bring the weight into the ideal range.

and we lose weight. Conversely, if we eat more food than we require for our energy needs, the excess fuel is stored (mainly in our adipose tissue), and we gain weight (Fig. 1.8).

When we draw on our adipose tissue to meet our energy needs, we lose approximately 1 lb whenever we expend approximately 3,500 calories more than we consume. In other words, if we eat 1,000 calories less than we expend per day, we will lose about 2 lb/week. Because the average individual's food intake is only about 2,000 to 3,000 calories/day, eating one-third to one-half the normal amount will cause a person to lose weight rather slowly. Fad diets that promise a loss of weight much more rapid than this have no scientific merit. In fact, the rapid initial weight loss the fad dieter typically experiences is attributable largely to loss of body water. This loss of water occurs in part because muscle tissue protein and liver glycogen are degraded rapidly to supply energy during the early phase of the diet. When muscle tissue (which is approximately 80% water) and glycogen (approximately 70% water) are broken down, this water is excreted from the body.

IV. DIETARY REQUIREMENTS

In addition to supplying us with fuel and with general-purpose building blocks for biosynthesis, our diet also provides us with specific nutrients that we need to remain healthy. We must have a regular supply of vitamins and minerals and of the essential fatty acids and essential amino acids. "Essential" means that they are essential in the diet; the body cannot synthesize these compounds from other molecules and therefore must obtain them from the diet. Nutrients that the body requires in the diet only under certain conditions are called "conditionally essential."

The Recommended Dietary Allowance (RDA) and the Adequate Intake (AI) provide quantitative estimates of nutrient requirements. The RDA for a nutrient is the average daily dietary intake level necessary to meet the requirement of nearly all (97–98%) healthy individuals in a particular gender and life stage group. Life stage group is a certain age range or physiologic status (i.e., pregnancy or lactation). The RDA is intended to serve as a goal for intake by individuals. The AI is a recommended intake value that is used when not enough data are available to establish an RDA.

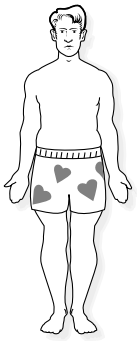
A. Carbohydrates

No specific carbohydrates have been identified as dietary requirements. Carbohydrates can be synthesized from amino acids, and we can convert one type

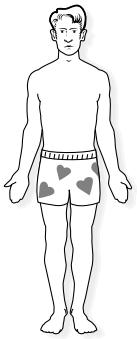
Malnutrition, the absence of an adequate intake of nutrients, occurs in the United States principally among children of families with incomes below the poverty level, the elderly, individuals whose diet is influenced by alcohol and drug usage, and those who make poor food choices. More than 13 million children in the United States live in families with incomes below the poverty level. Of these, approximately 10% have clinical malnutrition, most often anemia resulting from inadequate iron intake. A larger percentage have mild protein and energy malnutrition and exhibit growth retardation, sometimes as a result of parental neglect. Childhood malnutrition may also lead to learning failure and chronic illness later in life. A weight for age measurement is one of the best indicators of childhood malnourishment because it is easy to measure, and weight is one of the first parameters to change during malnutrition.

The term *kwashiorkor* refers to a disease originally seen in African children suffering from a protein deficiency. It is characterized by marked hypoalbuminemia, anemia, edema, pot belly, loss of hair, and other signs of tissue injury. The term *marasmus* is used for prolonged protein–calorie malnutrition, particularly in young children.

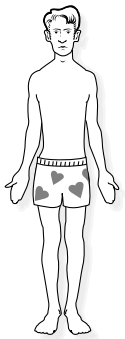
Are **Ivan Applebod** and **Ann O'Rexia** gaining or losing weight?



Positive caloric balance
Consumption > Expenditure



Caloric balance
Consumption = Expenditure



Negative caloric balance
Consumption < Expenditure

Fig. 1.8. Caloric balance.

Ivan Applebod's weight is classified as obese. His BMI is 264 lb × 704/70 in^2 = 37.9. **Ann O'Rexia** is underweight. Her BMI is 99 lb × 704/67 in^2 = 15.5.

Mr. Applebod expends about 2,952 kcal/day and consumes 4,110. By this calculation, he consumes 1,158 more kcal than he expends each day and is gaining weight. **Miss O'Rexia** expends 1,909 kcal/day while she consumes only 615. Therefore, she expends 1,294 more kcal/day than she consumes, so she is losing weight.

of carbohydrate to another. However, health problems are associated with the complete elimination of carbohydrate from the diet, partly because a low-carbohydrate diet must contain higher amounts of fat to provide us with the energy we need. High-fat diets are associated with obesity, atherosclerosis, and other health problems.

B. Essential Fatty Acids

Although most lipids required for cell structure, fuel storage, or hormone synthesis can be synthesized from carbohydrates or proteins, we need a minimal level of certain dietary lipids for optimal health. These lipids, known as essential fatty acids, are required in our diet because we cannot synthesize fatty acids with these particular arrangements of double bonds. The essential fatty acids α-linoleic and α-linolenic acid are supplied by dietary plant oils, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are supplied in fish oils. They are the precursors of the eicosanoids (a set of hormone-like molecules that are secreted by cells in small quantities and have numerous important effects on neighboring cells). The eicosanoids include the prostaglandins, thromboxanes, leukotrienes, and other related compounds.

C. Protein

The RDA for protein is approximately 0.8 g high-quality protein per kilogram of ideal body weight, or approximately 60 g/day for men and 50 g/day for women. "High-quality" protein contains all of the essential amino acids in adequate amounts. Proteins of animal origin (milk, egg, and meat proteins) are high quality. The proteins in plant foods are generally of lower quality, which means they are low in one or more of the essential amino acids. Vegetarians may obtain adequate amounts of the essential amino acids by eating mixtures of vegetables that complement each other in terms of their amino acid composition.

1. ESSENTIAL AMINO ACIDS

Students often use mnemonics to remember the essential amino acids. One common mnemonic is "Little TV tonight. Ha!" or **LIL** (**l**ysine-**i**soleucine-**l**eucine) **TV** (**t**hreonine-**v**aline) **T**o (**t**ryptophan) **PM** (**p**henyl- alanine-**m**ethionine). **(HA)** (**h**istidine-**a**rginine)!

Different amino acids are used in the body as precursors for the synthesis of proteins and other nitrogen-containing compounds. Of the 20 amino acids commonly required in the body for synthesis of protein and other compounds, nine amino acids are essential in the diet of an adult human because they cannot be synthesized in the body. These are lysine, isoleucine, leucine, threonine, valine, tryptophan, phenylalanine, methionine, and histidine.

Certain amino acids are conditionally essential, that is, required in the diet only under certain conditions. Children and pregnant women have a high rate of protein synthesis to support growth, and require some arginine in the diet, although it can be synthesized in the body. Histidine is essential in the diet of the adult in very small quantities because adults efficiently recycle histidine. The increased requirement of children and pregnant women for histidine is therefore much larger than their increased requirement of other essential amino acids. Tyrosine and cysteine are considered conditionally essential. Tyrosine is synthesized from phenylalanine, and it is required in the diet if phenylalanine intake is inadequate, or if an individual is congenitally deficient in an enzyme required to convert phenylalanine to tyrosine (the congenital disease phenylketonuria). Cysteine is synthesized by using sulfur from methionine, and it also may be required in the diet under certain conditions.

2. NITROGEN BALANCE

The proteins in the body undergo constant turnover; that is, they are constantly being degraded to amino acids and resynthesized. When a protein is degraded,

its amino acids are released into the pool of free amino acids in the body. The amino acids from dietary proteins also enter this pool. Free amino acids can have one of three fates: they are used to make proteins, they serve as precursors for synthesis of essential nitrogen-containing compounds (e.g., heme, DNA, RNA), or they are oxidized as fuel to yield energy. When amino acids are oxidized, their nitrogen atoms are excreted in the urine principally in the form of urea. The urine also contains smaller amounts of other nitrogenous excretory products (uric acid, creatinine, and NH_4^+) derived from the degradation of amino acids and compounds synthesized from amino acids (Table 1.5). Some nitrogen is also lost in sweat, feces, and cells that slough off.

Nitrogen balance is the difference between the amount of nitrogen taken into the body each day (mainly in the form of dietary protein) and the amount of nitrogen in compounds lost (Table 1.6). If more nitrogen is ingested than excreted, a person is said to be in positive nitrogen balance. Positive nitrogen balance occurs in growing individuals (e.g., children, adolescents, and pregnant women), who are synthesizing more protein than they are breaking down. Conversely, if less nitrogen is ingested than excreted, a person is said to be in negative nitrogen balance. A negative nitrogen balance develops in a person who is eating either too little protein or protein that is deficient in one or more of the essential amino acids. Amino acids are continuously being mobilized from body proteins. If the diet is lacking an essential amino acid or if the intake of protein is too low, new protein cannot be synthesized, and the unused amino acids will be degraded, with the nitrogen appearing in the urine. If a negative nitrogen balance persists for too long, bodily function will be impaired by the net loss of critical proteins. In contrast, healthy adults are in nitrogen balance (neither positive nor negative), and the amount of nitrogen consumed in the diet equals its loss in urine, sweat, feces, and other excretions.

D. Vitamins

Vitamins are a diverse group of organic molecules required in very small quantities in the diet for health, growth, and survival (Latin *vita*, life). The absence of a vitamin from the diet or an inadequate intake results in characteristic deficiency signs and, ultimately, death. Table 1.7 lists the signs or symptoms of deficiency for each vitamin, its RDA or AI for young adults, and common food sources. The amount of each vitamin required in the diet is small (in the microgram or milligram range), compared with essential amino acid requirements (in the gram range). The vitamins are often divided into two classes, water-soluble vitamins and fat-soluble vitamins. This classification has little relationship to their function but is related to the absorption and transport of fat-soluble vitamins with lipids.

Most vitamins are used for the synthesis of coenzymes, complex organic molecules that assist enzymes in catalyzing biochemical reactions, and the deficiency symptoms reflect an inability of cells to carry out certain reactions. However, some vitamins also act as hormones. We will consider the roles played by individual vitamins as we progress through the subsequent chapters of this text.

Although the RDA or AI for each vitamin varies with age and sex, the difference is usually not very large once adolescence is reached. For example, the RDA for

Table 1.6. Nitrogen Balance

Positive Nitrogen Balance	Growth (e.g., childhood, pregnancy)	Dietary N > Excreted N
Nitrogen Balance	Normal healthy adult	Dietary N = Excreted N
Negative Nitrogen Balance	Dietary deficiency of total protein or amino acids; catabolic stress	Dietary N < Excreted N

Table 1.5. Major Nitrogenous Excretion Products

Urea
Creatinine
Uric acid
NH_4^+

Multiple vitamin deficiencies accompanying malnutrition are far more common in the United States than the characteristic deficiency diseases associated with diets lacking just one vitamin, because we generally eat a variety of foods. The characteristic deficiency diseases arising from single vitamin deficiencies were often identified and described in humans through observations of populations consuming a restricted diet because that was all that was available. For example, thiamine deficiency was discovered by a physician in Java, who related the symptoms of beri-beri to diets composed principally of polished rice. Today, single vitamin deficiencies usually occur as a result of conditions that interfere with the uptake or utilization of a vitamin or as a result of poor food choices or a lack of variety in the diet. For example, peripheral neuropathy associated with vitamin E deficiency can occur in children with fat malabsorption, and alcohol consumption can result in beri-beri. Vegans, individuals who consume diets lacking all animal products, can develop deficiencies in vitamin B_{12}.

In the hospital, it was learned that **Mr. Percy Veere** had lost 32 lb in the 8 months since his last visit to his family physician. On admission, his hemoglobin (the iron-containing compound in the blood, which carries O_2 from the lungs to the tissues) was 10.7 g/dL (reference range, males = 12 – 15.5), his serum iron was 38 μg/dL (reference range, males = 42 – 135), and other hematologic indices were also abnormal. These values are indicative of an iron deficiency anemia. His serum folic acid level was 0.9 ng/mL (reference range = 3 – 20), indicating a low intake of this vitamin. His vitamin B_{12} level was 190 pg/mL (reference range = 180 – 914). A low blood vitamin B_{12} level can be caused by decreased intake, absorption, or transport, but it takes a long time to develop. His serum albumin was 3.2 g/dL (reference range = 3.5 – 5.0), which is an indicator of protein malnutrition or liver disease.

