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Physiology of Aging
Invited Review: Aging and energy balance

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Wilson, Margaret-Mary G., and John E. Morley. Invited Review: Aging and energy balance. *J Appl Physiol* 95: 1728–1736, 2003; 10.1152/japplphysiol.00313.2003.—Humans over 70 yr of age often lose weight. This appears to be due to a physiological anorexia of aging as well as a loss of lean mass (sarcopenia) and, to a lesser extent, fat mass. The causes of the physiological anorexia of aging include changes in taste and smell and a decrease in adaptive relaxation of the fundus of the stomach, which leads to more rapid antral filling and early satiation. In addition, basal and stimulated levels of the satiating hormone, cholecystokinin, are increased. In men, the decline in testosterone leads to an increase in leptin and a loss of lean mass. Although resting metabolic rate declines with aging, this is mainly due to the decline in lean body mass. Energy metabolism is also decreased due to a decline in Na^+-K^+-ATPase activity, decreased muscle protein turnover, and possibly changes in mitochondrial membrane protein permeability. Physical energy expenditure declines with aging. Meal-induced thermogenesis shows a delay to peak, possibly due to a delay in gastric emptying. Inadequate data are available on the effect of aging in humans on other energy-producing mechanisms such as adaptive thermogenesis. These physiological changes place older men and women at major risk of developing pathological weight loss when they develop disease states, especially those associated with cytokine elaboration.

anorexia; sarcopenia; thermogenesis

> "The leading principle in the use of food is that we should eat to live, but not live to eat . . . with very little food, animals, or human beings, can live for a long time. But prolonged underfeeding may be quite as dangerous as overfeeding."
>
> A. Lorand
> "Old Age Deferred"
> Philadelphia, PA: FA Davis, 1921

Many normal-weight healthy older men and women decrease their energy intake below their energy expenditure and thus lose weight. This weight loss is associated with loss of both muscle and fat mass (55, 83, 106). Weight loss in older individuals is associated with frailty (16, 18, 53), functional impairment (56), and mortality (34, 57, 86). Older men and women who lose weight are more likely to develop pressure ulcers (92), hip fractures (25), and cognitive impairment (66) and have a poor quality of life (1, 9, 14, 93). Overall, weight loss generally portends poor outcomes in older persons.

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This concept needs to be balanced against findings in a number of organisms, including rodents, that dietary restriction extends life span (71, 99, 100). Although controversial, dietary restriction in primates appears to slightly reduce total daily energy expenditure even when adjusted for the decline in body weight (63). This reduction appears to be true only during the first 1 or 2 yr of caloric restriction (71). Although caloric restriction has no overall effect on locomotor activity, activity is increased around meal times in calorically restricted primates, which is balanced by a decrease at other times. In addition, caloric restriction in primates reduces body temperature by 1.5°C.

Thus one of the conundrums of aging is that dietary restriction may prolong life, but weight loss in older men and women shortens life. This review examines the changes in energy metabolism that occur with aging that place the older person at risk for developing weight loss. In general, those over 70 yr of age are considered old and those 21–40 yr of age are considered young. Those 40–70 yr of age are considered to be intermediate in age. However, many studies have included individuals who are 60–70 yr as old. In many cases, studies have been done in men, but studies are needed in women to determine the magnitude of gen-

der differences, as women comprise the majority of the aging population.

ENERGY EXPENDITURE AND AGING

Antiquated philosophical theories infiltrating the ranks of modern science propagate the myth that aging is the quintessential representation of human decay. Consequently, misleading extrapolations have been made from the assumption that the metabolic profile of older adults is merely a less efficient version of that observed in younger humans. Thankfully, with the increasing stronghold on science gained by gerontologists, the unique metabolic characteristics of older adults are gaining recognition.

Although the precise effects of age on metabolic efficiency and energy expenditure are yet to be fully elucidated, improved techniques for evaluating energy expenditure provide helpful data for age-specific comparisons (Fig. 1). Metabolic chamber studies and double-labeled water techniques, although expensive and technically complex, provide the most accurate data in confined subjects (11, 68, 77). Longitudinal studies that use these techniques are needed to more fully define the changes in energy metabolism with aging. It should also be recognized that these techniques have a relatively large coefficient of variation. A 1% change in energy metabolism over a decade or so can produce large changes in body mass; therefore, it needs to be recognized that until more sensitive techniques are available, our interpretation of the data generated needs to be very cautious (11, 20)

