Metabolic Basis of Obesity
This book is dedicated to my family, mentors, colleagues and trainees, who have all contributed to my professional and scientific development. I am especially thankful to Grace, FAS, OH, Dedaa, Osei, Opare and Patrick, for making this and other endeavors worthwhile.
Preface

Overweight, defined as body-mass index (BMI) greater than 25, and obesity, defined as BMI greater than 30, are characterized by excessive fat accumulation which poses adverse risks to health. Worldwide, there are more than one billion overweight and 300 million obese adults. Obesity is a major risk factor for diabetes, cardiovascular disease, sleep apnea, non-alcoholic fatty liver disease, arthritis, cancer and other diseases, and has been associated with enormous health costs, premature death, reduction in the quality of life and disability. The increasing global incidence of child obesity is also a major concern. The obesity epidemic is not just a problem for industrialized societies. Indeed, obesity rates have risen three times or more over the past two decades in some developing countries. Although the growing obesity epidemic undoubtedly reflects profound changes in diet and lifestyle over recent decades, genetic factors are important in determining a person’s susceptibility to weight gain and adverse health consequences of obesity.

The goal of this book is to highlight the pathophysiology of obesity and associated diseases. While a completely comprehensive discussion of the metabolic basis of obesity is beyond the scope of this book, we present in-depth reviews of a wide range of topics, including energy homeostasis and intermediary metabolism, adipocyte biology, central neuronal pathways, adipokines, cytokines, classical hormones, abnormal glucose and lipid metabolism, and dysregulation of major organs, with an emphasis on human obesity. We believe these topics will be interesting and provide critical information on the metabolic basis of obesity to researchers, clinicians, students, and the public at large.

Philadelphia, Pennsylvania, USA

Rexford S. Ahima
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Introduction

Energy is defined as the ability of a system to perform work. Energy is present in many forms, such as luminous energy coming from the sun or kinetic energy obtained from wind and water. Humans obtain their energy from foods which is stored in the CH bonds of carbohydrates, lipids, proteins, and alcohol. To obtain the energy to live, grow, and reproduce, organisms must extract it in a usable form from plants and/or animal foods. This potential chemical energy is liberated inside cells through oxidative pathways that convert these CH bonds to energy-rich molecules such as creatine phosphate and adenosine triphosphate (ATP). The energy released from the breakdown of ATP is then used to power muscle activity, to synthesize many molecules necessary for cell structure and function, and create concentration gradients between the intra- and extra-cellular spaces (e.g., Na⁺, K⁺, or Ca²⁺ gradients). During these energy conversion processes, i.e., from foods to utilizable energy, and from utilizable energy to mechanical work, part of the energy is converted to heat. Thus, the energy utilized can be measured by the work generated or heat released. Work is measured in Joule (J), 1 J being the work necessary to give a mass of 1 kg an acceleration of 1 m/s traveling through a distance of 1 m. Heat is measured in calories, with 1 cal being the amount of heat required to raise the temperature of 1 g of water from 14.5 to 15.5°C. One calorie is equivalent to 4.184 J. Multiples of 1,000 (kilojoules (kJ) or kilocalories (kcal)) or one million (megajoules (MJ)) are used in human nutrition.

To obtain the energy from foods, mammals such as humans have evolved complex processes to maximize the energy supply [1]. Foods contain the energy in the form of carbohydrate, fat, and protein. These macromolecules need to be processed into small molecules before being absorbed from the gastrointestinal tract. The process of digestion is facilitated when foods are cooked, and then by
chewing and mixing with saliva and gastric movements, which ensure that the foods are properly mixed into a semifluid mass, known as chyme. Once the chyme gets to the duodenum and in contact with enzymes released from the gallbladder and pancreas, carbohydrate, fat, and protein are digested into smaller molecules, i.e., nutrients, which can be absorbed. From the bloodstream, the nutrients are taken up by cells to supply the energy required for cellular metabolism and survival. Within the cell, glucose, fatty acids, and amino acids are hydrolyzed in the presence of oxygen to release ATP, water, carbon dioxide, and heat [2]. Not all the energy contained in foods is available as utilizable energy, because some of the energy is lost during digestion and absorption [3]. Moreover, proteins are not completely oxidized to carbon dioxide and water; therefore, the intermediary metabolite of protein digestion still contains energy that is lost in the urine in the form of urea. The heat of combustion of exogenous nutrients, which is equivalent to their energy content measured using a bomb calorimeter is 4.2 kcal/g of carbohydrate, 9.4 kcal/g of fat, and 4.2–5.1 kcal/g of protein. However, after taking into account the intestinal absorption and urinary losses, the amount of energy available to be utilized by cells is approximately 4, 9, and 4 kcal for carbohydrate, fat, and protein, respectively [4].

