Focus on Nutrition

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John E. Morley, MB, BCh
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Contributors

Adil Abbasi, MD
Department of Medicine
Medical College of Wisconsin
Milwaukee, WI

Marie A. Bernard, MD
Department of Medicine
University of Oklahoma College of Medicine
Oklahoma City, OK

Larry E. Johnson, MD, PhD
Department of Family Medicine
University of Cincinnati Medical Center
Cincinnati, OH

Roger J.M. McCarter, PhD
Department of Physiology
University of Texas Health Science Center
San Antonio, TX

Douglas K. Miller, MD
Division of Geriatric Medicine
Saint Louis University Health Sciences Center
St. Louis, MO

John E. Morley, MB, BCh
Division of Geriatric Medicine
Saint Louis University Health Sciences Center
St. Louis, MO

Patricia M.K. Morley, BS
Division of Geriatric Medicine
Saint Louis University Health Sciences Center
St. Louis, MO

Rahmawati, Sih, MD
Division of Geriatric Medicine
Saint Louis University Health Sciences Center
St. Louis, MO

Margaret-Mary G. Wilson, MBBS
School of Medicine
Saint Louis Univeristy Health Sciences Center
St. Louis, MO

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CHAPTER 1

Introduction

JOHN E. MORLEY AND DOUGLAS K. MILLER
DIVSION OF GERIATRIC MEDICINE
SAINT LOUIS UNIVERSITY HEALTH SCIENCES CENTER

In the last decade there have been exciting advances in the understanding of appropriate approaches to nutrition among seniors. Many of these have lead to a reversal of advice previously given to seniors concerning good health. For example, as delineated in Chapters, 2, 4 and 5, it is much better to be slightly overweight than underweight when persons are over the age of 70 years. Also, as pointed out in the final chapter of this volume, there is now skepticism concerning whether lowering cholesterol in persons over 70 years has any benefit. In fact, it has been suggested that cholesterol lowering may lead to a number of adverse effects, including protein energy malnutrition, dementia, and depression.

The essays in this volume attempt to provide an in-depth view of some of the exciting frontiers of geriatric nutrition. One chapter (Chapter 8) stresses that nutrition cannot be considered in isolation from energy utilization. There is increasing evidence that moderate exercise, even in 90 year olds in nursing homes, can play a salutary role in improving health outcomes (Fiatarone et al, 1994). The appropriate nutritional intake in an exercising senior and the potential role of free radical scavengers in this group is yet to be determined. In Chapter 7, the role of vitamins in maintaining health, both as nutrients and as pharmacological agents utilized to minimize oxidative damage, is explored in detail.

Of the ten major causes of death in the United States, only accidents cannot be the result of or have their course modified by nutrient intake. The increasing awareness of the importance of the necessity of adequate and appropriate nutrition to maintain the integrity of the immune system has led to mounting attention being paid to the nutritional needs of the acutely and chronically ill older person. This area was highlighted recently by the report that older persons who were malnourished often had atypi-

TABLE 1.1 Comparison Between Changes in Immune Function with Aging and Protein Energy Undernutrition

	Aging	**Protein Energy Undernutrition**
Thymus	Atrophy	Atrophy
Delayed skin hypersensitivity	Decreased	Decreased
Helper/inducer T cells (CD_4+)	Unchanged	Decreased
CD_4+/CD_8+ T cells	Increased	Decreased
Mitogen lymphocyte proliferation	Decreased	Decreased
Interleukin-2	Decreased	Decreased
Immunization response	Decreased	Decreased

cal infections or infections requiring prolonged courses of antibiotics and that this could be related to the development of a CD_4^+ T cell lymphocytopenia (Kaiser & Morley, 1994). These patients had decreased CD^+_4 to CD^+_8 cell ratios that approximated the levels seen in young patients with AIDS. This and the other immune system deficits found in older malnourished persons (Table 1.1) has led to the suggestion that malnutrition leads to an Acquired Immune Deficiency Syndrome of Aging.

Numerous studies have highlighted the nutritional differences in various ethnic groups around the world. These nutritional differences have been utilized both in the past and the present to glean clues to those diets that are most nutritionally appropriate. Thus, the lower rate of heart disease in France, resulted in the "red wine" hypothesis (Anonymous, 1993), and the high fish intakes in some populations resulted in the awareness that eicosapentanoic and docosahexanoic acids may protect against heart disease (Kromhout, Bonschieter, & de Lezenne-Cocelander, 1985). Burkitt (1976) developed his beliefs about the protective effects of fiber based on his sojourn in Africa. The importance of salt in the pathogenesis of hypertension was recognized when ethnic differences in salt intake were related to the prevalence of hypertension in these populations (Eyer, 1975). In addition, it is now well recognized that providing ethnically appropriate foods to seniors is an important component of maintaining nutritional health in the extremes of old age. Chapter 4 explores the importance of nutrition in the older African American population. This chapter highlights the interaction of poverty with ethnic diversity as a potential cause of poor nutritional intake.

FOOD RESTRICTION AND AGING

Since the seminal studies by McCay and colleagues (1939), it is now well established that food restriction in rodents prolongs life (Masoro, 1993). The key to these studies is that moderate food restriction decreases cancer and kidney damage. In no cases has the level of food restriction approached protein energy malnutrition. It has been suggested that, in the past, food restriction produced its effects by decreasing free radical production (Lee & Yu, 1990). Food restriction delays the development of immunosenescence. Moderate caloric restriction results in preservation of the lymphoid cell proliferative responses (Fernandes, Yunis & Good, 1976). Food restriction delays the increase in prostaglandins and facilitates the maintenance of high affinity interleukin-2 receptors (Fernandes & Venkatraman, 1994). Many of the immunoregulatory effects of food restriction may be due to alterations in lipid composition of immune cells.

Recently, there has been an increased enthusiasm for replacing hormones that decrease with age in an attempt to delay the physiological declines associated with aging. Rudman, Feller and Nagraj (1990) initially reported exciting results with growth hormone administration in older men. However, by one year, many of these men had discontinued use because of development of carpal tunnel syndrome or gynecomastia (Cohn, Feller, Draper, & Reidman, 1993). A Stanford study reported a similar dismal outcome for growth hormone replacement therapy in older persons (Holloway, Butterfield, Hintz, Gesundheit & Marcus, 1994). A careful review of the food restriction literature would suggest that this was a likely outcome. Food restriction tends to produce early decreases in hormonal values similar to those seen with aging (Morley, 1993). These changes are delineated in Table 1.2. This suggests that the hormonal decreases seen with aging may represent a physiological decrease which may play a protective role in slowing down the aging process.

Whether all hormone decreases are protective is at present unknown. It would seem that the estrogen decrease at the time of the menopause may, in fact, be harmful. Numerous studies have suggested that estrogen replacement therapy for the first ten years following menopause will decrease osteoporosis, bone fractures, and cardiovascular disease (Barrett-Connor, 1992). Recently, it has become clear that like females, males have a decrease in the male hormone testosterone, around fifty years of age (Korenman et al., 1990). This so-called male menopause or viropause has led to the concept that testosterone replacement therapy may reverse some

TABLE 1.2 Comparison of the Effects of Food Restriction and Aging on Hormones in Rodents (↓ = Decrease, ↑ = Increase, NC = No Change)

Hormone	Food Restriction	Aging
Growth hormone	↓	↓
Insulin growth factor I	↓	↓
Thyroxine	↓	↓
Triiodothyronine	↓	↓
$25(OH)_2$ Vitamin D	NC	↓
Testosterone (males)	↑	↓
Estradiol (females)	↓	↓
Norepinephrine	NC	↑
Insulin	↓	↓
Glucagon	NC	↑
Corticosterone	↑	↑

of the physiological changes associated with male aging. Short-term studies have shown that testosterone will reverse a variety of aging-related deficits, including the decline in muscle strength (Morley et al., 1993). Dehydroepiandrosterone also declines with age, and preliminary studies have suggested positive effects on immune function when this hormone is replaced (Casson et al., 1993).

DIABETES MELLITUS

Diabetes is the most common nutritional disorder occurring in older persons. As one ages, there is a deterioration in the ability of the body to store glucose, leading to the hyperglycemia of aging. This is due predominantly to a decreased ability of insulin to drive glucose into cells secondary to a post-receptor defect (Morley & Perry, 1991). Approximately 80% of this hyperglycemia of aging is due to environmental factors such as excessive accumulation of adipose tissue and decreased physical activity associated with aging (Shimokata et al., 1989; Zaravoni et al., 1991).

True diabetes, as opposed to the hyperglycemia of aging, occurs in approximately 18% of persons over the age of 65 years (Harris, Hadden, Knowler, & Bennett, 1987). Diabetes in older persons is usually due to insulin resistance (Type II), but unlike the situation in middle-aged persons with Type II diabetes mellitus, many older persons with this disease are not obese. The diagnosis of diabetes mellitus is missed by physicians

in approximately half of persons over the age of 65 years. Diabetics over the age of 65 years have an increased relative risk of death and a higher institutionalization rate (Harris, 1990; Waugh, Dallas, Jung, & Newton, 1989).

Diabetes mellitus can produce many deleterious effects in older persons, such as hyperglycemic hyperosmolar coma, retinopathy, neuropathy, nephropathy, accelerated atherosclerosis, and direct effects of hyperglycemia (Morley & Perry, 1991, Table 1.3). It appears that in older persons diabetes interacts with age to produce the secondary complications (i.e., retinopathy, nephropathy, neuropathy) almost twice as quickly as occurs in younger diabetics (Naliboff & Rosenthal, 1989). Hyperglycemia has been demonstrated to lead to cognitive dysfunction in older persons (Morley & Flood, 1990). Animal studies have suggested that this is secondary to a direct effect of hyperglycemia on memory processing (Flood, Mooradian, & Morley, 1990). When glucose levels are returned to within the normal range in human diabetics, there is documented improvement in memory function (Gradman, Laws, Thompson, & Reaven, 1993; Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993).

While diabetes has historically been considered to be a disease that is responsive to dietary changes, the role of dietary intervention has been poorly determined in older persons. In a limited study, Coulston and colleagues (1990) could find no difference in glycemic control in older nursing home residents, whether or not they were fed an American Diabetes Association Diet. Chen, Halter, and Porte, Jr. (1987) found an improvement in glycemic control when carbohydrate intake was markedly increased. Others have found that a high monounsaturated fat diet (50% fat) more effectively lowered glucose and triglycerides than did a high carbohydrate diet (Reaven, 1988). Bantle and colleagues (1983) have found that the glycemic effects of simple sugars are markedly attenuated when taken with a mixed meal. A combination of chromium and nicotinic acid has been demonstrated to improve glucose tolerance in older persons (Urberg & Zemel, 1987). Vitamin E reduced fasting glucose and glycosylated hemoglobin in a group of patients with Type II diabetes and a mean age of 71 years (Paolisso, Gugliano, & D'Amore, 1993). It was postulated that Vitamin E produced these effects by reducing lipid peroxidation which is thought to play a role in the development of poor metabolic control in diabetes. Zinc deficiency, due to reduced zinc absorption and hyperzincuria, occurs in 10 % to 20% of diabetics (Kinlaw, Levine, Morley, Silvis, & McClain, 1983; Niewoehner, Allen, Boosalis, Levine, & Morley, 1986).

TABLE 1.3 Complications of Hyperglycemia in Older Persons with Diabetes Mellitus

COMA
- Hyperosmolar
- Ketoacidosis
- Lactic acidosis

GLUCOSE TOXICITY
- Pain
- Incontinence
- Cognitive impairment
- Infection
- Accelerated atherosclerosis
- Increased platelet adhesiveness
- Decreased red cell deformability
- Cataracts
- Zinc and magnesium deficiency
- Tissue glycation (accelerated aging)

MICROVASCULAR DISEASE
- Retinopathy
- Nephropathy
- Neuropathy
- Cardiomyopathy
- Amputation

Zinc deficiency does not appear to alter metabolic control but may play a role in the pathogenesis of poor wound healing and the immune deficiency commonly present in diabetes mellitus. The ideal diet for the older diabetic has not been established. High-quality controlled trials are desperately required to enhance the care of the older diabetic.

The Diabetes Control and Complications Trial has demonstrated that returning blood glucose within the normal range markedly slows the development of secondary complications of diabetes in young Type I diabetics (Harris, Eastman, & Siebert, 1994). More recently, a Japanese group has demonstrated in a 5-year prospective trial that the better the diabetic control in persons over the age of 60 years with Type II diabetes, the less likely it is that retinopathy will progress (Morisaki et al., 1994). Overall, there is now strong evidence for the aggressive management of diabetes mellitus in older persons.

OSTEOPOROSIS

With age, there is a generalized loss of bone mass which is termed osteoporosis. Type I osteoporosis occurs between the ages of 50 to 65 years, occurs predominantly in women, and is due to estrogen deficiency (Gunby & Morley, 1994). Type II osteoporosis occurs in both males and females and involves loss of both trabecular and cortical bone. It occurs in persons over 70 years of age and is commonly associated with hip fractures. Type II osteoporosis is clearly a nutritional disorder. Chapuy, Arlott, and Deboeuf, (1992) have demonstrated that treatment of nursing home residents with a combination of vitamin D and calcium markedly decreases the incidence of hip fractures. In addition, there is increasing evidence that protein energy malnutrition predisposes to the risk of having a hip fracture (Barstow, Rawlings, & Allison, 1983) and that aggressive refeeding following hip fracture can lead to improved rehabilitation outcomes (Delmi, Rapin, Bengoa, Delmas, Vasey, & Bonjour, 1990).

NUTRITION AND BEHAVIOR

Nutritional deficiencies have been demonstrated to produce effects on behavior. The classic study of Goodwin, Goodwin, and Garry (1983) found that older persons who had poor intakes of protein, ascorbate, thiamine, riboflavin, pyridoxine, niacin and/or folate intake had poorer performance on cognitive tests than did those with superior intakes. Persons with borderline pyridoxine levels have been shown to have improved memory when given pyridoxine (Deijen, van der Beck, Orfebeke, & Van den Berg, 1992). Thiamine replacement in older Irish women improved their energy levels (Smidt, Cremin, Grivetti, & Clifford, 1991). Alcohol is a toxic nutrient that can produce memory disturbances and confabulation (Korsakoff's syndrome). Carbohydrate appears to decrease alertness and attention in older persons, possibly due to increasing the entry of the serotonin precursor, tryptophan, into the central nervous system (Spring, Maller, Wurtman, Digman, & Cozolino, 1983).

Flood, Smith, and Morley (1987) demonstrated that if an animal is fed immediately after learning a task, they will have enhanced memory of the task 7 days later. Food has also been demonstrated to enhance memory in older humans with borderline cognitive ability. Food causes the release of the gastrointestinal hormone cholecystokinin (CCK) from the duodenum.

CCK has been shown to enhance memory when injected intraperitoneally into rodents. The ability of food to enhance memory is blocked by a CCK antagonist, suggesting that this is a physiological effect (Flood & Morley, 1989). The effect of CCK on memory enhancement is blocked by vagotomy, by injecting betaendorphin into the amygdala or by cutting the fibers in the stria terminalis. These experiments suggest that the pathway by which food enhances memory is as follows:

Food → CCK → activates ascending vagal fibers → nucleus tractus solitarius → stria terminalis → amygdala → hippocampus.

Teleologically, the ability of food to enhance memory makes sense, as it would enhance the ability of an animal to remember the details of a successful hunt. In older persons with borderline food intake, the paucity of food intake could interact with age-related memory deficits to decrease functional ability.

THIRST AND DEHYDRATION

Older persons have an increase in morbidity and death related to disturbances in salt and water metabolism. Dehydration is particularly common during febrile episodes in the nursing home and appears to be associated with an increased mortality (Weinberg, Pals, Levesque, Beal, Cunningham, & Minaker, 1994). Dehydration has been identified as an independent risk factor for the development of delirium in hospitalized elderly medical patients (Inouye, Viscoli, Horwitz, Hurst, & Tinetti, 1993). Older persons also struggle to excrete a water load and thus are more vulnerable than younger persons are to develop hyponatremia (Crowe et al., 1987).

Water is a key nutrient essential to maintain homeostasis. With advancing age, there is a decrease in total body water from 80% at birth to 60% to 70% in the eighth decade (Chernoff, 1994). Both intra- and extracellular water are reduced with advancing age. The original studies by Phillips and colleagues (1984, 1991), clearly demonstrated that older persons have a reduced thirst perception following overnight fluid deprivation or the infusion of a hypertonic solution.

Mack, Weseman, Langhans, Scherzer, Gillen, and Nadel (1994) found that older persons had a higher osmolality and decreased thirst following a dehydration period resulting in a 2.4% decrease in body weight. They

found that fluid intake during the repletion intake was related to thirst in a similar manner to that seen in younger persons. These studies suggest that older persons have a shift in the control point for thirst, leading to a lower overall sensation of thirst.

In contrast, in nonstressed conditions, de Castro (1992) found no differences in fluid intake over a 7-day period in a large group of individuals aged 20 to 80 years. Fluid intake in response to solid food ingestion was identical for young and old individuals. Older persons had a blunted circadian rhythm of fluid ingestion compared to younger persons. Older persons in this study ingested more coffee and less soda and alcohol than younger persons.

The neurotransmitter regulation of fluid intake is extremely complex. Studies in rodents by Silver, Flood, and Morley (1991) suggested that a failure of the mu opioid drinking drive may be responsible for the decreased fluid intake with aging. They then investigated the effects of the opioid antagonist, naloxone, on fluid intake in a group of young subjects (aged 23 to 39 years) and a group of older subjects who were healthy nonsmoking men (Silver & Morley, 1992). After overnight fluid deprivation and administration of naloxone, fluid intake was diminished by 42% in the younger subjects and only 7% in older subjects. This study strongly suggested that hypodipsia in older persons is due to a deficit in the opioid drinking drive.

Animal studies have failed to find a major difference in the angiotensin II fluid drive between young and old rodents (Silver, Guillen, Kahl, & Morley, 1993). Studies in humans on hemodialysis have suggested that angiotensin II may be responsible for the hyperdipsia seen in some patients with chronic renal failure (Yamamoto, Shimizu, Morioka, Kitano, Wakabayashi, & Aizawa, 1986). This hyperdipsia can be reduced with an angiotensin-converting enzyme (ACE) inhibitor. This suggests that ACE inhibitors may precipitate dehydration in older persons secondary to hypodipsia.

Physical restraints are commonly used in older persons. Physical restraints have been associated with dehydration (Evans & Strumpf, 1989). Recently, we found that when physical restraints were applied to healthy young persons, there was a dramatic decrease in fluid intake (Guitierrez, Morley, & Perry, unpublished observations).

Overall, it needs to be recognized that many elderly persons live in a water desert. Their reduced thirst perception often coupled with restricted mobility, places the older person at major risk for developing dehydration when exposed to stressors that increase the propensity to water loss.

OBESITY

Obesity is a major health problem of middle-aged persons. The major increase in body fat occurs in the fifth and sixth decades (Silver et al., 1993). Old age is associated with a loss in body mass, a decrease in stature, and a loss of muscle and skeletal mass (Going & Lohman, 1994). Andres (1980) has pointed out that obesity has a lesser detrimental impact on mortality in the young-old, compared to the old-old. A Swedish study has found that in males between the ages of 70 and 80 years, there is a U-shaped curve with the same level of mortality occurring at a body mass index of 20 and 33 (Steen, 1994). Increasing body mass index was not associated with increased mortality in older women. The major complications of obesity are listed in Table 1.4.

