# Basic Medical Biochemistry

## A CLINICAL APPROACH


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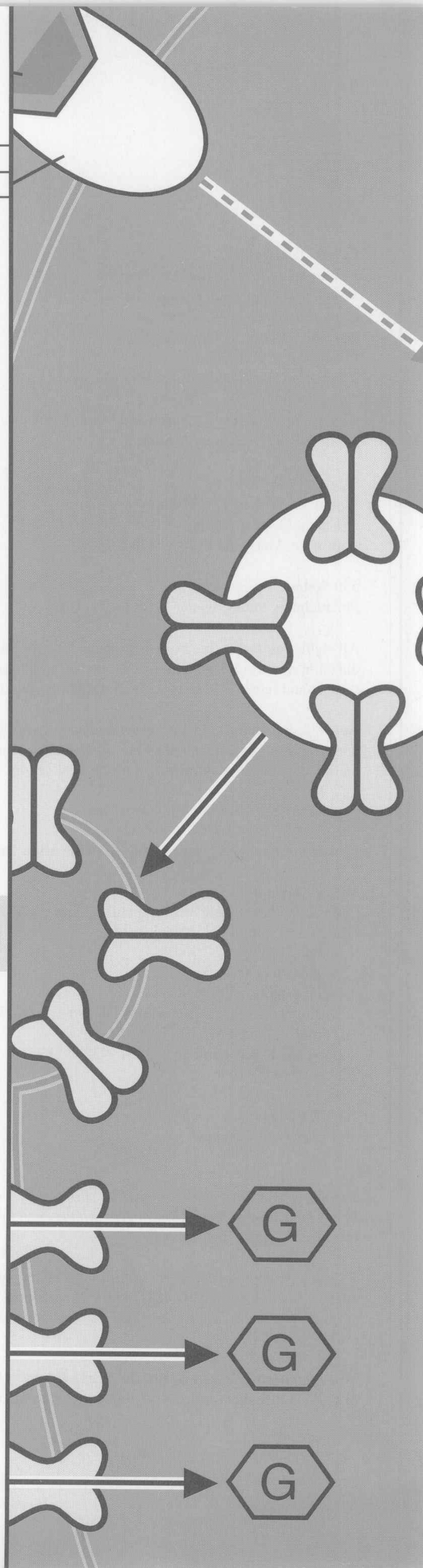


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# Preface

This book is intended to cover human biochemistry in a reasonably comprehensive fashion, but without excessive detail. The aim of the book is to help students learn to use biochemistry in the process of clinical problem solving. The basic text follows a somewhat traditional format to provide students with a comprehensive, coherent base of information. Other components of the book are designed to encourage students to use this information within a clinical context.

A major unifying concept of the book is fuel metabolism. What happens when we eat, when we fast, or when we fast for long periods of time? How does the body get the energy and precursors it needs to keep functioning, to survive? The regulation of metabolic pathways by intracellular and hormonal mechanisms is emphasized because an understanding of metabolic regulation is essential if students are to grasp the implications of biochemistry for pathological conditions.

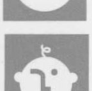
The clinical material is presented in the form of "real patients," who are composites of the patients seen by one of the authors (A.D. Marks) in his many years of practicing internal medicine. The patients in the book have names intended to serve as mnemonics that help students remember the case histories. As the chapters evolve, the patients appear and reappear as their problems are examined in the light of the biochemical concepts covered in the text. Many of the patients are seen repeatedly throughout the book with exacerbations or new facets of their original problem or with totally unrelated problems that require medical attention. The patients are not just dry initials, but people with personalities and quirks that must be considered in their treatment. Some patients comply with their treatment plan, and some do not. Some are cured, some get progressively worse in spite of appropriate treatment, and, as in real life, some die.

## HOW TO USE THIS BOOK

Icons identify the various components of the book: the patients who are presented at the start of each chapter; the clinical notes, biochemical notes, questions, and answers that appear in the margins; and the clinical and biochemical comments that are found at the end of each chapter.