**Energy Expenditure**

Energy is expended in multiple processes occurring to sustain life. The major components of the human energy budget include the obligate energy required to keep us alive and that required to provide locomotion (Fig. 1). A description of these and other constituents of energy expenditure are discussed below.

![Fig. 1](image_url) Contribution of basal metabolic rate (BMR), thermic effect of food (TEF), and physical activity to total energy expenditure in a 70-kg young man having a sedentary or active physical activity level
Principles of Human Energy Metabolism

Basal and Resting Metabolic Rate

The basal metabolic rate (BMR) is the energy expended by a subject under standard conditions that include being awake in the supine position after 10–12 h of fasting and 8 h of physical rest, and being in a state of mental relaxation in a room with environmental temperature that does not elicit heat-generating or heat-dissipating processes. The measurement of BMR requires specific conditions that are not always feasible. In contrast, resting metabolic rate (RMR) can be measured under less restricted conditions than BMR, and do not require that the subject spend the night sleeping in the testing facility prior to the measurement.

The BMR includes the cost of maintaining the integrated systems of the body at homeothermic temperature at rest. These processes are essential for life and include cation exchange to maintain gradient concentrations between the cellular compartments, muscle tone, protein synthesis and degradation, RNA and DNA turnover, cellular signaling, gluconeogenesis, synthesis of urea, fuel cycling, and many other biochemical processes [5]. In sedentary adults, these processes account for approximately 60–70% of daily energy expenditure [6]. The close correlation between BMR and body size has been known for many years and has formed the basis for the development of widely used equations to predict BMR from weight [7–9]. The equations derived from Schofield’s work [8] are conventionally accepted [10] (Table 1). The studies to derive these equations were mostly performed in Western Europe and North America. Almost half of the data used to generate the equations for adults were from studies carried out in the late 1930s and early 1940s on Italian men with relatively high BMR values, hence questions have been raised about the universal applicability of those equations [10].

Predictive equations derived from a database with broader geographical and ethnic representation have been evaluated [11]. The accuracy of the latter equations

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Equations for estimating BMR from body weight (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>n</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>162</td>
</tr>
<tr>
<td>3–10</td>
<td>338</td>
</tr>
<tr>
<td>10–18</td>
<td>734</td>
</tr>
<tr>
<td>18–30</td>
<td>2,879</td>
</tr>
<tr>
<td>30–60</td>
<td>646</td>
</tr>
<tr>
<td>&gt;60</td>
<td>50</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>137</td>
</tr>
<tr>
<td>3–10</td>
<td>413</td>
</tr>
<tr>
<td>10–18</td>
<td>575</td>
</tr>
<tr>
<td>18–30</td>
<td>829</td>
</tr>
<tr>
<td>30–60</td>
<td>372</td>
</tr>
<tr>
<td>&gt;60</td>
<td>38</td>
</tr>
</tbody>
</table>
and those from Schofield were compared with published measurements of BMR in adults from different parts of the world, which were not part of the databases used to generate the predictive equations [12]. Although the new equations had some merits, such as reductions in prediction error and overestimation bias among men, these were not robust enough to justify the replacement of Schofield’s equations.

In our search for the possible mechanisms underlying the intersubject variability in BMR, we have explored the impact of body composition, gender, physical training, age, muscle metabolism, sympathetic nervous system (SNS) activity, and body temperature. Fat-free mass (FFM) accounts for two-third of the intersubject variance in BMR [6, 13] (Fig. 2). Additional predictors of BMR are fat mass and age. In combination, these three factors account for over 70% of the BMR variance in humans [13]. Keys et al. [14] investigated the effect of age and concluded that the decline in BMR with aging was less than 1–2% per decade from the second to the seventh decade of life. Subsequent work supported Keys’ conclusion that the decrease in BMR seen in elderly people can be explained largely by decreases in FFM [15, 16].