Table 1.7. VITAMINS [a]

Vitamin	Dietary Reference Intakes (DRI) Females (F) Males (M) (18–30 yrs old)	Some Common Food Sources	Consequences of Deficiency (Names of deficiency diseases are in bold)
Water-soluble vitamins			
Vitamin C	**RDA** F: 75 mg M: 90 mg **UL:** 2 g	Citrus fruits; potatoes; peppers, broccoli, spinach; strawberries	**Scurvy:** defective collagen formation leading to subcutaneous hemorrhage, aching bones, joints, and muscle in adults, rigid position and pain in infants.
Thiamin	**RDA** F: 1.1 mg M: 1.2 mg	Enriched cereals and breads; unrefined grains; pork; legumes, seeds, nuts	**Beri-beri:** (wet) Edema; anorexia, weight loss; apathy, decrease in short-term memory, confusion; irritability; muscle weakness; an enlarged heart
Riboflavin	**RDA** F: 1.1 mg M: 1.3 mg	Dairy products; fortified cereals; meats, poultry, fish; legumes	**Ariboflavinosis:** Sore throat, hyperemia, edema of oral mucusal membranes; cheilosis, angular stomatis; glossitis, magenta tongue; seborrheic dermatitis; normochromic normocylic anemia
Niacin[b]	**RDA** F: 14 mg NEQ M: 16 mg NEQ **UL:** 35 mg	Meat: chicken, beef, fish; enriched cereals or whole grains; most foods	**Pellagra:** Pigmented rash in areas exposed to sunlight; vomiting; constipation or diarrhea; bright red tongue; neurologic symptoms
Vitamin B_6 (pyridoxine)	**RDA** F: 1.3 mg M: 1.3 mg **UL:** 100 mg	Chicken, fish, pork; eggs; fortified cereals, unmilled rice, oats; starchy vegetables; noncitrus fruits; peanuts, walnuts	Seborrheic dermatitis; microcytic anemia; epileptiform convulsions; depression and confusion
Folate	**RDA** F: 400 μg M: 400 μg	Citrus fruits; dark green vegetables; fortified cereals and breads; legumes	Impaired cell division and growth; **megaloblastic anemia**; neural tube defects
Vitamin B_{12}	**RDA** F: 2.4 μg M: 2.4 μg	Animal products[c]	**Megaloblastic anemia** Neurologic symptoms
Biotin	**AI** F: 30 μg M: 30 μg	Liver Egg yolk	Conjunctivitis; central nervous system abnormalities; glossitis; alopecia; dry, scaly dermatitis
Pantothenic acid	**AI** F: 5 mg M: 5 mg	Wide distribution in foods, especially animal tissues; whole grain cereals; legumes	Irritability and restlessness; fatigue, apathy, malaise; gastiointestinal symptoms; neurological symptoms
Choline	**AI** F: 550 mg M: 425 mg **UL**: 3.5 g	Milk; liver; eggs; peanuts	Liver damage
Fat-soluble vitamins			
Vitamin A	**RDA** F: 700 μg M: 900 μg **UL**: 3000 μg	Carrots; Dark green and leafy vegetables; sweet potatoes and squash; broccoli	Night blindness; **xerophthalmia;** keratinization of epithelium in GI, respiratory and genitourinary tract, skin becomes dry and scaly
Vitamin K	**RDA** F: 90 μg M: 120 μg	Green leafy vegetables; cabbage family (brassica); Bacterial flora of intestine	Defective blood coagulation; hemorrhagic anemia of the newborn
Vitamin D	**AI**[d] F: 5 μg M: 5 μg **UL:** 50 μg	Fortified milk; Exposure of skin to sunlight	**Rickets** (in children); inadequate bone mineralization (osteomalacia)
Vitamin E	**RDA** F: 15 mg M: 15 mg **UL:** 1 g	Vegetable oils, margarine; wheat germ; nuts; green leafy vegetables	Muscular dystrophy, neurologic abnormalities.

Dietary Reference Intakes (DRI): Recommended Dietary Allowance (RDA); Adequate Intake (AI); Tolerable Upper Intake Level (UL)

[a]Information for this table is from Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride (1997), Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001). Washington, DC: Food and Nutrition Board, Institute of Medicine, National Academy Press.

[b]neq = niacin equivalents. Niacin can be synthesized in the human from tryptophan, and this term takes into account a conversion factor for dietary tryptophan.

[c]Vitamin B_{12} is found only in animal products.

[d]Dietary requirement assumes the absence of sunlight.

riboflavin is 0.9 mg/day for males between 9 and 13 years of age, 1.3 mg/day for males 19 to 30 years of age, still 1.3 mg/day for males older than 70 years, and 1.1 mg/day for females aged 19 to 30 years. The largest requirements occur during lactation (1.6 mg/day).

Vitamins, by definition, cannot be synthesized in the body, or are synthesized from a very specific dietary precursor in insufficient amounts. For example, we can synthesize the vitamin niacin from the essential amino acid tryptophan, but not in sufficient quantities to meet our needs. Niacin is therefore still classified as a vitamin.

Excessive intake of many vitamins, both fat-soluble and water-soluble, may cause deleterious effects. For example, high doses of vitamin A, a fat-soluble vitamin, can cause desquamation of the skin and birth defects. High doses of vitamin C cause diarrhea and gastrointestinal disturbances. One of the Reference Dietary Intakes is the Tolerable Upper Intake Level (UL), which is the highest level of daily nutrient intake that is likely to pose no risk of adverse effects to almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases. Table 1.7 includes the UL for vitamins known to pose a risk at high levels. Intake above the UL occurs most often with dietary or pharmacologic supplements of single vitamins, and not from foods.

E. Minerals

Many minerals are required in the diet. They are generally divided into the classifications of electrolytes (inorganic ions that are dissolved in the fluid compartments of the body), minerals (required in relatively large quantities), trace minerals (required in smaller quantities), and ultratrace minerals (Table 1.8).

Sodium (Na^+), potassium (K^+), and chloride (Cl^-) are the major electrolytes (ions) in the body. They establish ion gradients across membranes, maintain water balance, and neutralize positive and negative charges on proteins and other molecules.

Calcium and phosphorus serve as structural components of bones and teeth and are thus required in relatively large quantities. Calcium (Ca^{2+}) plays many other roles in the body; for example, it is involved in hormone action and blood clotting. Phosphorus is required for the formation of ATP and of phosphorylated intermediates in metabolism. Magnesium activates many enzymes and also forms a complex with ATP. Iron is a particularly important mineral because it functions as a component of hemoglobin (the oxygen-carrying protein in the blood) and is part of many enzymes. Other minerals, such as zinc or molybdenum, are required in very small quantities (trace or ultra-trace amounts).

Sulfur is ingested principally in the amino acids cysteine and methionine. It is found in connective tissue, particularly in cartilage and skin. It has important functions in metabolism, which we will describe when we consider the action of coenzyme A, a compound used to activate carboxylic acids. Sulfur is excreted in the urine as sulfate.

A dietary deficiency of calcium can lead to osteoporosis, a disease in which bones are insufficiently mineralized and consequently are fragile and easily fractured. Osteoporosis is a particularly common problem among elderly women. Deficiency of phosphorus results in bone loss along with weakness, anorexia, malaise, and pain. Iron deficiencies lead to anemia, a decrease in the concentration of hemoglobin in the blood.

Which foods would provide Percy Veere with good sources of folate and vitamin B_{12}?

Table 1.8. Minerals Required in the Diet

Electrolytes	Minerals	Trace Minerals	Ultratrace or Trace Minerals[a]
Sodium	Calcium	Iodine	Manganese
Potassium	Phosphorus	Selenium	Fluoride
Chloride	Magnesium	Copper	Chromium
	Iron	Zinc	Molybdenum
	Sulfur		Others?

[a]These minerals are classified as trace or as ultratrace.

A: Folate is found in fruits and vegetables: citrus fruits (e.g., oranges), green leafy vegetables (e.g., spinach and broccoli), fortified cereals, and legumes (e.g., peas) (see Table 1.7). Conversely, vitamin B_{12} is found only in foods of animal origin, including meats, eggs, and milk.

Minerals, like vitamins, have adverse effects if ingested in excessive amounts. Problems associated with dietary excesses or deficiencies of minerals are described in subsequent chapters in conjunction with their normal metabolic functions.

F. Water

Water constitutes one half to four fifths of the weight of the human body. The intake of water required per day depends on the balance between the amount produced by body metabolism and the amount lost through the skin, through expired air, and in the urine and feces.

V. DIETARY GUIDELINES

Dietary guidelines or goals are recommendations for food choices that can reduce the risk of developing chronic or degenerative diseases while maintaining an adequate intake of nutrients. Many studies have shown an association between diet and exercise and decreased risk of certain diseases, including hypertension, atherosclerosis, stroke, diabetes, certain types of cancer, and osteoarthritis. Thus, the American Heart Institute and the American Cancer Institute, as well as several other groups, have developed dietary and exercise recommendations to decrease the risk of these diseases. The "Dietary Guidelines for Americans (2000)", prepared under the joint authority of the US Department of Agriculture and the US Department of Health and Human Services, merges many of these recommendations. Recommended servings of different food groups are displayed as the food pyramid (Fig. 1.9). Issues of special concern for physicians who advise patients include the following:

A. General Recommendations

- Aim for a healthy weight and be physically active each day. For maintenance of a healthy weight, caloric intake should balance caloric expenditure. Accumulate at least 30 minutes of moderate physical activity (such as walking 2 miles) daily. A regular exercise program helps in achieving and maintaining ideal weight, cardiovascular fitness, and strength.
- Choose foods in the proportions recommended in the food pyramid, including a variety of grains and a variety of fruits and vegetables daily.
- Keep food safe to eat. For example, refrigerate leftovers promptly.

B. Vegetables, Fruits, and Grains

- Diets rich in vegetables, fruits, and grain products should be chosen. Five or more servings of vegetables and fruits should be eaten each day, particularly green and yellow vegetables and citrus fruits. Six or more daily servings of grains should be eaten (starches and other complex carbohydrates, in the form of breads, fortified cereals, rice, and pasta). In addition to energy, vegetables, fruits, and grains supply vitamins, minerals, protective substances (such as carotenoids), and fiber. Fiber, the indigestible part of plant food, has various beneficial effects, including relief of constipation.
- The consumption of refined sugar in foods and beverages should be reduced to below the American norm. Refined sugar has no nutritional value other than its caloric content, and it promotes tooth decay.

C. Fats

- Fat intake should be reduced. For those at risk of heart attacks or strokes, fat should account for no more than 30% of total dietary calories, and saturated fatty acids

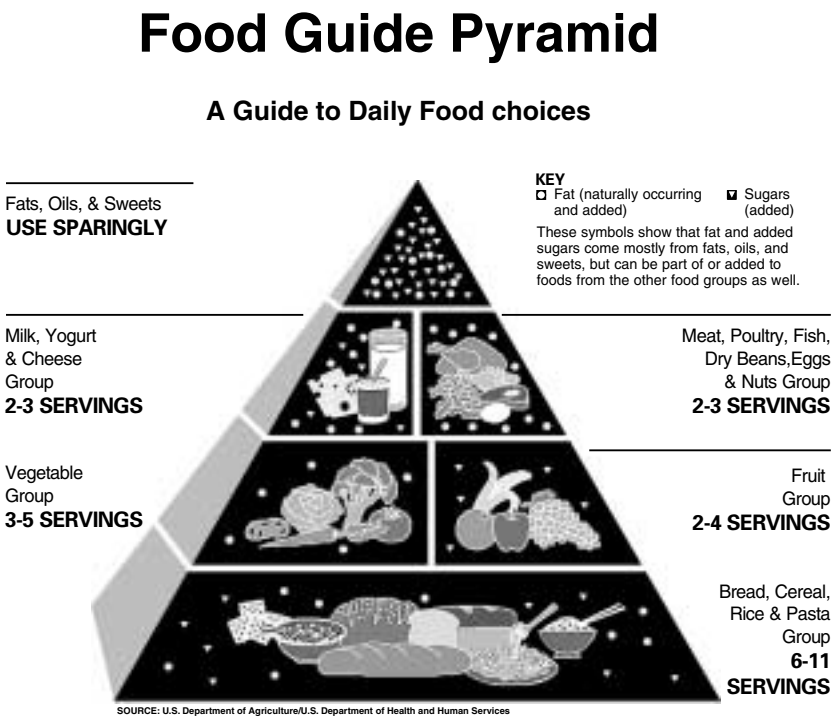


Fig. 1.9. The Food Guide Pyramid. The pyramid shows the number of servings that should be eaten each day from each food group. Within each group, a variety of foods should be eaten. Some examples of serving size: Grain products—1 slice of white bread or ½ cup of cooked rice; Vegetable group—½ cup cooked vegetables; Fruit group—1 apple or banana; Milk Group—1 cup of milk or 2 oz processed cheese; Meat and Beans Group—2–3 oz cooked lean meat or fish or 1 egg or 2 tbsp peanut butter. Nutrition and Your Health: Dietary Guidelines for Americans, 2000. Washington, DC: Dietary Guidelines Committee: The U.S. Department of Agriculture and the U.S. Department of Health and Human Services.

should account for 10% or less. Foods high in saturated fat include cheese, whole milk, butter, regular ice cream, and many cuts of beef. Trans fatty acids, such as the partially hydrogenated vegetable oils used in margarine, should also be avoided.

- Cholesterol intake should be less than 300 mg/day in subjects without atherosclerotic disease and less than 200 mg/day in those with established atherosclerosis.

Cholesterol is obtained from the diet and synthesized in most cells of the body. It is a component of cell membranes and the precursor of steroid hormones and of the bile salts used for fat absorption. High concentrations of cholesterol in the blood, particularly the cholesterol in lipoprotein particles called low density lipoproteins (LDL), contribute to the formation of atherosclerotic plaques. These plaques (fatty deposits on arterial walls) are associated with heart attacks and strokes. A high content of saturated fat in the diet tends to increase circulatory levels of LDL cholesterol and contributes to the development of atherosclerosis.

