Nutritional and Metabolic Bases of Cardiovascular Disease

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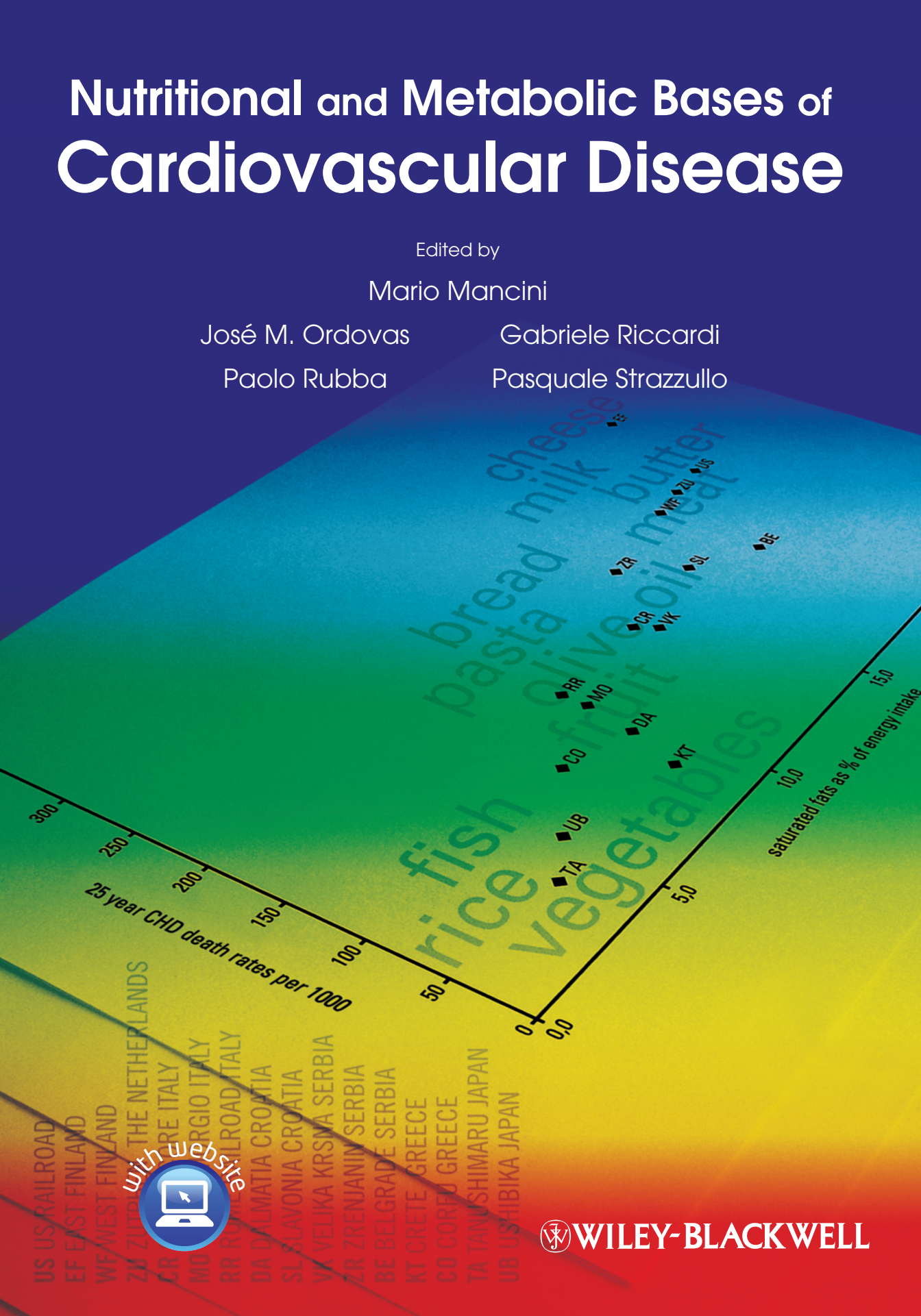

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Foreword

Examination of trends in cardiovascular disease indicates that this is in many ways the best of times, while the worst of times may loom in the future. Fifty years after William Kannel first introduced the term "risk factor," enormous strides have been made in controlling the epidemic of cardiovascular disease in industrialized countries by preventive measures and increasingly successful treatments focused on the cardinal risk factors of dyslipidemia, hypertension and smoking and on their atherosclerotic sequelae. Age-adjusted death rates for some major cardiovascular events have been reduced by more than 50% and the relative focus of research efforts is shifting toward cancer and other conditions.