Each chapter starts with an abstract that summarizes the information so that students can recognize the key words and concepts they are expected to learn. The next component of each chapter is a "Waiting Room," containing patients with complaints and a description of the events that lead them to seek medical help.


indicates a female patient


indicates a male patient


indicates a patient who is a baby or a young child

As each chapter unfolds, icons appear in the margin, identifying information related to the material presented in that portion of the text.

indicates a clinical note, usually related to the patients who appear in the waiting room for that chapter. These notes explain the signs or symptoms of a patient or give some other clinical information relevant to the text.

indicates a book note, which elaborates on some aspect of the basic biochemistry presented in the text. These notes provide tidbits, pearls, or just reemphasize a major point of the text.

"Questions" and "Answers" also appear in the margin and should help to keep students thinking as they read the text.


indicates a question, numbered so that the appropriate answer can be identified.


indicates the answer to the question of the same number. It is usually located at some distance from the question (further down the page or on a subsequent page) so it is difficult for the student to simply read the question and the answer without pausing to think in between.

Each chapter ends with "Clinical Comments" and "Biochemical Comments."

indicates clinical comments that give additional clinical information, often describing the treatment plan and the outcome.

indicates biochemical comments that add biochemical information not covered in the text or that explore some facet of biochemistry in more detail or from a more philosophical angle.

"Suggested Readings" are listed at the end of the chapter, for students who would like to pursue a particular topic in more depth. The references suggested are generally recent review articles at the level most suitable for beginning medical students. Due to space limitations, we were unable to appropriately credit the original investigators or to list more advanced review articles.

Finally, "Problems" are presented, usually of a clinical nature, that ask the student to apply the biochemistry covered in the chapter to problems more complex than those that appear as questions in the margin. Generally, "Answers" are given for each problem.

# Acknowledgments

*We would like to thank the many students, patients, and colleagues who inspired the design of the manuscript. We would also like to thank the staff at Williams & Wilkins (particularly Tim Satterfield, Nancy Evans, Anne Stewart Seitz, and Janet Krejci) and the reviewers who patiently aided us with the strenuous task of turning our ideas into the pages of a textbook. We are especially grateful to Matthew Chansky, the artist who, with amazing speed, turned our scribbles into crisp illustrations.*

*Dawn B. Marks*
*Allan D. Marks*
*Colleen M. Smith*

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SECTION I

# Fuel Metabolism

In order to survive, we require fuel to provide the energy that drives the chemical reactions of our bodies. These reactions enable us to carry out such diverse functions as seeing, moving, thinking, and reproducing. Without fuel, life ends. The source of our fuel is obvious: our food provides us with energy. But what happens when we are not eating—between meals, and while we sleep? What is the source of our energy during these periods? And what happens when we fast for an extended period—when we cannot afford the local supermarket prices, or when we are sick? How long can the hunger-striker in the morning headlines expect to survive, or the 1,400-lb person who gets stuck in the bathroom doorframe and vows not to eat until he can fit into normal spaces? Are the skeletal fashion models who parade through our magazine and TV ads in metabolic danger?

We will deal with these questions by describing 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 they will be joined by others as we delve deeper into the subject of biochemistry.

# 1 Metabolic Fuels and Dietary Components

*We obtain our fuel mainly from the 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 foodstuffs to carbon dioxide ($CO_2$) and water ($H_2O$), molecular oxygen ($O_2$) is required. We breathe in order to obtain this oxygen and to eliminate the $CO_2$ that is produced by the oxidation of our foodstuffs.*

*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 and liver, 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.*

*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.*

*In addition to providing energy, the diet provides precursors from which the body's components are derived. Among these are the essential fatty acids and amino acids, which the body needs but cannot synthesize. The diet also supplies vitamins, minerals, and water. Water is the solvent of life.*

---

**Ronald Templeton** is a 25-year-old medical student who was very athletic during high school and college. However, since he started medical school, he has been gaining weight, and he has decided to consult a physician at the student health service before the problem gets worse.

