PRESENT KNOWLEDGE IN NUTRITION

SEVENTH EDITION

EDITED BY

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AND

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Present Knowledge in Nutrition

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Ekhard E. Ziegler and L. J. Filer, Jr., Editors

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Present Knowledge in Nutrition

Foreword

The International Life Sciences Institute is a nonprofit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. By bringing together scientists from academia, government, industry, and the public sector, ILSI seeks a balanced approach to solving problems of common concern for the well-being of the general public.

Since its inception ILSI has had a major interest in nutrition issues as they relate to public health and safety. The ILSI Human Nutrition Institute has programs in micronutrient malnutrition, complex carbohydrates, child nutrition and physical activity, and other areas. The ILSI Allergy and Immunology Institute supports research to advance the understanding, prevention, and treatment of food allergy. ILSI's worldwide branches and its focal point in China have sponsored activities pertaining to nutrition and food safety, including dietary fats and carbohydrates, functional foods, dietary fiber, antioxidants, macronutrient substitutes, nutritional epidemiology, aging, obesity, and improved detection and control of such foodborne pathogens as *Listeria monocytogenes* and *Escherichia coli* O157:H7.

ILSI participated in the 1992 International Conference on Nutrition and is implementing a number of the recommendations in the Plan of Action resulting from that landmark meeting, including the alleviation of micronutrient deficiencies and creation of a process that individual countries can use to create dietary guidelines appropriate for their populations. ILSI is working with the World Health Organization and the Food and Agriculture Organization of the United Nations to develop food-based strategies to improve micronutrient nutrition.

ILSI publishes the premier review journal in nutrition science and policy. *Nutrition Reviews,* edited at Tufts University and published monthly, monitors and reports on major developments for its global readership of nutrition and dietetics professionals and students.

Given ILSI's extensive involvement in nutrition issues, I am especially pleased to make available the seventh edition of *Present Knowledge in Nutrition,* with its comprehensive and up-do-date examination of nutrition science today. First published in 1953, *Present Knowledge in Nutrition* has become a standard reference work in classrooms, laboratories, clinics, and practitioners' offices around the world. With previous editions translated into Spanish, Japanese, Indonesian, Korean, and Chinese, *Present Knowledge in Nutrition* has become one of the most widely used authoritative reference works on nutrition published.

I am confident that the information contained in this latest edition will contribute to understanding the complex and rapidly evolving science of nutrition.

Alex Malaspina, President
International Life Sciences Institute

Preface

The seventh edition of *Present Knowledge in Nutrition* reflects the growth in the science base and application of nutrition science to a wide variety of related disciplines. As medicine has evolved from a focus on treatment to prevention, principles of nutrition have evolved from the identification of specific nutrients and understanding of their role in preventing deficiency states to the prevention of chronic rather than acute disease states.

The principles of nutrition have driven the development of advances in food safety, food technology, biotechnology, disease prevention, and public policy as the latter relates to assessment of the health and well-being of population groups, nutrition education programs, and public assistance programs.

This growth process has dictated, and will continue to dictate, the size and content of the seventh and future editions of *Present Knowledge in Nutrition.* Four chapters published in the sixth edition were eliminated; however, 13 new chapters were prepared for the seventh edition to accommodate the expanding information base and present the cutting edge of the nutrition sciences.

The fact that the majority of chapters were prepared by authors residing in North America reflects the primary readership of the text and its use in educational programs. There is no question that each chapter is current and comprehensive, and written to both inform and challenge the reader. The information in the book has been organized and presented to maximize its usefulness as both a text and a reference for students, researchers, and practitioners in basic nutrition sciences, clinical nutrition, dietetics, and related areas.

It would not have been possible to develop and finalize this edition of *Present Knowledge in Nutrition* without the unselfish support of the author or authors of each chapter who gave generously of their time and expertise to produce this insightful volume. The editors are deeply indebted to each of these contributors. Initial guidance provided by an editorial panel was helpful in the identification of chapter titles and potential authors.