Studies in younger persons have suggested that those persons with a lower waist-to-hip ratio (pear shape) have a lesser mortality than those with a high waist-to-hip ratio (apple shape). Pear-shaped persons have less diabetes mellitus, hyperlipidemia, and a lower incidence of stroke and myocardial infarction (Bjorntorp, 1992). With aging, there is a shift towards higher waist-to-hip ratios (Borkan, Hults, Gurzof, & Robbins, 1985; Enzi et al., 1986). The role of this shift in the increased prevalence of hyperglycemia with aging has not been studied.

Overall, the available studies suggest that the approach to obesity not associated with diabetes in older persons should be cautious. Exercise, as discussed in Chapter 8, appears to be the most appropriate treatment modality. Drugs and surgery are not indicated for the management of obesity in older persons. When a reduction in caloric intake is indicated in an older person, care needs to be taken to make sure that the diet is protein sparing, albumin levels should be followed at monthly intervals, and the patient should receive a multivitamin.

ETHICAL ISSUES: THE REFUSAL OF FOOD AND WATER

The disciplined examination of value dilemmas in health care is an extremely important area for the care of older persons. However, it is only since the late 1960s that bioethics emerged from the academic halls to claim a place in full-stream society as a guiding light in developing health policy. In the mid-1980s, the practical ethical issues facing older persons were placed on a firm ethical footing with a special issue of *Social Thought*

TABLE 1.4 Major Complications of Obesity

1. Functional Impairment
2. Psychosocial problems
3. Intertrigo
4. Decubitus ulcers
5. Osteoarthritis
6. Deep vein thrombosis
7. Pulmonary embolus
8. Increased surgical risk
9. Gallbladder disease
10. Impaired diagnostic accuracy
11. Sleep apnea
12. Hypertension
13. Hyperlipidemia
14. Diabetes mellitus
15. Coronary artery disease
16. Increased incidence of certain cancers (e.g., endometrial, breast, ovarian, and prostate)
17. Syndrome X (hypertension, hypertriglyceridemia, hyperinsulinemia)

on ethics and aging (Fahey, 1985), and one in *Generations* (Moody, 1985). The following year a selected bibliography of recent articles on ethics and geriatrics was published in the *Journal of the American Geriatrics Society* (Cassel, Meier, & Traines, 1986).

One of the most hotly debated areas in bioethics has been the issues of death and dying. Among the elderly this issue is made more complex by the problem of diminished mental capacity. The major ethical issue around the time of death revolves around the advances in medical technology that have resulted in the need to make difficult decisions concerning the forging of treatment to the active withdrawal of treatment modalities. Moody (1992) summarized the general consensus of opinion as being that patient autonomy should allow the shortening of life by either withholding or withdrawing treatment. Ethically it has been established that there is little difference between withholding or withdrawing, although there are clearly different emotional connotations to these two behaviors. Legally, it is also now clearly established that competent patients have the right to refuse treatment.

The right to refuse or withdraw food and water is one of the most complex and difficult areas of bioethics and legal practice. The right for the

competent person to refuse food and water is now well accepted. The more difficult ethical questions revolve around the use of artificial hydration and feeding and the right of surrogate decision makers to refuse nourishment for the incompetent person. A subsection of this argument is whether artificial hydration (intravenous lines) and feeding (nasogastric, G-tubes, parenteral nutrition) represent food or medical treatment. The emerging common consensus of both ethicists and the law (based on the Cruzan case) (Thomasma, 1990) is that if the person had previously expressed a desire not to be kept alive by extraordinary measures, withdrawal of artificial feeding is acceptable. However, if the person has not expressed any wishes, the strict legal ruling is that the surrogate cannot decide to disallow artificial feeding. Many ethicists would argue that the role of beneficence should allow the proxy to withdraw or refuse artificial feeding when it would appear to be in the best interests of an incompetent subject and compatible with a general, though not specifically expressed belief, of what the subject would have wanted.

While these general rules are useful, a number of situations are commonly observed where their application is not straightforward:

(1) *Short-term use of artificial feeding and/or hydration*: When an older person becomes febrile, it is common practice to provide rehydration by intravenous fluids without asking permission of the person even if they have already refused artificial nourishment. Often the fluids are given under the guise of a vehicle for antibiotic treatment. At the other end of the spectrum is the person who refuses short-term artificial feeding while still wanting to be resuscitated and being prepared to accept artificial ventilation. Many older persons have separated artificial feeding from other medical therapies. While in some cases this may be rational, in others it is clearly irrational and often fueled by inappropriate press publicity and the poor knowledge that the average health care physician has concerning the importance of nutrition in the treatment of disease and maintenance of quality of life.

(2) *Refusal of food by the depressed patient*. Some consider the refusal of food by a depressed patient a suicidal gesture and therefore an unacceptable request. In this case, the autonomous wishes of the person are deferred until the depression is treated on the grounds that the principle of nonmaleficence is being followed. Others argue that most depressed persons do not change their viewpoints

regarding medical decisions following treatment, and, therefore, the principle of autonomy should apply from the outset. This area is further obfuscated by the fact that anorexia and weight loss are among the most common presentations of depression in older persons.

McCann, Hall, and Groth-Juneker (1994) have gathered empirical data in patients terminally ill with cancer to argue that food and water withdrawal is an acceptable approach to terminal care. In 32 patients, they found that 63% never experienced hunger or thirst, while 34% only had hunger symptoms initially. In all persons, symptoms could be alleviated with ice chips or small amounts of food.

Unfortunately, the above study does not provide insight into chronic starvation over long periods in persons who do not have a terminal illness. In our experience, many of these persons have an extremely poor quality of life secondary to the development of decubitus ulcers and recurrent infections. There is a need for well-designed empirical studies to determine the human and fiscal costs of food withdrawal.

Callahan (1987) has argued for setting limits of care for older persons on the grounds that society cannot afford the costs of their care. Based on his arguments, one could conclude that withdrawal of life support, including food and water, from persons with endstage Alzheimer's disease would be appropriate to save society the burden of the costs. When societal justice is allowed to replace autonomy, we are surely entering onto the slippery slope where individual beneficence will no longer guide health care practice.

As will be pointed out in Chapter 4, our society has already failed to meet the basic tenets of justice by not providing food security for all older persons. At present, we see this situation being further eroded as Congress attempts to remove programs such as food stamps under the guise of cutting "big government." If ethicists are to survive as a leading force in guiding policy, their voices have to be heard, loudly decrying such policies that are clearly maleficent.

CONCLUSION

Physicians have had minimal training in the care of older persons (geriatrics) and in nutrition. This often leads to older persons' nutritional needs

being ignored. The exciting advances in our knowledge concerning the nutritional needs of older persons suggests that such behavior is no longer acceptable. It is hoped that this volume will give health care professionals the ability to develop a rational approach to the nutritional care of older persons.

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CHAPTER 2

Nutritional Epidemiology

DOUGLAS K. MILLER AND JOHN E. MORLEY
DIVISION OF GERIATRIC MEDICINE
SAINT LOUIS UNIVERSITY HEALTH SCIENCES CENTER

> A proud and resourceful nation can no longer ask its older people to live in constant fear of illness. We owe them the right of dignity in sickness as well as in health. Too many elderly people. . . . skimp on food at a time when their health requires greater quantity, variety and balance in their diets.
>
> —John F. Kennedy

Aging is a physiological process that inexorably leads to decline and eventually death of the individual organism. The rate of physiological aging can be adversely effected by a variety of disease processes. Over this century there has been remarkable progress in extending the lifespan of human populations. This appears to have been accompanied by an improved quality of life of many, if not all older persons. Studies by epidemiologists have concentrated on identifying factors that are both capable of being manipulated and may result in an alteration in lifespan. Two areas which have been particularly fruitful in this regard have been the study of nutritional intakes and levels of physical activity. This chapter explores some of these epidemiological clues to longevity extension.

Fries (1984) has pointed out that our focus needs to be more on compression of morbidity rather than on extension of lifespan. Unfortunately, most epidemiological studies have utilized as their endpoints either death or a variety of diseases. Only recently have epidemiologists turned their attention to attempting to determine the factors that are associated with disability.

A major caveat to the interpretation of epidemiological studies is that these findings only provide circumstantial evidence to the possible causes of an event. Controlled intervention trials are necessary to confirm the findings of epidemiological studies. A caution concerning both epidemiologi-

cal and intervention studies is that a specific endpoint may be improved while others may have a less salutary outcome. This has been best demonstrated by the cholesterol studies where clear evidence exists, at least in younger persons, that lower cholesterol levels are associated with better cardiovascular outcomes but not with improvement in total mortality (Kaiser & Morley, 1990).

AGING AND MORTALITY

In the Bronze Age the human life expectancy was 18 years; this rose to 33 years in England during the Middle Ages, 35.5 years in the 18th century and 40.9 years in the 19th century. (Dublin, Lotka, & Spiegelman, 1936).

There has been a further marked increase in longevity this century, with life expectancy increasing from 49.2 years at the turn of the century to 75.7 in 1991. At the turn of the twentieth century 4% of the United States population was over the age of 65 years.

By 1976, 11% of United States citizens were over 65 years and by the year 2000 it is estimated that seniors will comprise 14% of the population (Munro, 1992). Seventy percent of all deaths occur in persons over 65 years of age, with the majority being from heart, neoplastic and cerebrovascular disease. While industrialized countries have the greatest relative percent of their populations being over 65 years of age, it needs to be recognized that the majority of older persons live in developing countries. By the year 2000, two-thirds of seniors will live in developing countries (Morley, 1991). Both China (with over 160 million persons over 60 years in 1980) and India (over 100 millions) will have gained an additional 270 million older persons by the year 2000. By the year 2020, Mexico will have the ninth largest elderly population in the world.

Life expectancies for men and women from various countries around the world are given in Figure 2.1a,b. As can be seen, the Japanese have the longest lived population. The United States does not make the top ten countries in life expectancy from birth and has a life expectancy of 2.4 years less for females and 3.1 years less for males than in Japan. Even over the age of 65 years the United States has a relatively poor life expectancy compared to other countries, finishing 12th on the list at 15 years compared to the 16.5 years of Japan, 16 years of Iceland, and 15.7 years of France (Fig. 2.2).

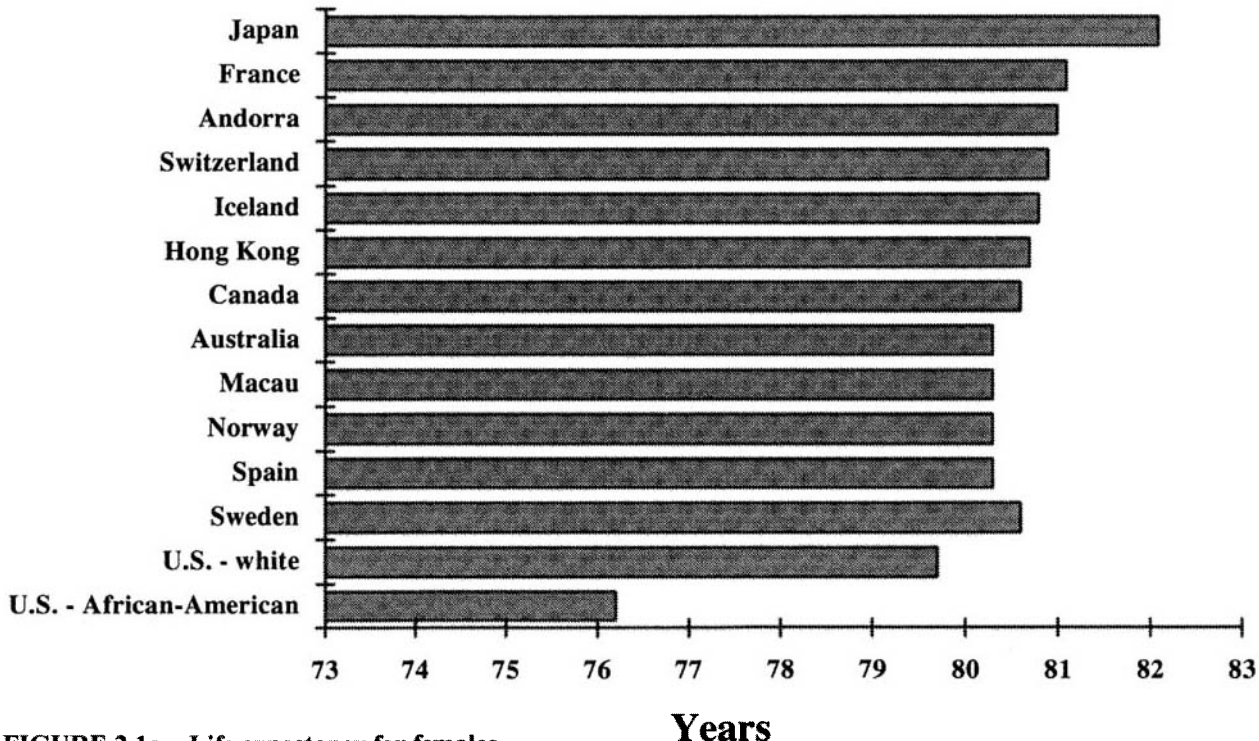

FIGURE 2.1a Life expectancy for females

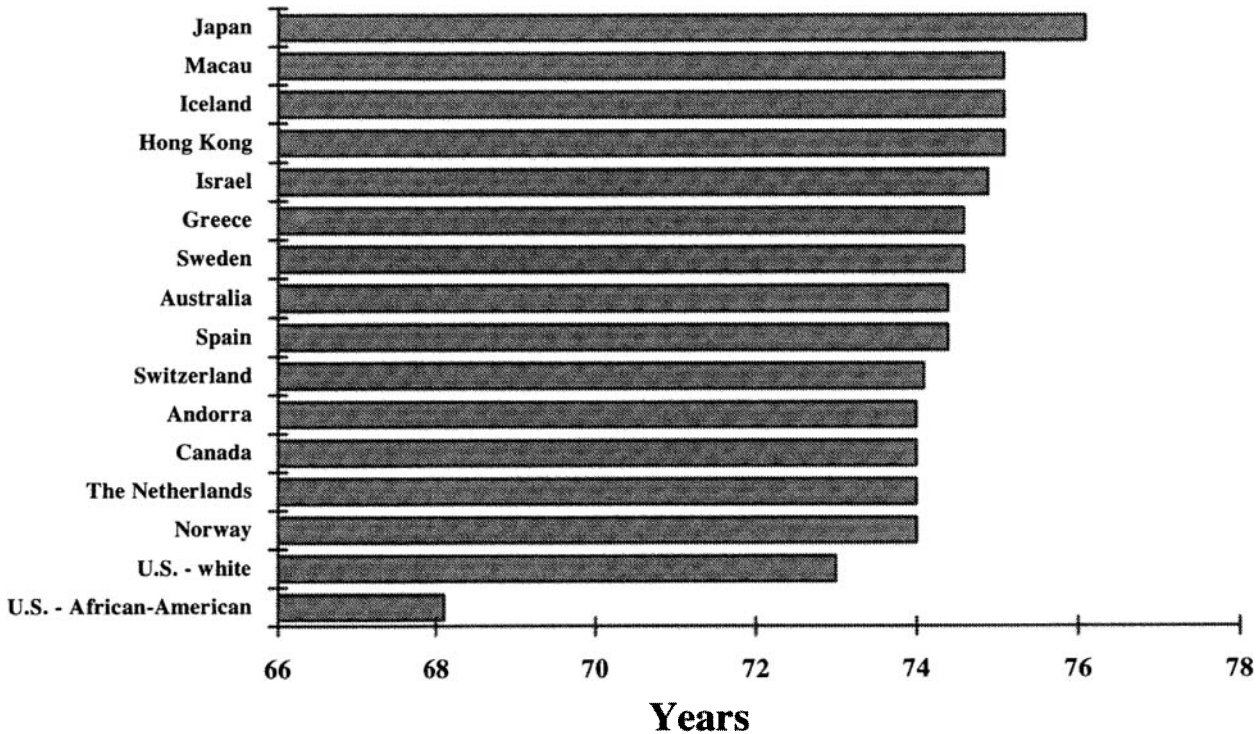

FIGURE 2.1b Life expectancy for males

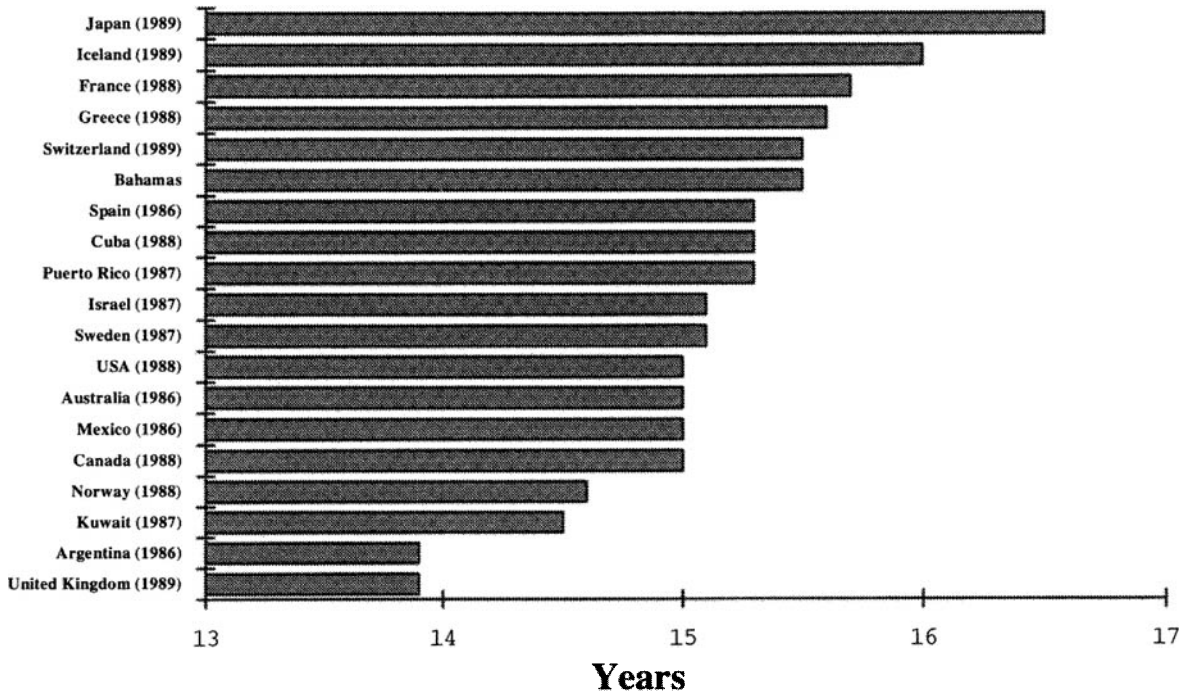

FIGURE 2.2 Life expectancy at 65 years of age. Source: Abstracted from *World Health Statistical Annual*, 1990.

The reasons for the poorer life expectancy in the United States compared to the rest of the world are obviously multifactorial. While some of these such as inappropriate high technological interventions and polypharmacy in older persons are not associated with nutrition, a number of possible causes are clearly nutritionally related. Only the Greeks (3,775 calories) eat more calories per day than do people living in the United States (3,642 calories) (Figure 2.3). However, calorie intake when not associated with obesity is not necessarily bad. A number of studies have found that increased calorie consumption leads to a decrease in myocardial infarction (McGee, Reed, Yarno, Kagan, & Tillotson, 1984; Shekelle, Mispell, Paul, Shyrock, & Stamler, 1985). In fact, epidemiologically, eating more is more protective of not having a heart attack than is having a low cholesterol level! The obvious explanation for this conundrum is that the increased food intake represents an increase in exercise.