**Thomas Appleman** is a 56-year-old accountant who has been morbidly obese for a number of years. His major recreational activities are watching TV, while drinking Scotch and soda, and doing some 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 was found to weigh 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).

**Priscilla Twigg** is a 23-year-old buyer for a woman's clothing store. Despite the fact that she is 5 feet 7 inches tall and currently weighs 99 lb, she is convinced that 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.

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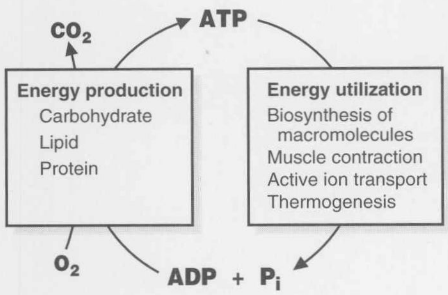



**Fig. 1.1.** The ATP-ADP cycle.

**Teresa Livermore** is a 49-year-old homemaker who was in good health until her husband died suddenly a year ago. Since that time she has experienced an increasing degree of fatigue and has lost interest in many of the activities she previously enjoyed. Shortly after her husband's death, her only child married and moved far from home. Since then, Mrs. Livermore has had little appetite for food. When a neighbor found Mrs. Livermore sleeping in her clothes, unkempt, and somewhat confused, she called an ambulance. Mrs. Livermore was admitted to the hospital psychiatry unit with a diagnosis of mental depression associated with dehydration and malnutrition.

## DIETARY FUELS

The major fuels we obtain from our diet are carbohydrates, proteins, and lipids. 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). 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 biochemical reactions, muscle contraction, and active transport across membranes. As these processes utilize energy, ATP is converted back to ADP and inorganic phosphate ($P_i$). The generation and utilization of ATP is referred to as the ATP-ADP cycle (Fig. 1.1).

The oxidation of fuels to generate ATP is called respiration (Fig. 1.2). The pathways for oxidizing these dietary components have many features in common. Most of the oxidation of fuels occurs in a series of reactions termed the tricarboxylic acid (TCA) cycle (see Chapter 19). Electrons 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" and we will abbreviate it "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.

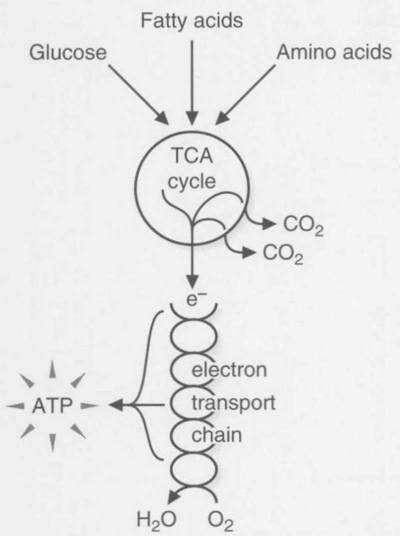



**Fig. 1.2.** Generation of ATP from fuels during respiration. Dietary carbohydrates are converted mainly to glucose, dietary lipids to fatty acids, and dietary protein to amino acids. The TCA cycle is described in Chapter 19, and the electron transport chain is discussed in Chapter 20. $e^-$ = electrons.

### Carbohydrates

The major carbohydrates in the human diet are starch, sucrose, lactose, fructose, glucose, and indigestible fiber, such as cellulose. 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. 1.3).

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 (see Fig. 1.3).

"Calorie" meaning kilocalorie was originally spelled with a capital C (to indicate "large" calories), but the capitalization was dropped as the term became popular.

Nutritional "calories" = kilocalories.