RESTING METABOLIC RATE AND AGING

Much of the research on age-related factors modulating energy balance focuses on energy intake and appetitive factors. Limited data exist regarding the modulating effect of age on energy production. Early studies have suggested that resting metabolic rate (RMR) and total energy expenditure decline with aging (61). These studies suggested a decrease of 13–20% in RMR between the ages of 30 and 80 yr, with men exhibiting a greater decrease and an earlier onset in the decline in RMR. Because fat-free mass accounts for over one-half of the observed interindividual variation in RMR, age-related sarcopenia is an attractive explanation for these observations (101). More recent studies suggest a loss of association between age and RMR, if body composition and maximal aerobic capacity are kept constant. However, in older men subjected to endurance training, RMR may increase by as much as 10% from baseline. Unlike young adults, this increase in RMR resulting from exercise is less likely to result in negative energy balance, as evidence indicates a compensatory restriction in physical activity after a period of vigorous exercise in older adults (59). Although much of the decrease in RMR with aging is corrected by comparison to lean body mass, there is most probably also a small intrinsic loss of RMR because of a decline in the Na^+-K^+-ATPase activity, a decrease in skeletal muscle protein turnover, and possibly changes in mitochondrial membrane proton permeability (19, 60, 82). In addition, fat oxidation is decreased in older persons (6). There is a major need to study the biochemical effectors of energy metabolism in fat and muscle biopsies in older compared with younger men and women.

Energy expenditure in older adults has been examined in relation to energy intake. Older subjects exhibit a relatively smaller increase in resting energy expenditure in response to overfeeding when compared with younger subjects. Similarly, maintenance energy expenditure, defined as mean resting energy expenditure averaged over fasting and fed states, shows a similar relative reduction in older subjects. In underfed subjects, the reciprocal increase in maintenance energy expenditure is disproportionately lower than expected based on overfeeding data, regardless of age. However, maintenance energy expenditure in older underfed subjects is still significantly lower than that observed in younger underfed subjects. On the basis of these

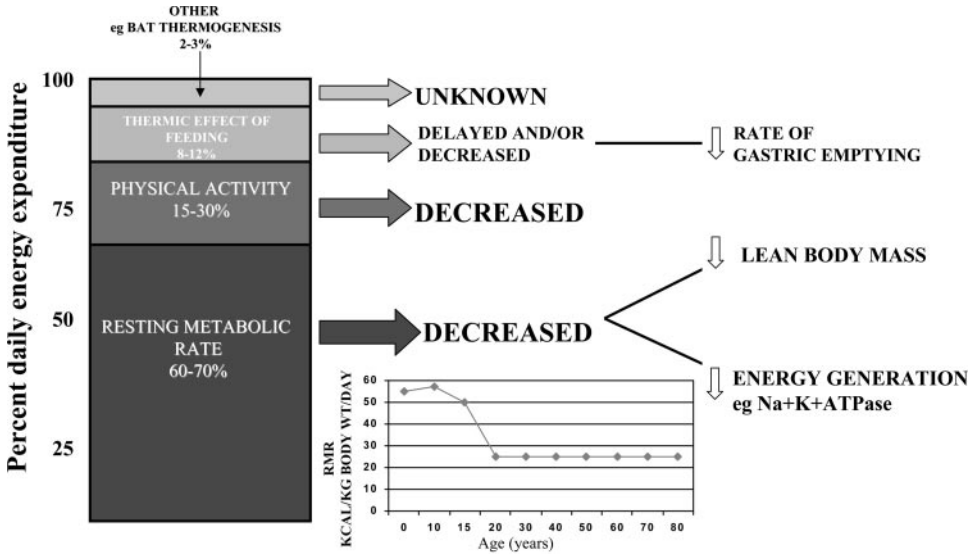

Fig. 1. Effects of aging on energy expenditure. BAT, brown adipose tissue; RMR, resting metabolic rate.

observations, intrinsic homoeostatic mechanisms triggered by inadequate energy intake appear to be more effective than mechanisms targeting excess energy intake in all age groups. However, aging may lead to blunting of both mechanisms, thereby placing the older adult at increased risk of impaired energy regulation and consequent progressive weight loss (69).

Chronic disease in aging humans leads to further disruptions in regulation of energy expenditure. Negative energy balance and subsequent weight loss accompany most chronic illnesses in the elderly. Although the precise pathophysiological mechanisms remain unclear, emerging evidence in this area raises several questions. Earlier studies implicated resting hypermetabolism as a major contributory factor to weight loss in chronic disease. However, the utilization of doubly labeled water methods in the measurement of total daily energy expenditure has yielded conflicting evidence.