D. Proteins

- Protein intake for adults should be approximately 0.8 g/kg ideal body weight per day. The protein should be of high quality and should be obtained from sources low in saturated fat (e.g., fish, lean poultry, and dry beans). Vegetarians should eat a mixture of vegetable proteins that ensures the intake of adequate amounts of the essential amino acids.

E. Alcohol

- Alcohol consumption should not exceed moderate drinking. Moderation is defined as no more than one drink per day for women and no more than two drinks per day for men. A drink is defined as 1 regular beer, 5 ounces of wine (a little over ½ cup), or 1.5 ounces of an 80-proof liquor, such as whiskey. Pregnant women should drink no alcohol.

The ingestion of alcohol by pregnant women can result in fetal alcohol syndrome (FAS), which is marked by prenatal and postnatal growth deficiency, developmental delay, and craniofacial, limb, and cardiovascular defects.

F. Vitamins and Minerals

- Sodium intake should be decreased in most individuals. Sodium is usually consumed as salt, NaCl. Individuals prone to salt-sensitive hypertension should eat less than 3 g sodium per day (approximately 6 g NaCl).
- Many of the required vitamins and minerals can be obtained from eating a variety of fruits, vegetables, and grains (particularly whole grains). However, calcium and iron are required in relatively high amounts. Low-fat or nonfat dairy products and dark green leafy vegetables provide good sources of calcium. Lean meats, shellfish, poultry, dark meat, cooked dry beans, and some leafy green vegetables provide good sources of iron. Vitamin B_{12} is found only in animal sources.
- Dietary supplementation in excess of the recommended amounts (for example, megavitamin regimens) should be avoided.
- Fluoride should be present in the diet, at least during the years of tooth formation, as a protection against dental caries.

The high intake of sodium and chloride (in table salt) of the average American diet appears to be related to the development of hypertension (high blood pressure) in individuals who are genetically predisposed to this disorder.

VI. XENOBIOTICS

In addition to nutrients, our diet also contains a large number of chemicals called xenobiotics, which have no nutritional value, are of no use in the body, and can be harmful if consumed in excessive amounts. These compounds occur naturally in foods, can enter the food chain as contaminants, or can be deliberately introduced as food additives.

Dietary guidelines of the American Cancer Society and the American Institute for Cancer Research make recommendations relevant to the ingestion of xenobiotic compounds, particularly carcinogens. The dietary advice that we eat a variety of food helps to protect us against the ingestion of a toxic level of any one xenobiotic compound. It is also suggested that we reduce consumption of salt-cured, smoked, and charred foods, which contain chemicals that can contribute to the development of cancer. Other guidelines encourage the ingestion of fruits and vegetables that contain protective chemicals called antioxidants.

CLINICAL COMMENTS

Physicians have an average lifespan that is longer than the general population, and generally practice healthier behaviors, especially with regard to fat consumption, exercise, alcohol consumption, and smoking. Physicians who practice healthy behaviors are more likely to counsel patients with respect to these behaviors and are better able to motivate their patients.

Otto Shape. Otto Shape sought help in reducing his weight of 187 lb (BMI of 27) to his previous level of 154 lb (BMI of 22, in the middle of the healthy range). Otto Shape was 5 feet 10 inches tall, and he calculated that his maximum healthy weight was 173 lbs. He planned on becoming a family physician, and he knew that he would be better able to counsel patients in healthy behaviors involving diet and exercise if he practiced them himself. With this information and assurances from the physician that he was otherwise in good health, Otto embarked on a weight loss program. One of his strategies involved recording all the food he ate and the portions. To analyze his diet for calories, saturated fat, and nutrients, he used the Interactive Healthy Eating Index, available online from the USDA Food and Nutrition Information Center.

Ivan Applebod. Ivan Applebod weighed 264 lb and was 70 inches tall with a heavy skeletal frame. For a male of these proportions, a BMI of 18.5 to 24.9 would correspond to a weight between 129 and 173 lb. He is currently almost 100 lb overweight, and his BMI of 37.9 is in the obese range.

Mr. Applebod's physician cautioned him that exogenous obesity (caused by overeating) represents a risk factor for atherosclerotic vascular disease, particularly when the distribution of fat is primarily "central" or in the abdominal region (apple

shape, in contrast to the pear shape, which results from adipose tissue deposited in the buttocks and hips). In addition, obesity may lead to other cardiovascular risk factors such as hypertension (high blood pressure), hyperlipidemia (high blood lipid levels), and type 2 diabetes mellitus (characterized by hyperglycemia). He already has a mild elevation in both systolic and diastolic blood pressure. Furthermore, his total serum cholesterol level was 296 mg/dL, well above the desired normal value (200 mg/dL).

Mr. Applebod was referred to the hospital's weight reduction center, where a team of physicians, dieticians, and psychologists could assist him in reaching his ideal weight range.

Ann O'Rexia. Because of her history and physical examination, Ann O'Rexia was diagnosed as having early anorexia nervosa, a behavioral disorder that involves both emotional and nutritional disturbances. Miss O'Rexia was referred to a psychiatrist with special interest in anorexia nervosa, and a program of psychotherapy and behavior modification was initiated.

Percy Veere. Percy Veere weighed 125 lb and was 71 inches tall (without shoes) with a medium frame. His BMI was 17.5, which is significantly underweight. At the time his wife died, he weighed 147 lbs. For his height, a BMI in the healthy weight range corresponds to weights between 132 and 178 lb.

Mr. Veere's malnourished state was reflected in his admission laboratory profile. The results of hematologic studies were consistent with an iron deficiency anemia complicated by low levels of folic acid and vitamin B_{12}, two vitamins that can affect the development of normal red blood cells. His low serum albumin level was caused by insufficient protein intake and a shortage of essential amino acids, which result in a reduced ability to synthesize body proteins. The psychiatrist requested a consultation with a hospital dietician to evaluate the extent of Mr. Veere's marasmus (malnutrition caused by a deficiency of both protein and total calories) as well as his vitamin and mineral deficiencies.

BIOCHEMICAL COMMENTS

Dietary Reference Intakes. Dietary Reference Intakes (DRIs) are quantitative estimates of nutrient intakes that can be used in evaluating and planning diets for healthy people. They are prepared by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI) of the Food and Nutrition Board, Institute of Medicine, and the National Academy of Science, with active input of Health Canada. The four reference intake values are the Recommended Dietary Allowance (RDA), the Estimated Average Requirement (EAR), the Adequate Intake (AI), and the Tolerable Upper Intake Level (UL). For each vitamin, the Committee has reviewed available literature on studies with humans and established criteria for adequate intake, such as prevention of certain deficiency symptoms, prevention of developmental abnormalities, or decreased risk of chronic degenerative disease. The criteria are not always the same for each life stage group. A requirement is defined as the lowest continuing intake level of a nutrient able to satisfy these criteria. The EAR is the daily intake value that is estimated to meet the requirement in half of the apparently healthy individuals in a life stage or gender group. The RDA is the EAR plus 2 standard deviations of the mean, which is the amount that should satisfy the requirement in 97 to 98% of the population. The AI level instead of an RDA is set for nutrients when there is not enough data to determine the EAR.

The Tolerable Upper Intake Level (UL) refers to the highest level of daily nutrient intake consumed over time that is likely to pose no risks of adverse effects for almost all healthy individuals in the general population. Adverse effects are defined as any significant alteration in the structure or function of the human organism. The

The prevalence of obesity in the U.S. population is increasing. In 1962, 12.8% of the population had a BMI equal to or greater than 30 and therefore were clinically obese. That number increased to 14.5% by 1980 and to 22.5% by 1998. An additional 30% were pre-obese in 1998 (BMI = 25.0 − 29.9). Therefore, more than 50% of the population is currently overweight, that is, obese or pre-obese.

Increased weight increases cardiovascular risk factors, including hypertension, diabetes, and alterations in blood lipid levels. It also increases the risk for respiratory problems, gallbladder disease, and certain types of cancer.

An example of the difference between the AI and the EAR is provided by riboflavin. Very few data exist on the nutrient requirements of very young infants. However, human milk is the sole recommended food for the first 4 to 6 months, so the AI of the vitamin riboflavin for this life stage group is based on the amount in breast milk consumed by healthy full-term infants. Conversely, the riboflavin EAR for adults is based on a number of studies in humans relating dietary intake of riboflavin to biochemical markers of riboflavin status and development of clinical deficiency symptoms.

UL does not mean that most individuals who consume more than the UL will suffer adverse health effects, but that the risk of adverse effects increases as intake increases above the UL.

Suggested References

A good, comprehensive textbook on nutrition is Shils ME, Olson JA, Shike M, Ross, AC. Modern nutrition in health and disease. Baltimore: Williams & Wilkins, 1999. Extensive nutrition tables, including Metropolitan Height and Weight Tables, are available in the appendices.

Recent Dietary References Intakes prepared by the Food and Nutrition Board of the National Academy of Science (1997–2001) are available in several volumes published by the National Academy Press (see Table 1.7) and may be consulted online at http://books.nap.edu/.

To analyze diets for calories and nutrient contents, consult food databases and resource lists made available by the USDA. The site www.nal.usda.gov/fnic provides lists of resources on food composition, such as the database U.S. Department of Agriculture, Agricultural Research Service. 2001. USDA Nutrient Database for Standard Reference, Release 14. Nutrient Data Laboratory Homepage, http://www.nal.usda.gov/fnic/foodcomp. This site also provides lists of resources for diet analysis, and links to the Interactive Healthy Eating Index, which is a program students can use to analyze their diets (http://147.208.9.133). A useful computer program for evaluating the diet of individuals, the MSU Nutriguide, can be obtained from Department of Nutrition, Michigan State University.

Dietary recommendations change frequently as new data become available. Current Dietary Recommendations are available from the following sources: Food and Nutrition Information Center, National Agricultural Library, USDA (www.fns.usda.gov); National Heart, Lung, and Blood Institute Information Center (www.nhlbi.nih.gov); American Heart Association (www.Americanheart.org); American Institute for Cancer Research (www.aicr.org); and the American Diabetes Association (www.diabetes.org). Another reliable source for nutrition information on the internet is www.navigator.tufts.edu.

A number of medical schools in the United States have received Nutrition Academic Awards from the National Institute of Heart, Blood and Lung, National Institutes of Health (www.nhlbi.nih.gov/funding/naa). These schools are developing products for medical nutrition education.

REVIEW QUESTIONS—CHAPTER 1

Directions: For each question below, select the single best answer.

1. In the process of respiration, fuels

   (A) are stored as triacylglycerols.
   (B) are oxidized to generate ATP.
   (C) release energy principally as heat.
   (D) combine with CO_2 and H_2O.
   (E) combine with other dietary components in anabolic pathways.

2. The caloric content per gram of fuel

   (A) is higher for carbohydrates than triacylglycerols.
   (B) is higher for protein than for fat.
   (C) is proportionate to the amount of oxygen in a fuel.
   (D) is the amount of energy that can be obtained from oxidation of the fuel.
   (E) is higher for children than adults.

3. The resting metabolic rate is

   (A) equivalent to the caloric requirement of our major organs and resting muscle.
   (B) generally higher per kilogram body weight in women than in men.
   (C) generally lower per kilogram body weight in children than adults.
   (D) decreased in a cold environment.
   (E) approximately equivalent to the daily energy expenditure.

4. The RDA is

   (A) the average amount of a nutrient required each day to maintain normal function in 50% of the U.S. population.
   (B) the average amount of a nutrient ingested daily by 50% of the U.S. population.
   (C) the minimum amount of a nutrient ingested daily that prevents deficiency symptoms.
   (D) a reasonable dietary goal for the intake of a nutrient by a healthy individual.
   (E) based principally on data obtained with laboratory animals.

5. A 35-year old sedentary male patient weighing 120 kg was experiencing angina (chest pain) and other signs of coronary artery disease. His physician, in consultation with a registered dietician, conducted a 3-day dietary recall. The patient consumed an average of 585 g carbohydrate, 150 g protein, and 95 g fat each day. In addition, he drank 45 g alcohol. The patient

   (A) consumed between 2,500 and 3,000 kcal per day.
   (B) had a fat intake within the range recommended in current dietary guidelines (i.e., year 2000).
   (C) consumed 50% of his calories as alcohol.
   (D) was deficient in protein intake.
   (E) was in negative caloric balance.