The unexplained variance in BMR may be partially accounted for by the differences in organ size between subjects with similar FFM. Table 2 shows the relative contributions of various organs to BMR [5]. About half of FFM is skeletal muscle, however, this tissue accounts for only one-fifth of the BMR. In contrast, liver and brain constitute less than 5% of total body mass, but together account for two-fifth of BMR. New technologies, such as magnetic resonance imaging, are now being used to estimate organ sizes and better determine the differences in BMR among individuals [17, 18].

![Fig. 2](Image)

**Fig. 2** Relationship between BMR and fat-free mass (FFM) in humans. Relationships by simple regression analysis between 24-h energy expenditure (24EE), BMR, sleeping metabolic rate, and FFM in 177 subjects. The slopes are statistically different from each other whereas the intercepts are not different. By multiple regression analysis, the effect of percent activity × weight on 24EE is given for 118 subjects.
The activity of the SNS is involved in the regulation of BMR [19, 20]. Using a direct measurement of SNS activity via microneurography, we found that the variability in energy expenditure was related to the variability of muscle sympathetic nerve activity [21]. The variability in BMR after adjustment for differences in FFM, fat mass, and age was also related to the variability in body temperature, indicating that body temperature could be a marker for high or low relative metabolic rate [22]. Some of the remaining variance was explained by family membership, suggesting that BMR is at least partly determined by genetics [23, 24].

**Thermic Effect of Food**

The thermic effect of food (TEF) is the increase in energy expenditure observed after a meal. The TEF includes the energy required for ingestion and digestion of food, and for absorption, transport, interconversion, oxidation, and deposition of nutrients. The TEF has also been called “specific dynamic action” of food or “dietary-induced thermogenesis.” The TEF accounts for 5–15% of the BMR over 24 h [25, 26]. Many factors influence the TEF, including the meal size and composition, palatability of food, time of the meal, subject’s genetic background, age, physical fitness, and insulin sensitivity. Brundin et al. [27] showed that TEF is also a function of the heat leakage across the abdominal wall, which is inversely related to the thickness of the abdominal adipose tissue layer. These factors together with the techniques of energy measurement, e.g., the position of the subject and the duration of the measurement, make TEF the most difficult and least reproducible component of daily energy expenditure to assess [26].