Alzheimer's disease is one of the leading causes of unintentional weight loss in the elderly. Reduced energy intake, although a contributory factor, fails to account for the extent of weight loss in most cases. Early theories suggested that elevated energy expenditure resulting from increased inappropriate physical activity such as wandering, pacing, or agitation, fosters long-term negative energy balance, thereby resulting in progressive weight loss. Recent studies, which used more sophisticated techniques, counter these theories. Several investigators studying energy regulation in ambulatory patients with Alzheimer's disease demonstrated a reduction in both RMR and total daily energy expenditure, when compared with healthy controls (13, 62, 93, 104). Parkinson's disease raises similar issues. Unintentional weight loss in Parkinson's disease is likely multifactorial. Regardless, weight loss is often attributed to increased energy expenditure resulting from persistent tremors. Indeed, current evidence undermines the magnitude of tremor-induced thermogenesis. Although patients with Parkinson's disease exhibit resting hypermetabolism, daily energy expenditure drops because of an ~50% reduction in physical activity energy expenditure (95).

Congestive cardiac failure and chronic obstructive pulmonary disease are frequently cited as disease models of resting hypermetabolism. Consequently, the occurrence of cachexia in either of these conditions is often erroneously attributed to increased RMR. Toth and colleagues (96), examining a cohort of community-dwelling subjects with moderate to severe heart failure, identified a total daily reduction in energy expenditure, even in patients with cardiac failure associated with significant weight loss. Similarly, emerging evidence challenges previous hypotheses of increased total energy expenditure in chronic obstructive disease. Tang et al. (90), using indirect calorimetry, failed to demonstrate a difference in either RMR or total energy expenditure between a cohort of patients with chronic obstructive pulmonary disease and healthy controls. Their findings suggest that negative energy balance occurring in the setting of longstanding cardiopulmonary disease is more likely a reflection of inadequate energy intake, underscoring the importance of early and aggressive nutritional intervention (90). A single study in older malnourished persons suggested that resting energy expenditure corrected for fat-free mass being increased in these patients but not being altered in middle-aged malnourished persons (76). This suggests that changes in energy expenditure may play a role in the pathogenesis of cachexia in older persons.

MEAL-INDUCED THERMOGENESIS AND AGING

Few definitive data exist relating to the effect of aging on meal-induced thermogenesis. After meal ingestion, the resultant increase in metabolic rate extends over a period of ~6 h. Although the thermic effect of meals is generally assessed as ~10% of the total energy consumed, the macronutrient composition of meals influences thermogenesis. Fat consumption results in a lower thermic effect compared with either protein or carbohydrate ingestion. This is attributed to the fact that, after fat consumption, energy storage is more efficient and does not require further metabolic interconversion (21). Meal-induced thermogenesis correlates negatively with age in male subjects. This is attributed to age-related blunting in sympathetic mediation. In female subjects, although meal-induced thermogenesis fails to exhibit any direct association with age, a negative correlation has been identified with fat mass and upper body obesity, both of which are anthropometric characteristics found commonly in older females (65, 91). More recently, a kinetic analysis of thermic response curves has been conducted (31). Comparative studies of area-under-the-curve profiles suggest that observed age-related changes in meal-induced thermogenesis arise from a delay to peak thermogenesis and not a quantitative reduction in thermic effect as proffered by earlier workers (31). This delay in peak thermogenesis may be due to the delayed gastric emptying in older persons when large meals are ingested (8). Nevertheless, although defective thermogenesis in older adults is an attractive concept on which to base age-related energy dysregulation, most of the available evidence is inconsistent and poorly reproducible (42).

Diet-induced thermogenesis is the phenomenon whereby excess energy intake is dissipated by heat. It results from the metabolic costs associated with depositing excess energy as fat and, in rodents, is generated from metabolically active brown adipose tissue. In rodents, there is a decline in diet-induced thermogenesis of 10–20% in older compared with younger animals. This aspect of energy metabolism has not been adequately studied in older humans. Studies are needed on adaptive thermogenesis (both cold induced and diet induced) in older persons. The potential role of skeletal muscle in adaptive thermogenesis also needs to be explored. Although humans have brown adipose cells dispersed in white cell depots, there is inadequate evidence to support the role of brown adipose tissue in human adaptive thermogenesis.