While there is cause for celebration, there is an even greater need at present to recognize the storm clouds on the horizon. The world-wide epidemics of obesity and diabetes are laying the groundwork for a new "rising tide" of cardiovascular disease stimulated by mechanistic pathways that are at present only incompletely understood, and in general poorly managed by either preventive or therapeutic strategies. To meet this challenge, there is a pressing need for those interested in cardiovascular disease to learn what is known and to identify the many gaping gaps in knowledge about the new driving forces of the future cardiovascular disease epidemic.

In this context, the present textbook entitled *Nutritional and Metabolic Bases of Cardiovascular Disease* makes a timely and extremely important contribution by bringing together in one source a comprehensive examination of the factors driving the emerging second epidemic of cardiovascular disease. The Editors, led by Professor Mario Mancini, have drawn together an international array of experts who provide up-to-date profiles of the state of the knowledge about a wide array of topics. The vast range of topics related to nutritional and metabolic aspects of cardiovascular disease are addressed with sensible grouping of chapters that consider Nutritional Habits and Obesity; the Metabolic Syndrome and Diabetes; Hypercholesterolemia and Early Atherosclerosis; Nutrition, Hypertension and Cerebrovascular Disease; Hemostasis and Thrombosis; and Nutrition, Metabolism and the Aging Process. The comprehensive nature of *Nutritional and Metabolic Bases of Cardiovascular Disease* and its thoughtful arrangement make it an outstanding source for readers who need up-to-date information on a focused topic, those who seek a multifaceted view of one or more of the above topic areas, and for others who want to be comprehensively informed about the basis of the coming wave of metabolically-driven cardiovascular disease.

Richard B. Devereux, M.D.

Preface

At the dawn of the third millennium, cardiovascular disease still represents the main cause of disability and death.

This condition is mostly mediated by atherosclerosis and the ensuing atherothrombosis that leads to ischemic heart, cerebral, and peripheral vascular disease. Our current understanding of the etiopathogenesis of atherosclerosis and the related coronary and extracoronary ischemic complications has greatly progressed, allowing us to make a strong and determined commitment to primary and secondary prevention.

Malnutrition due to excess saturated fat intake is undoubtedly the primary risk factor, as very keenly perceived and highlighted by Ancel Keys in Naples back in the 1950s. Here, he had the insight that the Mediterranean Diet played a protective role toward coronary heart disease. In fact, this was quite a rare condition in southern Italy in those days contrarily to the United States and northern European countries such as the Netherlands or Finland, where the habitual consumption of saturated fat was remarkably higher than in southern Italy. A family predisposition to cardiovascular diseases does indeed exist and is generally mediated by hyperlipidemia, high blood pressure, and thrombophilia; however, even in cases of clear family history, dietary habits contribute to improve or worsen the underlying metabolic conditions that are eventually responsible for the injury to the heart or vessels. The growing prevalence of obesity and diabetes, along with the increase in the elderly population, has further contributed to the current high trend in cardiovascular diseases worldwide.

Scientific research has made giant steps in understating the interaction between nutrition, metabolism, and molecular genetics in relation to the causes of cardiovascular diseases; we therefore felt that the most significant evidence produced in recent years deserved to be put together in a monograph. These data have been subdivided into six separate sections, spacing from nutrition to obesity (*section 1*), the metabolic syndrome to diabetes (*section 2*), hypercholesterolemia to atherogenesis (*section 3*), high blood pressure to cardio-cerebrovascular diseases (*section 4*), hemostasis to atherothrombosis (*section 5*), and diet to aging processes (*section 6*).

There is clearly a common thread in all the sections: the close relationship between type of dietary habits, metabolic processes of the nutrients, and the possibly severe pathogenic consequences on the cardiovascular system.

We are grateful to all of the authors who participated in this initiative with their scientific contributions, and to Wiley-Blackwell who welcomed our proposal to publish this book, which we dedicate to the memory of Ancel Keys, with gratitude from all his scholars.