**Table 1.1. Caloric Content of Dietary Components**

| | kcal/g |
|---|---|
| Carbohydrate | 4 |
| Protein | 4 |
| Fat | 9 |
| Alcohol | 7 |

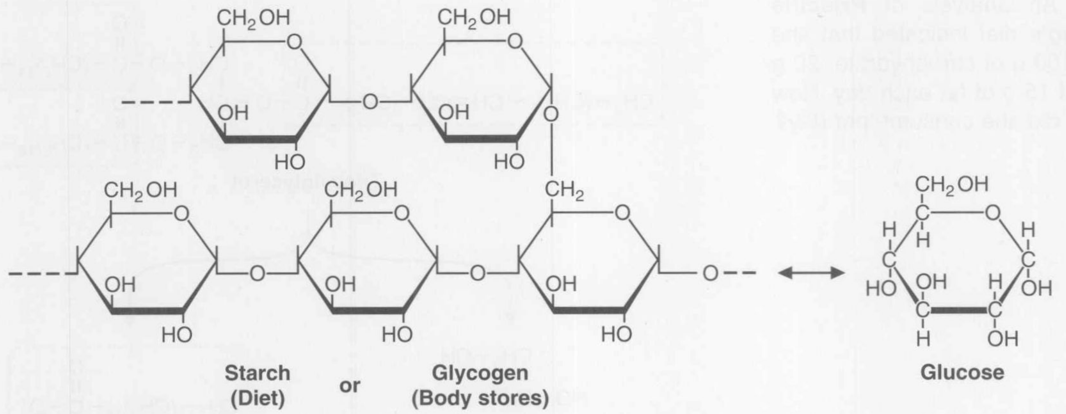



**Fig. 1.3.** General structure of the major carbohydrates. Glucose is a monosaccharide. Two monosaccharides may be linked together to form a disaccharide. Polysaccharides, such as starch or glycogen, are composed of many monosaccharides linked together.

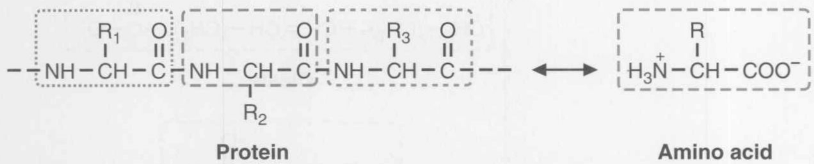



**Fig. 1.4.** General structure of proteins and amino acids. R = side chain. Different amino acids have different side chains. For instance, $R_1$ might be $-CH_3$; $R_2$, –⟨O⟩; $R_3$, $-CH_2-COO^-$.

## Proteins

Proteins are composed of amino acids that are joined to form linear chains (Fig. 1.4). In addition to carbon, hydrogen, and oxygen, proteins contain about 16% nitrogen by weight. The digestive process breaks down proteins to their constituent amino acids, which enter the bloodstream. The complete oxidation of proteins to $CO_2$ and $H_2O$ in the body produces approximately 4 kcal/g.

## Lipids

The lipids in our diet consist mainly of triacylglycerols (also called triglycerides). A triacylglycerol molecule contains 3 fatty acids esterified to one glycerol moiety (Fig. 1.5).

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 produces approximately 9 kcal/g, more than twice the energy produced by an equivalent amount of carbohydrate or protein.

## Alcohol

Many people used to believe that alcohol (ethanol, in the context of the diet) has no caloric content (Fig. 1.6). In fact, alcohol is oxidized to $CO_2$ and $H_2O$ in the body and yields about 7 kcal/g, that is, more than carbohydrate but less than fat.

# BODY FUEL STORES

Although some of us may try, it is virtually impossible to eat constantly. Therefore, it is fortunate that we carry supplies of fuel within our bodies (Fig. 1.7). These fuel

> **Q** 1.1: An analysis of **Priscilla Twigg's** diet indicated that she ate 100 g of carbohydrate, 20 g of protein, and 15 g of fat each day. How many calories did she consume per day?