2 The Fed or Absorptive State

The Fed State. *During a **meal**, we ingest carbohydrates, lipids, and proteins, which are subsequently **digested** and **absorbed**. Some of this food is **oxidized** to meet the immediate **energy** needs of the body. The amount consumed in **excess** of the body's energy needs is transported to the **fuel depots**, where it is stored. During the period from the start of absorption until absorption is completed, we are in the **fed**, or absorptive, state. Whether a fuel is oxidized or stored in the fed state is determined principally by the concentration of two **endocrine hormones** in the blood, **insulin** and **glucagon**.*

Fate of Carbohydrates. *Dietary carbohydrates are digested to monosaccharides, which are absorbed into the blood. The major monosaccharide in the blood is **glucose** (Fig 2.1). After a meal, glucose is **oxidized** by various tissues for energy, enters biosynthetic pathways, and is **stored** as **glycogen**, mainly in liver and muscle. Glucose is the major biosynthetic precursor in the body, and the carbon skeletons of most of the compounds we synthesize can be synthesized from glucose. Glucose is also converted to **triacylglycerols**. The liver packages triacylglycerols, made from glucose or from fatty acids obtained from the blood, into very low-density lipoproteins (VLDL) and releases them into the blood. The fatty acids of the VLDL are mainly stored as triacylglycerols in adipose tissue, but some may be used to meet the energy needs of cells.*

Fate of Proteins. *Dietary proteins are digested to **amino acids**, which are absorbed into the blood. In cells, the amino acids are converted to **proteins** or used to make various **nitrogen-containing compounds** such as neurotransmitters and heme. The carbon skeleton may also be **oxidized** for energy directly, or converted to glucose.*

Fate of Fats. *Triacylglycerols are the major lipids in the diet. They are digested to fatty acids and 2-monoacylglycerols, which are resynthesized into **triacylglycerols** in intestinal epithelial cells, packaged in **chylomicrons**, and secreted by way of the lymph into the blood. The **fatty acids** of the chylomicron triacylglycerols are stored mainly as triacylglycerols in **adipose** cells. They are subsequently oxidized for energy or used in biosynthetic pathways, such as synthesis of membrane lipids.*

Hormones are compounds that are synthesized by the endocrine glands of the body. They are secreted into the bloodstream and carry messages to different tissues concerning changes in the overall physiologic state of the body or the needs of tissues.

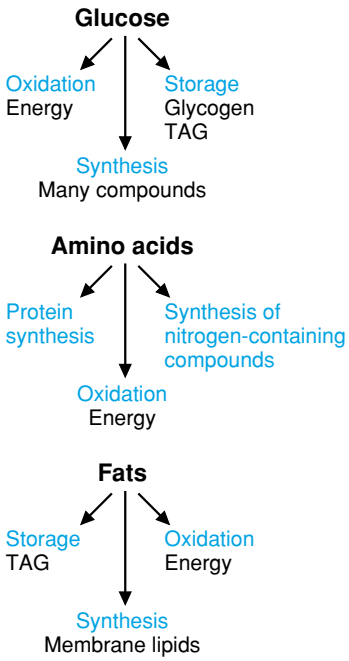


Fig. 2.1. Major fates of fuels in the fed state.

THE WAITING ROOM

Ivan Applebod returned to his doctor for a second visit. His initial efforts to lose weight had failed dismally. In fact, he now weighed 270 lb, an increase of 6 lb since his first visit 2 months ago (see Chapter 1). He reported that the recent death of his 45-year-old brother of a heart attack had made him realize that he must pay more attention to his health. Because

Mr. Applebod's brother had a history of hypercholesterolemia and because Mr. Applebod's serum total cholesterol had been significantly elevated (296 mg/dL) at his first visit, his blood lipid profile was determined, his blood glucose level was measured, and a number of other blood tests were ordered. (The blood lipid profile is a test that measures the content of the various triacylglycerol- and cholesterol-containing particles in the blood.) His blood pressure was 162 mm Hg systolic and 98 mm Hg diastolic or 162/98 mm Hg (normal = 140/90 mm Hg or less). His waist circumference was 48 inches (healthy values for men, less than 40; for women, less than 35).

The body can make fatty acids from a caloric excess of carbohydrate and protein. These fatty acids, together with the fatty acids of chylomicrons (derived from dietary fat), are deposited in adipose tissue as triacylglycerols. Thus, **Ivan Applebod's** increased adipose tissue is coming from his intake of all fuels in excess of his caloric need.

I. DIGESTION AND ABSORPTION

After a meal is consumed, foods are digested (broken down into simpler components) by a series of enzymes in the mouth, stomach, and small intestine. The products of digestion eventually are absorbed into the blood. The period during which digestion and absorption occur constitutes the fed state (Fig. 2.2)

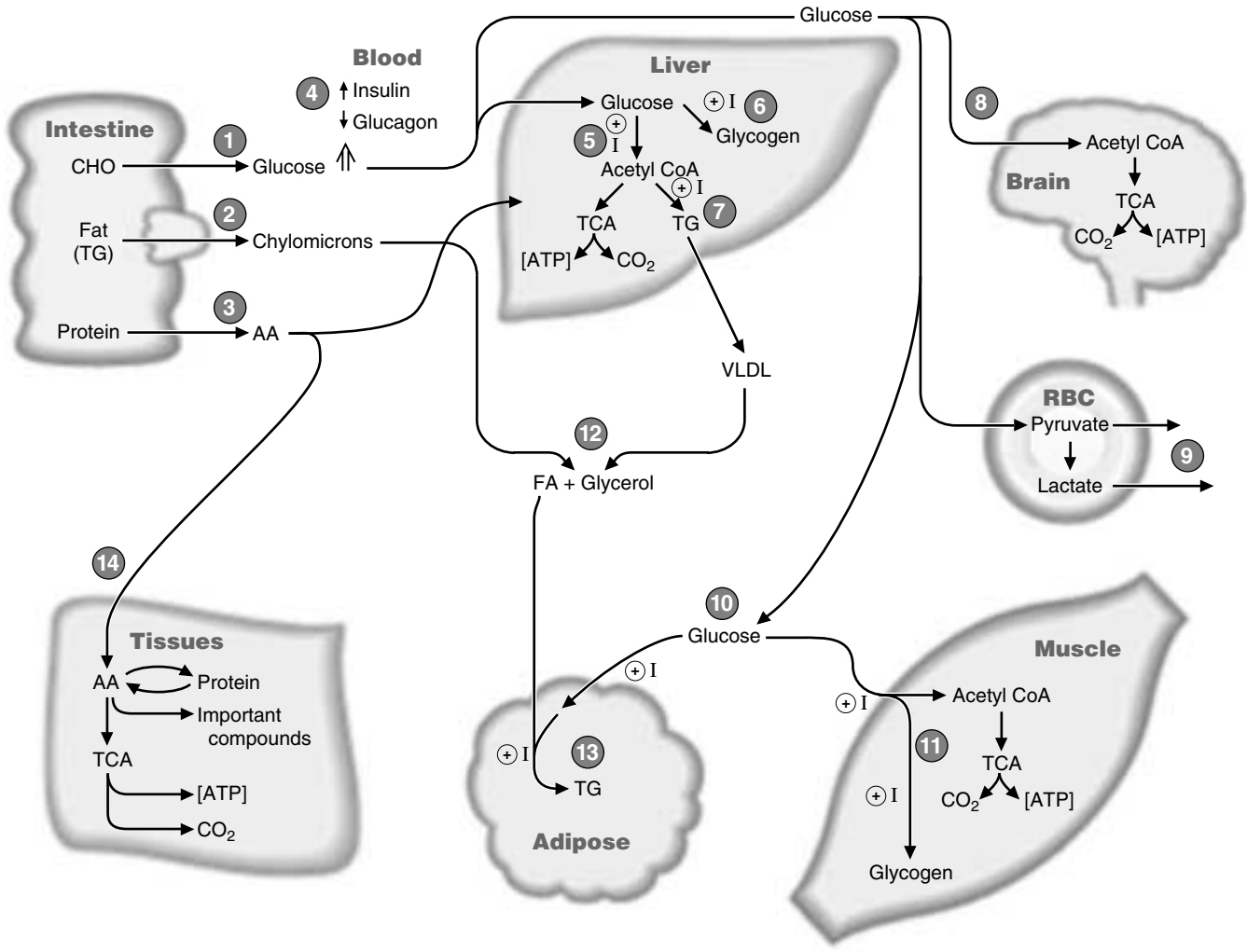


Fig. 2.2. The fed state. The circled numbers indicate the approximate order in which the processes occur. TG = triacylglycerols; FA = fatty acid; AA = amino acid; RBC = red blood cell; VLDL = very-low-density lipoprotein; I = insulin; ⊕ = stimulated by.

Digestive enzymes convert complex sugars to single sugar units for absorption. Sugars are saccharides, and the prefixes "mono" (one), "di" (two), "tri" (three), "oligo" (some), and "poly" (many) refer to the number of sugar units linked together.

Enzymes are proteins that catalyze biochemical reactions; in other words, they increase the speed at which reactions occur. Their names usually end in "ase."

Proteins are amino acids linked through peptide bonds. Dipeptides have two amino acids, tripeptides have three amino acids, and so on. Digestive proteases are enzymes that cleave the peptide bonds between the amino acids (see Chap.1, Fig. 1.5).

Fats must be transported in the blood bound to protein or in lipoprotein complexes because they are insoluble in water. Thus, both triacylglycerols and cholesterol are found in lipoprotein complexes.

The laboratory studies ordered at the time of his second office visit show that **Ivan Applebod** has hyperglycemia, an elevation of blood glucose above normal values. At the time of this visit, his 2-hour postprandial blood glucose level was 205 mg/dL. (Two-hour postprandial refers to the glucose level measured 2 hours after a meal, when glucose should have been taken up by tissues and blood glucose returned to the fasting level, approximately 80–100 mg/dL.) His blood glucose determined after an overnight fast was 162 mg/dL. Because both of these blood glucose measurements were significantly above normal, a diagnosis of type 2 diabetes mellitus, formerly known as non–insulin-dependent diabetes mellitus (NIDDM), was made. In this disease, liver, muscle, and adipose tissue are relatively resistant to the action of insulin in promoting glucose uptake into cells and storage as glycogen and triacylglycerols. Therefore, more glucose remains in his blood.

A. Carbohydrates

Dietary carbohydrates are converted to monosaccharides. Starch, a polymer of glucose, is the major carbohydrate of the diet. It is digested by salivary α-amylase, and then by pancreatic α-amylase, which acts in the small intestine. Di-, tri-, and oligosaccharides produced by these α-amylases are cleaved to glucose by digestive enzymes located on the surface of the brush border of the intestinal epithelial cells. Dietary disaccharides also are cleaved by enzymes in this brush border. Sucrase converts the disaccharide sucrose (table sugar) to glucose and fructose, and lactase converts the disaccharide lactose (milk sugar) to glucose and galactose. Monosaccharides produced by digestion and dietary monosaccharides are absorbed by the intestinal epithelial cells and released into the hepatic portal vein, which carries them to the liver.

B. Proteins

Dietary proteins are cleaved to amino acids by proteases (see Fig. 2.2, circle 3). Pepsin acts in the stomach, and the proteolytic enzymes produced by the pancreas (trypsin, chymotrypsin, elastase, and the carboxypeptidases) act in the lumen of the small intestine. Aminopeptidases and di- and tripeptidases associated with the intestinal epithelial cells complete the conversion of dietary proteins to amino acids, which are absorbed into the intestinal epithelial cells and released into the hepatic portal vein.

C. Fats

The digestion of fats is more complex than that of carbohydrates or proteins because they are not very soluble in water. The triacylglycerols of the diet are emulsified in the intestine by bile salts, which are synthesized in the liver and stored in the gallbladder . Pancreatic lipase converts the triacylglycerols in the lumen of the intestine to fatty acids and 2-monoacylglycerols (glycerol with a fatty acid esterified at carbon 2), which interact with bile salts to form tiny microdroplets called micelles. The fatty acids and 2-monoacylglycerols are absorbed from these micelles into the intestinal epithelial cells, where they are resynthesized into triacylglycerols. The triacylglycerols are packaged with proteins, phospholipids, cholesterol, and other compounds into the lipoprotein complexes known as chylomicrons, which are secreted into the lymph and ultimately enter the bloodstream (see Fig. 2.2, circle 2).

II. CHANGES IN HORMONE LEVELS AFTER A MEAL

After a typical high carbohydrate meal, the pancreas is stimulated to release the hormone insulin, and release of the hormone glucagon is inhibited (see Fig. 2.2, circle 4). Endocrine hormones are released from endocrine glands, such as the pancreas, in response to a specific stimulus. They travel in the blood, carrying messages between tissues concerning the overall physiologic state of the body. At their target tissues, they adjust the rate of various metabolic pathways to meet the changing conditions. The endocrine hormone insulin, which is secreted from the pancreas in response to a high-carbohydrate meal, carries the message that dietary glucose is available and can be used and stored. The release of another hormone, glucagon, is suppressed by glucose and insulin. Glucagon carries the message that glucose must be generated from endogenous fuel stores. The subsequent changes in circulating hormone levels cause changes in the body's metabolic patterns, involving a number of different tissues and metabolic pathways.

III. FATE OF GLUCOSE AFTER A MEAL

A. Conversion to Glycogen, Triacylglycerols, and CO_2 in the Liver

Because glucose leaves the intestine via the hepatic portal vein, the liver is the first tissue it passes through. The liver extracts a portion of this glucose from the blood. Some of the glucose that enters hepatocytes (liver cells) is oxidized in adenosine triphosphate (ATP)-generating pathways to meet the immediate energy needs of these cells and the remainder is converted to glycogen and triacylglycerols or used for biosynthetic reactions. In the liver, insulin promotes the uptake of glucose by increasing its use as a fuel and its storage as glycogen and triacylglycerols (see Fig. 2.2, circles 5, 6, and 7).