**Physical Activity**

Physical activity, the most variable component of daily energy expenditure, can account for a significant amount of calories in very active people. However, sedentary adult individuals exhibit a range of physical activity, which represents only 20–30%
of total energy expenditure (TEE) (Fig. 1). Until the introduction of the doubly labeled water method for measuring 24-h energy expenditure in free-living conditions [28], there was no satisfactory method to assess the impact of physical activity on daily energy expenditure. Physical activity level (PAL) can be measured or estimated from the 24-h TEE to BMR ratio (PAL = TEE/BMR). Multiplying the PAL by the BMR gives the actual daily energy requirements. For example, a male with PAL value of 1.75 and BMR value of 1,697 kcal/day would have an energy requirement of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Examples of activities performed by sedentary, moderate, or vigorous lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily activities</td>
<td>Time (h)</td>
</tr>
<tr>
<td><strong>Sedentary or light active lifestyle</strong></td>
<td></td>
</tr>
<tr>
<td>Sleeping</td>
<td>8</td>
</tr>
<tr>
<td>Dressing, showering</td>
<td>1</td>
</tr>
<tr>
<td>Eating</td>
<td>1</td>
</tr>
<tr>
<td>Cooking</td>
<td>1</td>
</tr>
<tr>
<td>Office work, tending shop</td>
<td>8</td>
</tr>
<tr>
<td>General household work</td>
<td>1</td>
</tr>
<tr>
<td>Driving car to/from work</td>
<td>1</td>
</tr>
<tr>
<td>Walking at varying paces without a load</td>
<td>1</td>
</tr>
<tr>
<td>Watching TV, chatting</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
</tr>
<tr>
<td><strong>Active or moderately active lifestyle</strong></td>
<td></td>
</tr>
<tr>
<td>Sleeping</td>
<td>8</td>
</tr>
<tr>
<td>Dressing, showering</td>
<td>1</td>
</tr>
<tr>
<td>Sleeping</td>
<td>8</td>
</tr>
<tr>
<td>Walking at varying paces without a load</td>
<td>1</td>
</tr>
<tr>
<td>Low intensity aerobic exercise</td>
<td>1</td>
</tr>
<tr>
<td>Watching TV, chatting</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
</tr>
<tr>
<td><strong>Vigorous or vigorously active lifestyle</strong></td>
<td></td>
</tr>
<tr>
<td>Sleeping</td>
<td>8</td>
</tr>
<tr>
<td>Dressing, showering</td>
<td>1</td>
</tr>
<tr>
<td>Eating</td>
<td>1</td>
</tr>
<tr>
<td>Cooking</td>
<td>1</td>
</tr>
<tr>
<td>Nonmechanized agricultural work (planting, weeding, gathering)</td>
<td>6</td>
</tr>
<tr>
<td>Collecting water/wood</td>
<td>1</td>
</tr>
<tr>
<td>Nonmechanized domestic chores (sweeping, washing clothes and dishes by hand)</td>
<td>1</td>
</tr>
<tr>
<td>Walking at varying paces without a load</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous light leisure activities</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
</tr>
</tbody>
</table>
1.75 × 1,697 = 2,970 kcal/day. Schulz and Schoeller [29] have provided data on more than 200 subjects showing a wide variability in TEE and physical activity. In a review of 574 doubly labeled water measurements, Black et al. [30] compiled data to establish the limits of sustainable human energy expenditure, determine the average range of habitual energy expenditure in relation to age and sex, and evaluate the lifestyle and activity patterns associated with different levels of physical activity. From this review, Black et al. showed a modal value for PAL of 1.60 (range 1.55–1.65) for both men and women from affluent societies in developed countries, with a predominantly sedentary lifestyle. A joint FAO/WHO/UNU report on Human Energy Requirements [10] classified as sedentary or light activity lifestyle, individuals with a PAL value between 1.40 and 1.69. Active or moderately active lifestyle corresponds to PAL value between 1.70 and 1.99, and vigorously active lifestyle corresponds to PAL values between 2.00 and 2.40. The PAL values that can be sustained for a long period of time in free-living adult populations fall in the range of 1.40–2.40. It is thought that PAL values of 1.70 or higher will reduce the risk of becoming overweight and developing a variety of noncommunicable chronic diseases often associated with obesity. Table 3 shows typical activities performed under a sedentary, moderate, or vigorous lifestyle conditions. Table 4 shows the frequency, duration, and intensity of physical activity recommended by selected organizations.

Table 4  Minimum frequency, duration, and intensity of physical activity recommended by different organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organization (2002)</td>
<td>30 min of moderate activity every day</td>
</tr>
<tr>
<td>World Cancer Research Fund/American Institute for Cancer Research (1997)</td>
<td>30 min of vigorous or 60 min of moderate activity daily, plus additional 30–60 min of vigorous activity once a week</td>
</tr>
<tr>
<td>Unites States Centers for Disease Control and Prevention (1996)</td>
<td>30 min of moderate activity on all or most days of the week</td>
</tr>
<tr>
<td>American College of Sports Medicine (1998)</td>
<td>For cardio-respiratory fitness and body composition: 20–60 min of continuous or intermittent (bouts of at least 10 min) aerobic activity at 55–90% maximum heart rate, or at 40–85% maximum oxygen uptake, 3–5 days/week For muscular strength and endurance, body composition and flexibility: one set of 8–10 exercises, with 8–12 repetitions of each exercise, 2–3 days/week</td>
</tr>
<tr>
<td>International Agency for Research on Cancer (2002)</td>
<td>To maintain healthy body weight: 60 min moderate activity on all or most days of the week For cancer prevention: Substitute moderate for vigorous activity several times per week</td>
</tr>
<tr>
<td>International Association for the Study of Obesity (2002)</td>
<td>To prevent weight regain in formerly obese individuals: 60–90 min of moderate daily activity or shorter periods of vigorous activity To prevent transition to overweight or obesity: 45–60 min of moderate activity daily or 1.7 PAL. For children, more activity time is recommended</td>
</tr>
</tbody>
</table>
Measurement of Energy Expenditure

Energy expenditure can be measured by several methods; however, those with higher accuracy and precision are more expensive.