Eight of the ten countries with the longest life expectancy consume 1% or more or their calories from fish (Figure 2.3). Japan consumes 6.9% of its total calories in fish products. There is reasonable epidemiological evidence that fish consumption is associated with a decrease in cardiovascular disease (Kromhout, Bonschieter, & de Lezenne-Cocelander, 1985; Norell, Ahlborn, Feyehting, & Pedersen, 1986). The Netherlands (20.2%), Sweden (20.1%), Israel (19.1%), France (18.9%), Canada (18.5%), Greece (18.4%), and Switzerland (18.3%) all ingest a higher percentage of their calories as fats (oils) than does the United States (18.1%). The Japanese ingest 11.2% of their total calories as fats. Both Sweden (15.3%) and Iceland (15.8%) ingest more of their calories from dairy products than does the United States (11.4%). Only 6.2% of calories ingested by Japanese comes from dairy products.

Alcohol consumption per capita is higher in the United States than in Japan but not in some European countries such as France, Switzerland, and Spain. Canadians smoke more (4.5 kg tobacco per capita per year) than United States citizens (4.2 kg). Japanese, however, have a lower utilization of tobacco products (3.3 kg).

Overall, international comparisons suggest that a substantial opportunity to extend the lifespan may exist in our ability to modify dietary intake. However, before the nutritional evangelists take over, it would be reasonable to remember that the overall ideal diet would appear to be one in which moderation predominates and extremes are avoided.

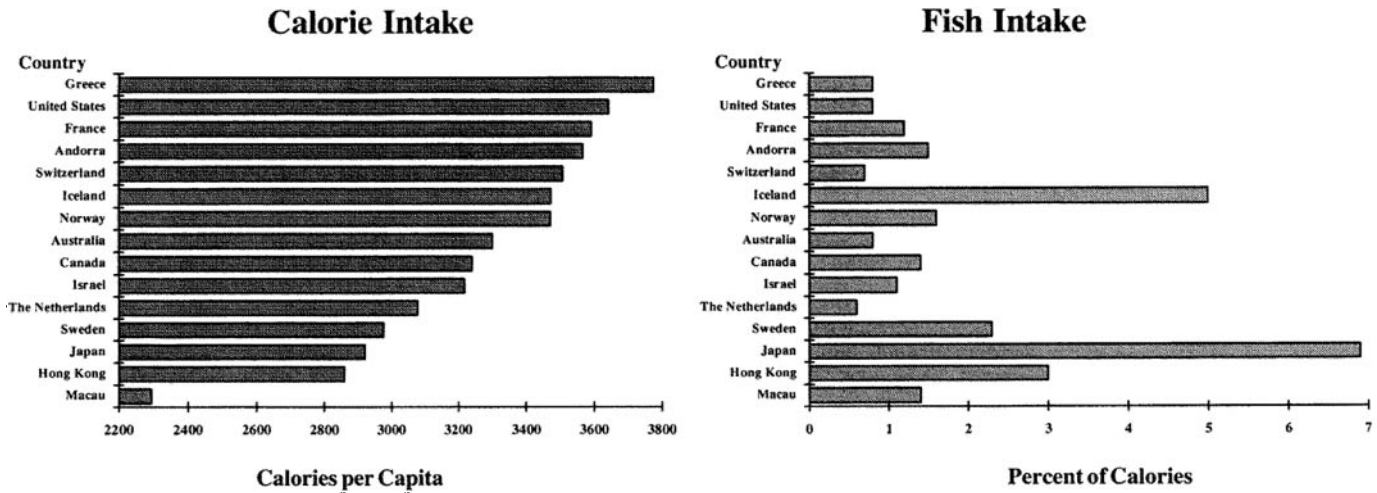

FIGURE 2.3 Food intake for the countries included in Figures 2.1a and 2.1b.

POVERTY AND NUTRITIONAL RISK

The inability to be able to afford food is a clear nutritional risk factor. This is discussed in detail in Chapter 4. Federal entitlement spending on social security ($335 billion), medicare ($177 billion), medicaid ($96 billion), federal retirement ($76 billion), and supplemental security income ($34 billion) has substantially reduced the number of poor persons over the age of 65 years. In 1970, the percentage of older persons living in poverty was twice that of all persons, whereas by 1990, fewer older persons were living in poverty than the rest of the population (Table 2.1). Similarly, median household incomes for older persons have risen at the same rate as middle-aged persons since 1967 and at a greater rate than for persons under the age of 44 years when adjusted to constant dollars. Despite this, certain segments of the older population such as African Americans, are at a substantially higher risk of living in poverty.

Approximately 38% of income for persons over 65 years comes from Social Security. Their remaining income is made up of assets 26%, pensions 16%, earning 17%, and miscellaneous 3% (Grad, 1986).

AGING FACTORS ASSOCIATED WITH NUTRITIONAL RISK

A variety of psychological factors can lead to poor nutritional intake. Approximately 3% to 6% of older persons living in the community are clinically depressed (Fitten, Morley, Gross, Petry, & Cole, 1989). Depression is less common in older than younger persons, but older persons are more likely to develop weight loss when they are depressed. Approximately 30% of older persons live alone. Eating alone and social isolation are risk factors for decreased nutritional intake. Dementia occurs in 5% of persons over the age of 65 years (Graves & Kukull, 1994). By the age of 85 years, between 25% to 40% of the older population will have some degree of dementia associated with functional impairment. Cognitive impairment is present in approximately two-thirds of institutionalized individuals (Gurland & Cross, 1982). Alcoholism occurs in between 5% to 15% of the older population. Thirty-five percent of the population over 65 years of age are widowed and therefore at risk of developing the dysphoria and anorexia often associated with bereavement.

Approximately 8% of older persons are impaired in their basic activities of daily living and 4.4% in their instrumental activities of daily living

TABLE 2.1 Prevalence of Poverty in the United States Population

	Year		
	1970	1980	1990
		(Percentage)	
Persons over 65 years	24.5	15.7	12.2
All persons	12.6	13.0	13.5

(Miller, Morley, & Rubenstein, 1995). Under the age of 65 years 2.4% of noninstitutionalized persons require assistance with everyday activities; by age 65 to 69 years 9.3% require help, and over the age of 85 years, 45.4% are in need of assistance. Two percent of community-dwelling older persons cannot feed themselves without assistance. In nursing homes, nearly one-third of persons need assistance with feeding (Rabin & Stockton, 1987). Help with preparing meals is required by 7% of older persons and difficulty with shopping experienced by 11%. Half of older persons are edentulous, 35% have difficulty chewing and 16% have inadequate dentures (Lowenstein & Schrier, 1982).

The listing of these simple facts makes it clear that the physiological aging processes and disease process place many older persons at extremely high nutritional risk.

BODY MASS INDEX AND MORTALITY

Andres, Elahi, Tobin, Muller, and Brant (1985) analyzed the data from The Build Study and found that with advancing age the body mass index associated with lowest mortality increased. Thus the optimum BMI for 20- to 29-year-old males was 21.4kg/m^z and for 60- to 69-year-olds was 26.6 kg/m^z. Similarly, the optimum BMI for women aged 20 to 29 years was 19.5 kg/m^z and 27.3kg/m^z for 60- to 69-year-olds. Of interest, sex did not significantly alter the associations of BMI to lowest mortality.

Numerous studies have demonstrated that when BMI is plotted against the mortality ratio the data are best fitted by a quadratic (U-shaped) curve than by simple regression (Build Study 1980; Dyer, Stamler, Bertison, & Lindberg, 1975; Keys, 1980). In African American men a similar J-shaped curve was found for BMI and relative mortality (Wienpahl, Ragland, & Sidney, 1990). However, in African American females the association between BMI and mortality was essentially flat. These findings remained in most of the populations when corrected for smoking or antecedent illness.

Tayback and colleagues (1990) analyzed the 1971 through 1975 National Health and Nutrition Examination Survey (NHANES I) data on men and women aged 55 to 74 years at the time of examination and follow-up data collected in 1982 to 1984 as part of the National Health Examination Epidemiologic Follow-up Survey (NHEFS). Their analysis, when controlling for hypertension, smoking, and poverty, found that women with a body mass index of equal to or greater than 30 kg/m^2 had no additional mortality risk. Males in the upper decile of body mass index had a small additional relative risk of 1.1 to 1.2. A body mass index of less than 22 kg/m^2 was associated with an increase in mortality in men aged 55 to 64 years and 65 to 74 years with a relative risk ratio of 1.3 to 1.6.

Kinney and Caldwell (1990) examined the relationship between body mass index and mortality in males aged 75 to 98 years old. Follow-up was for 28.6 months. A low Quetelet's index and glucose intolerance were related to mortality. Preexisting morbid conditions appeared to account for the increased mortality.

A study of 1,723 nonsmokers aged 65 years (followed from 1 to 23 years) as part of the Framingham Heart Study examined the relationship of body mass index to mortality. Both high and low extremes of body weight were associated with increased mortality (Harris, Cook, Garrison, Higgins, Kannel, & Goldman, 1988). For those in the lower weight ranges relative death risks were much higher in the first few years following 65 years of age, suggesting a role of premorbid conditions in producing the increased mortality.

Overall these studies support the concept that underweightedness is a major predictor of mortality in older persons. However, whether or not this is due to preexisting disease has not as yet been clearly elucidated. Overweightedness seems to be much less associated with mortality in older persons.

WEIGHT LOSS AND MORTALITY

Weight loss has been associated with lowering of blood pressure and glucose. Felson, Zhang, Anthony, Naimork, & Anderson (1992), utilizing the Framingham Study cohort, found that weight loss over 70 years was associated with a decreased risk for symptomatic osteoarthritis, and weight gain increased the risk for osteoarthritis. Weight loss, in conjunction with increased physical activity in older adults, lowered total cholesterol and

increased HDL cholesterol (Goldman, Aylie-Rosett, Swencionis, & Dornelas, 1992). These findings have generally lead to public health advocates arguing that overweight older persons should attempt to lose weight.

Recently, Pamuk et al. (1992) studied the relationship between weight loss and subsequent mortality in 2,140 males and 2,550 females who took part in the First National Health and Nutrition Examination Survey (1971 to 1975) and were surveyed for at least 5 years. Mortality was measured up until 1987. For those persons whose body mass index was between 26 and 29, mortality increased with increasing weight loss. Weight loss of greater than 15% doubled the death rate. With higher body mass indices, weight loss increased mortality in women. Men with a body mass index greater than 29 had a decrease in mortality for weight loss between 5% to 15%. In a follow-up study, the authors found that smoking status did not alter these findings (Pamuk, Williamson, Serdula, Madans, & Byers, 1993). However, when extension of the period before mortality was examined from 5 to 8 years, the association of weight loss with death from noncardiovascular causes was weakened. Nevertheless, for some persons, weight loss continued to be associated with mortality even after deaths in the first 8 years were excluded.

Harris, Ballard-Barbasch, Madans, Makue, and Feldman (1993) examined the data of older women 65 to 74 years of age from the same data set. Women with a body mass index greater than 29 had increased risk of coronary heart disease compared to those with an index less than 21. However, thin women who lost weight also had an increased risk for coronary heart disease. In a second study, they found that the increased mortality that occurs in older women was present only among those who lost at least 8.55% of their reported maximum lifetime weight (Rumpel, Harris, & Madans, 1993). This finding was independent of smoking. Mortality is less common in lean older women with stable weight.

CENTRAL ADIPOSITY

There is evidence in young persons that those who have the majority of their adipose tissue around their waist (high waist-to-hip ratio), have a higher prevalence of diabetes mellitus, hypertension, and coronary artery disease than those who have predominantly hip adiposity (Bjorntrop, 1992). The Baltimore Longitudinal Study found that there is increasing upper and

central body fat distribution with aging (Shimokata, Tobin, Muller, Elahi, Coon, & Andres, 1989). Women have an acceleration of this trend following menopause. Males have higher waist-to-hip ratios than women. Cigarette smoking was associated with a higher waist-to-hip ratio despite being associated with a lower overall body mass (Shimokata, Muller & Andres, 1989). This suggests that smoking has deleterious effects on body fat distribution. The longitudinal increase in waist-to-hip ratios is strongly correlated with weight changes. In males, the major changes are in waist circumference (Shimokata, Andres, Coon, Elahi, Muller, & Tobin, 1989). In women, waist and hip circumferences change in parallel, resulting in smaller waist-to-hip increases in women with aging.

Prineas, Folsom and Kaye (1993) examined the four-year risk of fatal coronary artery disease in 32,898 women aged 55 to 69 years. Women in the highest tertile of waist-to-hip ratio had 3.3 times higher risk of coronary artery disease mortality than those in the lowest tertele. This association of central adiposity, with the risk of coronary artery disease, was independent of its association with hypertension and obesity.

Folsom et al. (1993) examined the role of body fat distribution on mortality in a random sample of 41,837 Iowan women aged 55 to 69 years followed for 5 years. As expected, total mortality rates were elevated in both thin and overweight persons. Waist-to-hip ratio was positively correlated with mortality. This correlation remained after correcting for smoking, alcohol, and estrogen use. Weight loss patterns did not alter this relationship. This study supports the concept that high waist-to-hip ratios is an independent risk for death in late middle-aged and young old women.

SERUM ALBUMIN AND MORTALITY IN COMMUNITY-DWELLING OLDER PERSONS

Albumin functions to maintain the oncotic pressure of plasma and as a transport substance for many endogenous and exogenous substances. Albumin is produced by the liver at a rate of 130 to 200 mg/kg body weight per day (Rothschild, Oratz, & Schreiber, 1988). Albumin has a half-life of approximately 20 days. The role of albumin as a nutritional marker is controversial. Small declines in circulating albumin levels may occur with aging, but no study has clearly demonstrated that this is not due to minor degrees of protein energy malnutrition (Shibata et al., 1991). Clear falls in albumin levels are often only seen late in persons with protein calorie

malnutrition (Lemonnier et al., 1991). The best explanation for this conundrum is that protein is spared during food deprivation resulting in a marasmus-like picture (weight loss without hypoproteinemia) in malnourished older persons. Albumin is also a negative acute phase reactant. The cytokines interleukin-1, tumor necrosis factor-$^{\alpha}$ and interleukin-6 lead to a reduction in albumin gene expression, increased catabolism and a redistribution of albumin into the extravascular space (Roubenoff, Grimm, & Roubenoff, 1994). Decreased albumin levels are more related to catabolism and redistribution than decreased synthetic rate (Dahn et al., 1985). In our studies (Boosalis et al., 1989), we found that serum albumin was related to the severity of underlying illness and the underlying nutritional status. It would appear that illness is more likely to result in hypoalbuminemia in persons who have previously had a poor caloric intake or who decrease their caloric intake dramatically at the time of the illness. Despite the above controversies, albumin, as demonstrated below, is a useful marker for potential mortality in older persons.

Corte, Guralnik, Salive, and Sorkin (1994) studied 1,486 males and 2,630 females over the age of 70 years who were participants from the Established Populations for Epidemiologic Studies of the Elderly and had a mean follow-up of 27 years. They found that a serum albumin level less than 35 g/L had a significantly higher mortality risk than was seen in those with an albumin level greater than 43 g/L. They also reported that within the normal serum albumin range (35 g/L to 50 g/L) there was a decreasing mortality rate with increasing albumin levels. This study also found that decreasing albumin and increasing physical disability level appeared to be synergistic in predicting mortality.

Klonoff-Cohen, Barnett-Conner and Edelstein (1992) studied 2,342 healthy subjects aged 50 to 89 years in a 3-year prospective study. They found that for every standard deviation fall in albumin, there was a relative odds ratio of dying of 1.24. This appeared to be independent of preexisting disease.

A number of studies have suggested that albumin levels are a potent predictor of inhospital mortality. These data are summarized in Table 2.2. Overall, these data suggest that an albumin of 3.2 g/dl or less is highly predictive of dying in hospital. In addition, two studies have found that hypoalbuminemia is a major predictor of delirium occurring during hospitalization (Dickson, 1991; Levkoff, Safron, & Cleary, 1988).

Mortality in persons with hip fracture has also been associated with hypoalbuminemia. Foster, Heppinstahl, and Friedenberg (1990) found a

TABLE 2.2 Serum Albumin Levels as a Predictor of Mortality in Older Hospitalized Patients

Author	Age (yr)	n	Mean Albumin (g/dl) Died	Survived	Comments
Intensive Care Unit					
Boosalis et al. (1989)	32–88	78	3.1	3.5	—
Murray et al. (1985)	20–91	111	3.0	3.2	—
General Hospital					
Reinhart et al. (1980)	21–90	509	—	—	Veterans; 62% mortality rate is albumin <2.0g/dl
Agarwal, Acevedo, Leighton, Cayten, & Ptichumoni (1988)	85–100	80	—	—	Albumin <3.0 g/dl predicts mortality
Herrmann, Safran, Levkoff, & Minaker (1992)	67±14	15,511	—	—	14% died if albumin <3.4 g/dl; 4% died if albumin >3.4 g/dl
Constans, Bacq, & Brechot (1992)	M78.8± 5.4	128	3.2	3.6	—
Cederholm, Jagren, & Hellstrom (1995)	75±1	205	3.3	3.4	Malnutrition as identified by having at least 3/5 nutritional indices below the norm was much more predictive of mortality (44% vs 18% p<0.001)
Surgical					
Lai, Tam, & Paterson (1990)	67±14	96	3.1	3.6	Preoperative
Christou, Tellado-Rodriguez, & Christiano (1989)	64.9±12.	245	2.9	3.6	Preoperative
Rich, Keller, & Schechtman (1989)	75–90	92	—	—	Albumin <3.5g/dl mortality 31%; 73.5 g/dl mortality 13%
Hip Fracture					
Foster et al. (1990)	45–97	40	2.8	3.5	

mean serum albumin level of 2.8 g/dl in persons who died compared to 3.5 g/dl in those who survived for 11 months following a hip fracture. Patients with hip fracture who were protein depleted were more likely to die within 1 year of the fracture and had longer hospital stays (Patterson, Cornell, & Carbone, 1992). In a British study of 744 females with femoral neck fracture, subsequent mortality was correlated with poor food intake and lower serum albumin levels (Barstow, Rawlings, & Allison, 1983).

NUTRIENT INTAKES

Analysis of the NHANES II data of nonsmoking men and women has demonstrated a decrease in energy intake from the ages of 19 to 24 years (Subar, Harlan, & Matson, 1990). Males decreased their intake to a greater extent than females. Similar decreases in coloric intake were found in male subjects from the Baltimore Longitudinal Study aged 20 to 99 years (McGandy et al., 1966). In a 3-decade longitudinal study of this group it was found that there was a decrease in calories/kg body weight over the lifespan (Hallfrisch, Muller, Drinkwater, Tobin, & Andres, 1990).

A Swedish study demonstrated a 600-calorie decrease in calorie intake in males between the age of 70 to 76 years (Sjogren, Osterburg, & Stean, 1994). Women decreased their caloric intake by approximately 440 calories over the same 6-year period. This group also studied the differences in energy intake in two 70-year-old cohorts 10 years apart. There was an increase in caloric intake in both men and women who had been born a decade later.

Preliminary data is now available from the first phase of NHANES III (Anonymous, 1994). There was a linear decrease in food intake in males from a peak ingestion at 16 to 19 years of 3,097 to 1,776 kcalories in those over 80 years of age. By the sixth decade caloric intake had reduced by 32% and in those over 80 years by 39%. In females caloric intake decreased from 1958 kcalories at 16 to 19 years of age to 1329 kcalories in those over 80 years of age. By the sixth decade calorie intake had decreased by 14% and by 22% in those over 80 years. In older women fat accounted for between 31.3% to 32.8% of total calories.

The New Mexico Aging Process Study has followed nutrient intakes in a highly healthy population aged 63 to 84 years from 1980 to 1987 (Koehler, 1994). Energy intake in women declined by 19.3 kcal/day per year and in men by 25.1 kcal/day per year. Both total fat and cholesterol

intake fell over time and this was associated with a fall in plasma cholesterol levels.