SECTION I

Nutrition and Obesity

CHAPTER 1

Basics of Energy Balance

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Introduction

The aim of this chapter is to concisely discuss the basic concepts related to the utilization of energy in the human body. In addition, background information is provided about the practical use of these concepts. These issues are considered in more detail in chapters of books and other major publications on human nutrition to whom the reader may refer for further explanations [1–9]. Other references are indicated in the text only for more specific points. The human being needs energy to sustain life and maintain the structural and functional integrity of the body. The energy is used by cells to perform chemical work (synthesis and degradation of molecules), mechanical work (muscular contraction), and electrical work (maintenance of ionic gradients across membranes), and eventually lost in the form of heat or external work or is stored (mostly in the adipose tissue as triacylglycerols) if energy balance is positive.

The first law of thermodynamics states that energy cannot be created or destroyed, but only transformed. Human body attains energy from foods where it is stored in the chemical bonds of macronutrients (carbohydrates, fats, and proteins) and alcohol. Through biochemical transformation the energy of nutrients is made available to the body mostly as adenosine triphosphate (ATP), but this conversion into high-energy biochemical compounds is an inefficient process, with 50% of the original energy lost as heat. Furthermore, since a certain percentage of ATP is needed for the transport, storage, and recycling of macronutrients, actual ATP yields correspond to 90%, 75%, and 55% of those expected on the basis of pure oxidation of fats, carbohydrates, and proteins, respectively. In other words, the synthesis of one mole of ATP that can be used by the body requires about 20 kcal for fats, 24 kcal for carbohydrates, and 33 kcal for proteins.

Since all the energy used by the body is ultimately lost as heat (including that related to external work), energy is usually expressed using the calorie, which is defined as the amount of heat energy needed to raise the temperature of 1 ml of water at 15 °C by 1 °C. Actually, according to the SI system, the unit for energy is the joule (J), which measures energy in terms of the mechanical work required to accelerate a mass of 1 kg with a force of 1 newton through 1 m along the direction of the force. Because calorie and joule are small units, considering energy balance, for practical reasons, kilocalorie (kcal = 1,000 cal), kilojoule (kJ = 1,000 J), and sometimes megajoule (MJ = 1,000,000 J) are commonly used in human nutrition. The equivalence is indicated as 1 kcal = 4.184 kJ (in some texts, 4.186) with the inverse ratio of 0.239.

Food Energy

The *gross energy of food* is the energy contained in the chemical bonds of macronutrients (carbohydrates, fats, and proteins) and alcohol and can be determined using a bomb calorimeter, which is an instrument that measures heat production due to complete oxidation of organic molecules. The gross energy of food (in kcal/g: 4.10 for carbohydrates, 9.45 for fats, 5.65 for proteins, and 7.10 for

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alcohol) is not entirely available to the body. First, some energy is lost in feces because of incomplete absorption of macronutrients from the digestive tract; the energy available after ingestion of food is termed *digestible energy*. The absorption rate of macronutrients is usually considered very high–97% for carbohydrates, 95% for fats, and 92% for proteins–but it could be much lower for high-fiber diets, especially with respect to protein digestibility. Once in the body, carbohydrates and fats are completely oxidized to water and carbon dioxide, but this is not the case for proteins. Nitrogen is not oxidized to nitrogen oxides, which are toxic, but to urea, which is much less toxic, and this molecule still contains a quarter of the chemical energy of original proteins. Small amounts of other, not completely oxidized nitrogenous molecules such as amino acids, 3-methyl-hystidine, and creatinine are also lost in the urine. The energy made available to the body after taking into account losses in feces and urine is termed *metabolizable energy*; the corresponding energy values (kcal/g) are the ones commonly used in human nutrition: 3.75 for monosaccharides, 3.94 for disaccharides, 4.13 for starch, 9.00 for fats (triglycerides composed of long-chain fatty acids), 4.00 for proteins, and 7.00 for alcohol. A figure of about 1.5 kcal/g has also been proposed for dietary fiber, as it can be metabolized (fermented) in the large bowel by bacteria to short-chain fatty acids, which can be subsequently absorbed and utilized in the body.

Components of Total Energy Expenditure

Total energy expenditure (TEE), usually expressed as 24-hour energy expenditure, comprises three main components (basal metabolic rate, thermic effect of food, and energy expenditure due to physical activity), plus a number of additional components that may be relevant in specific circumstances (Table 1.1).