**Direct Calorimetry**

The measurement of the energy expenditure was first made in the late eighteenth century by Lavoisier, who discovered that respiration was the basis of all life-sustaining processes, and that life was a form of chemical combustion [31]. Lavoisier measured the rate at which heat was lost from the body to the environment [31]. Heat loss from the body includes non-evaporative heat loss, and evaporative heat loss in the form of water vapor. Non-evaporative heat loss is determined from the temperature gradient across the walls of a well-insulated chamber. Evaporative heat loss is measured by determining the increase in water content in the air in the test chamber and calculating its latent heat of condensation. Heat loss is estimated from the sum of evaporative and non-evaporative loss. Although very accurate, the measurement of energy expenditure by direct calorimetry is not done often, because an easier estimation of the energy expenditure can be obtained from the chemical reactions that release heat.

**Indirect Calorimetry**

The transformation of food nutrients to a usable source of energy requires oxygen. One liter of oxygen consumed generates approximately 5 kcal (~21 kJ). Given that there is proportionality between $\text{VO}_2$ and ATP synthesis, and because each mole of ATP synthesized is accompanied by a given amount of heat, it is possible to calculate heat production from $\text{VO}_2$ measurements alone. However, the heat produced by the utilization of 1 L of oxygen varies according to the proportion in the diet of carbohydrate, fat, and protein. By measuring carbon dioxide production, oxygen consumption, and urinary nitrogen excretion, it is possible to determine the proportion of the different nutrients that are oxidized, and the energy produced can be precisely calculated [6, 31]. This indirect calorimetry method takes into account the heat released by the oxidation of the three macronutrients. Three measurements must be carried out: oxygen consumption, carbon dioxide production, and protein oxidation. Gas exchange is measured using oxygen and carbon dioxide analyzers and flow, while protein oxidation is estimated from urinary nitrogen excretion rate. Indirect calorimetry predicts heat production (energy expenditure) from the rates of respiratory gas exchange and nitrogen excretion. The subject is kept in a sealed room or a canopy is placed over his head. The chamber or canopy is ventilated with a constant supply of fresh air. The subject's respiratory gas exchange is measured by comparing the composition of well-mixed air in the chamber with the composi-
Principles of Human Energy Metabolism

The measurement of air entering the chamber, together with the flow rate of air through the system. After determining how much oxygen is consumed, carbon dioxide produced, and urinary nitrogen excreted, energy expenditure can be calculated using one of many equations. A difference less than 4% in energy expenditure is observed between equations due to slightly different constants for the amounts of oxygen consumed and carbon dioxide produced during oxidation of the three classes of nutrients, i.e., fat, carbohydrate, and protein [31].

\[
\text{MR (kcal / day)} = 3.941 \text{VO}_2 (\text{L / day}) + 1.106 \text{VCO}_2 (\text{L / day}) - 2.17 \text{N}_{\text{urine}} (\text{g / day}),
\]

where MR is the metabolic rate; \( \text{VO}_2 \), oxygen consumption; \( \text{VCO}_2 \), carbon dioxide production; and \( \text{N}_{\text{urine}} \) is the nitrogen excreted in urine.

The correction for urinary nitrogen resulting from incomplete combustion of protein is small, and a value of 12 g/day (0.5 g/h) is often used for the calculation of metabolic rate.

The ratio between carbon dioxide and oxygen is known as the respiratory quotient (RQ) or respiratory exchange ratio. Each nutrient requires a given amount of oxygen to be oxidized and releases a given amount of carbon dioxide. The oxygen and carbon dioxide exchange in a system can then indicate the proportion of nutrients participating in the ATP production. Because proteins are not completely oxidized, the ratio between \( \text{VCO}_2 \) and \( \text{VO}_2 \) is calculated only for fat and carbohydrate, which is known as the nonprotein RQ. The RQ in healthy humans usually ranges between 0.7 and 1.0, and its variability depends on the availability of carbohydrate, fat, and protein for oxidation. When fat is the only nonprotein fuel available, this ratio approaches 0.7, whereas, when carbohydrate is solely oxidized, RQ is equal to 1.0. The proportion of energy coming from carbohydrate and fat, and the kilocalories expended per liter of oxygen consumed can be calculated using these equations [4]:

\[
\text{CHO\%} = \frac{504.7(\text{npRQ} - 0.707)}{[5.047(\text{npRQ} - 0.707) + 4.686(1.00 - \text{npRQ})]}
\]

\[
\text{Fat\%} = \frac{468.6 (1.00 - \text{npRQ})}{[5.047(\text{npRQ} - 0.707) + 4.686(1.00 - \text{npRQ})]}
\]

\[
\text{kcal} = 4.686 + \left( \frac{(\text{npRQ} - 0.707)}{0.293} \right) 0.361
\]

where CHO % is the proportion of energy coming from carbohydrate; Fat %, proportion of energy coming from fat; kcal, kilocalories expended per liter of oxygen consumed; and npRQ, nonprotein respiratory quotient, nonprotein \( \text{VCO}_2 / \text{nonprotein VO}_2 \).