As glucose is being oxidized to CO_2, it is first oxidized to pyruvate in the pathway of glycolysis. Pyruvate is then oxidized to acetyl CoA. The acetyl group enters the tricarboxylic acid (TCA) cycle, where it is completely oxidized to CO_2. Energy from the oxidative reactions is used to generate ATP.

Liver glycogen stores reach a maximum of approximately 200 to 300 g after a high-carbohydrate meal, whereas the body's fat stores are relatively limitless. As the glycogen stores begin to fill, the liver also begins converting some of the excess glucose it receives to triacylglycerols. Both the glycerol and the fatty acid moieties of the triacylglycerols can be synthesized from glucose. The fatty acids are also obtained preformed from the blood. The liver does not store triacylglycerols, however, but packages them along with proteins, phospholipids, and cholesterol into the lipoprotein complexes known as very-low-density lipoproteins (VLDL), which are secreted into the bloodstream. Some of the fatty acids from the VLDL are taken up by tissues for their immediate energy needs, but most are stored in adipose tissue as triacylglycerols.

In the liver and most other tissues, glucose, fats, and other fuels are oxidized to the 2-carbon acetyl group ($CH_3-\overset{\overset{O}{\|}}{C}-$) of acetyl CoA. CoA, which makes the acetyl group more reactive, is a cofactor (coenzyme A) derived from the vitamin pantothenate. The acetyl group of acetyl CoA is completely oxidized to CO_2 in the TCA cycle (see Fig 1.4). Adenosine triphosphate (ATP) is the final product of these oxidative pathways. It contains energy derived from the catabolic energy-producing oxidation reactions and transfers that energy to anabolic and other energy-requiring processes in the cell.

B. Glucose Metabolism In Other Tissues

The glucose from the intestine that is not metabolized by the liver travels in the blood to peripheral tissues (most other tissues), where it can be oxidized for energy. Glucose is the one fuel that can be used by all tissues. Many tissues store small amounts of glucose as glycogen. Muscle has relatively large glycogen stores.

Insulin greatly stimulates the transport of glucose into the two tissues that have the largest mass in the body, muscle and adipose tissue. It has much smaller effects on the transport of glucose into other tissues.

Fuel metabolism is often discussed as though the body consisted only of brain, skeletal and cardiac muscle, liver, adipose tissue, red blood cells, kidney, and intestinal epithelial cells ("the gut"). These are the dominant tissues in terms of overall fuel economy, and they are the tissues we describe most often. Of course, all tissues require fuels for energy, and many have very specific fuel requirements.

1. BRAIN AND OTHER NEURAL TISSUES

The brain and other neural tissues are very dependent on glucose for their energy needs. They generally oxidize glucose via glycolysis and the TCA cycle completely to CO_2 and H_2O, generating ATP (see Fig. 2.2, circle 8)). Except under conditions of starvation, glucose is their only major fuel. Glucose is also a major precursor of neurotransmitters, the chemicals that convey electrical impulses (as ion gradients) between neurons. If our blood glucose drops much below normal levels, we become dizzy and light-headed. If blood glucose continues to drop, we become comatose and ultimately die. Under normal, nonstarving conditions, the brain and the rest of the nervous system require roughly 150 g glucose each day.

2. RED BLOOD CELLS

Glucose is the only fuel used by red blood cells, because they lack mitochondria. Fatty acid oxidation, amino acid oxidation, the TCA cycle, the electron transport chain, and oxidative phosphorylation (ATP generation that is dependent on oxygen

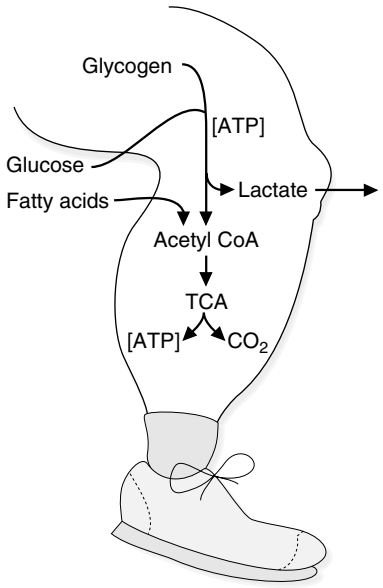


Fig. 2.3 Oxidation of fuels in exercising skeletal muscle. Exercising muscle uses more energy than resting muscle, and, therefore fuel utilization is increased to supply more ATP.

and the electron transport chain) occur principally in mitochondria. Glucose, in contrast, generates ATP from anaerobic glycolysis in the cytosol and, thus, red blood cells obtain all their energy by this process. In anaerobic glycolysis, the pyruvate formed from glucose is converted to lactate and then released into the blood (see Fig. 2.2, circle 9).

Without glucose, red blood cells could not survive. Red blood cells carry O_2 from the lungs to the tissues. Without red blood cells, most of the tissues of the body would suffer from a lack of energy because they require O_2 to completely convert their fuels to CO_2 and H_2O.

3. MUSCLE

Exercising skeletal muscles can use glucose from the blood or from their own glycogen stores, converting glucose to lactate through glycolysis or oxidizing it completely to CO_2 and H_2O. Muscle also uses other fuels from the blood, such as fatty acids (Fig. 2.3). After a meal, glucose is used by muscle to replenish the glycogen stores that were depleted during exercise. Glucose is transported into muscle cells and converted to glycogen by processes that are stimulated by insulin.

4. ADIPOSE TISSUE

Insulin stimulates the transport of glucose into adipose cells as well as into muscle cells. Adipocytes oxidize glucose for energy, and they also use glucose as the source of the glycerol moiety of the triacylglycerols they store (see Fig. 2.2, circle 10).

IV. FATE OF LIPOPROTEINS IN THE FED STATE

Two types of lipoproteins, chylomicrons and VLDL, are produced in the fed state. The major function of these lipoproteins is to provide a blood transport system for triacylglycerols, which are very insoluble in water. However, these lipoproteins also contain the lipid cholesterol, which is also somewhat insoluble in water. The triacylglycerols of chylomicrons are formed in intestinal epithelial cells from the products of digestion of dietary triacylglycerols. The triacylglycerols of VLDL are synthesized in the liver.

When these lipoproteins pass through blood vessels in adipose tissue, their triacylglycerols are degraded to fatty acids and glycerol (see Fig. 2.2, circle 12). The fatty acids enter the adipose cells and combine with a glycerol moiety that is produced from blood glucose. The resulting triacylglycerols are stored as large fat droplets in the adipose cells. The remnants of the chylomicrons are cleared from the blood by the liver. The remnants of the VLDL can be cleared by the liver, or they can form low-density lipoprotein (LDL), which is cleared by the liver or by peripheral cells.

Most of us have not even begun to reach the limits of our capacity to store triacylglycerols in adipose tissue. The ability of humans to store fat appears to be limited only by the amount of tissue we can carry without overloading the heart.

V. FATE OF AMINO ACIDS IN THE FED STATE

The amino acids derived from dietary proteins travel from the intestine to the liver in the hepatic portal vein (see Fig. 2.2, circle 3). The liver uses amino acids for the synthesis of serum proteins as well as its own proteins, and for the biosynthesis of nitrogen-containing compounds that need amino acid presursors, such as the

Ivan Applebod's total cholesterol level is now 315 mg/dL, slightly higher than his previous level of 296. (The currently recommended level for total serum cholesterol is 200 mg/dL or less.) His triacylglycerol level is 250 mg/dL (normal is between 60 and 160 mg/dL). These lipid levels clearly indicate that Mr. Applebod has a hyperlipidemia (high level of lipoproteins in the blood) and therefore is at risk for the future development of atherosclerosis and its consequences, such as heart attacks and strokes.

nonessential amino acids, heme, hormones, neurotransmitters, and purine and pyrimidine bases (e.g., adenine and cytosine in DNA). The liver also may oxidize the amino acids or convert them to glucose or ketone bodies and dispose of the nitrogen as the nontoxic compound urea.

Many of the amino acids will go into the peripheral circulation, where they can be used by other tissues for protein synthesis and various biosynthetic pathways, or oxidized for energy (see Fig. 2.2, circle 14). Proteins undergo turnover; they are constantly being synthesized and degraded. The amino acids released by protein breakdown enter the same pool of free amino acids in the blood as the amino acids from the diet. This free amino acid pool in the blood can be used by all cells to provide the right ratio of amino acids for protein synthesis or for biosynthesis of other compounds. In general, each individual biosynthetic pathway using an amino acid precursor is found in only a few tissues in the body.

VI. SUMMARY OF THE FED (ABSORPTIVE) STATE

After a meal, the fuels that we eat are oxidized to meet our immediate energy needs. Glucose is the major fuel for most tissues. Excess glucose and other fuels are stored, as glycogen mainly in muscle and liver, and as triacylglycerols in adipose tissue. Amino acids from dietary proteins are converted to body proteins or oxidized as fuels.

CLINICAL COMMENTS

Ivan Applebod. Mr. Applebod was advised that his obesity represents a risk factor for future heart attacks and strokes. He was told that his body has to maintain a larger volume of circulating blood to service his extra fat tissue. This expanded blood volume not only contributes to his elevated blood pressure (itself a risk factor for vascular disease) but also puts an increased workload on his heart. This increased load will cause his heart muscle to thicken and eventually to fail.

Mr. Applebod's increasing adipose mass has also contributed to his development of type 2 diabetes mellitus, characterized by hyperglycemia (high blood glucose levels). The mechanism behind this breakdown in his ability to maintain normal levels of blood glucose is, at least in part, a resistance by his triacylglycerol-rich adipose cells to the action of insulin.

In addition to diabetes mellitus, Mr. Applebod has a hyperlipidemia (high blood lipid level—elevated cholesterol and triacylglycerols), another risk factor for cardiovascular disease. A genetic basis for Mr. Applebod's disorder is inferred from a positive family history of hypercholesterolemia and premature coronary artery disease in a brother.

At this point, the first therapeutic steps should be nonpharmacologic. Mr. Applebod's obesity should be treated with caloric restriction and a carefully monitored program of exercise. A reduction of dietary fat and sodium would be advised in an effort to correct his hyperlipidemia and his hypertension, respectively.

BIOCHEMICAL COMMENTS

Anthropometric Measurements. Anthropometry uses measurements of body parameters to monitor normal growth and nutritional health in well-nourished individuals and to detect nutritional inadequacies or excesses. In adults, the measurements most commonly used are: height, weight,

Ivan Applebod's waist circumference indicates he has the android pattern of obesity (apple shape). Fat stores are distributed in the body in two different patterns, android and gynecoid. After puberty, men tend to store fat in and on their abdomens and upper body (an android pattern), whereas women tend to store fat around their breasts, hips, and thighs (a gynecoid pattern). Thus, the typical overweight male tends to have more of an apple shape than the typical overweight female, who is more pear-shaped. Abdominal fat carries a greater risk for hypertension, cardiovascular disease, hyperinsulinemia, diabetes mellitus, gallbladder disease, stroke, and cancer of the breast and endometrium. It also carries a greater risk of overall mortality. Because more men than women have the android distribution, they are more at risk for most of these conditions. But women who deposit their excess fat in a more android manner have a greater risk than women whose fat distribution is more gynecoid.

Upper body fat deposition tends to occur more by hypertrophy of the existing cells, whereas lower body fat deposition is by differentiation of new fat cells (hyperplasia). This may partly explain why many women with lower body obesity have difficulty losing weight.

triceps skinfold thickness, arm muscle circumference, and waist circumference. In infants and young children, length and head circumference are also measured.

To obtain reliable measures of skinfold thickness, procedures are carefully defined. For example, in the triceps measurement, a fold of skin in the posterior aspect of the nondominant arm midway between shoulder and elbow is grasped gently and pulled away from the underlying muscle. The skinfold thickness reading is taken at a precise time, 2 to 3 seconds after applying the caliper, because the caliper compresses the skin. Even when these procedures are performed by trained dieticians, reliable measurements are difficult to obtain.

The **waist-to-hip ratio** has been used instead of the waist circumference as a measure of abdominal obesity in an attempt to correct for differences between individuals with respect to body type or bone structure. In this measurement, the waist circumference is divided by the hip circumference (measured at the iliac crest). The average waist-to-hip ratio for men is 0.93 (with a range of 0.75–1.10), and the average for women was 0.83 (with a range of 0.70–1.00). However, the waist circumference may actually correlate better with intraabdominal fat and the associated risk factors than the waist-to-hip ratio.

Weight and height. Weight should be measured by using a calibrated beam or lever balance-type scale, and the patient should be in a gown or in underwear. Height for adults should be measured while the patient stands against a straight surface, without shoes, with the heels together, and with the head erect and level. The weight and height are used in calculation of the body mass index (BMI).

Skinfold thickness. Over half of the fat in the body is deposited in subcutaneous tissue under the skin, and the percentage increases with increasing weight. To provide an estimate of the amount of body fat, a standardized calipers is used to pinch a fold of the skin, usually at more than one site (e.g., the biceps, triceps, subscapular, and suprailiac areas). Obesity by this physical anthropometric technique is defined as a fatfold thickness greater than the 85th percentile for young adults; that is, 18.6 mm for males and 25.1 mm for females.