Lastly, we acknowledge the support and efforts of Lisa Schomberg, who provided support services for the editorial work at the University of Iowa; Roberta Gutman, managing editor of ILSI Press, who managed the editorial and production activity at ILSI; and Judith Dickson, who undertook the herculean task of coordinating the copyediting effort to produce this comprehensive text and reference.

As editors, we experienced our share of highs and lows as we brought the volume into being and completion. We were both relieved and pleased with the end result. To all of the authors we extend our heartfelt thanks and appreciation for a job well done.

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Contents

Chapter 1

Energy Requirements

Raffaele Napoli and Edward S. Horton

Undernutrition remains a leading cause of mortality and morbidity in developing countries worldwide. It has been estimated that >400 million people worldwide are undernourished, and this number is expected to increase as overpopulation continues.[1] In the United States inadequate nutrition continues to be of concern for many segments of the population, such as pregnant women, young children, elderly adults, and those living below the poverty level. National and international health policies are attempting to address the critical issue of uneven distribution of food supplies among various segments of the population.

In industrialized countries such as the United States, the major nutritional problem is one of surfeit, with excess dietary energy and fat contributing to the disproportionate increase in metabolic disease prevalent in our society. The gift of modernization and technological advancements may, like the Trojan horse, carry the seeds of destruction for societies that traditionally have been free from the diseases of plenitude (obesity, non-insulin-dependent diabetes mellitus, hypertension, and hyperlipidemias). The toll for overindulgence is great in both human and financial terms.

Energy Needs

How efficiently a person can convert the potential energy available in foodstuffs into body energy stores is subject to individual variation and may explain the propensity toward or resistance to weight gain in different subjects over a long period of time. The so-called thrifty gene that may have had survival value for American Indians subject to harsh desert conditions with limited food sources may be considered maladaptive in present-day America, where food is plentiful and obesity is nearly endemic. Differences between lean and obese individuals in Na^+,K^+-ATPase pump activity, thermogenic responses to various hormonal and environmental stimuli, and possibly in substrate cycle activity may help us understand the biochemical nature of this metabolic efficiency.[2] Several studies in animals have indicated a role for the β_3-adrenoreceptor in the regulation of energy expenditure and fat accumulation.[3] Therefore, the identification of increased frequencies of mutations in the β_3-adrenoreceptor gene in populations of obese people suggests that abnormalities in the activity of this receptor may be involved in the susceptibility to obesity in humans.[4–6] Recently, the discovery of the genetic abnormality responsible for obesity in *ob/ob* mice has indicated interesting new directions for the search for the defect or defects responsible for human obesity.[7] However, as emphasized by Sims,[8] any discussion of obesity must acknowledge the heterogeneity present in obese individuals that may help to explain some of the divergent results reported in various studies.

Energy Balance

Food is required as a fuel for the maintenance of energy-requiring processes that sustain life. Energy is required for maintaining the physicochemical environment of the intact animal, the so-called internal milieu, and for sustaining the electromechanical activities that define the organism. In the late 18th century, Lavoisier made the landmark discovery that the life-sustaining process of respiration was merely a form of chemical combustion and as such could be measured precisely. By the end of the next century, Rubner[9] was measuring the excretion rates of expired carbon dioxide and urinary nitrogen to estimate energy expenditure in human subjects. This method, known as indirect calorimetry, estimates metabolic rate from measurements of oxygen consumption and carbon dioxide production. When urinary nitrogen excretion is also measured, net rates of substrate oxidation can be calculated by using the tables of Lusk.[10]

For measurements of resting metabolic rate (RMR) in a supine, resting subject, the ventilated-hood system was shown to be accurate (2–5% error) with minimal inconvenience to the subject during relatively long-term measurements (several hours).[11] A steady state of carbon dioxide production and respiratory exchange must be reached, and subjects should have normal acid-base balance. For longer time periods, indirect calorimetry chambers are used. This technique was described by Ravussin et al.[12] The chambers are large

enough to allow subjects to move freely and perform normal daily activities (i.e., sleeping, eating, and mild exercise) and to allow for precise measurement of energy expenditure over 24 hours. An advantage of the chamber is the ability to estimate physical activity with a radar-detection device.