Indirect calorimetry is largely used to measure BMR or RMR for short periods of time (minutes to hours). Using respiratory chambers, energy metabolism can be measured for longer periods, up to several days. However, subjects confined to a metabolic chamber have an energy expenditure which is usually not fully represen-
Doubly Labeled Water

Free-living energy expenditure can be measured by doubly labeled water [28, 32]. The method consists of giving a single oral dose of water enriched in two stable isotopes: deuterium (\(^2\)H) and \(^{18}\)Oxygen (\(^{18}\)O). Because the natural abundance of these isotopes is very low, body water is labeled by both isotopes. After equilibrium is reached in 3–6 h, the loss of \(^{18}\)O occurs as CO\(^{18}\)O and H\(_2^{18}\)O, since a rapid exchange of \(^{18}\)O between water and carbon dioxide takes place via the carbonic anhydrase enzyme, whereas deuterium is lost only in water. Enrichments in \(^{18}\)O and \(^2\)H are performed by isotope ratio mass spectrometry usually in urine or saliva. The calculation of carbon dioxide production rate is based on the difference in turnover rates between the oxygen and hydrogen labels. Because oxygen has two routes of elimination (expired carbon dioxide and water in urine, saliva, sweating, etc.), the disappearance rate of \(^{18}\)O will be faster than of \(^2\)H, which is eliminated as water in urine, saliva, sweating, etc. After log-transformation of isotope disappearance rates, the difference between the slopes for \(^2\)H and \(^{18}\)O is proportional to the amount of carbon dioxide produced in a given time (Fig. 3). Assuming a 24-h RQ value of 0.85, oxygen consumption and hence the energy expenditure can be calculated. The doubly labeled water method is an excellent field technique, which has been validated by comparing results to those obtained in a metabolic chamber [33].

Factorial Method

When experimental data on TEE are not available, it can be estimated by factorial calculations based on the time allocated to activities that are habitually performed and the energy cost of those activities. Factorial calculations combine two or more components or “factors,” such as the sum of the energy spent while sleeping, resting, working, doing social or discretionary household activities, and in leisure. Energy spent in each of these components may in turn be calculated by knowing the time allocated to each activity and its corresponding energy cost.

Energy Balance and Implications for Obesity

Energy homeostasis is disturbed when food supply is restricted or food intake is increased. In response to energy restriction, several compensatory mechanisms including increasing appetite, reduction of physical activity, and enhancement of
Fig. 3 Doubly labeled water technique. Theoretical time course of enrichments of isotopes of oxygen and hydrogen in body water after administration at time zero. Over an equilibration period of several hours the isotope enrichments reach a peak. If the amount of isotope administered is known, the peak enrichment can be used to estimate the volume of dilution space. After equilibration, the isotopes are washed out of the body along an exponential curve that is linear when expressed as log of the enrichment above background. The oxygen isotope leaves the body faster than the hydrogen isotope because it is washed out of the body by water and carbon dioxide. Carbon dioxide production and energy expenditure are estimated based on the divergence in enrichments at times 1 and 2. During the 4–14 days of the study in normal adults, they are free to engage in usual activities without being confined in a calorimetry chamber.
the coupling between oxidation and ATP synthesis are engaged. When negative energy balance is maintained for a longer period, the adaptation includes increasing energy efficiency, in order to prevent further weight loss [34, 35]. In contrast, overfeeding causes a suppression of appetite and an increase in energy expenditure, with probably a reduction in energy production efficiency [36]. However, such adaptation to energy surplus seems unable to prevent weight gain, in contrast to the ability of the metabolic response to energy deprivation to prevent weight loss.