Table 1.1 Components of energy expenditure.

Basal metabolic rate (BMR)
Thermic effect of food (TEF)
Energy expenditure due to physical activity (EEPA)
Exercise activity thermogenesis (EAT)
Nonexercise activity thermogenesis (NEAT), including fidgeting
Other thermogenic stimuli
Psychological thermogenesis
Cold-induced thermogenesis
Drug-induced thermogenesis

The term *diet-Induced thermogenesis* indicates the variations in BMR and TEF due to true metabolic adaptation to chronic underfeeding or overfeeding.

Basal Metabolic Rate

Basal metabolic rate (BMR) is by far the most important component of TEE in a very large percentage (60%–75%) of individuals, and more markedly in sedentary people. BMR corresponds to the energy needed in basal conditions to sustain the metabolic activities of cells and tissues and to maintain vital functions (e.g., circulatory, respiratory, gastrointestinal and renal processes, and body temperature) when the subject is awake and alert; sleeping metabolic rate is 5%–10% lower than BMR.

BMR is determined in standard conditions avoiding any effect of food or physical activity, with the subject lying at physical and mental rest in a comfortably warm environment (thermoneutral environment) and in the post-absorptive state. In practice, according to a realistic protocol, BMR is measured in the first part of the morning after the subject has been in the supine position for 30 minutes, at least 12 hours after eating food or taking any stimulants such as coffee or smoking. Heavy physical activity should also be avoided during the day prior to the test. Resting metabolic rate (RMR) is the term used when the conditions for the measurement of BMR are substantially but not completely met (e.g., because of a shorter fasting period and heavy physical exercise the day before). RMR is, therefore, expected to be slightly higher than BMR. BMR and RMR are usually expressed in kcal/min or, if extrapolated to 24 hours to be more meaningful, in kcal/day. In the latter case, the terms basal energy expenditure (BEE) and resting energy expenditure (REE) are usually (and more appropriately) used.

A number of factors cause the BMR to vary among individuals. By far, body size (i.e., body weight) is the most important one. Heavier people have higher metabolic rates than lighter ones. As metabolic processes that require energy occur

almost exclusively within the cytosol and mitochondria, BMR is strictly related to fat-free mass (i.e., body weight minus body lipids) and body cell mass. Brain, liver, kidney, and heart, which together represent 5%–6% of body weight, are the most metabolically active organs, accounting for more than 50% of BMR. For the same amount of tissue, their metabolic rate is much higher than that of skeletal muscles. Indeed, skeletal muscles contribute 20%–30% of BMR in adults because of its large mass, while adipose tissue (at least in people of average weigh) contributes to a small extent, as its metabolic rate per unit of weight is low. As far as metabolic processes are concerned, protein synthesis, Na-K ATPase pump, and gluconeogenesis account for a substantial proportion of energy utilization in basal conditions. Furthermore, BMR is subject to the control of the central nervous system and the sympathetic nervous system and is related to hormonal status (i.e., thyroid hormones and insulin).

In addition, for the same weight and height, BMR is higher in males than in females even after adjusting for body composition and, in women, is higher in the luteal compared to the follicular phase. Furthermore, BMR significantly declines with age in both genders. This trend is not entirely explained by the changes in body composition observed in older people; it may also be ascribed to a number of hormonal and metabolic changes related to senescence.

Thermic Effect of Food

The thermic effect of food (TEF) is the increase in energy expenditure occurring after the ingestion of energetic molecules (carbohydrates, fats, proteins, and alcohol) and is mostly associated with their digestion, absorption, and storage. An increase in energy expenditure can usually be observed from 4 to 6 hours after a mixed meal. Postprandial thermogenesis, specific dynamic action, thermic effect of feeding, and heat increment of feeding are other terms used to describe the same phenomenon.

TEF is influenced by the quantity and the type of macronutrients ingested. The thermogenic response is 5%–10% of ingested energy for carbohydrates, less than 5% for lipids, and 20%–30% for proteins, accounting on average for approximately 10%–15% of total energy intake (and TEE, if energy balance is neutral). The high TEF for proteins is due not only to the more complex processes of digestion and absorption but also to substantial postprandial changes in amino acid metabolism, leading to an overall increase of protein turnover.