The doubly labeled water technique, in which water is labeled with ^{2}H and ^{18}O, has been shown to measure energy expenditure in free-living subjects accurately over a period of several weeks.[13] This technique offers the potential for more studies of prolonged duration in subjects engaged in normal daily activities but is not widely available because of cost and the requirement for an isotope-ratio mass-spectrometry facility.

Direct calorimetry is probably the most accurate method for measuring energy expenditure (only 1–2% error) but is not widely used because of cost, limited chamber size, and slow response time. In addition, since the time of Atwater and Benedict,[14] many investigators have shown the close correlation between direct and indirect calorimetric measurements. Consequently, the former method is seldom used in present-day research studies. A novel version of the direct calorimeter, the space suit described by Webb et al.,[15] is intriguing but is still in the experimental stage.

Energy intake. Energy intake is a highly variable component of the energy balance equation and may be important in the causation and maintenance of the obese state. Danforth[16] emphasized the importance of the composition of food intake in addition to total energy intake in the pathogenesis of obesity.

Energy expenditure. Energy expenditure includes several components: RMR, the thermic effect of exercise (TEE), the thermic effect of food (TEF, formerly known as specific dynamic action), and facultative thermogenesis (also known as adaptive thermogenesis).

Resting metabolic rate. RMR is usually the greatest contributor (60–75%) to total daily energy expenditure. RMR is a measurement of the energy expended for maintenance of normal body functions and homeostasis plus a component for activation of the sympathetic nervous system. RMR is measured with the subject in a supine or sitting position in a comfortable environment several hours after a meal or significant physical activity. The basal metabolic rate, originally defined by Boothby and Sandiford,[17] is measured in the morning upon awakening, before any physical activity, and 12–18 hours after a meal. It may be slightly lower than RMR, but the difference is small and RMR is now the more commonly used measurement. Several factors are known to influence the RMR, including nutritional state, thyroid function, and sympathetic nervous system activity. Differences in RMR due to differences in body size, sex, or age are largely corrected if the data are related to fat-free mass (FFM).[12] Most studies do not find a difference between lean and obese subjects when RMR is expressed per kilogram FFM. This lack of difference highlights the importance of accurate body composition measurements when different groups of subjects are compared in the ongoing search for clues to explain and correct the obese state. The decrease in RMR with age is explained largely, but not exclusively,[18] by a decrease in lean body mass. Women have lower RMRs than do men because of smaller body size and lower lean body mass, although RMR seems to vary with the menstrual cycle.[19]

It was shown that differences in FFM, age, and sex may account for 83% of the variance in RMR between different individuals.[12] Of great importance, family membership contributes an additional 11% to the variance in RMR per kilogram FFM. Similar findings of a genetic component to RMR were reported in studies of monozygotic twins and in retrospective studies of adopted children in Denmark.[20,21] Subjects with lower RMRs appear to be more susceptible to weight gain over the period of follow-up in both adult and pediatric populations.[22,23] The authors speculate that weight gain in such subjects would reach a plateau once the increase in lean body mass and energy cost of bodily movement brought subjects into energy balance. This theory suggests one mechanism for positive energy balance and weight gain over a long period of time in genetically susceptible individuals.

RMR is dependent also on thyroid hormone status and sympathetic nervous system (SNS) activity. The major clinical use of energy-expenditure measurements during the early part of this century was to diagnose over- and underactivity of the thyroid gland. Recent studies showed a relationship between RMR and rates of norepinephrine turnover by use of infusions of radioactive norepinephrine, which is a better index of SNS activity than is measurement of catecholamine concentration in plasma. Chronic administration (2 weeks) of the β-adrenergic agonist terbutaline increases RMR by 8% in humans,[24] whereas pharmacological blockade of the SNS by the acute administration of α- and β-blocking drugs appears to have little effect on RMR.[25] It was shown in animals that β_3-adrenergic stimulation, obtained by administration of specific β_3-agonists, induces an increase in RMR.[3] The identification of mutations in the β_3-adrenoreceptor gene associated with human obesity suggests that the abnormalities in RMR seen in obesity might be linked to inefficient β_3-adrenergic stimulation.[4–6]