The EURONUT-SENECA study examined the nutritional status of Europeans living in 19 small towns (Dirren, 1984). Daily energy intake varied from 1,920 kcal to 2,660 kcal for men in the different towns with between 25% to 43% coming from fat and 12.4% to 16.6% coming from protein. Caloric intakes in women varied from 1,490 kcal to 2,140 kcal with fat accounting for 26.3% to 44.7% and protein for 12.9% to 18.3%. Cholesterol intakes varied from 186 mg to 402 mg in men and 162 mg to 341 mg in women.

The data on energy intake in older persons is summarized in Table 2.3.

DIETARY INTAKE AND MORTALITY

Kant, Schatzkin, Harris, Ziegler, and Block (1994) examined the role of dietary diversity in relationship to mortality. They found that the failure to include at least three of the five major food groups (dairy, meat, grain, fruit, and vegetables) was associated with an increased mortality.

A German study found that older strict vegetarians had a lower mortality than moderate vegetarians (Chang-Claude & Frentzel-Beyme, 1993). In a population of Seventh Day Adventists who do not smoke and drink and are predominantly vegetarians, very lean males did not show the classical association with increased mortality (Lindsted, Tonstad, & Kuzma, 1991). This study demonstrated that over the age span of 50 to 90 years, the persons in the lowest quintile had the lowest mortality. There was a decrease in the protective effect of low body weight with advancing age.

There has been a recent enthusiasm for the concept that ingestion of free radical scavengers will slow the aging process and delay mortality (Morley, 1992). Vitamins and minerals are well recognized free radical scavengers. Kim, Williamson, Byers, and Koplan (1993) examined the effects of vitamin and mineral supplementation on mortality in the United States population, utilizing data from the First National Health and Nutrition Examination Survey (1971 to 1975). Supplements were used regularly by 22.5% and irregularly by 10%. Regular supplement use could not be shown to be associated with decreased mortality. This study calls into question the strength of the free radical hypothesis of aging.

TABLE 2.3 Energy Intake in Older Persons in Different Studies

CALORIC INTAKE (kcal)

MALES

Age group (years)	NHANES III(a) (1988–1991)	NHANES II(b) (1982–1984)	Baltimore (c) (1961)	Sweden (d) (1971)	Sweden (d) (1981)	UK (e) (1969–1972)
20–29	3025	2947	2688	—	—	—
55–74	—	1998	—	—	—	—
60–69	2110	—	2297	—	—	—
65–74	—	—	—	—	—	2386
70–79	1887	—	2093	2210	2501	—
75+	—	—	—	—	2082	2214
>=80	1776	—	—	—	—	—

FEMALES

Age group (years)	NHANES III (1988–1991)	NHANES II (1982–1984)	Sweden (1971)	Sweden (1981)	UK (1969–1972)
20–29	1957	1667	—	—	—
55–74	—	1360	—	—	—
60–69	1578	—	—	—	—
65–74	—	—	—	—	1786
70–79	1435	—	1841	1983	—
75+	—	—	—	1757	1698
>=80	1329	—	—	—	—

a) Anonymous, 1994
b) Subar et al., 1990
c) McGandy et al., 1966
d) Sjogren et al., 1994
e) MacLeod, 1974

NUTRITIONAL STATE AND DISABILITY

Recently, two studies have begun to examine the potential role of protein energy undernutrition in the pathogenesis of the development of disability in older persons. In addition, Vellas et al. (1994) have found that protein energy undernutrition predisposes to falls, and Barstow, Rawlings, and Allison (1983) found a similar association with hip fracture.

Galanos, Pieper, Coroni-Huntley, Bales, and Fillenbaum (1994) undertook a secondary data analysis of the National Health and Nutrition Examination Survey–I Epidemiologic follow-up study (1982–1984). The study included 3,061 persons aged 65 to 86 years. Functional status was

assessed utilizing a 26-item battery and compared to body mass index. Functional disability was found to be strongly correlated with those individuals who had a body mass index less than the 15th percentile. Extremely low body mass indices (less than the 5th percentile) had the highest relative risk of having functional impairment. These relationships remained even after removal of those individuals who died within two years of completing the survey. Of additional interest was the finding that persons on a special diet had an increased risk of having functional limitations (O.R. 1.27 [1.01–1.61]). Overall, this study demonstrated that body mass index is related to the functional capabilities of community-dwelling elderly.

Hubert, Block, and Fries (1993) utilized the same data set linked to the first National Health and Nutrition Examination Survey (NHANES I) (1971–1975) to identify risk factors for physical disability 10 years later in a 50- to 77-year-old population. Major nutritional risk factors that were predictive of physical disability 10 years in the future included: low nonrecreational and recreational activity, high body mass index at age 40, low caloric intake, low serum albumin, and glycosuria. These studies again support the concept that the extremes of nutritional status (i.e., obesity or protein energy undernutrition) both predict and perhaps play a role in the pathogenesis of functional disability.

DEHYDRATION AND MORTALITY

Dehydration is a common problem in older persons. Warren et al. (1994) studied 1991 Medicare files to determine the relationship of dehydration to hospitalization. Dehydration was associated with at least 6.7% of hospitalizations. This suggests a minimal rate of dehydration of 236.2 per 10,000 older persons per year. Infection was the most common concomitant diagnoses. Approximately half of the persons admitted with dehydration were dead within one year of hospitalization.

A British study found a lower rate for dehydration in hospitalized elders with an incidence of 0.3% (Long, Mann, Bayer, Shetty, & Pathy, 1991). The most common causes of dehydration were infection, altered level of consciousness, and diuretics. In-hospital mortality rate was 54% in those older persons with dehydration.

In a nursing home 29.1% of residents admitted to an acute hospital were dehydrated (Lavizzo-Mourney, Johnson, & Stolley, 1988). Risk factors for dehydration included being over 85 years of age, taking more than four

medications, being bedridden, and being unable to feed oneself. A British study of a 2-year follow-up of residents in a continuing care facility found increased mortality in residents with dehydration (O'Neil et al., 1990).

PHYSICAL ACTIVITY AND MORTALITY

Paffenbarger et al. (1993) has followed lifestyle changes of 10,269 male Harvard alumni aged 45 to 84 years in 1977. The follow-up occurred in 1985. Moderately vigorous sports activity (greater than 4.5 metabolic equivalents) led to a 23% lower death rate compared to those not in sports.

An analysis of the 10.5-year follow-up of the 12,138 middle-aged men in the multiple risk factor intervention trial (MRFIT) found that the least active men had excess mortality rates for cardiovascular disease (22%) and all-cause mortality (15%) compared to all others (Leon & Connett, 1991). However, those men doing the highest level of activity had no decreased risk of death compared to those in the middle group.

An Italian study followed up 1,712 males aged 40 to 59 years for 25 years (Seccareccia & Menotti, 1992). Sedentary workers had a 1.23 relative risk of all-cause death and a 1.72 coronary artery death compared to heavy workers. The odds ratio for all cause death for forced expiratory volume was 0.65 and for heart rate was 1.32.

Analysis of the Established Populations for Epidemiologic Studies of the Elderly data found that moderate recreational activity was associated with a decreased mortality over 6 years and reduced risk of physical impairment over 3 years (Simonsick et al., 1993).

Two studies have looked at the relationship of physical activity to mortality in women. This analysis utilized data from 1,404 women aged 50 to 74 years who were participants in the Framingham Heart Study and were followed for 16 years (Sherman et al., 1994). The most active quartile had a relative risk of mortality of 0.67 compared to the least active quartile. Relative risk ratios for the two middle quartiles were 0.95 and 0.63. This suggested the possibility of a J-shaped curve though insufficient data is available to substantiate this.

Analysis of NHANES I (1971–1975) and the 1982–1984 NHANES I Follow-up Survey found that for older men and women (65 to 74 years) nonrecreational physical activity was a predictor of survival time (Davis et al., 1994). Overall these studies support the concept that moderate physical activity decreases mortality in middle-aged and young-old persons.

OBESITY

Kuczmarski, Fiegal, Campbell, and Johnson (1994) have examined the prevalence of overweight in adults in the United States utilizing data from the first phase of the third National Health and Nutrition Examination Survey (NHANES III). They then compared their data to three earlier surveys, namely, the first National Health Examination NHANES I (1971 to 1974) and NHANES II (1976–1980). They used a body mass index of >27.8 for men and >27.3 for women as being overweight.

The highest prevalence of overweight in men was in the 60- to 69-year-old group (42.2%). The prevalence of overweight declines thereafter so that in 70- to 79-year-olds the prevalence was 35.9% and in those over 80 years it was 18.0%. In females the highest prevalence of overweight was in 50- to 59-year-olds (52.0%). The prevalence of overweight then declined in each of the next three decades (42.5%, 37.2%, and 26.2%, respectively). In males over the age of 60 years the highest prevalence of overweight was in Mexican American men with the lowest in non-Hispanic black men. In women the highest rates of overweight were in African American women closely followed by Mexican American women.

Over the 30-year period from 1960 to 1991 there has been a marked increase in overweight prevalence in men aged 60 to 74 years from 23.0% to 40.9%. Females, on the other hand, actually showed a decline in the prevalence of overweight from 45.6% to 41.3%. However lower levels of obesity were reported for females in both the 1971–1974 and 1976 to 1980 surveys (39.0% and 37.3%, respectively).

Data on the prevalence of overweight and obesity in Swedish males and females were reported for 1980–1981 (Kuskowska-Wolk & Rossner, 1990). The criteria they used for obesity were a body mass index greater than 30 for men and greater than 28.6 for females. One in 4 females and 1 in 10 males aged 65 to 74 years were obese. This age group had the highest prevalence of obesity. Older persons (75 to 84 years) had lesser rates of obesity.

Table 2.4 (p. 41) compares the body mass index in older persons from Sweden to those from the United States. As can be seen older males and females in the United States were heavier than those living in Sweden.

DIABETES MELLITUS

Diabetes mellitus represents one of the commonest nutritionally related diseases in the United States. Diabetes is the fifth most common chronic condition affecting persons over the age of 65 years in the United States (Harris, 1990). The cost of health care services provided to older persons with diabetes is approximately $5.16 billion annually (Weinberger, Cowper, Kirkman, & Vinicor, 1990). Older persons with diabetes are much more likely to be hospitalized than nondiabetics in any given year (31.4% compared to 20.1%) (Taylor, 1987). Persons with diabetes mellitus spend 2 days longer in hospitals than those who do not have diabetes (Sinnock, 1985). Diabetes occurs more commonly in nursing home residents than in age-matched community residents (Von Nostrand, 1985).

The prevalence of diabetes mellitus in the United States increases with age. Approximately 2% of persons aged 20–44 years have diabetes mellitus and 17.7% of those aged 65 to 74 years have diabetes (Harris et al., 1987). This study also demonstrated that almost half of the diabetes mellitus in persons aged 65 to 74 years was undiagnosed (9.3% diagnosed versus 8.4% undiagnosed). The rates of diabetes mellitus in African Americans and Mexican Americans is at least twice as high as in whites over the age of 65 years (Harris, 1990). In addition to the high prevalence of diabetes in persons over the age of 65 years, 22.7% have impaired glucose intolerance.

A Finnish study had similar findings concerning the prevalence of diabetes mellitus in persons aged 65 to 74 years (Mykkanen, Laakso, Uusitupa, & Pyorala, 1990). In males the prevalence of diabetes mellitus was 15.7% and in females, 18.8%. The presence of obesity or a waist-to-hip ratio greater than 0.98 in men or 0.89 in women doubled the prevalence of Type II diabetes mellitus.

Another study examined the association of diabetes with mortality in 637 Finnish males aged 65 to 84 years who were followed for 5 years (Stengard et al., 1992). The relative death rate for diabetic men was 2.10 compared to those with normal glucose tolerance.

BONE LOSS AND ASSOCIATED MORBIDITY

Hip fracture is the most dangerous outcome associated with bone loss. The vast majority of fractures occur over the age of 70 years, and if a person

TABLE 2.4 Comparison of Mean Body Mass Index in Older Persons in Sweden and the United States

	Body Mass Index ($kg\ m^{-2}$)			
	MEN		WOMEN	
Age	Sweden	United States	Sweden	United States
55–64	25.9		26.2	
60–69		26.9		27.3
65–74	25.6		26.1	
70–79		26.5		26.7
75–84	25.1		25.4	
80+		24.7		24.8

lives to 90 years of age, they have a 30% chance of developing a hip fracture (Cummings, Black, & Rubin, 1989). There is a 10% to 20% excess mortality associated with hip fracture. In women over 50, death rates from hip fracture are the same as those from breast cancer (Gallagher et al., 1980). Up to one-quarter of women experiencing a hip fracture lose their independence (Cummings, 1987) and in one prospective study of persons over 75 years of age, only 26% of the survivors regained their prefracture functional status (Jette, Harris, Cleary, & Campion, 1987).

The incidence of all types of fractures increases with aging. Vertebral fractures occur in 0.5% of white women aged 50 to 54 years and 2.5% of those aged 80 to 84 years (Riggs et al., 1982). Hip fracture rates increase exponentially after the age of 50 years, with one study finding an incidence of 1.63 per thousand in white women at 65 years of age and 35.4 per thousand at 95 years of age (Jacobsen, Goldberg, Miles, Brody, Stiers, & Rimm, 1990). Peripheral wrist fractures (Colles fractures) have an incidence of 355.4 per thousand in women age 50 to 54 years of age, increasing to 688.2 per thousand in those over 85 years of age (Owen, Melton, Johnson, & Ilstrup, 1982). Fracture rates are lower in males with aging. Both vertebral (Bengner, Johnell, & Redlung-Johnell, 1988) and hip fractures (Jacobsen et al., 1990) increase at approximately half the rate in men compared with women.

Ethnic variations are particularly marked in hip fracture incidence. Fracture rates in white women are 2 to 3 times more common than in black women, and black men are half as likely to have a hip fracture compared to white men (Gunby & Morley, 1994). One study found that white women have a greater risk of hip fracture (140.7 in 100,000) than Hispanic (49.7

in 100,000) or Asian (85.4 in 100,000) women (Silverman & Madison, 1988). Japanese have approximately the hip fracture rate of American whites (Ross et al., 1991). Besides the United States, other countries with particularly high hip fracture rates are those in Western Europe, Israel, and New Zealand (Lewinnek, Kelsey, White, & Kreiger, 1980). South African Bantu have the lowest rates of hip fracture (Bloom & Pogrund, 1982).

Bone density is a key factor in determining the potential age-associated risk of fracture. Mean bone density declines with age in the distal radius, lumbar spine and femoral neck (Gunby & Morley, 1994). Persons who fracture either the spine or femur tend to have lower bone densities than age-matched persons who have not had a fracture. Recently, we have found that approximately one-quarter of African American women have bone densities in the range that places them at high risk for hip fracture (H.M. Perry, III, & J.E. Morley, unpublished observations). Women who have a bone density 1 standard deviation below the mean for their age have a 7-fold greater chance of fracturing their hip than those with a bone density 1 standard deviation above the mean (Cummings et al., 1993). However, it needs to be recognized that bone density alone is insufficient to predict fracture rates. Other age-related factors that predict fracture are the increased risk of falling, alterations in adaptive response to falling, and alterations in the intrinsic shock absorbers (i.e., reduced muscle and fat mass about the hip).

Calcium intake is a key element in the lifetime prevention of osteoporosis. Retrospective studies have found that higher calcium intakes in childhood and early adulthood results in a 3% to 8% greater bone mass later in life (Matkovic, Fontana, Tominoc, Goel, & Chestnut, 1990; Sandler et al., 1985) and a lower fracture rate (Matkovic et al., 1990). Data from the NHANES I Epidemiologic follow-up study found an approximately 50% decrease in hip fracture rate in the highest compared to the lowest quartile of calcium intake in persons aged 50 to 74 years at baseline (Looker, Harris, Madans, & Sempos, 1993). In Toulouse, France, both a high calcium intake and moderate overweight were found to be protective of hip fracture in persons over 50 years of age (Ribot et al., 1993). Calcium supplementation in one of two identical twins resulted in a greater rate of bone mass gain in the supplemented twin (Slemenda, Christian, & Williams, 1991). Besides the role of calcium in increasing peak bone mass, it has also been demonstrated that at the time of menopause, a urinary calcium leak develops (Horowitz, Need, Morris, & Nordin, 1993). Calcium

replacement following menopause reduces the rate of both cortical and trabecular bone loss (Nordin & Heaney, 1990; Nordin et al., 1991). Calcium intakes below 400 mg per day were associated with an increased fracture rate in Chinese women (Lau, Donnan, Barker, & Cooper, 1988).

Calcium intakes in postmenopausal women are highly variable with mean ranges in the neighborhood of 530 to 720 mg per day (Dawson-Hughes, Jacques, & Shipp, 1987; Sandler et al., 1985). Similar levels have been reported in postmenopausal women in the United Kingdom (Stevenson et al., 1988). In France, intakes of 518–604 mg per day were found in men and women over 65 years of age (Chapuy, Chapuy, & Meunier, 1987). Higher daily intakes of calcium are seen in Australia (669–774 mg; Polley, Nordin, Baghurst, Walker, & Chatterton, 1987), Norway (742–887 mg; Nes et al., 1988) and Denmark (mean intake 910 mg; Nilas, Christianson, & Rodbro, 1984).

Factors other than calcium intake can influence the amount of calcium absorbed or secreted. Higher protein intakes such as those seen in developed or industrialized countries increase the urinary excretion of calcium (Schuette, Zemel, & Linkswiler, 1980). High dietary fiber intakes may reduce calcium absorption. Average dietary intakes of phosphorous are insufficient to alter calcium balance, but persons ingesting large amounts of cola drinks, which contain phosphoric acid, may need higher calcium intakes. Increased sodium intake results in an increase in calcium excretion (Shortt, Madden, Flynn, Morrissey, 1988). Caffeine intake increases the urinary excretion of calcium (Heaney & Recker, 1982).

Vitamin D plays a key role in the maintenance of the integrity of bone. A number of community-based studies have found a tendency for $25(OH)_2$ vitamin D levels to decrease with age (Morley, 1989). Goldray et al. (1989) found that vitamin D levels decrease with age even in a sunny climate such as Israel. They also found that $25(OH)_2$ vitamin D levels are even lower in immobile housebound or institutionalized elderly compared to mobile elderly. Numerous factors lead to the decrease in Vitamin D levels with aging. These include the use of sunscreen lotions to prevent skin cancer, a decrease in the ability of older skin to manufacture cholecalciferol when exposed to ultraviolet light and a deficiency in 1-alpha-hydroxylase with aging leading to a decreased conversion of $25(OH)_2$ vitamin D to 1.25(OH) vitamin D. In addition, many older individuals have a decreased dietary intake of vitamin D. Vitamin D (800 IU) and calcium therapy have been demonstrated to remarkably reduce occurrence of hip fractures in elderly nursing home residents in France (Chapuy, Arlot, Delmas, & Meunier, 1994).

Overall, osteoporosis and hip fracture are the conditions which have most clearly been demonstrated to be preventable by nutritional intervention. Optimally, appropriate nutritional intake of calcium needs to begin before adolescence to allow the individual to obtain an optimal bone mass. However, it appears that even in extreme old age, increased calcium and vitamin D intake may slow bone loss and prevent the development of hip fracture. This is not an inconsequential nutritional disorder, as up to 25% of persons with a hip fracture are still institutionalized one year later (Cummings, Kelsey, Nevitt, & O'Dowd, 1985). Hip fractures have been shown to cost approximately $8.7 billion a year in direct costs in the United States (Gunby & Morley, 1994).