A number of other factors have been indicated to affect TEF, for instance, overfeeding and underfeeding or physical exercise on the days prior to the test. Several studies have also shown variations due to age, genetic factors, weight changes, and physical fitness. Although these studies are relevant to metabolic and physiological knowledge, from a practical perspective, it is unlikely that in healthy individuals, and in the long term, differences in TEF may significantly influence TEE and energy balance.

Physical Activity

The third main component of TEE is the energy expenditure due to physical activity (EEPA), which is the energy expenditure for physical activities of all kinds. It is important to stress that physical activity does not always match the strict definition of muscular work, which implies external work performed on the environment. In fact, an increase in energy expenditure can also occur without any work in the case of just tensed and stretched muscles (e.g., isometric thermogenesis for standing up and dynamic thermogenesis for climbing down a ladder, respectively).

Energy expenditure due to physical activity can be further split into two components: Exercise activity thermogenesis (EAT) is the energy used during sport or fitness exercises, while non-exercise activity thermogenesis (NEAT) is due to occupational activities, leisure activities, and any other activity related to everyday life. In particular, NEAT also comprises fidgeting (spontaneous physical activity), which is a condition of restlessness, as manifested by continuous movements particularly of body segments. Finally, excess post-exercise oxygen consumption (EPOC) is an additional small increase in energy expenditure even after exercise has ceased, which is related to exercise intensity and duration.

EEPA, which widely varies among individuals as well as from day to day, depends on the type and intensity of a certain physical activity and on the combination of different physical activities over the day. It may also be influenced by the individual

habits of motion, as well as the speed and dexterity with which an activity is performed. The energy cost of each physical activity is commonly expressed as a multiple of BMR, and the term correspondingly used by the World Health Organization (WHO) [1] is physical activity ratio (PAR). The term *metabolic equivalents* (METs) is often used in the same way but is somewhat different. As a matter of fact, METs are multiples of resting oxygen consumption and the latter is not measured but calculated using a fixed rate of oxygen consumption (in adults, 3.5 mL/kg of body weight per minute). This means roughly 1.0 kcal/kg of body weight per hour, or 1.2 kcal/min in a man weighing 70 kg and 1.0 kcal/min in a woman weighing 60 kg. Comprehensive tables on the energy cost of different activities are easily available [1,2]. In general, PAR (or METs) ranges from 1 to 5 (e.g., 1.4 for standing, 3.3–4.5 for walking) but can reach much higher values (>8) for jogging, running, and selected occupational activities.

The overall level of physical activity can be defined by computing the ratio of TEE to BEE, termed physical activity level (PAL), or sometimes physical activity index (PAI). PAL can be used to describe physical activity habits, or to express how sedentary is the lifestyle of individuals. The Institute of Medicine [2] identified four categories in adults: sedentary, low active, active, and very active with respective PAL ranges of 1.0–1.3, 1.3–1.6, 1.6–1.9, and >1.9. The WHO proposed alternative classification criteria [1]: sedentary or light activity lifestyle for PAL = 1.40–1.69, active or moderately active lifestyle for PAL = 1.70–1.99, and vigorous or vigorously active lifestyle for PAL >2.00. For instance, performing one hour of moderate to vigorous activity every day (brisk walking to jogging/running, aerobic dancing, cycling, etc.) is sufficient to maintain an active lifestyle. Indeed, PALs of >2.00 are uncommon in industrialized countries.

Other Components of TEE

In addition to the three components already referred to, other minor thermogenic stimuli may be mentioned: psychological thermogenesis, as anxiety and stress increase BMR; cold-induced thermogenesis, due to exposure to low temperature; and drug-induced thermogenesis, for instance, related to the consumption of caffeine, nicotine, or alcohol. The actual impact of these factors on TEE is questionable and cannot easily be evaluated in the single individual.

In terms of energy balance, additional energy needs should be considered in specific circumstances, such as growth, pregnancy, and lactation. Briefly, the energy cost of growth is very high in the first three months of life but declines rapidly to 5% of energy intake in the second year of life, and then to 1%–2% until puberty, including both the cost to synthesize new tissues and the energy deposited in those tissues. The overall energy cost of pregnancy is on average approximately 75,000 kcal, being higher in the second and third trimesters, while during the first six months postpartum, on average an additional 675 kcal/day are needed for milk production if infants are exclusively breastfed.