Thermic effect of exercise. TEE is the second largest component of energy expenditure. It represents the cost of physical activity above basal levels. In a moderately active individual it comprises 15–30% of total energy requirements. Of all the components of energy expenditure, TEE is most variable and therefore most amenable to alteration. Increases in energy expenditure 10–15 times above the RMR can be achieved with intense

exercise. Few, if any, factors appear to affect TEE except the amount of work done. Several studies compared TEE in lean and obese subjects, and in most cases no differences in the efficiency of exercise were found when the energy cost of moving the increased body weight of obese subjects was taken into account.[26] Previous exercise may increase metabolic rate for at least 18 hours and potentiates the thermic response to insulin-glucose infusions for >14 hours.[27,28]

The degree of spontaneous physical activity appears to be another variable that may allow for positive energy balance and weight gain in subjects prone to obesity. Earlier studies suggested that obese girls were less active during periods of recreation than were their lean schoolmates.[29] Using the indirect calorimetry chamber, Ravussin et al.[12] demonstrated a wide range in spontaneous physical activity, termed "fidgeting," among individuals. Fidgeting accounted for between 418 and 3347 kJ/d (between 100 and 800 kcal/d) in their subjects.

Thermic effect of food. TEF refers to the increase in energy expenditure above RMR that occurs for several hours after the ingestion of a meal. The earlier term "specific dynamic action" was initially applied to dietary protein, but it is now recognized that ingestion of each macronutrient (protein, fat, and carbohydrate) results in a thermogenic effect. TEF is the result of energy expended to digest, transport, metabolize, and store food. On average TEF accounts for ≈10% of daily energy expenditure and varies depending on the metabolic fate of ingested substrate. The cost of storing the fat contained in a meal in adipose tissue amounts to only 3% of the energy content of a meal. If glucose is directly oxidized, all the energy is available, whereas if it is first stored as glycogen, 7% of the available energy is lost.[30] Evidence suggests that only about one-third of liver glycogen repletion in rats starved for 24 hours occurs via the direct pathway from glucose; the remainder comes from triose phosphate intermediates and other mechanisms.[31] The cost of the indirect pathway of glycogenesis from triose phosphate intermediates is greater than the cost of direct synthesis of glycogen from glucose.

Theoretically, excess dietary carbohydrate can result in de novo lipogenesis, resulting in an increase in adipose tissue fat stores. However, this process is energy inefficient, requiring 26% of the ingested energy.[30] In addition, it was shown that carbohydrate overfeeding results in very little net lipogenesis over 24 hours.[32] Thus, fat balance remains negative at least in the short term after carbohydrate overfeeding because lipid oxidation continues. These considerations led Danforth[16] to conclude that the composition of the diet is at least as important as its energy content in determining whether a positive fat balance is maintained. Of the three macronutrients, dietary protein produces the greatest TEF.[33] This effect appears to be due to the high energy cost of protein degradation and synthesis, which require ≈24% of available energy.

The SNS appears to play an important role in TEF, especially after carbohydrate ingestion. Glucose ingestion and intravenous glucose-insulin infusions result in a 5–7% increase in energy expenditure above RMR, and up to 70% of this increase can be inhibited by administration of β-adrenergic–blocking drugs such as propranolol.[25,34] Increases in norepinephrine turnover correlate with the thermic response to a meal. TEF is also increased during treatment with β_3-agonists in rats, suggesting a possible role of β_3-adrenoreceptors in the regulation of this component of energy expenditure, in addition to their role in the regulation of RMR.[3]

Although subjects with insulin resistance demonstrate a decreased TEF, this impairment becomes normal if either insulin or glucose concentrations are increased sufficiently to result in normal rates of glucose disposal.[35] TEF after ingestion of fructose, which does not require insulin for cellular uptake, is normal in insulin-resistant subjects, again suggesting that the major determinant of TEF after carbohydrate ingestion is substrate metabolism rather than insulin secretion or action per se. Whether previous studies showed a decreased TEF in obese compared with lean subjects may have depended on the degree of insulin resistance present in the obese group.[35] Insulin is capable of stimulating Na^+,K^+-ATPase pump activity directly, and may exert thermogenic effects by direct stimulation of insulin-sensitive areas of the hypothalamus.[36]

TEF varies greatly among individuals, and even repeated measurements in the same individual under the same laboratory and nutrient intake conditions show a high degree of variability. Therefore, studies comparing TEF between different populations, such as lean and obese subjects, must be interpreted cautiously.