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CHAPTER 3

Nutrition in the Nursing Home

ADIL ABBASI
DEPARTMENT OF MEDICINE
MEDICAL COLLEGE OF WISCONSIN
MILWAUKEE

Approximately 5% of Americans over age 65, and 22% over age 85 currently reside in the nation's 20,000 nursing homes. The older population will continue to grow in the future. By the year 2000, persons 65 years and older will represent 13% of the total population of the United States and this is projected to climb to 22% by year 2030. With the anticipated increase in the older population, the number of nursing home beds needed to accommodate the frail elderly will also increase. Nursing home residents are the most frail group of elderly and it is not uncommon to find nutritional deficiencies in this population. Since nutritional deficiencies are associated with increased morbidity, mortality, and medical care expenditure, early recognition and treatment are essential (Bienia, Ratcliff, Barbour, & Kummer, 1982; Henderson, 1988).

NUTRITIONAL STATUS OF THE NURSING HOME POPULATION

The prevalence of protein, calorie, vitamin, and micronutrient deficiencies are common in the nursing home population. Table 3.1 summarizes the prevalence of various indicators of undernutrition in the United States. The prevalence of protein calorie undernutrition in Nursing homes varies from 45% to 85% (Abbasi & Rudman, 1993; Keller, 1993; Muncie & Carbonetto, 1982; Nelson, Coulston, Sucher, & Tseng, 1993; Sahyoun et al., 1988; Shaver, Loper, & Lutes, 1980; Smith, Wickiser, Korth, Grandjean, & Schaefer, 1984). As shown in Table 3.1, indicators of undernutrition including underweight, hypoalbuminemia such as low height-

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TABLE 3.1 Nutritional Deficiencies in the Nursing Home Population in the United States

Nutritional Indicator	Prevalence (%)
Protein-Calorie Undernutrition	45%–85%
Underweight (body weight < 80% of ideal)	12%
Hypoalbuminemia (serum albumin < 3.5 g/dl)	18%–60%
Weight//height ratio ≤ 90% of standard	40%
Triceps skin fold ≤ 90% of standard	21%
Mid-arm muscle circumference ≤ 90% of standard	55%

to-weight ratio, triceps skin fold, and mid-arm circumference are common in this population (Abbasi & Rudman, 1993; Muncie & Carbonetto, 1982; Shaver et al., 1980). Table 3.2 summarizes the vitamin and micronutrient status of the nursing home population in the United States. The deficiencies of various water-soluble vitamins and vitamin D are common among the nursing home population in the United States (Baker, Franke, & Jaslow, 1980; Baker, Franke, Thind, Jaslow, & Louria, 1979; Morgan et al., 1986; O'Dowd, Clemens, Kelsey, & Lindsay, 1993; Sahyoun et al., 1988; Smith et al., 1984). The micronutrient status of nursing home patients, however, is less well documented. Some studies suggest that there is a low intake of calcium as well as other essential micronutrients including zinc by the nursing home patients (O'Dowd et al., 1993; Sahyoun et al., 1988).

Despite overwhelming evidence that nutritional deficiencies are common in nursing home patients, physicians frequently fail to recognize and adequately treat them (Abbasi & Rudman, 1993). The author conducted a study in 26 Department of Veterans Affairs nursing homes located in the Department's Central Region to determine the prevalence of underweight and hypoalbuminemia in the Veterans Affairs nursing home residents of that region and the frequency with which physicians, nurses, and dietitians documented the presence of underweight and hypoalbuminemia. Three hundred and thirty-two (23%) of the patients were underweight (body weight < 80% of ideal) and 772 (27.5%) were hypoalbuminemic (serum albumin < 3.5 gm/dl). The prevalence of the two conditions varied widely across facilities. The prevalence of hypoalbuminemia ranged from 5% to 58% in the 26 nursing homes studied and the prevalence of body weight less than 80% of ideal ranged from 2% to 20%. In the region as a whole the dietitian's notes documented underweight in an average of 95% of affected cases. But the presence of hypoalbuminemia was documented in only 82% of cases. Nurses documented prevalence of underweight and

TABLE 3.2 Vitamin and Micronutrient Status of the Nursing Home Population in the United States

Nutrient	Intake below 2/3 of RDA %	Subnormal blood level (%)
Vitamins		
B_1 (Thiamine)	2%–4%	2%–5%
B_2 (Riboflavin)	0%–1%	1%–34%
B_6 (Pyridoxine)	73%	21%–57%
Folate	52%–65%	6%–24%
B_{12} (Cyanocobalamin)	2%–8%	4%–29%
C (Ascorbic acid)	3%–6%	0%–5%
D	18%	
Minerals		
Calcium (based on 800 mg/day as RDA)	4%–5%	
Zinc	49%–58%	

hypoalbuminemia in 80% and 45% cases, respectively. The documentation by physicians was most inadequate of the three health care providers compared. They did not document the presence of underweight and hypoalbuminemia in 48% and 64% cases, respectively. The frequency of documented awareness of underweight and hypoalbuminemia by nurses and physicians varied tremendously across the 26 nursing homes. This study confirmed the high prevalence of protein calorie undernutrition in nursing home population with wide variation across facilities and frequent lack of documentation of these nutritional deficiencies by physicians and nurses. In this study, the prevalence of underweight and hypoalbuminemia varied as much as ten-fold across 26 facilities compared. There are two possible explanations for this variation: Case-mix (intrinsic factors), and environmental/quality of care (extrinsic factors). The intrinsic or patient-related causes of undernutrition are usually unavoidable, such as terminal cancer, endstage chronic obstructive pulmonary disease, heart disease, renal failure, or hepatic cirrhosis. On the other hand the extrinsic or environmental causes of undernutrition usually involve one or more avoidable causes that are potentially treatable (Abbasi & Rudman, 1994). Alverno, Mattson, and Rudman (1992) compared adverse somatic outcomes in three Veterans Affairs nursing homes and found that despite similar case-mix (intrinsic factors), one of the three nursing homes compared had higher

incidence of underweight (body weight < 90% or 80% of ideal) and hypoalbuminemia (serum albumin < 3.5g/dl). In the nursing home with higher prevalence of undernutrition (underweight and hypoalbuminemia) the prevalence of bedsores and major loss of activities of daily living was also higher. The authors concluded that differences in the frequency of adverse outcomes among the nursing home facilities were accounted for by extrinsic factors related to quality of care (and therefore avoidable) and not due to intrinsic factors related to patient characteristics. Silver, Morley, Strome, Jones, and Vickers (1988) studied the nutritional status in an academic nursing home and compared their results with nonacademic nursing homes, and concluded that undernutrition is less common in an academic nursing home due to better surveillance and active intervention.

It is clear from the above discussion that nutritional deficiencies are common in the nursing home population; they are frequently not recognized by the health care providers and may be the result of extrinsic or avoidable cause(s).

AVOIDABLE CAUSES OF NURSING HOME UNDERNUTRITION

The avoidable causes of undernutrition in nursing home patients can be divided into two groups: those that cause increased nutritional requirements, and those that cause inadequate intake (Table 3.3).

Infections are common in nursing home patients and up to 15%–20% of nursing home residents have an active infection at any given point in time (Beisel 1977; Garibaldi, Brodine, & Matsumiya, 1981; Scrimshaw 1977; Yoshikawa, 1983). Infectious processes may cause delirium, anorexia, and hypophagia in the elderly and may lead to negative nitrogen balance (Yoshikawa & Norman, 1987). Sandman, Adolfsson, Nygren, Hallmans, and Winblad, (1987) studied the nutritional status of nursing home patients with Alzheimer's disease. These investigators reported that despite adequate nutritional intake (based on RDA) 40% of the subjects had low body weight and serum albumin. The degree of undernutrition was significantly related to the number of infectious illnesses during the preceding six months. To fulfill metabolic demands, the nutritional requirements are increased during infectious illness (Sandman et al., 1987, Scrimshaw, 1977). An infected, confused nursing home patient may not be able to consume adequate calories and proteins to maintain zero nitrogen balance. A declining nutritional

TABLE 3.3 Avoidable Causes of Undernutrition in Nursing Home Patients

Increased nutritional requirements:
• Infectious illness
• Inadequate caloric prescription during intercurrent illness
Decreased nutritional intake
Depression
Medications
Inappropriate use of restricted diets
Lack of feeding assistance
Inadequate caloric prescription
Poor oral and dental status
Staff unawareness
Suboptimal dining environment
Unmet need of a modified diet

status itself is a risk factor for recurrent infections (Chandra, 1991). A vicious cycle may develop between undernutrition and infection, if an intervention to improve nutritional intake during this period and to promptly treat the infectious illness is not undertaken by the health care providers. Infectious illnesses, even without fever, may cause a negative nitrogen balance that may last for as long as a month (Beisel, 1977). The nutritional requirements to adequately overcome the negative nitrogen balance sustained during infectious illness are up to 50% of the maintenance (Scrimshaw, 1977).

Some nursing home residents with neurologic illnesses are hyperactive (Fauman, 1978). Patients with dementia are often agitated and wandering. Patients with Parkinson's disease and some other neurologic illnesses are affected by involuntary movements. Such nursing home patients have increased caloric requirements but usually have inadequate intake due to their neurologic illness and at times unmet need for feeding assistance (Garfinkel, Garner, Kaplan, Rodin, & Kennedy, 1983).

Depression is common in nursing home patients (Rovner, Kafonek, Filipp, Lucas, & Folstein, 1986). It is frequently associated with poor oral intake. Morley and Kraenzle (1994) studied the causes of weight loss in a community nursing home and concluded that depression is the single most common cause of weight loss in a community nursing home.

Medications are commonly used in the nursing home setting, with an average of eight medications per nursing home patient (Beers et al., 1991). Mechanisms of drug-nutrient interactions include reduced intake as a re-

sult of drug side effects like anorexia, nausea, vomiting, and altered taste; interference with nutrient absorption, metabolism, and excretion (Roe, 1994; Varma, 1994). Some of the commonly prescribed drugs influencing nutritional status include: Digoxin, Captopril, and nonsteroidal antiinflammatory drugs, which are associated with decreased appetite; anti-Parkinsonian drugs, Tricyclic antidepressants, and antihistamines cause dryness of mouth; Captopril may also cause altered taste perception (Roe, 1994).

Coulston, Mandelbaum, and Reaven (1990) identified the inappropriate use of restricted diets in nursing homes as an avoidable cause of undernutrition. In this study, when the diet of 18 diabetic patients was changed from diabetic to a regular diet, no change in glycemic control was noted over a period of 8 weeks but caloric intake significantly improved. The authors concluded that the practice of routinely prescribing diabetic diets for patients with non-insulin-dependent diabetes mellitus and poor oral intake in nursing homes was often not necessary. Buckler, Kelber, and Goodwin (1994) studied the use of dietary restrictions in malnourished nursing home patients. They found that 75% of patients with hypoalbuminemia and 59% patients with weight loss > one pound per month were on one or more dietary restrictions.

Oral health problems may be responsible for undernutrition in the elderly (Sullivan, Martin, Flaxman, & Hagen, 1993). The changes in taste buds and olfactory sensation with advancing age influence the thresholds for recognition and discrimination, altering established food preferences (Schiffman & Covey, 1984). Chewing is slower and less effective in the elderly (Feldman et al., 1980). Xerostomia is a common problem in the elderly; it is associated with inadequate nutritional intake and is a risk factor for undernutrition (Rhodus & Brown, 1990).

Loss of manual dexterity is a common prelude to nursing home placement (Williams, Hadler, & Earp, 1982). In Siebens's study (Siebens et al., 1986) paralysis or contractures had caused impaired arm function in up to 30% of nursing home patients, and 40% of the nursing home patients required feeding assistance. In this group of nursing home patients, the nutritional status can be maintained or improved as shown by some investigators, provided adequate help for assisted feeding is available (Maclennan, Martin, & Mason, 1975; Nguyen, Flint, Prinsely, Wahlqvist, 1985, Siebens et al., 1986). Lack of staffing may, however, aggravate the eating problems of nursing home patients, especially among those who need feeding assistance (Davies & Snaith, 1980).

Shizgal, Martin, and Gimmon (1992) studied the effect of age on the caloric requirement of malnourished patients. The authors showed that at the age of 20 years in the presence of moderate malnutrition, the administration of 50 kcal/kg/day will increase the body cell mass at the rate of 161 g/day. This increase in body cell mass is reduced to 112 g/day at age 40, to 62 g/day at age 60, and 13 g/day at age 80. It can be concluded from this study that the caloric requirement of an older undernourished nursing home patient is significantly higher than a younger undernourished patient. Recently, Campbell et al. (1994) reported the protein requirements in elderly people and concluded that a safe protein intake for older adults would be 1.0–1.25 g/kg/day.

CONSEQUENCES OF UNDERNUTRITION

Undernutrition is associated with alteration in immune function and decline in cognitive function (Chandra, 1989; Chandra, 1991; Goodwin, Goodwin, & Garry, 1983). It therefore leads to recurrent infections, delayed wound healing, pressure sores, declining activities of daily living, increased dependence, poor quality of life, and ultimately death (Henderson, 1988; Morley, Mooradian, Silver, Heber, & Alfin-Slater, 1988). Chandra (1989, 1991) has studied the association of nutrition and immunity in different age groups and has shown that when elderly malnourished subjects were given appropriate nutritional advice and supplements for 1 year, their immune responses, including natural killer cell activity and interleukin-2 production, significantly improved. In another study of 34 malnourished adults between the ages of 61 and 97 years, 6 months of nutritional supplementation significantly increased the percentage of mature lymphocytes (Roebothan & Chandra, 1994). Goodwin et al. (1983) studied the association of nutritional status and cognitive function in 260 elderly noninstitutionalized men and women. These investigators documented the association of declining cognitive status with the low blood levels of vitamins C, B_{12}, riboflavin, and folic acid, and concluded that malnutrition may play a role in the depression of cognitive function in some elderly patients. Galanos, Pieper, Corroni-Huntley, Bales, and Fillenbaum (1994) studied the relationship between body mass index and the ability to perform activities of daily living in a sample of community-dwelling elderly. They demonstrated the relationship between nutritional status as determined by body mass index and functional status to be a U-shaped curve; they concluded that it is not only the person who is overweight who

is at risk for functional disability, but also the underweight person. They showed a persistent relationship between low and high body mass index with functional status when other pertinent variables were controlled through multivariant analysis.

The adverse consequences of undernutrition in the community-dwelling elderly as well as acutely ill hospitalized elderly have been recognized since the 1970s. Only recently has the association between undernutrition and adverse clinical outcomes in nursing home patients been documented (Table 3.4). Phillips (1986) demonstrated association of decreased mid-arm circumference and hypoalbuminemia with increased mortality in 82 patients admitted to a geriatric ward. Dwyer et al. (1987) studied 335 elderly long-term care residents and showed that a weight loss of more than 4.5 kg was associated with a decreased survival. Pinchcofsky-Devin and Kaminski (1986) studied 232 nursing home patients with pressure sores and concluded that undernutrition was significantly associated with the presence of pressure sores. Rudman et al. (1987) conducted a nutritional survey in a 200-bed VA nursing home and studied the association of mortality with various nutritional indicators. In this study 7 items were identified as significant predictors of death in the univariate analysis and included age, functional status, triceps and skin-fold, mid-arm circumference, albumin, cholesterol, and hematocrit. The decedents were older, more dependent, more depleted in adipose tissue and muscle mass and had lower serum albumin and cholesterol level. The death rate rose significantly when serum albumin was less than 4.0 gm/dl, cholesterol less than 160 mg/dl, or hematocrit less than 41%. When multivariate analysis was applied to the 7 mortality-related variables, the statistical model selected cholesterol first and hematocrit second. This study demonstrated the important prognostic significance of serum cholesterol less than 160 ml/dl in the nursing home population. Verdery and Goldberg (1991) concluded that nursing home residents with hypocholesterolemia (serum cholesterol less than 7.5 mml/L) had a ten-fold risk of dying. Katz, Beaton-Wimmer, Parmelee, Freidman, and Lawton (1993) studied 1,005 residents of a long-term care facility and concluded that decreased survival was associated with hypoalbuminemia and anemia.

CONCLUSION

Undernutrition is a common but infrequently diagnosed disease in nursing home patients. It is associated with adverse clinical outcomes and poor

TABLE 3.4 Adverse Consequences of Undernutrition in the Nursing Home Population

Author	Study Population	Adverse Outcome
1. Phillips, P. (1986). *Age Aging, 15;* 53.	82 patients in a geriatric ward, mean age = 82 yr	Decreased arm muscle circumference and hypoalbuminemia were associated with increased mortality.
2. Dwyer et al. (1987). *J Gerontol,* 42(3), 246.	335 elderly long-term care residents, mean age = 72 yr	Patients with weight loss ≥ 4.5 kg have a lower survival rate as compared to those who gained or maintained body weight.
3. Pinchcofsky-Devin & Kaminski, Jr. (1986). *J Am Geriatr Soc, 34;* 334.	232 nursing home patients, mean age = 72 yr	The presence of pressure sores was significantly correlated with malnutrition.
4. Rudman et al. (1987) *J Am Geriatr Soc, 35;* 496–502.	176 male residents of a VA nursing home, mean age = 69 yr	Body weight as percent of ideal, triceps skin fold, hematrocrit, serum albumin, and cholesterol were inversely related to death rate. Serum cholesterol below 160 mg/dl was the strongest predictor of mortality.
5. Verdery & Goldberg (1991).	227 nursing home residents, mean age: men = 68 yr, women = 74 yr	Hypocholesterolemia (serum cholesterol ≤ 7.5 mmol/L) was associated with a ten-fold risk of death.
6. Katz et al. (1993). *J Geriatr Psychiatry,*	1,035 residents of a long-term care facility, mean age = 84 yr	Patients with hypoalbuminemia and anemia had a higher mortality rate.

quality of life; therefore, it should be diagnosed and treated early by health care providers. More research is needed to enhance our knowledge about the causes, prevention, and treatment of undernutrition in the nursing home population.

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CHAPTER 4

Nutrition and the African American

MARIE A. BERNARD
DEPARTMENT OF MEDICINE, UNIVERSITY OF OKLAHOMA COLLEGE OF MEDICINE
OKLAHOMA CITY, OK

INTRODUCTION

The reader may query, why a chapter devoted to nutrition and the African American elderly? What makes this minority group worthy of focus? African American elderly presently comprise the largest group of minority elders in the United States (Bureau of the Census, 1990; Ryan & Bower, 1989). This group has a high prevalence of poverty and functional disability (Bernard, 1993; Corroni-Huntley et al., 1990; Fulton, Katz, & Hendershot, 1989; Leon, & Lair, 1990; Miles, & Bernard, 1992). Many studies have correlated physical health problems with dietary and nutritional deficiencies (Bianchetti, Rozzini, Carabellese, Zunetti, & Trubucchi, 1990; Davis, Randall, Forthofer, Lee, & Margen, 1985; Goodwin, 1989; Ries, 1990). Thus dietary and nutritional deficiencies are more likely among African American elders.

To the extent that underrepresented minorities (e.g., Latinos, Asian/Pacific Islanders, American Indian/Alaska Natives) have similar degrees of poverty and functional disability, nutrition in African Americans may be representative of nutrition in the other populations. African Americans are the largest minority group, and the best studied from a nutritional perspective. Examination of factors which may contribute to nutritional changes in this group may provide helpful insights into the nutritional status of other minority groups.

However, it should be noted that cultural factors also play an important role in determining overall nutritional state. Thus, study of one minority group will not be totally representative of findings in other minority groups. Additionally, none of the minority groups within the United States are homogeneous. African Americans have cultural attitudes and practices relat-

ing to food preparation and nutrition emanating from the southern United States, Caribbean, South America, and Africa. Thus, one can anticipate that study of the nutritional status of African Americans as a whole will only begin to approximate the nutritional state of one or another subgroup of the population.