Variability of TEE

To a very large extent, TEE varies even in people living in developed countries, where technology, which promotes a sedentary lifestyle, is commonly and widely used. All the factors that affect BEE (e.g., body weight and composition, age, and gender) also influence TEE, whereas TEF represents a quite constant and limited component. Large differences in TEE between subjects of the same gender, age, and weight (even >2,000 kcal/day) are accounted for mostly by variance in EEPA. In particular, differences in NEAT may be of great importance since most adults are not regularly involved in sporting-like activities (EAT). The between-subject differences in NEAT may be related to environmental and biological factors affecting both occupational and leisure-time activities, with fidgeting still very difficult to assess. It should be noted that extremely high values of TEE can be observed both in individuals with high levels of physical activity and in severely obese individuals (see below).

Energy Requirements

Energy requirement is defined by the Food and Agriculture Organization of the United Nations (FAO)/WHO/United Nations University (UNU) Consultation [1] as the amount of food energy needed to balance energy expenditure in order to maintain body size, body composition, and a level

of necessary and desirable physical activity consistent with long-term well-being and good health. This also includes the energy needed for growth (children and adolescents), deposition of tissues during pregnancy, and production of milk during lactation. According to this definition, energy requirement does not automatically correspond to TEE in a given individual, for instance, in underweight or obese or very sedentary people.

From a practical perspective, in order to avoid a negative outcome associated with underfeeding or overfeeding, it is crucial to assess TEE before commencing nutritional support in the single individual [9]. In this case, TEE could not correspond to energy requirement as above defined, for instance, in underweight or obese people (lower and higher than the desirable one, respectively).

Two different basic approaches may be used for the assessment of TEE [1,2,10], with an accuracy that is indeed still not completely known, especially in the single individual. In the first approach (simplified factorial method), BEE and PAL are considered [1,10]. BEE is measured by indirect calorimetry or estimated using predictive formulas including, in different combinations, easily measurable variables such as gender, age, weight, and height. As far as adult individuals are concerned, the most widely used among such formulas are still those published in 1919 by Harris and Benedict [11]. The equations proposed by Schofield et al. in 1985 [12] are frequently cited as well; they were derived for each gender and for different age ranges on the basis of a large number of data collected in several countries.

Once BEE is measured or estimated, PAL can be approximated by asking the subject to keep an activity diary or by using an appropriate questionnaire, and TEE is accordingly estimated by multiplying BEE by PAL. In the case of an activity diary, EEPA could also be calculated in absolute value (kcal/day) from recorded activities and their duration and then added to BEE.

The second approach for the assessment of TEE has been recently recommended by the Institute of Medicine as part of the Dietary Reference Intakes project [2]. In this case, BEE is neither measured nor estimated. Instead, as shown in Table 1.2, gender-specific equations for TEE are proposed, requiring four predictive variables: age, height, weight, and level of physical activity. The latter is expressed as a coefficient depending on the lifestyle category: sedentary, low active, active, and very active (see Table 1.2).

Energy Balance

The difference between the energy made available to the body (metabolizable energy) and TEE defines the energy balance. The traditional (static) energy balance equation is commonly expressed as

$$\text{Changes in energy stored in the body} = \text{metabolizable energy intake} - \text{total energy expenditure}$$

Neutral energy balance (or energy balance) is when the two factors are equivalent, with no changes in body energy stores. Because with common dietary habits, as observed in industrialized countries, there is little or no conversion of either proteins or carbohydrates to fatty acids, achieving neutral energy balance also means achieving neutral balance of each macronutrient.

Positive energy balance occurs when energy expenditure is low or energy intake is high, or with a combination of these two factors. The opposite is true for a negative energy balance. Short-term energy imbalance (over hours or days) is handled by the body through rapid changes in carbohydrate balance and glycogen stores, whereas over a prolonged period, there are changes in fat mass and fat-free mass. The amount of fat mass gained or lost depends on a number of factors, such as the extent of energy imbalance and the initial BMI. However, in normal conditions, fat-free mass and fat mass both increase during weight gain and decrease after weight loss.