Facultative thermogenesis. The final component of energy expenditure, facultative thermogenesis, is readily demonstrable in animals but is less well described in humans. It appears to account for ≤10–15% of total daily energy expenditure but may have significant effects on long-term weight changes. Facultative thermogenesis is the change in energy expenditure induced by changes in ambient temperature, food intake, emotional stress, and other factors. The best-described version of facultative thermogenesis is nonshivering thermogenesis in rodents exposed to cold environments, during which heat production is increased via SNS stimulation of brown adipose tissue (BAT). BAT mitochondria have a unique proton conductance mechanism that allows them to reversibly uncouple oxidation from ADP phosphorylation.[37] Under stimulation by the SNS, the intracellular concentration of free fatty acids is increased and proton conductance is uncoupled. Both thyroid hormone and insulin are required for norepinephrine to increase BAT

thermogenesis.[38] Glucagon may contribute to thermogenesis directly or indirectly by increasing catecholamine concentrations. The role of BAT in facultative thermogenesis in adult humans is questionable and is probably small in magnitude,[39] although BAT was histologically identified in adults chronically exposed to cold outdoor temperatures.[40] Use of immunocytochemical techniques revealed the presence of a mitochondrial uncoupling protein with a molecular weight of 32,000 in adult humans.[41] Intriguingly, elevated catecholamine concentrations in pheochromocytoma were shown to increase thermogenesis in the intraabdominal adipose tissue sites that are the same sites containing BAT in infants.[42]

Another form of facultative thermogenesis that is consistently shown in man occurs with altered nutritional intakes. Decreased energy intakes for prolonged periods result in a progressive decrease in RMR that is greater than can be accounted for by decreases in FFM. Associated with decreased energy intake is reduced insulin secretion and reduced activity of 5′-monodeiodinase, which converts the primary thyroid gland secretagogue 3,3′,5,5′-tetraiodothyronine (T_4) to the metabolically active thyroid hormone 3,3′,5-triiodothyronine (T_3).[43] Dietary carbohydrate is the primary nutrient regulating plasma concentrations of T_3. Recently, Danforth[44] showed that energy balance is more important than the absolute rate of energy intake or expenditure in altering T_3 concentrations. The decrease in T_3 is not entirely responsible for the decreased RMR during fasting, because restoring T_3 concentration to normal does not increase the RMR of starved rats.[45] Both an increase in T_3 and in nutrient ingestion are required for the increase in RMR to occur with refeeding. Underfeeding decreases the activity of the SNS, as determined by norepinephrine-turnover studies.[46] The finding that RMR may remain depressed for prolonged periods after dietary stabilization following rapid weight-reduction programs sounds a cautionary note regarding the clinical application of very-low-energy diets.[47] Furthermore, the maintenance of a reduced body weight in obese people is associated with compensatory changes in energy expenditure that oppose the maintenance of a body weight different from the usual weight.[48] These compensatory changes may account for the poor long-term efficacy of treatment of obesity.[48]

Experimental overfeeding in man has provided some valuable insights. Neumann[49] first used the term "luxus consumption" in 1902 and in the same year Rubner[9] in studies in dogs described the process whereby overfed lean animals were able to dissipate increased energy intake through heat loss. Although the convincing demonstration of this process in long-term studies has been difficult, studies yielding negative results have been criticized for inadequate duration or magnitude of overfeeding. As pointed out by Garrow[50] there appears to be a threshold of ≈84 MJ (≈20,000 kcal) of excess intake for the demonstration of luxus consumption, or diet-induced thermogenesis, in humans. In a review of earlier studies of overfeeding, Webb[51] concluded that only about one-half of the weight gain predicted from energy intake actually occurred. The Vermont study of experimental overfeeding of prisoners showed that previously lean subjects required about twice the daily energy intake of the spontaneously obese to maintain increased body weight, although there was a large degree of individual variation.[52] In addition, maintenance of an increased body weight, similar to that which occurs in maintenance of a reduced body weight, is associated with compensatory changes in energy expenditure opposing the change from the usual body weight.[48]