Mid-Arm Anthropometry. The arm muscle circumference (AMC), also called the mid upper arm muscle circumference (MUAMC), reflects both caloric adequacy and muscle mass and can serve as a general index of marasmic-type malnutrition. The arm circumference is measured at the midpoint of the left upper arm by a fiberglass flexible-type tape. The arm muscle circumference can be calculated from a formula that subtracts a factor related to the skinfold thickness (SFT) from the arm circumference:

$$\text{MUAMC (cm)} = \text{arm circumference (cm)} - (3.14 \times \text{SFT mm})/10$$

Where MUAMC is the mid upper arm muscle circumference in cm and SFT is the skinfold thickness, expressed in millimeters.

MUAMC values can be compared with reference graphs available for both sexes and all ages. Protein–calorie malnutrition and negative nitrogen balance induce muscle wasting and decrease muscle circumference.

Waist Circumference. The waist circumference is another anthropometric measurement that serves as an indicator of body composition but is used as a measure of obesity and body fat distribution (the "apple shape"), not malnutrition. It is the distance around the natural waist of a standing individual (at the umbilicus). A high-risk waistline is more than 35 inches (88 cm) for women and more than 40 inches (102 cm) for men.

Suggested References

Garrow JS. Obesity. In: Cohen RD, Lewis B, Alberti KGMM, Denman AM, eds. The metabolic and molecular basis of acquired disease. London: Bailliere Tindall, 1990.

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REVIEW QUESTIONS—CHAPTER 2

1. During digestion of a mixed meal,

   (A) starch and other polysaccharides are transported to the liver.
   (B) proteins are converted to dipeptides, which enter the blood.
   (C) dietary triacylglycerols are transported in the portal vein to the liver.
   (D) monosaccharides are transported to adipose tissue via the lymphatic system.
   (E) glucose levels increase in the blood.

2.2. After digestion of a high carbohydrate meal,

   (A) glucagon is released from the pancreas.
   (B) insulin stimulates the transport of glucose into the brain.
   (C) liver and skeletal muscle use glucose as their major fuel.
   (D) skeletal muscles convert glucose to fatty acids.
   (E) red blood cells oxidize glucose to CO_2.

3. Amino acids derived from digestion of dietary protein

   (A) provide nitrogen for synthesis of nonessential amino acids in the liver.
   (B) can be converted to glucose in most tissues.
   (C) cannot be converted to adipose tissue fat.
   (D) release nitrogen that is converted to urea in skeletal muscle.
   (E) are generally converted to body proteins or excreted in the urine.

4. Elevated levels of chylomicrons were measured in the blood of a patient. What dietary therapy would be most helpful in lowering chylomicron levels?

   (A) Decreased intake of calories
   (B) Decreased intake of fat
   (C) Decreased intake of cholesterol
   (D) Decreased intake of starch
   (E) Decreased intake of sugar

5. A male patient exhibited a BMI of 33 kg/m^2 and a waist circumference of 47 inches. What dietary therapy would you consider most helpful?

   (A) Decreased intake of total calories, because all fuels can be converted to adipose tissue triacylglycerols
   (B) The same amount of total calories, but substitution of carbohydrate calories for fat calories
   (C) The same amount of total calories, but substitution of protein calories for fat calories
   (D) A pure-fat diet, because only fatty acids synthesized by the liver can be deposited as adipose triacylglycerols
   (E) A limited food diet, such as the ice cream and sherry diet

3 Fasting

The Fasting State. *Fasting begins approximately 2 to 4 hours after a meal, when blood glucose levels return to basal levels, and continues until blood glucose levels begin to rise after the start of the next meal. Within about 1 hour after a meal, blood glucose levels begin to fall. Consequently,* ***insulin*** *levels decline, and* ***glucagon*** *levels rise. These changes in hormone levels trigger the* ***release of fuels*** *from the body stores.* ***Liver glycogen*** *is* ***degraded*** *by the process of* ***glycogenolysis****, which supplies glucose to the blood.* ***Adipose triacylglycerols*** *are* ***mobilized*** *by the process of* ***lipolysis****, which releases fatty acids and glycerol into the blood. Use of* ***fatty acids*** *as a fuel increases with the length of the fast; they are the* ***major fuel*** *oxidized during overnight fasting.*

Fuel Oxidation*. During fasting,* ***glucose*** *continues to be* ***oxidized*** *by* ***glucose-dependent tissues*** *such as the brain and red blood cells, and* ***fatty acids*** *are oxidized by tissues such as muscle and liver. Muscle and most other tissues oxidize fatty acids completely to CO_2 and H_2O. However, the* ***liver*** *partially oxidizes fatty acids to smaller molecules called* ***ketone bodies****, which are released into the blood. Muscle, kidney, and certain other tissues derive energy from completely oxidizing ketone bodies in the tricarboxylic acid (TCA) cycle.*

Maintenance of Blood Glucose*. As fasting progresses, the* ***liver produces glucose*** *not only by* ***glycogenolysis*** *(the release of glucose from glycogen), but also by a second process called* ***gluconeogenesis*** *(the synthesis of glucose from noncarbohydrate compounds. The major* ***sources of carbon*** *for gluconeogenesis are* ***lactate****,* ***glycerol****, and* ***amino acids****. When the carbons of the amino acids are converted to glucose by the liver, their* ***nitrogen*** *is converted to* ***urea****.*

Starvation*. When we fast for 3 or more days, we are in the starved state.* ***Muscle*** *continues to burn fatty acids but* ***decreases*** *its use of* ***ketone bodies****. As a result, the concentration of ketone bodies rises in the blood to a level at which the* ***brain*** *begins to* ***oxidize*** *them for energy. The brain then needs less glucose, so the liver decreases its rate of gluconeogenesis. Consequently, less* ***protein*** *in muscle and other tissues is degraded to supply amino acids for gluconeogenesis, Protein sparing preserves vital functions for as long as possible. Because of these changes in the fuel utilization patterns of various tissues, humans can survive for extended periods without ingesting food.*

Pathways named with the suffix "lysis" are those in which complex molecules are broken down or "lysed" into smaller units. For instance, in glycogenolysis, glycogen is lysed into glucose subunits; in glycolysis, glucose is lysed into two pyruvate molecules; in lipolysis, triacylglycerols are lysed into fatty acids and glycerol; in proteolysis, proteins are lysed into their constituent amino acids.

Gluconeogenesis means formation (genesis) of new (neo) glucose, and by definition, converts new (noncarbohydrate) precursors to glucose.

Degrees of protein–energy malnutrition (marasmus) are classified according to BMI.

Protein–energy Malnutrition	BMI (kg/cm^2)
I	17.0–18.4
II	16.0–16.9
III	<16.0

Percy Veere has grade I protein–energy malnutrition. At his height of 71 inches, his body weight would have to be above 132 lb to achieve a BMI greater than 18.5. **Ann O'Rexia** has grade III malnutrition. At 66 inches, she needs a body weight greater than 114 lb to achieve a BMI of 18.5.

THE WAITING ROOM

Percy Veere had been admitted to the hospital with a diagnosis of mental depression associated with malnutrition (see Chap. 1). At the time of admission, his body weight of 125 lb gave him a body mass index (BMI) of 17.5 (healthy range, 18.5–24.9). His serum albumin was 10% below the low end of the normal range, and he exhibited signs of iron and vitamin deficiencies.

Additional tests were made to help evaluate Mr. Veere's degree of malnutrition and his progress toward recovery. His arm circumference and triceps skinfold were measured, and his mid upper arm muscle circumference was calculated (see Chap. 2, Anthropometric Measurements). His serum transferrin, as well as his serum albumin, were measured. Fasting blood glucose and serum ketone body concentration were determined on blood samples drawn the next day before breakfast. A 24-hour urine specimen was collected to determine ketone body excretion and creatinine excretion for calculation of the creatinine–height index, a measure of protein depletion from skeletal muscle.

Ann O'Rexia was receiving psychological counseling for anorexia nervosa, but with little success (see Chap. 1). She saw her gynecologist because she had not had a menstrual period for 5 months. She also complained of becoming easily fatigued. The physician recognized that Ann's body weight of 85 lb was now less than 65% of her ideal weight. (Her BMI was now 13.7.) The physician recommended immediate hospitalization. The admission diagnosis was severe malnutrition secondary to anorexia nervosa. Clinical findings included decreased body core temperature, blood pressure, and pulse (adaptive responses to malnutrition). Her physician ordered measurements of blood glucose and ketone body levels and made a spot check for ketone bodies in the urine as well as ordering tests to assess the functioning of her heart and kidneys.

I. THE FASTING STATE

Blood glucose levels peak approximately 1 hour after eating and then decrease as tissues oxidize glucose or convert it to storage forms of fuel. By 2 hours after a meal, the level returns to the fasting range (between 80 and 100 mg/dL). This decrease in blood glucose causes the pancreas to decrease its secretion of insulin, and the serum insulin level decreases. The liver responds to this hormonal signal by starting to degrade its glycogen stores and release glucose into the blood.

If we eat another meal within a few hours, we return to the fed state. However, if we continue to fast for a 12-hour period, we enter the basal state (also known as the postabsorptive state). A person is generally considered to be in the basal state after an overnight fast, when no food has been eaten since dinner the previous evening. By this time, the serum insulin level is low and glucagon is rising. Figure 3.1 illustrates the main features of the basal state.

A. Blood Glucose and the Role of the Liver during Fasting

The liver maintains blood glucose levels during fasting, and its role is thus critical. Glucose is the major fuel for tissues such as the brain and neural tissue, and the sole fuel for red blood cells. Most neurons lack enzymes required for oxidation of fatty acids, but can use ketone bodies to a limited extent. Red blood cells lack mitochondria, which contain the enzymes of fatty acid and ketone body oxidation, and can use only glucose as a fuel. Therefore, it is imperative that blood glucose not decrease too rapidly nor fall too low.

Initially, liver glycogen stores are degraded to supply glucose to the blood, but these stores are limited. Although liver glycogen levels may increase to 200 to 300 g after a meal, only approximately 80 g remain after an overnight fast. Fortunately, the liver has another mechanism for producing blood glucose, known as gluconeogenesis. In gluconeogenesis, lactate, glycerol, and amino acids are used as carbon sources to synthesize glucose. As fasting continues, gluconeogenesis progressively adds to the glucose produced by glycogenolysis in the liver.

Percy Veere had not eaten much on his first day of hospitalization. His fasting blood glucose determined on the morning of his second day of hospitalization was 72 mg/dL (normal, overnight fasting = 80–100 mg/dL). Thus, in spite of his malnutrition and his overnight fast, his blood glucose was being maintained at nearly normal levels through gluconeogenesis using amino acid precursors. If his blood glucose had decreased below 50 to 60 mg/dL during fasting, his brain would have been unable to absorb glucose fast enough to obtain the glucose needed for energy and neurotransmitter synthesis, resulting in coma and eventual death. Although many other tissues, such as the red blood cell, are also totally or partially dependent on glucose for energy, they are able to function at lower concentrations of blood glucose than the brain.

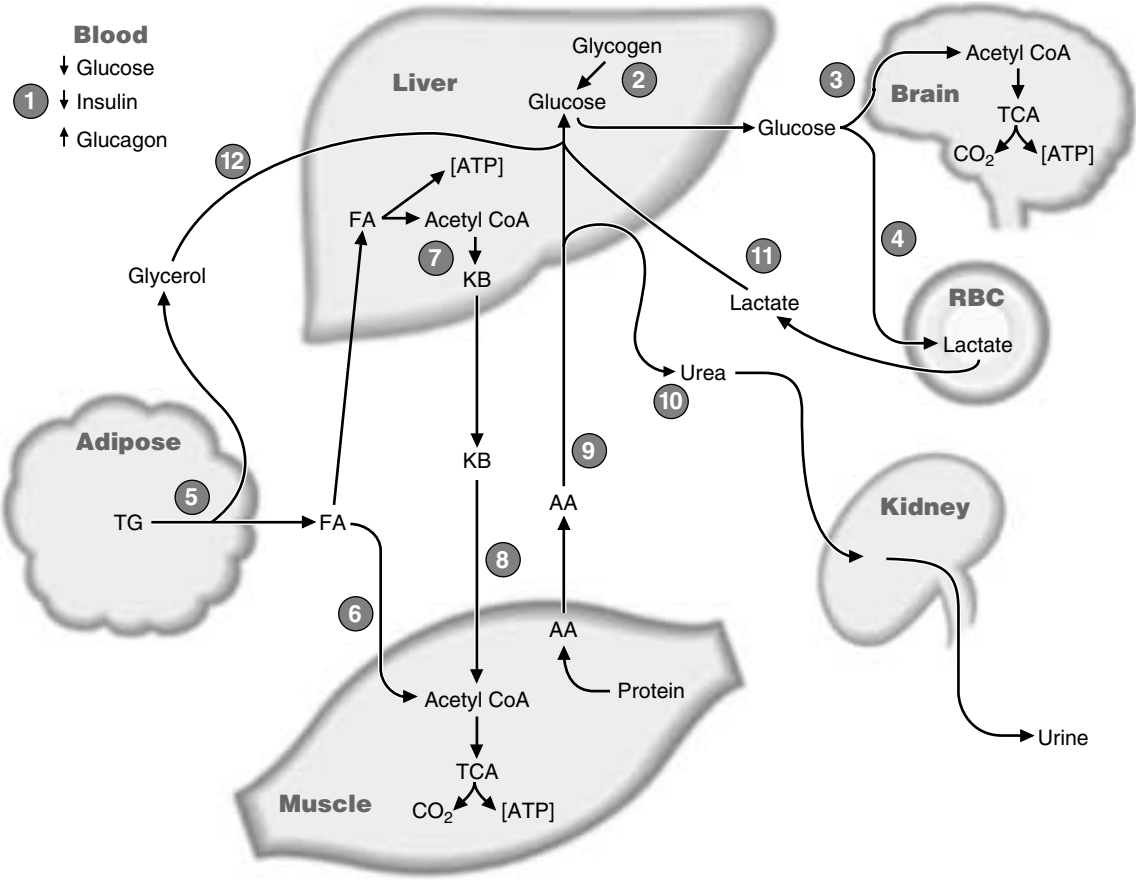

Fig. 3.1. Basal state. This state occurs after an overnight (12-hour) fast. The circled numbers serve as a guide indicating the approximate order in which the processes begin to occur. KB = ketone bodies. Other abbreviations are defined in Figure 2.1.