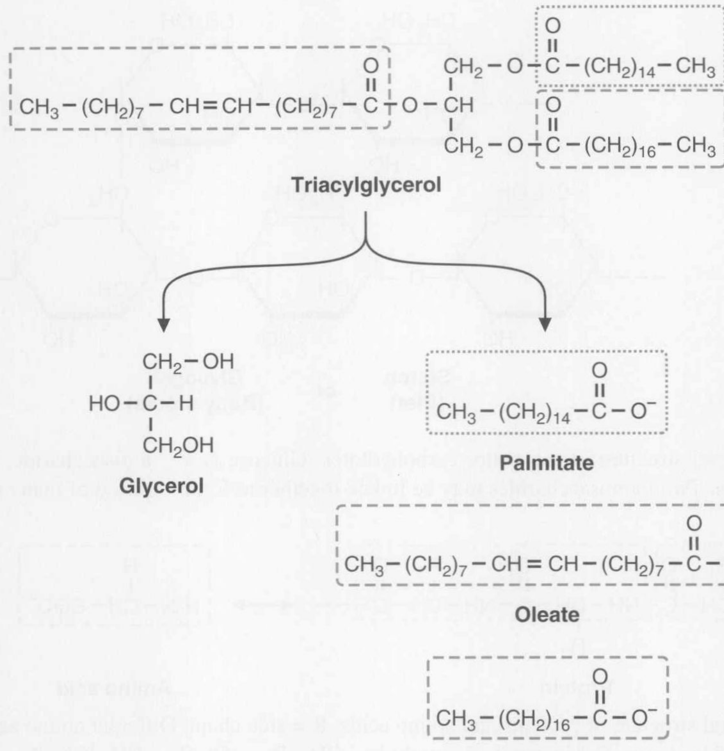
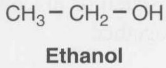



**Fig. 1.5.** Structure of a triacylglycerol. Palmitate and stearate are saturated fatty acids, i.e., they have no double bonds. Oleate is monounsaturated (one double bond). Polyunsaturated fatty acids have more than one double bond.



**Ethanol**

**Fig. 1.6.** Structure of ethanol.

> **Q** 1.2: An analysis of **Thomas Appleman's** diet indicated that he ate 585 g of carbohydrate, 150 g of protein, and 95 g of fat each day. In addition, he drank 45 g of alcohol. How many calories did he consume per day?

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 these familiar fat stores, we also have important although much smaller stores of carbohydrate in the form of glycogen located mainly in our liver and muscles. Glycogen consists of glucose residues joined together to form a large, branched polysaccharide. 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.

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

## Triacylglycerols

Our major fuel store is adipose triacylglycerol (triglyceride). The average 70-kg man has about 15 kg of stored triacylglycerol, which accounts for about 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. Muscle tissue contains about 80% water; adipose tissue contains about 15%. That means that the 70-kg man, who has 15 kg of stored triacylglycerol, has only about 18 kg of adipose tissue. What would happen if this man stored the same amount of energy as protein in muscle? The stored fuel itself would amount to about 34 kg of protein. In addition, there would be 4 times that weight in tissue water. Thus, the man would end up carrying a total of about 170 kg of extra muscle tissue, and he would weigh more than 3 times what he now weighs.

In biochemistry and nutrition, the standard reference is often the 70-kg (154 lb) man. This standard probably was chosen because in the early part 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.

### Glycogen

Our stores of glycogen in liver and muscle 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 about 150 g of muscle glycogen.

Adipose tissue contains:
- fat stores (9 kcal/g)
- only 15% water

### Protein

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

Protein:
- has essential roles other than providing fuel
- can be oxidized for energy in only limited amounts
- is 20% of muscle tissue (80% is water)

## 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 that meets our daily energy expenditure. The daily energy expenditure includes the energy to support our basal metabolism and our physical activities plus the energy required to process the food we eat (diet-induced thermogenesis).