The term adaptation describes the normal physiological responses of humans to different environmental conditions to preserve body functions and well-being as much as possible. Specifically, the maintenance of energy balance in spite of some alteration of the steady state may involve behavioral changes, variations in body composition, and true metabolic adaptation. For instance, changes of body weight per se are expected to modify different components of TEE in a direction that tends to oppose the original imbalance. Weight gain is

Table 1.2 Equations to estimate total energy expenditure (TEE) in adults as proposed by the Institute of Medicine.

Table not available in this electronic edition.

associated with an increase in fat-free mass as well as metabolically active tissues, leading to an increase in both BEE and the absolute energy cost of physical activity. On the other hand, true metabolic adaptation occurs when there are biochemical changes in cellular energy metabolism that cannot be related to other factors. In this regard, the term diet-induced thermogenesis has often been used to describe possible variations in BMR and TEF that are due to true adaptation to underfeeding or overfeeding.

A convincing, consistent example regarding adaptation and energy expenditure is offered by underfed adult subjects. It is a universal observation [13,14] that all the components of TEE are affected by chronic energy deficiency. The decrease in TEF is due to the reduced food intake and possibly to some true metabolic adaptation. BEE and EEPA decline because of the reduction in body mass, but EEPA declines also because of possible changes in spontaneous physical activity (unconscious economy of activity). Finally, and more interestingly, there is a decrease in BEE that is greater than it would be expected from the loss of body mass and fat-free mass [13,14]. This is a major factor in the protection against further weight loss, likely to be due to both

a reduction in cellular energy needs and changes in hormonal status (e.g., thyroid hormones) or in the activity of the sympathetic nervous system (leading to a true metabolic adaptation).

Much more difficult is to discuss the issue of adaptation during positive energy balance.

Since dietary energy excess may vary significantly from day to day, results obtained in experimental overfeeding studies can difficult to extrapolate to everyday life, for instance, because of peculiar characteristics of protocols such as very consistent daily energy surplus. Indeed, during short-term overfeeding, the increase in energy expenditure appears fairly small and possibly related to the type of nutrient, possibly greater for carbohydrates than fats [6].

Overall, adaptive variations in energy expenditure to contrast changes in body weight are more apparent and effective in chronic energy deficiency than chronic overfeeding, suggesting a clear priority in preventing the consequences of weight loss rather than those of excess body fat. This is in agreement with the observation that food shortages were more common than food abundance during early human evolution and more likely to be fatal in the short term.

Energy Expenditure and Obesity

Obesity is a heterogeneous disorder in which environmental, individual, and biological factors interact to influence both energy intake and energy expenditure. Long-term energy balance appears to be quite efficiently regulated in humans, with a number of sensitive mechanisms that act to oppose weight changes. In most average-weight people living in industrialized countries, body weight tends to remain quite constant despite that metabolizable energy made available to the body ranges between 600,000 and 1,000,000 kcal/yr. On the other hand, considering that even an energy surplus of only 80 kcal/day (3%–5% of total daily energy intake) is expected to cause a 4.5-kg increase in body weight over 12 months, it has been extensively discussed over the past decades whether alterations, even minor, in energy expenditure may play a role in the pathogenesis of overweight and obesity. In other words, are there abnormalities in TEE and any of its components that, at least in part, cause weight gain and lead to excess body fat?

Experimental Studies

Experimental studies in humans focus on different conditions: individuals before weight gain, already obese, or after weight loss. Few longitudinal data have indicated that low energy expenditure is a risk factor for weight gain in some groups of subjects who may be prone to obesity, such as adult Pima Indians and infants of overweight mothers, but there is no evidence of increased risk in the general population or unselected cohorts [15]. However, in pre-obese as well as post-obese subjects (i.e., subjects with a clinical predisposition to gain excess body fat), a trend toward more efficient energy storage and/or higher food intake associated with sedentarism has been suggested. In pre-obese as well as post-obese subjects, some studies have also suggested that low levels of NEAT and spontaneous physical activity represent a risk factor for weight gain, but data are still preliminary [15,16]. Taken together, these studies support a variable role of biological factors in the pathogenesis of human obesity. In fact, a positive association has been described between some genotypes and phenotypes typical of individuals predisposed to obesity. Nevertheless, nongenetic biological factors such as intrauterine factors, birth weight, and breastfeeding may facilitate the onset of obesity later in life.