PHYSICAL ENERGY EXPENDITURE AND AGING

Activity-related energy expenditure closely parallels functional status. However, several studies have suggested an independent inverse correlation between activity-related energy expenditure and fat mass. Likewise, lean body mass correlates positively with activity-related energy expenditure. Available data do not permit evaluation of the cause-effect relationship of these associations. Thus it remains unclear whether low energy expenditure encourages increased body fat or whether excess body fat triggers a reduction in energy expenditure. Regardless, the effect of physical activity on total energy expenditure is multifaceted. In addition to the obvious direct effect of physical exertion on increasing activity-related energy expenditure, physical activity also increases resting energy expenditure. In a group of older individuals, exercise training increased total daily energy expenditure from 40.8 to 43.5 $kcal \cdot kg^{-1} \cdot day^{-1}$ (17). This increase was still 1.7 $kcal \cdot kg^{-1} \cdot day^{-1}$ 6 mo after completion of the exercise program. Enhanced insulin sensitivity and increased sympathetic mediation have both been proffered as likely causes of activity-related resting hypermetabolism. The effect of physical activity on meal-induced thermogenesis is unclear (74).

Overall, available data indicate a reduction in total daily energy expenditure with normal aging. Superimposed disease processes may alter any of the components of total energy expenditure in a variety of ways. Ultimately, further reduction in total energy expenditure occurs in most disease processes, even in the face of resting hypermetabolism. In the absence of evidence to support a significant effect of meal-induced thermogenesis, it is likely that reduced physical energy expenditure is the primary factor leading to a decrease in total energy expenditure.

One study examined energy metabolism in very old men and women (91–96 yr) and compared the findings with those in 70-yr-old individuals (73). In the older group, the physical activity level was extremely low, but RMR results were not substantially different from those of 70-yr-old subjects. Total energy expenditure declined by 34% in older compared with younger women and 25% in men, whereas RMR was only 4.8% lower in women and 2.1% lower in men. Total energy expenditure was ~40% in 70-yr-old men and women but only 22% in the 91- to 96-yr old group. Adjustment of RMR for fat-free mass resulted in there being no differences between both the gender and age groups.

Future studies are needed to explore the precise mechanisms underlying age-related energy dysregulation and to characterize adequately energetic homeostatic mechanisms triggered by chronic disease in older adults. For now, the current state of evidence underscores the importance of geriatric nutritional intervention and management programs targeted toward ensuring energy balance and preventing weight loss.

ANOREXIA OF AGING

The concept that there is a physiological decline in food intake from the ages of 20–80 yr is now well established in both large populations and in highly healthy persons (45, 98). This has been termed the "anorexia of aging" and in most cases is an appropriate response to the decrease in physical activity that occurs over the lifespan (54). This decline in food intake is due to both early satiation that occurs in response to large meals and a decrease in intermeal snacking (8).

Some of this decline in food intake may be related to the increased number of older persons who eat alone. It has been shown that, when humans eat alone, they eat less than when they eat in social groups (10). In a study of older men and women receiving meals-on-wheels, it was demonstrated that when the person delivering the meal stayed with the person while the meal was eaten nutritional risk was reduced (85). In nursing homes, an improved environment during meals increased food intake (40). Also, it has been demonstrated that it can take up to 45 min to feed a single meal to a demented or severely functionally impaired person who requires feeding assistance (83). Paquet et al. (58) have shown that everyday emotions at the time of eating can have both positive and negative effects on food intake. These studies all highlight the fact that, in impaired older persons, social factors can play an important role in decreasing food intake. These social factors were highlighted in an algorithm, which was aimed at treating weight loss in nursing home residents (94).

Although the predominant feeding change seen with older persons is a decrease in food intake coupled with weight loss, Roberts et al. (70) have suggested that the major change with aging is a dysregulation of food intake (dysorexia). They found that older men and women who had been overfed tended to be less capable of decreasing their food intake and returning to their previous weight than younger men and women. Similarly, older persons who were underfed continued to eat less and failed to regain their lost weight.