This chapter is a review of literature based on the evaluation of books and articles, as well as a Medline search of the literature from 1988–1994. Search terms utilized were: *nutrition, black, enteral nutrition, diet,* and *parental nutrition.* Special emphasis was placed upon reports/studies which evaluated the protein-calorie nutritional status of blacks 65 years old and older.

The chapter is organized into the following parts: (1) demographics of African American elderly; (2) national studies which gave insight into the overall nutritional status of African Americans; (3) regional studies which review overall nutritional status, or selected aspects of nutritional status; (4) preliminary report from a cross-sectional evaluation of a cohort of old-old African Americans from the Oklahoma City area; and (5) review of areas where more information is required.

Demographics

African Americans are a progressively increasing population within the United States. Presently, African American elders comprise 8.5% of the elderly (2.5 million) (Bureau of Census 1990). It is anticipated that the proportion of elders who are African American will increase to 13% (4.5 million) by the year 2015. They are projected to remain the largest minority group of elders through the year 2030. However, this is a population with a high prevalence of disease and functional disability (Bernard, 1993; Fulton, 1989; Leon, 1990; Miles, 1992; Ries, 1990). In the National Medical Expenditure Survey, 26.3% of geriatric blacks had problems with at least one activity of daily living of instrumental activity of daily living (Leon, 1990). Ten percent of these individuals had difficulty with 2 or more activities of daily living, as compared to a prevalence of 6% in the general population. Similar data have been derived in other epidemiological studies of the elderly (Fulton, 1989; National Center for Health Statistics, 1981). Problems with activities of daily living and instrumental activities of daily living have been demonstrated to correlate with increased risk for poor nutritional intake (Goodwin, 1989). Additionally, African American

TABLE 4.1 Large Studies Addressing Nutrition of African American Elders

- 10-State Nutrition Survey
- Nationwide Food Consumption Surveys
- North Carolina EPESE
- National Health Interview Survey
- National Health and Nutrition Examination Surveys (NHANES) I–III

elders are a population with a high prevalence of poverty, which is a risk factor for poor nutritional intake (Coroni-Huntley, et al., 1990). In 1989, 66.4% of blacks 65 or older were poor, marginally poor, or economically vulnerable (income < $11,894 for a single individual; $15,002 for a couple) (Bureau of Census, 1990). The high prevalence of risk factors for malnutrition in this population deserves examination, as these problems are associated with increased cost for health care (Liu, Manton, & Liu, 1985; Macken, 1986; Manton, 1988).

Review of the Existing Literature: National Studies

There have been a number of national studies which have considered the nutritional status of African American elders (see Table 4.1). Each was designed to examine the total population of U.S. citizens. Therefore, the elderly, and particularly African American elderly, were often underrepresented.

The 10-State Nutrition Survey found that "the poorest nutrient intake and the highest prevalence of nutritional deficiencies occurred among lower income with little education" (Ten-State Nutrition Survey, 1972). The Nation-Wide Food Consumption Surveys of 1978–1980 and 1987–1988 demonstrated that African American elders had poorer intake of nutrients than non-Hispanic whites (Murphy, 1992; Windham, Wyse, Hansen, & Hurst, 1983a, Windham, Wyse, Hansen, & Hurst, 1983b). Poor intake of calcium and magnesium was demonstrated in the 1978–1980 study. The 1987–1988 study was flawed by a poor response rate (less than 35%). However, it demonstrated that race and education were strong predictors of adequacy of diet ($p < 0.01$). African Americans were a group that seemed at greater risk for poor intake. However, the degree to which these findings can be generalized is limited by the small number of African Americans > 50 years old ($n = 183$).

The North Carolina Established Populations for Epidemiologic Studies of Elderly (Corroni-Huntley, et al., 1990) gives minimal information regarding the nutritional status of African Americans. However, this study suggests that there should be concern about the nutrition of the population, given that 30%–40% of elderly black males and 40%–54% of black females were at nutritional risk, based on recent weight loss and gain of 10 lbs or more. Additionally, there was a 10% prevalence of hip fractures in black males and 6% among black females. However, there were no data relative to vitamin D levels, vitamin D metabolism, or falls risk in the population. Therefore, it is not clear whether there were nutritional factors which predisposed to this higher than previously reported prevalence of hip fractures in the population.

The National Health Interview Survey (NHIS) of 1987 included an African American population of 148 males and 217 females 65–79 years old; and 15 males and 52 females 80 years and older (Block & Subar, 1992; National Center for Health Statistics, 1985). The NHIS failed to demonstrate a decreased intake of energy or micronutrients in African American elders, as was the case in other surveys. NHIS did note that blacks seemed to have increased consumption of energy from sweets, such as pastries and soft drinks.

The National Health Nutrition Examination Survey (NHANES) I and II had upper age limits of 74 (National Center for Health Statistics, 1974, 1981). Both studies suggested that blacks consumed substandard quantities of calories and several other nutrients, when compared to recommended daily allowances; and when compared to non-Hispanic whites of the same age. NHANES II, which contains the most recent detailed information regarding nutritional status, included only 28 blacks aged 65–74 years.

The National Health and Nutrition Examination Survey (NHANES) III (Harris, Woteki, Briefel, & Kleinman, 1989) oversampled the elderly and ethnic minorities in an attempt to obtain better information regarding the nutritional status of these populations. However, results from this study are not yet available. Additionally, it is anticipated that there will be only 5,179 participants older than 60 years. If these participants are equally distributed among the fifty states, the number of black elders from any specific geographic region would be limited. Therefore, data that are derived from this study may need further confirmation for specific geographic areas.

TABLE 4.2 Proportions of Persons Who Met or Exceeded USDA Guidelines, Ages 55–74

Fruit and Vegetables (2 + fruits and 3 + vegetables)	
Black Males	8%
Black Females	8%
Vegetable Guidelines (3 or more servings)	
Black Males	23%
Black Females	20%
Fruit Guidelines (2 or more servings)	
Black Males	22%
Black Females	32%

Based on data as presented by Patterson et al. (1990) from the National Health and Nutrition Examination Survey (NHANES) II, *American Journal of Public Health, 30;* 1443–1449.

NHANES II has the most detailed recent nutritional information regarding elderly African Americans, and bears further discussion. Kumanyika, in evaluating those data, demonstrated that the most significant medical problem in African American elders, as with younger African Americans, is obesity (Kumanyika, 1987, 1989; Kumanyika, Wilson, & Guilford-Davenport, 1993). Defining obesity as 27.3 kg/meter^2 for women and 27.8 kg/meter^2 for men, 60.8% of black females 65–74, and 26.4% of black males 65–74, were obese. It has been demonstrated in other settings (Stevens, Kumanyika, & Keil, 1994) that there are striking differences in body size perception between elderly white and black females, which may contribute to the high prevalence of obesity in elderly black females. It has also been demonstrated that, as with whites, there is a relationship between excess BMI and mortality (Wienpahl, Ragland, & Sidney, 1990).

However, other evaluations of the NHANES II data reveal a number of findings suggestive of inadequate intake among elderly blacks. Patterson, Block, Rosenberger, Pee, and Kahle (1990) evaluated the intake of fruits and vegetables by participants in NHANES II (see Table 4.2). The intake of fruits and vegetables by black males and females ages 55–74 was found to be inadequate, as compared to U.S. Department of Agriculture guidelines. Only 20% of females and 23% of males consumed 3 or more servings of vegetables per day, as suggested by guidelines. Twenty-two percent of males an 32% of females consumed 2 or more servings of fruit, as per guidelines. However, only 8% of the population consumed the recommended number of servings of both fruits and vegetables.

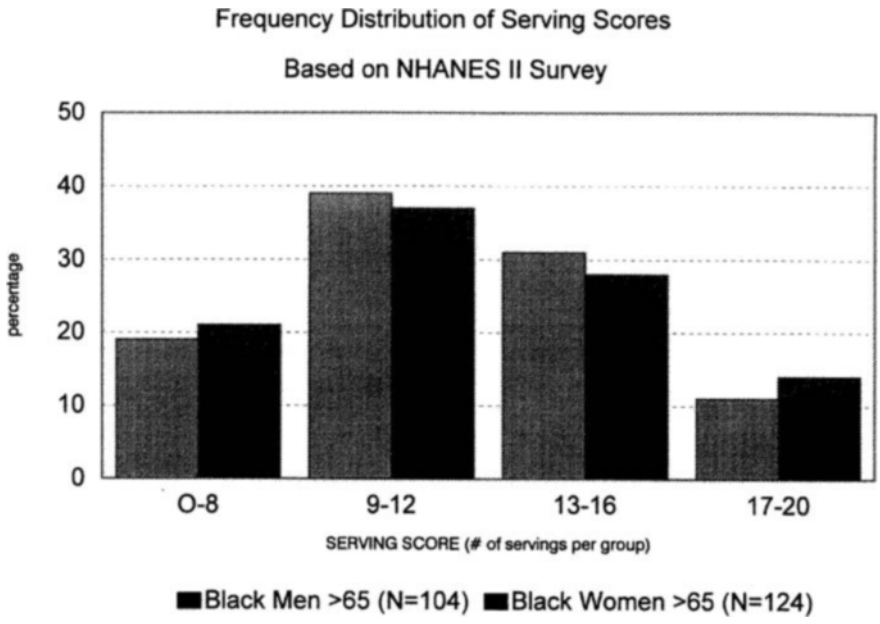

FIGURE 4.1 Proportion of individuals with adequate consumption. (*Source:* Based on data as presented by Kant et al. (1990), from the National Health and Nutrition Examination Survey (NHANES) II, *Journal of the American Dietetic Association, 91,* 1526–1536.)

Kant, Block, Schatzkin, Ziegler, and Nestle (1991) did a further evaluation of NHANES II data, examining the adequacy of consumption of the five food categories: dairy, meat, grain, fruits, and vegetables. They found that significant percentages of blacks ages 65–74 had suboptimal intake in each of these categories (n=228). Based on a 24-hour dietary recall, approximately 46% of males and 38% of females had no servings of dairy; 51% of males and 37% of females had no consumption of fruits; and 26% of males and 28% of females had no consumption of vegetables (see Figure 4.1). When these data were further refined to determine whether there were an adequate number of servings of food in each group, only 10% of black males and 15% of black females appeared to have adequate consumption in all five categories (see Figure 4.2). Given a maximum score of 20 for adequate consumption in all five food groups, 18% of black males

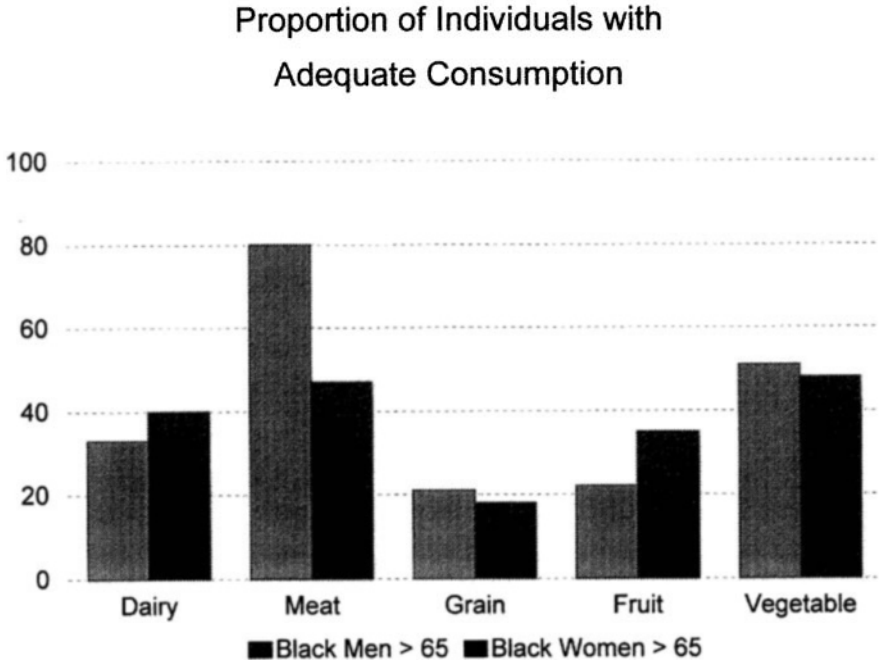

FIGURE 4.2 Frequency distribution of serving scores based on NHANES II survey. (*Source:* Based on data as presented by Kant et al. (1991), from the National Health and Nutrition Examination Survey (NHANES) II, *Journal of the American Dietetic Association, 91,*1526–1531.)

and 21% of black females scored 0–8. The best consumption was in the meats category, where 80% of males and 43% of females had adequate consumption.

Jerome (1988), in the classic book on black American elderly, thoroughly reviewed the NHANES studies data, and pointed out than the quality of diet is similar between elderly blacks and non-Hispanic whites. However, the content of diet may vary, with blacks consuming more food items such as mustard greens and collard greens, while whites consumed more lettuce and rye bread. Blacks consumed an average 300 fewer calories than

whites. A significant contributing factor to this calorie differential appeared to be a practice of skipping meals, found among blacks. As many as 40% of the black males skipped lunch, with elderly blacks missing other meals in lesser percentages. This led to inadequate consumption of calories, calcium, and B complex vitamins. Additionally, there was a low sodium intake, although the sodium to potassium ratio was high.

Review of the Existing Literature: Regional Studies

There have been a number of smaller studies addressing the nutritional status of African American elders (see Table 4.3). Greger and Sciscoe (1977) examined a cohort of elderly blacks and whites consuming meals at a congregate meal site (n=44). As contrasted with other studies, they found blacks consumed greater quantities of calories, fats, phosphorus, iron, and a variety of nutrients.

Hunter and Linn (1979) evaluated the diet of 94 blacks and 88 whites > 64 years old in Miami. They found that socioeconomic status predicted quality of nutritional intake, with those of higher socioeconomic class (whites) as having better nutritional intake than those of lower socioeconomic class (blacks).

Bailey and colleagues (1979) examined a cohort of 170 elderly blacks in Dade County, Florida, regarding nutritional factors that affected hematologic status. They found that iron status was normal. However, 60% of study participants were at high risk of folate deficiency; 11% were at median risk. Much of the folate deficiency was attributed to nutritional practices, such as consuming limited quantities of fresh fruits and vegetables, and the cooking of vegetables for prolonged periods of time.

Koh and Caples (1979) evaluated the frequency of consumption of food groups in 1,000 black households in Mississippi, 23% of which were headed by an individual of 65 years old or older. Using daily consumption of milk, green vegetables, fruits and juices, and meat as a standard for adequate diet, they found that their population consumed adequate quantities of those food groups in the following frequencies: 65% milk, 37.9% green vegetables; 42% fruits and juices; and 54% meats. They found that income and educational level were positively correlated with the adequacy of reported dietary intake.

Learner and Kivett (1981) examined rural North Carolina residents, 37% of whom were blacks 65–99 years old (n=149). They found blacks perceived their diet as inadequate more frequently than whites.

TABLE 4.3 Smaller Studies Addressing Nutrition of African American Elders

- Greger and Sciscoe (1977)
- Hunter and Linn (1979)
- Bailey et al., (1979)
- Koh and Caples (1979)
- Lerner and Kivett (1981)
- Jerome (1988)

Jerome (1988) did a follow-up evaluation of 30 black residents of Kansas City, Kansas > 59 years old, from 1980–1981. These subjects had previously been evaluated in 1970–1971. Study participants were extensively interviewed, and dietary intake data were reported over a protracted period of time. In the decade between surveys, the income of the population had decreased by 1/2 to 2/3. Living arrangements stayed approximately the same in the aggregate although there were some rearrangements due to deaths, causing some people to live alone, and some people to have moved in with relatives. There were significant changes in diet, with a decrease in pork, wild game, alcohol, total food intake, salt, sugar, fat, and citrus beverages. Consumption of core items remained essentially the same. However, there was the addition of some "health" food items, such as imitation bacon, egg substitutes, diet soda, decaffeinated coffee. Both males and females surpassed the recommended levels for protein intake. However, mean energy and calcium intake, as well as the intake of several other micronutrients and vitamins, were below recommended levels.

Summary of National and Regional Studies

What does this tell us about nutritional status of African American elders? Clearly, there are very few studies that examine the oldest-old African Americans. However, the data that are presently available indicate that African Americans often have inadequate intake of total energy, calcium, and potassium. Several other micronutrients may be consumed in suboptimal quantities.

Substandard calorie intake can ultimately lead to protein-calorie malnutrition, given that endogenous protein will be broken down to meet calorie needs with prolonged substandard intake (Cahill, 1970). Thus, the protein-calorie nutritional status of this population should be a point of concern, in spite of the high prevalence of obesity in the population.

The Oklahoma Data Base

To gain better insight into the health and nutritional status of old-old African Americans, a cross-sectional descriptive pilot study was performed evaluating 58 African Americans, ≥ 74 years old, residing in senior housing complexes in Oklahoma City (Bernard, Anderson, & Forgey, 1995). Fifty of the 58 participants were females; 8 were males. Orally administered questionnaires determined functional status, cognitive status, mood, the existence of alcohol abuse, and extent of support system. Nutritional variables that were measured included: frequency of food consumption, height, weight, mid-arm muscle circumference, triceps skin-fold thickness, serum albumin, and cholesterol levels. A subsample of randomly selected subjects also underwent a 24-hour dietary recall by a trained dietitian.

The population surveyed had a high functional status and good health habits, with > 50% consuming supplementary vitamins, and < 2% smoking and/or with evidence of alcohol abuse. Nonetheless, as nutritional status was evaluated, there were a number of findings which were of concern. Based on responses to the food frequency questionnaire, most study participants had a low fat and cholesterol intake, with a mean score equivalent to step one American Heart Association diet (Ammerman et al., 1991). However, in the subset of individuals in whom 24-hour dietary recall data was gathered, a contributor to the low fat intake may have been low overall intake. It was anecdotally noted by several participants that the congregate meals which were provided at the senior housing facilities were their major source of daily nutrients.

Anthropometric data were gathered and compared to National Health and Nutrition Examination (NHANES) II data. There may be variation in appropriate anthropometric standards for elderly blacks versus whites (Ortiz et al., 1992). However, as per the recommendations of the Nutrition Screening Initiative (Dwyer, 1991), NHANES II standards were utilized. Weight averaged 117% of ideal, as compared with NHANES II standards for individuals 65–74 years. Thirty-eight percent of subjects had a body weight which was at the 120th percentile or greater; 2 individuals had a body weight which was in the 80th percentile or lower. Triceps skinfold thicknesses averaged 117%, with 2 individuals having thicknesses at the lowest 20th percentile; 60% of subjects had thicknesses at the 100th percentile or higher. Mid-arm muscle circumference averaged at the 40th percentile (as compared to NHANES II standards for individuals 65–74).; 27% of subjects had a mid-arm muscle circumference in the lowest 20th percentile. The finding of a subset of individuals with low mid-arm muscle

circumferences (27%) was unexpected, and not previously reported. All serum albumin levels were within laboratory norms, averaging 4.29 gm/dl. However, 20% of the serum albumin levels were below 4 gm/dl. Serum cholesterol levels averaged 219 mg/dl, with 14% 160 mg/dl or lower.

Although no one individual had more than two anthropotemic or biochemical variables which were abnormal, there were a number of findings that led to concern regarding the overall nutritional status of the population:

(1) 27% of subjects had a mid-arm muscle circumference < 20th percentile;

(2) 20% of subjects had relatively low serum albumin levels, with serum albumin < 4 gm/dl;

(3) 14% of subjects had low serum cholesterol levels (Rudman et al., 1988);

(4) there were frequent anecdotal reports of overall low caloric intake, seemingly supported by the food frequency questionnaires and 24-hour dietary recall data.