Considering an achieved condition of excess body fat, it is widely accepted that BEE is increased in overweight and obese individuals. This is not surprising because not only do they have a greater fat-free mass, but in very obese people, fat mass also significantly contributes to energy expenditure, although the metabolic rate per unit of weight is low. The equations proposed by the Institute of Medicine [2] indicate an increase in BEE of 10.1 and 8.6 kcal/day for each kilogram of body weight gained in overweight/obese male and female individuals, respectively. Interestingly, after adjustment for body composition, there are no differences in BEE between overweight/obese individuals and their lean counterparts [15]. Overweight people also have a higher EEPA in absolute terms because they spend a larger amount of energy to move a greater mass, especially in weight-bearing activities. If PAL is taken into consideration, there is evidence that overweight subjects do not exhibit more sedentary lifestyles, possibly because of the low mean PAL observed in average-weight

individuals living in industrialized countries [15]. On the other hand, it should be noted that excess body fat is frequently a physically incapacitating factor in morbidly obese patients, leading to a reduction in physical activity. As far as adaptive thermogenesis is concerned, while the few data available seem to suggest a similar response to short-term overfeeding in lean and overweight individuals, several studies have demonstrated that TEF is abnormal in obese individuals [15]. However, the difference, possibly due to the presence of insulin resistance, is unlikely to be due to an altered adaptive thermogenesis, is small, and is unlikely to produce significant energy imbalance. Overall, when weight stability is present, TEE is on average much higher in overweight/obese individuals than in their average-weight counterparts (energy gap) [17].

Finally, the question of whether obese individuals may have decreased energy requirements after weight loss has also been addressed. All components of TEE decline in obese individuals with weight loss, for example, due to a decrease in body mass, fat-free mass, or energy intake. On the other hand, conflicting results are available concerning the hypothesis that post-obese people have a lower BEE than would be expected on the basis of their body composition, but this difference would indeed be very small and unlikely to affect energy balance to a significant extent [15]. Indeed, it is clear that in order to maintain energy balance, post-obese people have to reduce their energy intake compared to their previous overweight condition or substantially increase EEAT.

The Epidemiological Approach

Epidemiological studies have given significant results about the role of energy expenditure in the pathogenesis of obesity, which are also somewhat in contrast with those of experimental studies [18,19]. Randomized controlled studies and cohort studies have evaluated in adults and children the relationships between weight changes and physical activity (also in combination with diet), occupational and leisure activities, and household activities. Overall, there is substantial and consistent evidence that regular and sustained physical activity may protect, at least in part, against the increase of body fat and facilitate maintenance of weight loss in the long term. Since the measurement of physical activity is complex and usually not very accurate, the actual relationship could be stronger than the observed one. It should also be mentioned that physical activity may influence energy balance in different ways, not only by increasing energy expenditure but also by affecting the regulation of food intake.

Similarly, epidemiological studies have also shown that sedentary lifestyles, which means a high level of physical inactivity, are also related to weight gain [18,19]. Several studies in children, adolescents, and young adults show a higher risk of overweight/obesity with increased television viewing (usually >3 hr/day). Indeed, television viewing is a marker of physical inactivity but may also be associated with consumption of energy-dense foods and drinks.

Main Clinical Correlates

The evaluation of energy requirements is important not only from a theoretical point of view, but also for clinical purposes. Energy requirements should be evaluated before commencing every nutritional therapy, and this is true not only for underweight and overweight patients and also for those with conditions such as metabolic syndrome, type 2 diabetes, and hyperlipidemia. Physicians should always be aware of the potential error introduced in nutritional therapy by disregarding this issue, because the diet should always be tailored to the individual's energy needs.

Standardized procedures should be used for estimating BEE and PAL with predictive equations and questionnaires. The measurement of BEE using a specific device such as the ventilated hood system should be encouraged as a standard procedure in human nutrition to improve the evaluation of energy requirements in the single individual. EEAT could be assessed with accelerometers, but the validity of this approach in the single individual is still debated.

The increase in TEE due to being overweight is not a legend, but it is real and consistent. For instance, the equations proposed by the Institute of Medicine [2] indicate that for the same age, height, and PAL, TEE is significantly affected by weight not only in average-weight but also in overweight and obese individuals. Indeed, there are overweight and