With aging there is a small increase in taste threshold, which is more marked in persons who smoke or who are receiving medications (75). In addition, there is a decline in the ability to detect odors (88). Odor detection is a key component of the enjoyment of food, as release of aromatic amino acids from food in the mouth results in stimulation of the vomeronasal organ. There is much controversy on the exact effects of these alterations in taste and smell over the lifespan on the genesis of decreased food intake (5). However, it was recently shown that the addition of the taste enhancer monosodium glutamate to a single meal in a nursing home produced weight gain in nursing home residents (39). Over the past decade, there have been major advances in understanding the genesis of early satiation in older humans. Clarkston et al. (8) demonstrated that early satiation was related to a delay in gastric emptying that occurs in older men and women after large but not small meals. This represents a classical example of homeostatic preservation in older persons

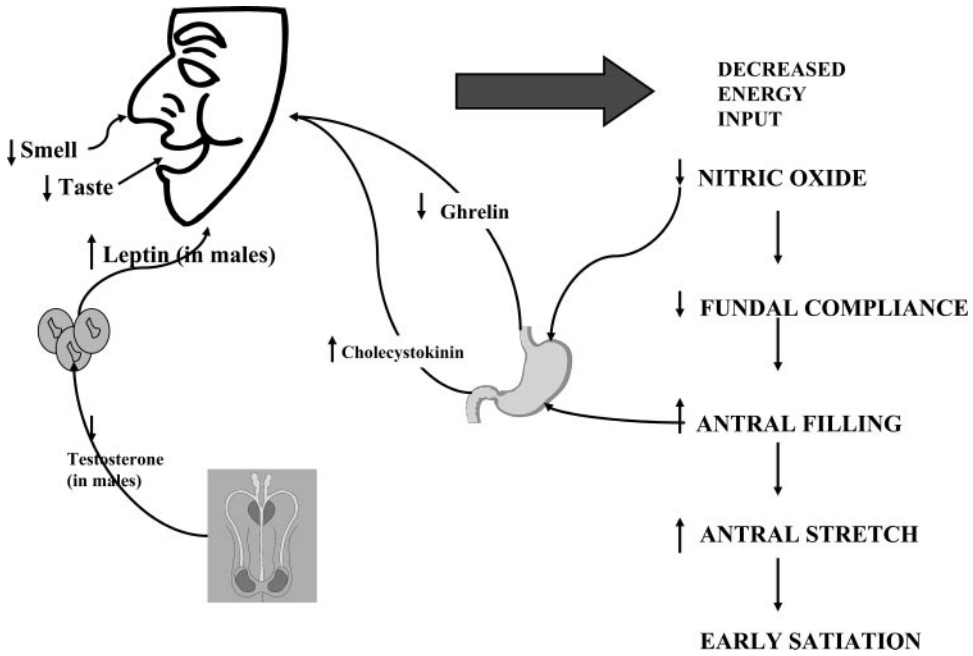

Fig. 2. Summary of the multiple factors involved in the pathogenesis of the physiological anorexia of aging and energy expenditure.

when they are not stressed (small meal) but homeostatic failure when stress is introduced (large meal).

In older men and women, there is a decrease in gastric fundal compliance leading to more rapid antral filling (64). This loss of adaptive relaxation, with aging, in response to food appears to be due to a failure of adequate production of nitric oxide in response to food and, therefore, a decrease in smooth muscle relaxation (51, 87). Antral stretch has been demonstrated to be the major factor responsible for signaling satiation to the central nervous system (27).

Ghrelin is a peptide hormone released from the fundus of the stomach that induces eating and release of growth hormone (72). Food in the fundus suppresses release of ghrelin (72). In older persons, ghrelin levels have been reported to be decreased (67).

Glucose in the duodenum appears to be less inhibitory of hunger in older compared with younger men and women (36). When a liquid carbohydrate diet is given immediately before a meal, it inhibits the amount eaten at the meal by the same amount as its calorie content (103). On the other hand, when given 60-min before the meal, both the full meal and the extra energy content of the liquid supplement are ingested.

When fat is infused into the duodenum, it releases the satiating hormone cholecystokinin (CCK) (35). Older men and women have higher basal levels of CCK and a greater release of CCK in response to fat compared with younger men and women (35). This is in contrast to other peptide gut hormones such as peptide YY and glucagon-like peptide I. The increase in CCK is due in part to delayed clearance of the hormone (37). Animal studies have suggested that CCK is a more effective satiating hormone in older compared with younger animals (79). Recently, CCK was shown to be more satiating in older than in younger humans (37).