During long-term energy balance, macronutrient oxidation has to eventually match macronutrient intake such that no macronutrients are stored or lost [37]. In other words, not only does 24-h energy expenditure have to be equal to 24-h energy intake, but 24-h RQ has to be equal to 24-h food quotient (FQ). The 24-h RQ corresponds to the mean proportion of macronutrient oxidized over a day whereas 24-h FQ represents the proportion of daily dietary macronutrients available for oxidation [4]. Many studies have shown that when people are in energy balance, 24-h RQ eventually matches 24-h FQ [38–42]. Both day-to-day variations in energy/macronutrient intake and day-to-day changes in energy expenditure lead to either slightly positive or negative energy balance. In response to these short-term variations in energy balance, carbohydrate and protein stores are closely regulated by an adjustment of oxidation to intake. Consequently, positive or negative energy balances are mostly buffered by changes in fat stores as evidenced by the tight correlation between fat storage and energy balance [43].

Obesity results from a chronic imbalance between energy intake and energy expenditure, resulting in weight gain, mostly as fat. If the origins of positive energy balance lies in a chronic imbalance of energy intake and expenditure, a key question is “How does this imbalance between intake and expenditure happen? An examination of the contribution of a particular nutrient to energy balance is only valid if that nutrient has a separate balance equation, implying a separate regulation (Fig. 4). Is each nutrient oxidized or stored in its own compartment (separate regulation), or does it get converted into another compartment for storage? This applies particularly to carbohydrate that can be converted to fat via de novo lipogenesis. The latter occurs only when large amounts of carbohydrate are ingested [44–47].

**Protein Balance**

Protein intake usually accounts 15% of total calories ingested, but protein stores in the body represent about one-third of the total stored calories in a 70-kg man. The daily protein intake amounts to a little over 1% of the total protein stores [48] (Fig. 4). The protein stores increase in response to growth hormone, androgens, and strength and weight bearing exercises, but do not increase simply from increased dietary protein. Protein stores are, therefore, tightly controlled and protein balance is maintained on a day-to-day basis [43]. It is doubtful that protein imbalance plays
Principles of Human Energy Metabolism

Carbohydrate Balance

Carbohydrate is often the main source of dietary calories, yet the body stores of glycogen are very limited: 500–1000 g of carbohydrate in the form of glycogen [48]. The daily caloric intake of carbohydrate corresponds to about 50–100% of carbohydrate stores [49] (Fig. 4). Thus, the carbohydrate stores fluctuate markedly over hours and days, compared to protein and fat stores. However, as with protein stores, carbohydrate stores are tightly controlled even if the mechanisms are unknown [43]. Whether carbohydrate control is based on humoral and/or neural signals exchanged between the muscle and liver and the brain remains to be established. Dietary carbohydrate intake stimulates both glycogen storage and glucose oxidation and suppresses fat oxidation [37]. That which is not stored as glycogen, is oxidized (not converted to fat), and carbohydrate balance is achieved. Like other nonfat nutrients, chronic imbalance between carbohydrate intake and oxidation is unlikely to be an explanation for weight gain, because storage capacity is limited and controlled.
Fat Balance

In marked contrast to glycogen and protein stores, fat stores are large. Fat intake represents less than 1% of the total fat stores [48] (Fig. 4). Fat stores are the energy buffer for the body. The daily surplus or deficit in energy intake is translated into surplus or deficit in fat stores [43, 50]. Energy balance and diet macronutrient composition are the main determinants for fat oxidation [43, 51]. For example, a deficit of 200 kcal of energy over 24 h means 200 kcal comes from the fat stores, and the same holds true for an excess of 200 kcal of energy, which ends up in the fat stores. Additionally, diets with high fat-to-carbohydrate ratios result in a progressive increase in fat oxidation over periods of days [52].

In summary, when energy balance in humans is considered under physiological conditions, fat is the main nutrient capable of sustaining a chronic imbalance between intake and oxidation, and thus contributing to an increase in adipose tissue. The other nutrients influence adiposity indirectly by their contribution to overall energy balance. The use of the fat balance equation, instead of the energy balance equation, offers a new framework for understanding the pathogenesis of obesity.

Metabolic Risk Factors for Weight Gain

An understanding of the etiology of human obesity demands longitudinal studies. Cross-sectional studies have added little to our understanding of the physiological mechanisms predisposing to weight gain [53]. Cross-sectional studies can only provide associations, whereas longitudinal studies reveal predictors or risk factors. Several studies have examined such predictors in Pima Indians, a population prone to obesity [54] (Fig. 5). Other studies have been done in African-American population, another population prone to obesity [55, 56].