On the second day of hospitalization, **Percy Veere's** serum ketone body level was 110 μM. (Normal valve after a 12-hour fast, is approximately 70 μM.) No ketone bodies were detectable in his urine. At this stage of protein–energy malnutrition, Mr. Veere still has remaining fat stores. After 12 hours of fasting, most of his tissues are using fatty acids as a major fuel, and the liver is beginning to produce ketone bodies from fatty acids. As these ketone bodies increase in the blood, their use as a fuel will increase.

Lactate is a product of glycolysis in red blood cells and exercising muscle, glycerol is obtained from lipolysis of adipose triacylglycerols, and amino acids are generated by the breakdown of protein. Because our muscle mass is so large, most of the amino acid is supplied from degradation of muscle protein. These compounds travel in the blood to the liver, where they are converted to glucose by gluconeogenesis. Because the nitrogen of the amino acids can form ammonia, which is toxic to the body, the liver converts this nitrogen to urea. Urea has two amino groups for just one carbon (NH_2-CO-NH_2). It is a very soluble, nontoxic compound that can be readily excreted by the kidneys and thus is an efficient means for disposing of excess ammonia.

As fasting progresses, gluconeogenesis becomes increasingly more important as a source of blood glucose. After a day or so of fasting, liver glycogen stores are depleted and gluconeogenesis is the only source of blood glucose.

B. Role of Adipose Tissue During Fasting

Adipose triacylglycerols are the major source of energy during fasting. They supply fatty acids, which are quantitatively the major fuel for the human body. Fatty acids are not only oxidized directly by various tissues of the body; they are also partially oxidized in the liver to 4-carbon products called ketone bodies. Ketone bodies are subsequently oxidized as a fuel by other tissues.

As blood insulin levels decrease and blood glucagon levels rise, adipose triacylglycerols are mobilized by a process known as lipolysis. They are converted to fatty acids and glycerol, which enter the blood.

It is important to realize that most fatty acids cannot provide carbon for gluconeogenesis. Thus, of the vast store of food energy in adipose tissue triacylglycerols, only the small glycerol portion travels to the liver to enter the gluconeogenic pathway.

Fatty acids serve as a fuel for muscle, kidney, and most other tissues. They are oxidized to acetyl CoA, and subsequently to CO_2 and H_2O in the TCA cycle, producing energy in the form of adenosine triphosphate (ATP). In addition to the ATP required to maintain cellular integrity, muscle uses ATP for contraction, and the kidney uses it for urinary transport processes.

Most of the fatty acids that enter the liver are converted to ketone bodies rather than being completely oxidized to CO_2. The process of conversion of fatty acids to acetyl CoA produces a considerable amount of energy (ATP), which drives the reactions of the liver under these conditions. The acetyl CoA is converted to the ketone bodies acetoacetate and β-hydroxybutyrate, which are released into the blood (Fig. 3.2).

The liver lacks an enzyme required for ketone body oxidation. However, ketone bodies can be further oxidized by most other cells with mitochondria, such as muscle and kidney. In these tissues, acetoacetate and β-hydroxybutyrate are converted to acetyl CoA and then oxidized in the TCA cycle, with subsequent generation of ATP.

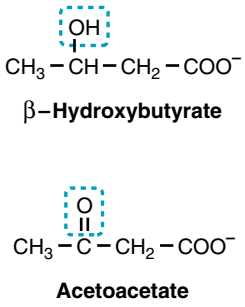

Fig. 3.2. β-Hydroxybutyrate and acetoacetate. These compounds are ketone bodies formed in the iner. A third ketone body, acetone (CH_3-CO-CH_3), is produced by nonenzymatic decarboxylation of acetoacetate. However, acetone is expired in the breath and not metabolized to a significant extent in the body.

C. Summary of the Metabolic Changes during a Brief Fast

In the initial stages of fasting, stored fuels are used for energy (see Fig. 3.1). The liver plays a key role by maintaining blood glucose levels in the range of 80 to 100 mg/dL, first by glycogenolysis and subsequently by gluconeogenesis. Lactate, glycerol, and amino acids serve as carbon sources for gluconeogenesis. Amino acids are supplied by muscle. Their nitrogen is converted in the liver to urea, which is excreted by the kidneys.

Fatty acids, which are released from adipose tissue by the process of lipolysis, serve as the body's major fuel during fasting. The liver oxidizes most of its fatty acids only partially, converting them to ketone bodies, which are released into the blood. Thus, during the initial stages of fasting, blood levels of fatty acids and ketone bodies begin to increase. Muscle uses fatty acids, ketone bodies, and (when exercising and while supplies last) glucose from muscle glycogen. Many other tissues use either fatty acids or ketone bodies. However, red blood cells, the brain, and other neural tissues use mainly glucose. The metabolic capacities of different tissues with respect to pathways of fuel metabolism are summarized in Table 3.1.

II. METABOLIC CHANGES DURING PROLONGED FASTING

If the pattern of fuel utilization that occurs during a brief fast were to persist for an extended period, the body's protein would be quite rapidly consumed to the point at which critical functions would be compromised. Fortunately, metabolic changes occur during prolonged fasting that conserve (spare) muscle protein by causing muscle protein turnover to decrease. Figure 3.3 shows the main features of metabolism during prolonged fasting (starvation).

B. Role of Liver During Prolonged Fasting

After 3 to 5 days of fasting, when the body enters the starved state, muscle decreases its use of ketone bodies and depends mainly on fatty acids for its fuel. The

The liver synthesizes a number of serum proteins and releases them into the blood. These proteins decrease in the blood during protein malnutrition. Two of these serum proteins, albumin and transferrin (an iron-binding transport protein), are often measured to assess the state of protein malnutrition. Serum albumin is the traditional standard of protein malnutrition. Neither measurement is specific for protein malnutrition. Serum albumin and transferrin levels decrease with hepatic disease, certain renal diseases, surgery, and a number of other conditions, in addition to protein malnutrition. Serum transferrin levels also decrease in iron deficiency. **Percy Veere's** values were below the normal range for both of these proteins, indicating that his muscle mass is unable to supply sufficient amino acids to sustain both synthesis of serum proteins by the liver and gluconeogenesis.

Table 3.1. Metabolic Capacities of Various Tissues

Process	Liver	Adipose Tissue	Kidney Cortex	Muscle	Brain	RBC
TCA cycle (acetyl CoA $\rightarrow CO_2 + H_2O$)	+++	++	+++	+++	+++	−−
β-Oxidation of fatty acids	+++	−−	++	+++	−−	−−
Ketone body formation	+++	−−	+	−−	−−	−−
Ketone body utilization	−−	+	+	+++	+++ (prolonged starvation)	−−
Glycolysis (glucose $\rightarrow CO_2 + H_2O$)	+++	++	++	+++	+++	−−
Lactate production (glucose → lactate)	+	+	−−−	+++ exercise	+	+++
Glycogen metabolism (synthesis and degradation)	+++	+	+	+++	+	−−
Gluconeogenesis (lactate, amino acids, glycerol → glucose)	+++	−−	+	−−	−−	−−
Urea cycle (ammonia → urea)	+++	−−	−−	−−	−−	−−
Lipogenesis (glucose → fatty acids)	+++	+	−−	−−	−−	−−

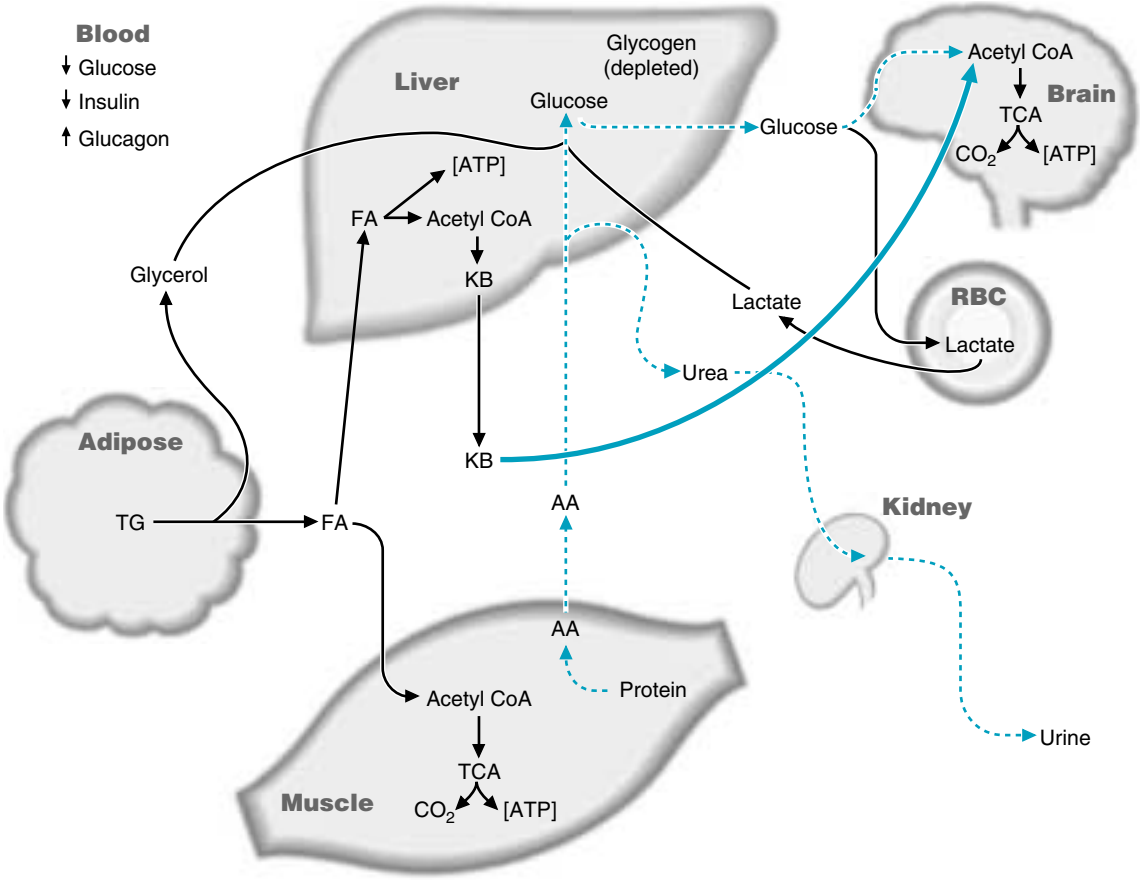

Fig. 3.3. Starved state. Abbreviations are defined in Figures 2.1 and 3.1. Dashed lines indicate processes that have decreased, and the heavy solid line indicates a process that has increased relative to the fasting state.

liver, however, continues to convert fatty acids to ketone bodies. The result is that the concentration of ketone bodies rises in the blood (Fig. 3.4). The brain begins to take up these ketone bodies from the blood and to oxidize them for energy. Therefore, the brain needs less glucose than it did after an overnight fast (Table 3.2).

Glucose is still required, however, as an energy source for red blood cells, and the brain continues to use a limited amount of glucose, which it oxidizes for energy and uses as a source of carbon for the synthesis of neurotransmitters. Overall, however, glucose is "spared" (conserved). Less glucose is used by the body, and, therefore, the liver needs to produce less glucose per hour during prolonged fasting than during shorter periods of fasting.

Because the stores of glycogen in the liver are depleted by approximately 30 hours of fasting, gluconeogenesis is the only process by which the liver can supply glucose to the blood if fasting continues. The amino acid pool, produced by the breakdown of protein, continues to serve as a major source of carbon for gluconeogenesis. A fraction of this amino acid pool is also being used for biosynthetic functions (e.g., synthesis of heme and neurotransmitters) and new protein synthesis, processes that must continue during fasting. However, as a result of the decreased rate of gluconeogenesis during prolonged fasting, protein is "spared"; less protein is degraded to supply amino acids for gluconeogenesis.