Daily energy expenditure = Energy expended at rest + physical activity + diet-induced thermogenesis

### Basal Metabolic Rate (BMR)

The basal metabolic rate is a measure of the energy required to maintain life: the functioning of the lungs and kidneys, the pumping of the heart, the maintenance of ionic gradients across membranes, the reactions of biochemical pathways, and so forth. The BMR is usually determined from a measurement of the rate at which oxygen is consumed or heat is produced by a resting person who has recently awakened

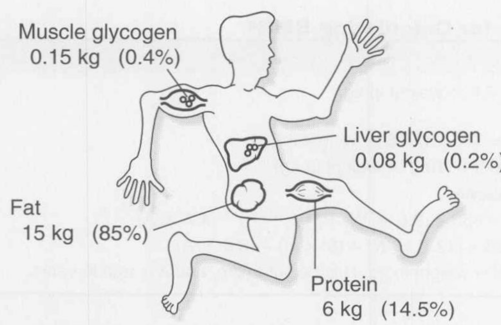



**Fig. 1.7.** Fuel composition of the average 70-kg man after an overnight fast (in kilograms and as percentage of total calories).

A 1.1: **Miss Twigg** consumed

| | |
|---|---|
| 100 × 4 = | 400 kcal as carbohydrate |
| 20 × 4 = | 80 kcal as protein |
| 15 × 9 = | 135 kcal as fat |
| | for a total of 615 kcal/day. |

A 1.2: **Mr. Appleman** 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. |

**Q** 1.3: What is **Mr. Appleman's** BMR? (Use the method for a rough estimate.)

in the morning after fasting for at least 12 hours. In practice, therefore, the BMR is really the resting metabolic rate (RMR).

BMR is usually expressed in kilocalories required per day. Obviously, the amount of energy required for basal functions in a large person will be greater than the amount required in a small person, a fact that restaurants and even hospitals often do not recognize when offering portions of food to their patrons.

Although an individual's BMR depends mainly on body weight, many other factors affect it (Table 1.2). The BMR is lower for women than for men of the same weight because women usually have more adipose tissue. Adipose tissue is much less metabolically active than is lean tissue. Body temperature also affects the BMR. Women who have passed on the saying "feed a fever; starve a cold" may have made some valid scientific observations, because the BMR increases by 12% with each degree centigrade increase in body temperature. The ambient temperature affects the BMR, which increases slightly in colder climates. Excessive secretion of thyroid hormone (hyperthyroidism) causes the BMR to increase, while 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 portion of their bodies is composed of brain, muscle, and other more metabolically active tissues. Whether the BMR decreases to a constant level by age 20 or continues to decline with age is somewhat controversial. Certainly, the BMR decreases in aging individuals whose metabolically active tissue is shrinking and body fat is increasing.

There are large variations in BMR from one adult to another. Nevertheless, it is clear that BMR depends on body weight. 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/hour. Other methods are also used by clinicians for calculating the BMR (Table 1.3). Such calculations are, of course, only estimates because of the wide variation among individuals.

**Q** 1.4: What is **Miss Twigg's** BMR? (Use the method for a rough estimate.)

## Physical Activity

In addition to the BMR, the energy required for physical activity contributes to the daily energy expenditure. The difference in physical activity between a student and a

**Table 1.2. Factors That Affect BMR/kg Body Weight**

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

**Table 1.3. Methods for Calculating BMR[a]**

**Rough Estimate:** BMR = 24 × weight in kg

**Owen Equations[b]:**

$$BMR_{WOMEN} = 795 + (7.18 \times \text{weight in kg})$$
$$BMR_{MEN} = 879 + (10.2 \times \text{weight in kg})$$

**Harris and Benedict Equations:**

$$BMR_{WOMEN} = 655 + (9.6 \times W) + (1.8 \times H) - (4.7 \times A)$$
$$BMR_{MEN} = 66 + (13.7 \times W) + (5 \times H) - (6.8 \times A)$$

where W is weight in kg, H is height in cm, and A is age in years.

[a]Units of BMR are kcal/kg/day.

[b]Owen uses the term RMR rather than BMR because the RMR (resting metabolic rate) is what is actually measured.