Low Metabolic Rate

The relation between metabolic rate and body size suggests that, at any given body size, individuals can have a “high,” “normal,” or “low” relative metabolic rate. From our own studies in adult nondiabetic Pima Indians, we found that a low relative metabolic rate adjusted for differences in FFM, fat-mass, age, and sex was a risk factor for body weight gain [57]. After 4 years of follow-up, the risk of gaining 10 kg was approximately eight times greater in subjects with the lowest RMR (lower tertile) compared with those with the highest RMR (higher tertile). According to a meta-analysis, formerly obese subjects have a 3–5% lower mean relative RMR than control subjects, which likely contributes to the high rate of weight regain in formerly obese persons [58]. Nevertheless, these data need to be
Interpreted with caution because the variability of baseline energy expenditure accounted for only 16% of the variability of weight gain. Theoretical estimates suggest that only 30–40% of the increase in body energy stores in people who gained weight can be attributed to the baseline “deficit” in energy expenditure. Furthermore, relatively low energy expenditure does not seem to be a predictor of weight gain in other adult populations [59, 60]. Together, the results suggest that a low metabolic rate may not be only a direct risk factor for body weight gain but also a marker for inactivity or hyperphagia.

**Low Physical Activity**

Reduced physical activity, as a cause of obesity is an attractive hypothesis. The energy expended in physical activity is quite variable and the secular increase in obesity parallels the increase in sedentary lifestyles. Physical activity may have decreased in many populations over the past few decades with the increased number of cars per household and the increase in the numbers of hours spent in front of television sets or personal computers [61]. However, Westerterp and Speakman concluded that decreased energy expenditure via decreased physical activity is unlikely the cause of the obesity epidemic [62]. Using doubly labeled water data, they could not find major differences in physical activity in
Westernized populations as well as developing countries. Furthermore, they could not find a decrease in physical activity measures over the past 3–4 decades. Swinburn et al. used data from 963 children and 1,399 adults to calculate the energy flux for given body weights [63, 64]. Using such equations to estimate changes in energy intake in the United States from 1970s to the 2000s, it was determined that virtually all the weight gain in the United States appeared to be due to increased energy intake rather than decreased energy expenditure. Whether a low level of physical activity is a cause or a consequence of obesity can only be tested in prospective studies. Some studies indicate that patients engaging in considerable amount of physical activity up to 80 min/day are successful at maintaining weight loss [65].

Another component of 24-h energy expenditure is the energy cost of spontaneous physical activity, that accounts for 8–15% of the total daily expenditure [6]. Consistent with the cross-sectional observation of a decrease in spontaneous physical activity in obese subjects, our longitudinal studies showed that even in the confined environment of a respiratory chamber, spontaneous physical activity is a familial trait and that a low level of spontaneous physical activity is associated with subsequent weight gain in males, but not in females [66]. Other data show that resistance to the development of obesity may be due to spontaneous physical activity, also called non-exercise activity thermogenesis (NEAT) [67, 68]. An increase in NEAT by 200 kcal/day would be the equivalent to engaging in 2.5 h/day of activities such as fidgeting or strolling.

**Low Fat Oxidation**

The composition of nutrient intake has been shown to be an important factor in the pathogenesis of obesity. Apart from the effect of diet composition, the RQ is also influenced by recent energy balance (negative balance causing more fat oxidation), sex (females tend to have reduced fat oxidation), adiposity (higher fat mass leads to higher fat oxidation), and family membership, suggesting genetic determinants [51, 69].

In a longitudinal study in Pima Indians, a high 24-h RQ predicted weight gain [51]. Those in the ninetieth percentile for RQ (“low fat oxidizers”) had a 2.5 times larger risk of gaining 5 kg or more body weight than those in the tenth percentile (“high fat oxidizers”). This effect was independent of a relatively low or high 24-h metabolic rate. In support of this observation, others have demonstrated that weight-reduced obese volunteers have high RQs, i.e., low rates of fat oxidation [70, 71], and those who are able to maintain weight loss have lower RQs compared to those experiencing weight relapse [72]. A low fat oxidation could lead to higher carbohydrate oxidation, which would decrease carbohydrate store. The size of carbohydrate store has been inversely related to food intake in mice [73] and humans [74], and prospective weight gain in humans [75]. Mechanisms accounting for this relationship remain unclear.