While converting amino acid carbon to glucose in gluconeogenesis, the liver also converts the nitrogen of these amino acids to urea. Consequently, because glucose production decreases during prolonged fasting compared with early fasting, urea production also decreases (Fig. 3.5).

B. Role of Adipose Tissue During Prolonged Fasting

During prolonged fasting, adipose tissue continues to break down its triacylglycerol stores, providing fatty acids and glycerol to the blood. These fatty acids serve as the major source of fuel for the body. The glycerol is converted to glucose, whereas the fatty acids are oxidized to CO_2 and H_2O by tissues such as muscle. In the liver, fatty acids are converted to ketone bodies that are oxidized by many tissues, including the brain.

A number of factors determine how long we can fast and still survive. The amount of adipose tissue is one factor, because adipose tissue supplies the body with its major source of fuel. However, body protein levels can also determine the length of time we can fast. Glucose is still used during prolonged fasting (starvation), but in greatly reduced amounts. Although we degrade protein to supply amino acids for gluconeogenesis at a slower rate during starvation than during the first days of a fast, we are still losing protein that serves vital functions for our tissues. Protein can become so depleted that the heart, kidney, and other vital tissues stop functioning, or we can develop an infection and not have adequate reserves to mount an immune response. In addition to fuel problems, we are also deprived of the vitamin and mineral precursors of coenzymes and other compounds necessary for tissue function. Because of either a lack of ATP or a decreased intake of electrolytes, the electrolyte composition of the blood or cells could become incompatible with life. Ultimately, we die of starvation.

Table 3.2. Metabolic Changes during Prolonged Fasting Compared with Fasting 24 Hours

Muscle	↓	Use of ketone bodies
Brain	↑	Use of ketone bodies
Liver	↓	Gluconeogenesis
Muscle	↓	Protein degradation
Liver	↓	Production of urea

Ann O'Rexia's admission laboratory studies showed a blood glucose level of 65 mg/dL (normal fasting blood glucose = 80 – 100 mg/dL). Her serum ketone body concentration was 4,200 μM (normal = ~70 μM). The Ketostix (Bayer Diagnostics, Mishawaha, IN) urine test was moderately positive, indicating that ketone bodies were present in the urine. In her starved state, ketone body use by her brain is helping to conserve protein in her muscles and vital organs.

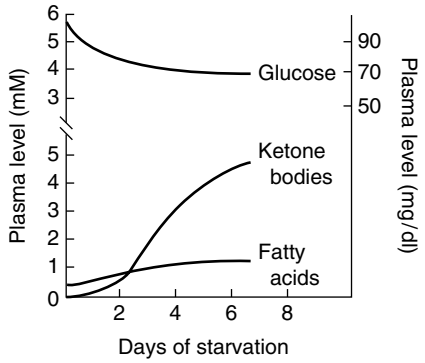

Fig. 3.4. Changes in the concentration of fuels in the blood during prolonged fasting.

Death by starvation occurs with loss of roughly 40% of body weight, when approximately 30 to 50% of body protein has been lost, or 70 to 95% of body fat stores. Generally, this occurs at BMIs of approximately 13 for men, and 11 for women.

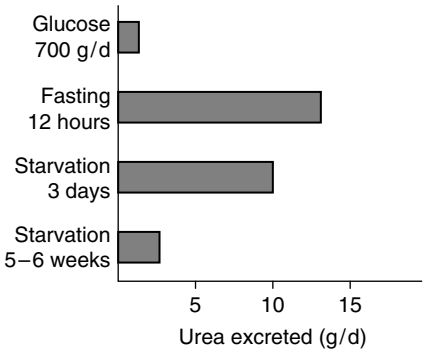

Fig. 3.5. Changes in urea excretion during fasting. Urea production is very low in a person consuming only glucose. It increases during fasting as muscle protein is broken down to supply amino acids for gluconeogenesis. However, as fasting progresses, urea synthesis decreases. Because the brain meets some of its energy needs by oxidizing ketone bodies after 3 to 5 days of fasting, gluconeogenesis decreases, sparing protein in muscle and other tissues.

Creatinine–Height Index. The most widely used biochemical marker for estimating body muscle mass is the 24-hour urinary creatinine excretion. Creatinine is a degradation product formed in active muscle at a constant rate, in proportion to the amount of muscle tissue present in a patient. In a protein-malnourished individual, urinary creatinine will decrease in proportion to the decrease in muscle mass. To assess depletion of muscle mass, creatinine excreted is expressed relative to the height, the creatinine–height index (CHI). The amount of creatinine (in milligrams) excreted by the subject in 24 hours is divided by the amount of creatinine excreted by a normal, healthy subject of the same height and sex. The resulting ratio is multiplied by 100 to express it as a percentage. **Percy Veere**'s CHI was 85% (80–90% of normal indicates a mild deficit; 60–80% indicates a moderate deficit; less than 60% of normal indicates a severe deficit of muscle mass).

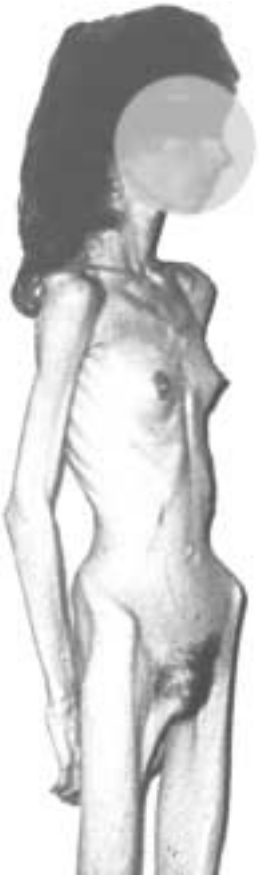

Fig. 3.6. Photograph of a patient with anorexia nervosa. From a MedCom slide, 1970.

CLINICAL COMMENTS

Percy Veere. As a result of his severely suppressed appetite for food, Percy Veere has developed a mild degree of protein–calorie malnutrition. When prolonged, this type of protein malnutrition can cause changes in the villi of the small intestine that reduce its absorptive capacity for what little food is ingested.

Despite his insufficient intake of dietary carbohydrates, Mr. Veere's blood glucose level is 72 mg/dL, close to the lower limit (80 mg/dL) of the normal range for a well-nourished, healthy person after a 12-hour fast. This is the finding you would expect; it reflects the liver's capacity to maintain adequate levels of blood glucose by means of gluconeogenesis, even during prolonged and moderately severe caloric restriction. Amino acids from degradation of protein, principally in skeletal muscle, supply most of the precursors for gluconeogenesis.

Percy Veere has several indicators of his protein malnutrition: his serum albumin and transferrin levels are below normal, his mid-upper-arm muscle circumference (MUAMC) is at the 12th percentile, and his creatinine–height index (CHI) was at 85%. The low levels of serum proteins reflect a low dietary protein intake, and possibly diminished capacity to absorb dietary amino acids. Consequently, amino acids are being mobilized from degradation of protein in muscle and other tissues to supply precursors for new protein synthesis as well as gluconeogenesis. The result is a loss of muscle mass, indicated by the MUAMC and the CHI, and decreased levels of serum proteins.

Fatty acids mobilized from adipose tissue are the major source of energy for most tissues. Because he is eating, and not in total starvation, his ketone bodies were only moderately elevated in the blood (110 μM vs. normal of 70 μM) and did not appear in the urine.

After several psychological counseling sessions, and the promise of an extended visit from his grandchild, Mr. Veere resumed his normal eating pattern.

Ann O'Rexia. Ann O'Rexia has anorexia nervosa, a chronic disabling disease in which poorly understood psychological and biologic factors lead to disturbances in the patient's body image. These patients typically pursue thinness in spite of the presence of severe emaciation and a "skeletal appearance" (Fig. 3.6). They generally have an intense fear of being overweight and deny the seriousness of their low body weight.

Amenorrhea (lack of menses) usually develops during anorexia nervosa and other conditions when a woman's body fat content falls to approximately 22% of her total body weight. The immediate cause of amenorrhea is a reduced production of the gonadotropic protein hormones (luteinizing hormone and follicle-stimulating hormone) by the anterior pituitary; the connection between this hormonal change and body fat content is not yet understood.

Ms. O'Rexia is suffering from the consequences of prolonged and severe protein and caloric restriction. Fatty acids, released from adipose tissue by lipolysis, are being converted to ketone bodies in the liver, and the level of ketone bodies in the blood is extremely elevated (4,200 μM vs. normal of 70 μM). The fact that her kidneys are excreting ketone bodies is reflected in the moderately positive urine test for ketone bodies noted on admission.

Although Ms. O'Rexia's blood glucose is below the normal fasting range (65 mg/dL vs. normal of 80 mg/dL), she is experiencing only a moderate degree of hypoglycemia (low blood glucose) despite her severe, near starvation diet. Her blood glucose level reflects the ability of the brain to use ketone bodies as a fuel when they are elevated in the blood, thereby decreasing the amount of glucose that must be synthesized from amino acids provided by protein degradation.

Ms. O'Rexia's BMI showed that she was close to death through starvation. She was therefore hospitalized and placed on enteral nutrition (nutrients provided through tube feeding). The general therapeutic plan, outlined in Chapter 1, of nutritional restitution and identification and treatment of those emotional factors leading to the patient's anorectic behavior was continued. She was coaxed into eating small amounts of food while hospitalized.

BIOCHEMICAL COMMENTS

Clinical Use of Metabolite Measurements in Blood and Urine. When a patient develops a metabolic problem, it is difficult to examine cells to determine the cause. To obtain tissue for metabolic studies, biopsies must be performed. These procedures can be difficult, dangerous, or even impossible, depending on the tissue. Cost is an additional problem. However, both blood and urine can be obtained readily from patients, and measurements of substances in the blood and urine can help in diagnosing a patient's problem. Concentrations of substances that are higher or lower than normal indicate which tissues are malfunctioning. For example, if blood urea nitrogen (BUN) levels are low, a problem centered in the liver might be suspected because urea is produced in the liver. Conversely, high blood levels of urea suggest that the kidney is not excreting this compound normally. Decreased urinary and blood levels of creatinine indicate diminished production of creatinine by skeletal muscle. However, high blood creatinine levels could indicate an inability of the kidney to excrete creatinine, resulting from renal disease. If high levels of ketone bodies are found in the blood or urine, the patient's metabolic pattern is that of the starved state. If the high levels of ketone bodies are coupled with elevated levels of blood glucose, the problem is most likely a deficiency of insulin; that is, the patient probably has type 1, formerly called insulin-dependent, diabetes mellitus. Without insulin, fuels are mobilized from tissues rather than being stored.

These relatively easy and inexpensive tests on blood and urine can be used to determine which tissues need to be studied more extensively to diagnose and treat the patient's problem. A solid understanding of fuel metabolism helps in the interpretation of these simple tests.

Suggested References

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REVIEW QUESTIONS—CHAPTER 3

You will need some information from Chapters 1 and 2, as well as Chapter 3, to answer these questions.

1. By 24 hours after a meal,

   (A) gluconeogenesis in the liver is the major source of blood glucose.
   (B) muscle glycogenolysis provides glucose to the blood.
   (C) muscles convert amino acids to blood glucose.
   (D) fatty acids released from adipose tissue provide carbon for synthesis of glucose.
   (E) ketone bodies provide carbon for gluconeogenesis.

2. The liver is the only tissue that

   (A) contains significant glycogen stores.
   (B) oxidizes fatty acids during overnight fasting.
   (C) oxidizes ketone bodies during overnight fasting.
   (D) converts ammonia to urea.
   (E) converts glucose to lactate.

3. In a well-nourished individual, as the length of fasting increases from overnight to 1 week,

   (A) blood glucose levels decrease by approximately 50%.
   (B) red blood cells switch to using ketone bodies.
   (C) muscles decrease their use of ketone bodies, which increase in the blood.
   (D) the brain begins to use fatty acids as a major fuel.
   (E) adipose tissue triacylglycerols are nearly depleted.

4. A hospitalized patient had low levels of serum albumin and high levels of blood ammonia. His CHI was 98%. His BMI was 20.5. Blood urea nitrogen was not elevated, consistent with normal kidney function. The diagnosis most consistent with these finding is

   (A) loss of hepatic function (e.g., alcohol-induced cirrhosis).
   (B) anorexia nervosa.
   (C) kwashiorkor (protein malnutrition).
   (D) marasmus (protein–energy malnutrition).
   (E) decreased absorption of amino acids by intestinal epithelial cells (e.g., celiac disease).

5. Otto Shape, an overweight medical student (see Chapter 1), discovered that he could not exercise enough during his summer clerkship rotations to lose 2 to 3 lb per week. He decided to lose weight by eating only 300 kcal/day of a dietary supplement that provided half the calories as carbohydrate and half as protein. In addition, he consumed a multivitamin supplement. During the first 3 days on this diet,

   (A) his protein intake met the RDA for protein.
   (B) his carbohydrate intake met the fuel needs of his brain.
   (C) both his adipose mass and his muscle mass decreased.
   (D) he remained in nitrogen balance.
   (E) he developed severe hypoglycemia.