Increases in thyroid hormone concentrations and SNS activity appear to play important roles in the mechanisms of luxus consumption. As mentioned above, carbohydrate is the major nutrient increasing T_3 production. Current attention is being focused on the activity of substrate cycles, such as the Cori cycle (glucose to lactate to glucose) and the glucose (glucose to glucose-6-phosphate) and fructose (fructose-1-phosphate to fructose-1,6-diphosphate) cycles to explain differences in energetics with altered nutritional states. Newsholme[53] points out that such cycles, formerly called futile cycles, are far from futile and probably play important roles in finely regulating substrate fluxes in opposing directions. Recent studies demonstrated increased activity of glucose and fructose cycles in experimental hyperthyroidism and increased activity of the lipid cycle (lipolysis to reesterification) in burn patients.[54,55] The latter was shown to be partly under the influence of the SNS and was partially inhibited by administration of propranolol. As mentioned above, the Na^+,K^+-ATPase pump is under the influence of hormonal regulation; thyroid hormones, insulin, phosphatidylinositol, and possibly norepinephrine exert effects on pump activity.[56]

The extent to which defective facultative thermogenesis can contribute to or maintain the obese state was briefly mentioned in relation to TEF. Impairments in TEF during feeding or insulin-glucose infusions in obesity appear to be largely secondary to insulin resistance and decreased glucose disposal and are improved by treatments such as diet and exercise, which improve insulin sensitivity.[57] Whether differences in substrate-cycle activity in either the fasting or postprandial state can explain a tendency toward weight gain in obesity requires further studies.

Perspectives

It was recently discovered that fat deposition in an animal model of obesity is regulated by a previously unknown protein, called leptin (from the Greek leptos,

meaning thin).[7] The administration of leptin to obese *ob/ob* mice, which do not produce this protein because of a genetic defect, rapidly normalizes their body weight.[58–60] This normalization occurs through an action on both components of the energy balance, i.e, reduction in food intake and increase in energy expenditure.[58,59] Interestingly, leptin production in normal mice increases after food ingestion, suggesting that a fine regulation of the appetite might be due to this protein.[60] In addition, increases in serum insulin, but not in glucose, stimulate the production of leptin.[61] One mechanism through which leptin acts in regulating food intake is inhibition of the synthesis and release by the hypothalamus of neuropeptide-Y, a substance involved in regulation of appetite.[62] Although an analogue of leptin was identified in humans, caution should be used in the extrapolation of animal data to humans for several reasons. First, human obesity is a heterogeneous disease, whereas obesity in *ob/ob* mice is due to a single gene defect. Second, resistance to the effect of leptin has been already described in *db/db* mice, and is likely due to a postulated defect in the leptin receptor present in these animals; similarly, resistance to leptin action might be present in humans. Third, human obesity seems to be associated with increased, rather than decreased, leptin plasma levels and leptin expression in fat cells, suggesting a more complicated regulatory role for this molecule.[63–65] However, the discovery of leptin has provided a new key for our understanding of the molecular mechanisms of obesity and it will be important to test the therapeutic effect of leptin in human obesity.

Summary

Although there are large interindividual differences in energy requirements, much of the variance can be accounted for by FFM, age, sex, and amount of physical activity. Genetic factors also appear to play an important role. Determining which factors help to explain the development or perpetuation of the obese state requires further investigation, but greater understanding will likely follow the improvements in technical capabilities and better-designed and controlled long-term studies in obese subjects. Because of an epidemic of obesity-associated metabolic diseases in Western societies, this improved understanding is essential for the health of the population.

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