What can one conclude from these data? These data raise the question of whether protein-calorie malnutrition is a significant problem in the current cohort of African American elders, who have a high prevalence of functional disability and poverty. The study population exhibited problems with obesity, which are also found in younger populations of African Americans. However, as noted above, there was a subset of individuals with low mid-arm muscle circumferences, relatively low serum albumin levels, low cholesterol levels, and poor overall caloric intake. Concern regarding risk for protein-calorie malnutrition would seem appropriate in this cohort. Whether these abnormalities were long-term and static, or progressive and associated with increased health risk, could not be determined in the cross-sectional evaluation.

Implications for Future Research

As is well summarized by Jerome (1988), there are a number of areas where further research would help clarify the nutritional status of African American elderly:

1) There are few data regarding food consumption of older blacks (>74)

from varying geographic areas. Given the heterogeneity of African Americans, and changes noted by Jerome (1988) in her longitudinal study, there is reason to believe that there may be geographic variation which could lead to differences in overall nutritional status.

2) There is a dearth of information regarding changes in food preparation and consumption patterns with aging in African Americans. Again, given some of the findings from the Jerome study, and abnormalities noted in the Oklahoma cohort, such changes could contribute to overall nutritional status.
3) There is a paucity of nutritional information regarding the moderate prevalence of hip fractures in this population (Corroni-Huntley et al., 1990). Perry and colleagues (1993) have begun to evaluate this problem. In a sample of 32 African Americans (68–93 y.o.), compared to 43 whites (70–89 y.o.), evidence was found for hypovitaminosis D with secondary hyperparathyroidism. However much more work needs to be done.
4) There is a need for data to account for the high prevalence of obesity among elderly blacks. NHANES data demonstrate frequent meal skipping among black elders. Most studies suggest that elderly African Americans consume fewer calories than non-Hispanic whites. Yet, as noted by Kumanyika and colleagues, elderly black women may have cultural attitudes regarding ideal body weight which contribute to problems with obesity. Much more work needs to be done to clarify the factors which cause elderly black women to have double the prevalence of obesity of elderly white women.
5) There is a need for data which evaluate elderly blacks longitudinally, to determine if there is a true risk for protein-calorie malnutrition. If there is such risk, it must be determined if this risk increases over time, and if it is associated with higher costs for health care.

CONCLUSION

There is a need to recognize that changes within one minority group *may not* be representative of all minority groups—although changes that relate to poverty and functional disability are likely to cross ethnic and cultural groupings. Additionally, within any particular ethnic group, there may be marked variations in eating patterns and thus nutritional status, related

to cultural practices, geographic location, and other less easily quantified factors. Thus, the abnormalities which have been noted with African American elderly need further evaluation in longitudinal studies. In addition, more careful examination of the overall nutritional status of other ethnic minority groups with a high prevalence of poverty and functional disability would appear appropriate.

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CHAPTER 5

Psychological and Social Factors in the Pathogenesis of Weight Loss

JOHN E. MORLEY AND PATRICIA M.K. MORLEY
DIVISION OF GERIATRIC MEDICINE
SAINT LOUIS UNIVERSITY HEALTH SCIENCES CENTER

> All human history attests that happiness for man—the hungry sinner—Since Eve ate apples, much depends on dinner.
>
> —Lord Byron

Food plays a central role in human existence. Since the beginning of time, the successful hunter or gatherer has been the survivor. When famines occurred, it was the person who had developed adequate fat stores who survived. Fat protects from environmental cold, as demonstrated by the fact that populations living nearer the poles are fatter than those living near the equator. Fat also acts as a relative armor plating, protecting the internal organs (and bones) from damage during trauma such as a fall. Overall, in prehistoric humans, natural selection favored those who could accumulate fat, and in modern times maintenance of fat stores appears to play an important role in the survival of older persons.

Besides providing fuel for the human body and decreasing the feeling of hunger, food plays an important role in many social functions. Food plays a central role in religious ceremonies, for example, the bread and wine of communion or the proscription of certain meat products. Food has also become a powerful symbol in our society, being offered almost universally when friends visit. Food is used to produce behavior modification in children where it can be used either as a reward, such as candy, or a punishment. Given the central role of food in humans, it is not surprising that the interaction of culture and biopsychosocial processes gone awry can often lead to malnutrition in older persons.

In this chapter, we will first review the human and animal evidence for the existence of a physiological anorexia of aging that places the older

persons at increased risk for developing severe weight loss. The second section will explore the role of social and cultural factors in precipitating hunger insecurity in older persons. Finally, the increasing evidence that psychological factors may be the most important treatable causes of malnutrition in older persons will be examined.

The importance of aggressive recognition and treatment of these psychosocial factors associated with undernutrition cannot be underestimated. A number of studies have shown that malnourished older persons have longer hospital stays, higher health care costs, more major complications and higher mortality rates (Buzby, Mullen, & Matthews, 1980; Cannon, Wissler, Woolridge, & Benditt, 1944; Christensen, 1986; Coe & Miller, 1984; Epstein, Read, & Hoefer, 1987; Reilly, Hull, & Albert, 1988; Rhoads & Alexander, 1955; Robinson, Goldstein, & Levine, 1987; Smith, Smith, & Toan, 1989). Despite these documented ravages of malnutrition in industrialized nations where there is not a food shortage, malnutrition is often not detected in the clinical setting nor considered a routine concern by many physicians.

THE ANOREXIA OF AGING

Both animal and human studies have demonstrated a physiological decrement in food intake with aging. This is thought to be a physiological response to the decrease in resting metabolic rate and total energy expenditure that occurs with aging (Morley & Silver, 1988).

The NHANES Study demonstrated that there was a linear decrease in food intake from age 19 to 74 years in nonsmokers (Subar, Harlan, & Mattson, 1990). The decrease in calories in males was nearly three times that seen in females and corresponds to the much smaller decrease in total energy intake that occurs in women compared to men with aging. This study could be criticized, as it involved dietary recall, and the health of the subjects was not defined.

Wurtman, Lieberman, Tsay, Nader, and Chew (1988) examined food intake in a laboratory situation comparing healthy elderly and young persons. They found that food intake was reduced in both older males and females. There was no change in protein intake. The largest decrease in calories was due to a decrease in fat (males 56% and females 54%). The decrease in carbohydrate was 41% for females and 39% for males.

Clarkston and colleagues found that healthy older persons demonstrated less hunger after an overnight fast and a greater satiation response after being refed a standardized meal. Older persons had a mild decrease in the rate of gastric emptying but no change in total transit time. The degree of hunger was related to the rate of gastric emptying. Older persons had mild abnormalities in their autonomic function which was postulated to be partly the cause of the altered perception of hunger and the delay in gastric emptying.

Roberts et al. (1994) overfed young and old subjects by approximately 4 MJ/day for 3 weeks. A second group were underfed by 3.17 MJ/day for the same time period. Following overfeeding, young, but not old men, developed hypophagia. After the underfeeding experiment, young persons had a hyperphagia that was not seen in older persons. As a consequence, the older men failed to regain the weight they had lost during the experimental underfeeding period. These studies strongly support the concept that there is an altered ability to control energy intake and energy balance with aging.

Animal studies have supported the concept that, at least in rodents, advanced age is associated with a physiological decrease in food intake, leading to weight loss (Gosnell, Levine, & Morley, 1983). This was originally demonstrated to be due to a decrease in the opioid feeding drive in both rats (Gosnell et al., 1983) and mice (Kavaliers & Herst, 1985). With aging, there is a decrease in opioid receptors in the hypothalamus, providing a biochemical mechanism for this occurrence (Morley, Flood, & Silver, 1990). The endogenous opioid feeding drive is due predominantly to Kappa opioid receptor-activation by dynorphin (dynis = most powerful, orphin = morphine) (Morley, Levine, Yim, & Lowy, 1983). The opioid feeding drive predominantly involves fat intake in both humans (Billington, Shafer, & Morley, 1990) and rodents (Romsos, Gosnell, Morley, & Levine, 1987). This is in keeping with the finding that the major decrease in calories in older persons is due to a decrement in fat intake (Wurtman et al., 1988).

Other studies have shown in mice that there is an increase in the satiating effect of the gastrointestinal hormone, cholecystokinin (CCK) with advancing age (Silver, Morley, Strome, Jones, & Vickers, 1988). CCK is the prototypic satiating hormone and accounts for approximately 15% to 20% of the satiating effect of a meal (Silver & Morley, 1991). Human studies found that CCK levels were elevated in anorectic older humans (Khalil et al., 1985), and these levels were normalized when older persons were not anorectic and of normal weight (Berthelmy et al., 1992).

Nitric oxide is a neurotransmitter responsible for the regulation of adaptive relaxation of the fundus of the stomach, that is, the dilatation of the fundus of the stomach in response to food being present in the fundus. We have previously noted that some older persons with early satiety have been able to eat more after taking nitrates (unpublished observation). In mice, nitric oxide has been shown to play a role in increasing food intake (Morley & Flood, 1991; Morley & Flood, 1992; Morley & Flood, 1994). Nitric oxide inhibitors have been shown to be more potent at inhibiting food intake in older rodents than young ones. This is associated with a decrease in the mRNA for nitric oxide synthase but no decrease in the enzyme level (unpublished observations). These data are compatible with nitric oxide playing a role in the early satiation seen in some older persons.

Amylin is a pancreatic peptide that decreases food intake and increases glucose levels (Edwards & Morley, 1992; Morley, Kaiser, & Perry, 1993). Amylin levels increase in older persons compared to middle-aged persons. Amylin may play a role in the decreased hunger seen in older persons.

The decline in lean body mass that occurs with aging is, in some cases, out of proportion to the anorexia. This often occurs when minor disease activity is present, such as rheumatoid arthritis. It is possible that in these situations the release of cytokines such as interleukin-1 and tumor necrosis factor may increase the anorexia and accelerated loss of lean body mass (Roubenoff & Rall, 1993).

Other hormonal changes may also play a role in developing the loss of lean body mass and the anorexia of aging. Growth hormone and insulin growth factor-1 levels decrease with aging (Kelijman, 1991; Rudman, 1985). Growth hormone administration to healthy older persons increases lean body mass (Rudman et al., 1990). Numerous studies have suggested a role for pharmacological administration of growth hormone to reverse severe malnutrition in older persons (Morley, Kaiser, & Perry, 1993).

The higher testosterone levels observed in males compared to females appears to account for the greater lean body mass in males. Testosterone also increases food intake. Testosterone levels decline over the lifespan (Korenman et al., 1990). This decline may play a role in the decrease in food intake and lean body mass that occurs with aging in males. Estrogen decreases food intake. Thus the decrease in estrogen after the menopause may account for the relative lower decrease in food intake in women compared to men with aging.

Finally, alterations in taste and olfaction will lead to a decrease in food intake with aging (Morley & Silver, 1988). Sensory-specific satiety is the

ability of the person to eat a novel food after being satiated on a familiar food. Rolls and McDermott (1991) found that older persons did not demonstrate a decrease in the pleasantness of the taste of eaten compared to uneaten foods. This suggests that aging is associated with a decline in the sensory-specific satiety seen in younger persons.

The regulation of appetite is extremely complex, involving both a peripheral satiation system and a central feeding drive system. With advancing age, a number of disturbances in these systems appear to lead to a physiological anorexia of aging. The pathogenesis of this condition is summarized in Table 5.1.

SOCIAL FACTORS

The major social factor that is associated with decreased food intake is poverty. While 16% of the total population ingests less than 1,000 calories per day, this rises to over 30% in those whose income is below the poverty level (Abraham, Carroll, & Dresser, 1977). Utilizing the nutrition risk index, we have found that older African Americans living in the inner city in the St. Louis area are at a much greater risk of malnutrition than are whites and that this is predominantly due to the poverty level (Miller, Miller, Rossites, Morley, & Core, 1994). A study in a New York City Municipal hospital found that 23% of subjects were chronically hungry secondary to low income (Rosenberg & Bernabo, 1992). Homelessness, physical problems, and not enjoying eating by oneself were also associated with chronic hunger in this population.

The term *food insecurity* has now replaced the concept which was loosely labeled as hunger. Food insecurity exists when access to enough food at all times to allow the person to lead an active, healthy life is limited or uncertain (Campbell, 1991). To have food *security* (the opposite of food insecurity), the minimum needs include that nutritionally adequate and safe foods are readily available and that personally acceptable food can be obtained in a socially acceptable manner. The major risk factors for food insecurity are household resources and the part of those resources that need to be spent on non-food expenditures (i.e., housing, health care, emergencies, taxes, and discretionary income). Household resources include not only sufficient money to obtain food, but also adequate time to shop for food and appropriate information concerning the construction of an adequate diet. The sources of household resources are the private sec-

TABLE 5.1 The Pathogenesis of the Physiological Anorexia of Aging and Decrease in Lean Body Mass Associated with Aging (↓ = Decrease)

Factors	Change in Aging	Anorexia of Aging → (↓ in Fat > Carbohydrate > Protein)	Decreased Lean Body Mass
Kappa opioids (Dynorphin)	↓	Decreased intake (specifically involves fat intake)	—
Cholecystokin	↑	Increased effect, leading to early satiation	—
Nitric Oxide	Mild ↓	Decreased effect leading to early satiation	—
Cytokines (TNFa)*	↑	Anorexia	Increased protein catabolism lipolysis
Amylin (compared to middle age)	↑	Anorexia	Decreased protein anabolism due to insulin antagonism
Decreased taste and smell	↓	Decreased food intake	—
Growth hormone/IGF-1*	↓	Decreased food intake anabolism	Decreased protein
Testosterone	↓	Decreased food intake (males)	Decreased protein anabolism
Estrogen	↓	Increased food intake (females)	—

*IGF-1 = insulin growth factor I. TNFα = Tumor necrosis

tor, (including employment, retirement income, and investments) and the public sector (employment, social security, food stamps, supplemental security income, nutrition program for the elderly—Title 3c). Nontraditional (alternative) food sources are private foundation support, gifts from family and friends, gardening, and scavenging. This conceptualization of the risk factors for food insecurity is depicted visually in Figure 5.1.

A relative form of poverty occurs when an older person on a fixed income is prescribed an expensive drug by the physician. Often the only potential discretionary income is the older person's food budget. This may result in a situation where the older person decreases their food intake to allow for the purchase of the medication. Alternatively, the older person is noncompliant with the medication. Cycles in which the older person is intermittently noncompliant, alternating with food insecurity, are not unusual.

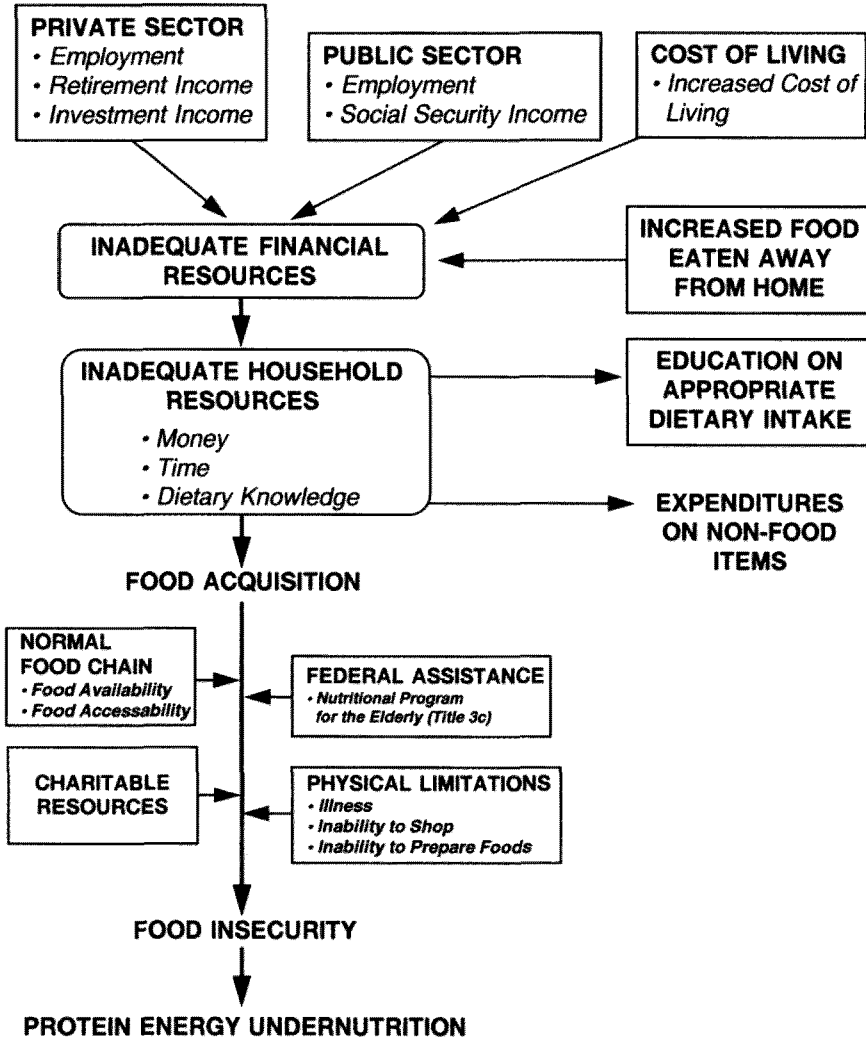

FIGURE 5.1 Conceptualization of social factors leading to food insecurity and protein energy undernutrition. (Based on an original concept by C.C. Campbell, [1991]. *Journal of Nutrition, 121;* 408–415.

Food consumption in the elderly is affected by national food consumption trends. Most older persons in the United States were born at a time (1900–1935) when the predominant calorie source was crops, with a low animal product consumption (Kinsey, 1994). They then lived through the dramatic increase in animal food product ingestion that occurred in midcentury, and have now been affected by the national publicity of possible health risks associated with animal products, which has in turn lead to a decrease in animal compared to crop product consumption. Overall, there has been an increase in both household incomes and total dollars spent on food in the last 30 years, but much of this increase has resulted in an increase in expenditures on food eaten away from home. The quality and caloric quantity of food ingested have also altered with an increase in frozen foods, bananas, lowfat milk, and nonwhite bread; and a decrease in whole milk and meat ingestion.

Roe (1990) examined the causes of food insecurity in inner-city elderly in New York. She found that in this population, food insecurity was due to a decrease in physical mobility in addition to poverty and a lack of in-home assistance. Davies (1984) identified poverty, lack of mobility, and anorexia (possibly disease associated) as the causes of food insecurity in the homebound older person in the United Kingdom. Posner (1979) identified that in addition to poverty, disabilities further decrease the ability of older persons to meet their nutritional requirements. Lack of access to cooking facilities has also been identified as a cause of food insecurity in older persons (Schlenker, 1984). Aging has been associated with a progressive inability to prepare food (Piper & Thorner, 1965). It has been estimated that at a minimum of at least 10% of older persons have substantial problems in preparing a hot meal (Grant, 1968).

Social isolation is another important factor resulting in dietary inadequacy. McIntosh, Shifflett, and Picou (1989) found that financial well-being and extensive friendship networks were both important factors in producing adequate diets. Companionship also appeared to be a buffer against the negative effects of poor appetite on dietary intake. Social isolation can be caused by many factors, including economic factors, disabilities, language, and cultural factors. Social impairment may also lead to social isolation. The socially impaired include older persons who are homeless, live in single-room apartments, have been deinstitutionalized, are alcoholics or drug abusers, and those who have suffered elder abuse (Balsam & Rodgers, 1988).

Elder abuse may commonly present directly as malnutrition due to associated depression or because the abuser is withholding food or financial resources from the older person. Socially isolated persons have a higher disease burden, are often psychologically and physically impaired, and die sooner than socially integrated individuals. A number of programs are available that may be utilized to decrease social isolation, including congregate Nutrition Centers, Meals-on-Wheels Programs, Senior Centers; Transportation Services, for example, Older Adults Transport Services (OATS); Volunteer Friendly Visitor Programs such as the Retired Senior Volunteer Program, the Senior Companion Program, and Foster Grandparent Program, Adult Day Centers, Churches, Older Adult Educational Programs like University of the Third Age, Community Colleges, Elder Hostel, and outreach programs such as the Home Assessment Program for Successful Aging of the Sepulveda VAMC (Farbacher et al., 1994). Remember that socially isolated persons are often difficult to locate, making it important to have successful outreach and referral programs. Human beings are social beings, and it has been demonstrated that social situations result in increased food intake (de Castro, Brewer, Elmore, & Orazco, 1990).