There is a greater decrease in food intake in men compared with women over the life span. One reason for this appears to be the decline in testosterone that occurs over the life span (41, 49). Besides being a major cause of the loss of muscle mass, i.e., sarcopenia, that occurs in older men (3, 26, 30), testosterone has also been shown to be associated with an increase in leptin levels (2). Leptin is a peptide hormone produced from adipocytes that decreases food intake and increases metabolic rate (52). The increased leptin levels can modulate neuropeptide Y and nitric oxide within the hypothalamus to reduce food intake (47). Testosterone

Table 1. *Pathological causes of anorexia*

Central nervous system
Depression
Dementia
Anorexia tardive (nervosa)
Late-life paranoia
Gastrointestinal
Helicobacter pylori
Small intestine bacterial overgrowth
Dysphagia
Gallstones
Major disease
Uremia
Liver failure
Cardiac cachexia
Metabolic
Hypercalcemia
Hyperthyroidism
Hypoadrenalism
Infections
Tuberculosis
Clostriium difficile
Medications (e.g., digoxin, fluoxetine, theophylline, and ametidine)
Cancer

Some weight loss can also be due to malabsorption, hypermetabolism, or social problems.

administration to older men who are hypogonadal lowers leptin levels (78). Further studies of the interaction of testosterone, leptin, and appetite in humans are required to confirm or reject this hypothesis. The role of both estrogen and testosterone in the regulation of energy intake and metabolism in older humans also needs further study.

Within the central nervous system are a number of neurotransmitters that appear to be responsible for the regulation of food intake (43, 44). Animal studies have suggested that some of these, such as the orexigenic agents, opioid peptides, neuropeptide Y, and the anorexic neuropeptide, cocaine amphetamine-related transcript, are altered with aging (22, 23, 46, 48). However, studies in humans have not successfully demonstrated alterations in antral nervous system neurotransmitters associated with the anorexia of aging. Although evidence shows that opioid peptides are involved in the hypodypsia of aging (81), we could find no differential effect of opioid suppression on feeding in older compared with younger individuals (38).

Figure 2 summarizes the multiple factors involved in the pathogenesis of the physiological anorexia of aging and energy expenditure.

PATHOLOGICAL ANOREXIA

An in-depth review of the pathological causes of aging is beyond the scope of this short review. It is important to recognize that multiple cytokines such as interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor-α, and ciliary neurotrophic factor are anorectic (24, 45). These cytokines also decrease albumin levels and produce a general catabolic state.

In older humans, it now appears that depression is the most common cause of anorexia, which leads to weight loss (4, 50, 102). Other common pathological causes of weight loss are summarized in Table 1. In some persons with progressive weight loss, appetite can be stimulated by the use of orexigenic drugs. Megestrol acetate is a drug that inhibits cytokines and increases appetite and weight gain in older men and women (29, 105). Unfortunately, in men, it markedly decreases testosterone, with the result that some of the weight gain is fat and not muscle (32, 33). Dronabinol, a cannabinoid compound, stimulates the endogenous cannabinoid (ananamide) CB_1 receptor to increase food intake (11). One study suggested that Dronabinol may increase food intake in older humans (97). Growth hormone is an anabolic agent that was originally thought to have a role in the management of malnourished, anorectic older persons (7, 28). Unfortunately, it appears to produce increased mortality (89).

CONCLUSION

Physical activity declines over the lifespan. This is associated with a physiological anorexia, which is inadequate to prevent obesity in many middle-aged men and women. In contrast, physiological anorexia in older men and women may outstrip the reduction of physical activity, leading to weight loss and sarcopenia in the elderly. In general, there are minimal changes in extraction of energy from food with aging. If these problems are to be attenuated, a lifetime increase in physical activity, with a focus on resistance exercise, appears to be essential (15, 84).

The field of energy metabolism and aging is slowly emerging from the dark ages. Although data are limited, there are clear-cut directions in which future studies should be directed: *1*) longitudinal studies of energy metabolism over the lifespan that utilize modern technologies; *2*) studies of changes in adaptive thermogenesis with aging; *3*) biochemical studies of alterations in energy metabolism and its mechanisms in muscle and adipose tissue biopsies over the lifespan; *4*) studies of the role of reproductive hormones (estrogen, testosterone, progesterone, and perhaps dehydroepiandrosterone) on energy intake and metabolism with aging; *5*) more detailed studies of the role of the failure of fundal compliance in the pathogenesis of the anorexia of aging; *6*) studies of the putative role of CCK antagonists and ghrelin in reversing the anorexia of aging; and *7*) studies in animals to determine the alterations in central nervous system neurotransmitters with aging and their effect on energy intake and metabolism.

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