About 5% of persons over 55 years of age utilize alcohol excessively (Klein & Iber, 1991). Thirty percent of persons over 75 years of age drink alcohol. Alcoholism results in decreased social functioning and impaired cognitive function. Cirrhosis of the liver is often associated with decreased albumin levels and impaired zinc status. Alcoholism can lead to folate deficiency. Alcohol displaces utilizable calories, decreases discretionary income, and can increase nutrient requirements. The diagnosis of alcoholism, especially when of recent onset in older persons, is often difficult. The Michigan Alcohol Screening Test has been adapted for older persons. We have found the CAGE questions surprisingly useful in detecting older alcoholics:

C—Have you **c**ut down on your drinking?
A—Do people's comments on your drinking **a**nnoy you?
G—Do you feel **g**uilty about drinking?
E—Do you need an **e**ye opener?

Inability to carry out certain activities of daily living clearly can result in nutritional insecurity. Of the Instrumental Activities of Daily Living, inability to shop and prepare meals clearly limits the ability to maintain an adequate diet. Fifty percent of persons over 85 years of age need help preparing meals and 73% need help shopping. In addition, 47% need help

managing money. In the 75- to 84-year-old group, 16% need help preparing meals, 29% need help shopping, and 12% need help managing their finances. In addition to these chronic disabilities, we have increasingly seen older persons being discharged home alone from the hospital in an acutely debilitated condition. They have no food in the house and little likelihood of being able to obtain food in the near future. The ability of an older person to carry out his or her instrumental activities of daily living related to food procurement and preparation needs to be explored in all older persons coming into contact with the health care system. Where it is possible, this should include a home visit by a member of the health care team, as this will often uncover otherwise undisclosed causes of malnutrition (e.g., bare cupboards, stale or spoiled food). Social interventions can include homemaker and chore services, meals-on-wheels, and a variety of case management services which can attempt to match the individual's needs to community services. Volunteer services including churches, neighbors, and relatives are often crucial to overcoming these barriers.

Approximately 7% of persons over 85 years of age and 2% of those between 65 to 84 years of age need assistance eating. This may be due to physical or cognitive difficulties. In some cases, caused by physical disabilities, an assistive device may be sufficient to overcome the inability to feed oneself. For example, a heavy handled spoon may help a person with a severe tremor, a rocker bottom knife may allow a person with a stroke to cut their meat, and straws or feeder cups may enhance intake of liquids. In-home health aides, homemaker services, adult day care respite services, and volunteers may all be able to play a role in assisting with feeding of the severely limited individual.

When an older person is institutionalized, a number of social factors may result in deterioration in food intake (Morley, 1990). Some older persons isolate themselves in their rooms and eat poorly. When integrated into the nursing home community, their food intake improves. Failure to recognize ethnic food preferences of older persons can lead to weight loss. Some residents decrease their food intake due to the inability to eat in the vicinity of demented patients who have obnoxious eating habits or around residents with physical disabilities or those with catheters or colostomy bags. Monotony of institutionalized food may also lead to decreased food intake.

The social causes of poor nutrient intake are summarized in Table 5.2.

TABLE 5.2 The Social Causes of Poor Nutrient Intake

1. POVERTY
   - Low income
   - Secondary to medication costs
   - Pension utilized to support other members of the household
   - Homelessness
2. EDUCATION
   - National food consumption trends
   - Inadequate dietary knowledge
   - Inaccurate knowledge concerning dietary restriction and low cholesterol diets
3. POOR MOBILITY
4. SOCIAL ISOLATION
5. ELDER ABUSE
6. ALCOHOLISM
7. LIMITATIONS IN ACTIVITIES OF DAILY LIVING
   - Eating
   - Food preparation
   - Food procurement (shopping)
8. INSTITUTIONAL FACTORS
   - Social isolation
   - Ethnic food preferences
   - "Disgust" at other residents
   - Monotony of institutionalized food

NUTRITION SCREENING INITIATIVE: A SOCIOPOLITICAL EDUCATIONAL CAMPAIGN TO INCREASE AWARENESS OF MALNUTRITION IN THE OLDER PERSON

The Nutrition Screening Initiative (NSI) was initiated in 1990 in response to the 1988 Surgeon General's Workshop on Health Promotion and Aging and the U.S. Department of Health and Human Services Report, *Healthy People 2000,* both of which called for increased nutrition screening and education. It was sponsored by the American Academy of Family Physicians, The American Dietetic Association, and the National Council of the Aging and supported by 27 other agencies. It was financially supported by Ross Laboratories, a company who makes food supplements and as such had a clear financial interest in the success of this program. The stated objective of the NSI is "to accelerate the rate at which nutrition screening

and care are incorporated into this nation's health and social service system. . . . specifically focused on improving nutritional care available to older adults" (Nutrition Screening Initiative, 1992).

The major contribution of the NSI has been the development of the DETERMINE Your Nutritional Health checklist:

D isease
E ating poorly
T oothless/Mouth pain
E conomic hardship
R educed social contact
M ultiple medicines
I nvoluntary weight loss/gain
N eeds assistance in self-care
E lder years above age 80

This was eventually translated into a 10-point scale whose validity as an epidemiological screening tool for older persons at nutritional risk has been established (Posner, Jette, Smith, & Miller, 1993). Its sensitivity and specificity for use in individuals has not been determined.

After the development of the instrument, the NSI held a national consensus conference where presentations of the concept were made to consumer focus groups at over 100 meetings of health professionals. This was accompanied by substantial media publicity.

By 1992, over 235,000 screening checklists had been distributed. The NSI clearly represents a highly successful program in educating both the public and health professionals concerning the presence of malnutrition among older persons. It has subsequently developed a nutritional intervention program which is coupled with the nutrition screening (Nutrition Screening Initiative, 1994). Whether this educational program will eventually lead to improvement in nutritional care of older persons is yet to be determined.

A highly innovative method of delivering the nutrition screening message into the hands of the public was developed by Albert Barrocas, M.D. He convinced Schwegmann Supermarkets in New Orleans to place the "Determine Your Nutritional Health" message on grocery bags for one month. During January, 1995 one million bags were circulated in the greater New Orleans area. With spin-offs such as this, the NSI message

will clearly continue to educate persons about the importance of adequate nutritional intake for older persons and the risks of a poor nutrient intake.

PSYCHOLOGICAL CAUSES

The major psychological causes of weight loss and malnutrition in older individuals are listed in Table 5.3.

Depression

Depression is less common in older persons than younger persons living in the community (Fitten, Morley, Gross, Petry, & Cole, 1989). However, the diagnosis of depression is often missed in older persons, both because of the unusual ways in which it can present and the difficulty younger health care professionals have in recognizing depression in older persons (Miller, Morley, Rubenstein, Pietruszka, & Strome, 1990). In young individuals, depression results in weight loss in approximately 60% of cases, while in older individuals weight loss is a presenting feature in 90% of cases (Blazer, Bachas, & Hughes, 1987). In North American older persons, a decreased appetite is the most common presenting feature of depression (Zung, 1967).

Depression has been demonstrated to be the major cause of undernutrition both in nursing homes (Morley & Kraenzle, 1994) and in older persons visiting their physician (Wilson, Miller, & Morley, unpublished observations). Katz et al. (1994) found in an epidemiological study in nursing homes that depression strongly correlated with weight loss. Silver, Flood, and Morley (1988) found that depression was present in 14% of those nursing home residents under 20% of average body weight compared to 10% of those of normal weight. Numerous symptoms reported in older males with depression may lead to weight loss. In a Finnish study (Kivela et al., 1986) depression was noted to result in the following complaints: diarrhea 20%; constipation 36%; stomach pain 37%; nausea 27%; vomiting 10%; loss of appetite 22%; and weakness 61%. Kaplan and Tuckman (1986) have pointed out that depression results in a loss of some of the positive symbolism associated with food such as warmth, caring, acceptance, and sharing. Preoccupation with self-cleansing can lead to laxative abuse in older, depressed persons. Refusal to eat can be used as a suicidal

TABLE 5.3 Psychological Causes of Weight Loss

1. Depression
2. Dysthymia
3. Bereavement
4. Alcoholism
5. Dementia
   - wandering
   - inability to eat
   - forgetting to eat
   - psychotropic drug withdrawal
6. Late life paranoia
7. Late life mania
8. Anorexia nervosa/tardive
9. Sociopathy (loss of sense of control)
10. Excessive burden of life (food refusal)
11. Cholesterol phobia (often a precipitant of anorexia tardive)
12. Globus hystericus
13. Choking phobias

gesture (subintentional death wish) in the older depressed person (Kaplan & Tuckman, 1986).

Corticotropin releasing factor (CRF) is a potent anorectic agent when administered into the central nervous system in animals (Krahn, Gosnell, Levine, & Morley, 1988; Morley & Levine, 1982). Elevations in CRF have been associated with the development of anorexia nervosa (Morley, 1987). In depressed persons, increased activity of the hypothalamic-pituitary-adrenal axis is often present (Carroll et al., 1981), and levels of CRF have been found to be elevated in the cerebrospinal fluid (Nemeroff, Bissetti, & Widerov, 1984). Increased activity of hypothalamic CRF appears to play an important role in the pathogenesis of anorexia associated with depression.

Weight loss and protein energy undernutrition due to depression can be life-threatening. Where extreme weight loss has occurred, electroconvulsive therapy is considered the treatment of choice. In less extreme cases of weight loss, either psychotherapy or pharmacotherapy can be attempted. The selective serotonin uptake inhibitors (i.e., fluoxetine, sertraline, paroxetine) all can cause weight loss and are very expensive. For this reason, we prefer the use of the tricyclics with less cholinergic activity, for example, desipramine (this is substantially cheaper than nortryptiline) for

the treatment of depression associated with weight loss. Trazodone may be preferred if the person is having problems sleeping. The major side effect of these agents in malnourished older persons is orthostatic hypotension.

Bereavement

Bereavement is often associated with a short period of dysphoria and anorexia. When these behaviors continue for more than 3 months, a diagnosis of major depression needs to be entertained. The danger of undereating following the loss of a loved one has long been recognized. The Irish wake represents an example of prevention where the guests at the funeral bring food into the house to make sure that there is sufficient food left in the house for the first week following the funeral. This decreases the chance that a vicious cycle will develop where the grieving person reduces his or her food intake resulting in the development of ketosis. The ketone bodies, in turn, result in a further suppression of intake. The development of "bereavement squads"—organized community groups which bring food into the house of a recent widow(er) and/or invite them to go out to dinner—represents a modern innovation that can prevent bereavement-induced malnutrition. The bringing of food into the home represents an important gesture of renewal indicating that life must continue despite the recent loss.

Rosenbloom and Whittington (1993) studied fifty recently widowed persons and the same number of married controls. Both groups were over 60 years of age. Dietary intake was recorded for three days. The major effect of widowhood was an alteration in the social environment. This resulted in a decrease in the importance that food held for them as part of a social ritual. These social changes resulted in a negative effect on eating behaviors and a decrease in nutrient intake.

Dementia

Dementia is commonly associated with weight loss. Dietary intake studies had suggested that this may be due to an increased metabolism associated with Alzheimer's disease (Sandman, Adolfsson, Nygren, Halimans & Umbiac, 1987). However, recent studies using sophisticated techniques

have demonstrated that increased resting metabolism is not present in Alzheimer's disease (Niskanen, Piirainen, Koljonen, & Uusitupa, 1993; Poehlman, 1993). A small subset of older demented patients who wander incessantly do have an increased metabolism. In some cases, their wandering is the equivalent of running a marathon! This leads to a marked increase in caloric need. Some of these persons will not sit down long enough to ingest sufficient calories to maintain their body mass. Demented patients who receive phenothiazines and develop tardive dyskinesia may have increased energy utilization secondary to their abnormal movements (Morley & Kraenzle, 1994).

Sandman et al. (1987) have suggested that the major reason for weight loss in dementia is due to failure to eat. The failure to eat may be due to indifference (failure to care about eating), memory loss (failure to remember to eat), and impaired judgment (inability to recognize the need to eat). Some demented subjects develop apraxia, that is they forget to swallow the food once it is in their mouth. Other demented patients develop delusional behavioir that inhibits eating. One of our nursing home residents would not eat as she believed she did not have sufficient money to pay for her food. Food price may also be associated with dementia. Coprophagia is not rare. For these reasons, demented patients are often dependent on others to help them obtain adequate nutrition. Inability to self-feed has been identified as a key reason for institutionalization, as it leads to caregiver exhaustion (Chenoweth & Spencer, 1986). Cognitive impairment is associated with loss of independence of eating in institutionalized patients (Siebens et al., 1986). When at home, the time spent feeding severely demented persons is approximately 99 minutes per day compared to only 18 minutes spent feeding them when they are residents in a nursing home (Hu et al., 1986).

In Sandman et al.'s (1987) study, half of the demented patients were malnourished and the mean-weight of his subjects was 85% of ideal body weight. Another study found that demented patients had low levels of B vitamins, zinc and iron (Greer, McBride, & Shenkin, 1986). Zinc deficiency is associated with anorexia and as such this could aggravate the poor food intake in demented persons (Essatara, McClain, Levine, & Morley, 1984). Equally, these vitamin deficiencies may aggravate the deterioration in mental status of these individuals. Silver et al. (1988) found that elderly nursing home residents who weigh less than 80% average body weight were more likely to be demented (43%) than those of average body weight (18%).

Norepinephrine has been demonstrated to increase food intake in rodents when administered directly into the paraventricular nucleus of the hypothalamus (Leibowitz, 1992). Norepinephrine levels are reduced in the hypothalamus of persons with Alzheimer's disease (Yates, Ritchie, & Simpson, 1981). These findings suggest that norepinephrine may be the neurotransmitter responsible for the decreased food intake in Alzheimer's disease.

Excessive use of antipsychotic drugs (phenothiazines or butysophenones) to control agitated behaviors in demented persons can lead to weight loss. Recently, Morley and Kraenzle (1994) reported that some individuals undergoing psychotropic drug reduction as mandated by OBRA '87 (Office of Budget Reconciliation Act) developed severe weight loss without any other signs of mental deterioration. Weight returned to normal with reinstitution of the neuroleptic drug.

Late Life Paranoia

Some older persons develop new onset of paranoid delusions either as the only finding (late-life paranoia) or in association with dementia. A not uncommon form of this paranoia is the belief that food is being poisoned, leading to refusal to eat. One of our elderly clients was convinced that the children in the neighborhood were going to steal her potted plants. This led to her standing at the front door and opening it every few minutes to try to catch the children in the act of stealing her plants. This left no time to eat, and she developed severe weight loss. She gained weight when her late-life paranoia was treated with a low dose of haloperidol (0.5 mg daily). Late life paranoia classically responds very well to low doses of butysophenones.

Late-life mania

New onset of mania can occur in old age. This condition is often associated with prolonged periods of sleeplessness and continuous rapid movements. This can lead to severe weight loss due to increased energy utilization. Lithium is the treatment of choice for these patients.

Anorexia nervosa/tardive

The first report of anorexia nervosa beyond the age of 60 years was that of Bernstein (1972). This 94-year-old woman had mixed features of anorexia nervosa and depression and had a positive response to electroconvulsive therapy. Our previous review of anorexia nervosa in late life (Morley, Silver, Miller, & Rubenstein, 1989), found 7 cases of whom one was a male. In 4 of these cases, an alternate diagnosis of depression or bereavement could have been entertained.

Riemann, McNally and Meier (1993) reported that a 72-year-old male had had a 20-year history of low body weight, feelings of being fat when he weighed 93 pounds, laxative abuse, self-induced vomiting, and excessive exercise. Depression did not appear to be a factor. Gowers and Crisp (1990) reported the case of an 80-year-old woman who had had anorexia nervosa in adolescence, went into remission at aged 30 years, and had a recurrence at 80 years of age as part of an acute grief reaction. White, Harries, and Allen (1990) reported an older person with extreme weight loss and psychological abnormalities suggestive of anorexia nervosa. A 67-year-old female presented with weight loss, preoccupations with calorie intake, a fear of becoming obese, and a distorted body image (Ramell & Brown, 1988). Cosford and Arnold (1991) reported a woman who at 73 years old had a recurrence of anorexia nervosa similar to an episode she had at 23 years of age. The reported cases of anorexia nervosa are summarized in Table 5.4.

Anorexia tardive has been suggested as an alternative term for late-life onset of anorexia nervosa (Dally, 1984). He reported 11 cases ranging from 41 to 80 years of age. Many of these patients had concomitant depression. In some cases, the anorexia was being utilized as a manipulative behavior. Sex was a duty and avoided where possible. A desire for death was common in these persons.

These studies support the contention that full-blown anorexia nervosa (or tardive) is a real syndrome in older persons. In our experience, this often is a recurrence and careful check of history can uncover a similar episode (usually called asthenia) in the teenage years. Depression appears to be a major concomitant feature in many of these cases.

In addition to the rather rare, clear cases of anorexia nervosa, Miller, Morley, Rubenstein, and Pietreszka (1991) have reported that in males over 70 years of age who were underweight, 3% to 9% had abnormal responses on the EAT-26 and 9% to 26% had inappropriate eating attitudes such as

TABLE 5.4 Reports of Anorexia Nervosa Occurring in Older Persons

Reference	Year	Age	Comments
Ryle, *Lancet 2,* 893	1936	59	—
Bernstein, *Minn Med 55,* 552	1972	94	Depression
Kellett et al., *Br J Psychiat 128,* 555	1976	52	Classic
Launer, *Br J Med Psychol 51,* 375	1978	70	Classic
Price et al., *J Am Geriatr Soc 33,* 213	1985	68	Bereavement
Price et al., *J Clin Psychiat 8,*144	1986	60	Depression
		62	Depression
Russell et al., *Med J Aust 148,* 199	1988	70	Small cell cancer
Nagaratham & Ghougassian, *Br Med J 296,* 1443	1988	69	Male
Ramell & Brown, *Post Grad Med J 64,* 48	1988	67	Classic
Gowers & Crisp, *Br J Psychiat 158,* 286	1990	80	Recurrence
Cosford & Arnold, *Br J Psychiat 159,* 296	1991	73	Recurrence
Riemann et al., *Int J Eating Disorders 14,* 581	1993	72	Bulimia nervosa
Morley, *J Am Geriatr Soc 41,* 1012	1993	85	Sociopathy; life long restriction

a preference for the stomach to be empty, avoiding eating when hungry, and engaging in dieting behavior. Sixty percent of undernourished older males acknowledged maintaining self-control in the presence of food. These undernourished subjects scored high on the Oral Control Subscale but had normal scores on the Dieting and Bulimia and the Food Preoccupation subscales. The reasons for these attitudes have not been adequately explored but may include lifelong attitudes to food intake or newly developed attitudes related to the belief that weight loss may prolong life. The popular press accounts of dietary restriction prolonging life in rodents appears to have played a role in these beliefs.

We have now studied the responses to the EAT-26 in a population of older males and females in St. Louis (Morley, Morley, & Flood, 1993). Our preliminary results demonstrated that older malnourished subjects scored significantly higher on the Oral Control subscale than the younger subjects. Multiple regression analysis demonstrated that the single most important factor explaining the Oral Control subscale was increasing age.

Depressive symptoms also played a role in defining the Oral Control subscale. Issues of oral control were more often associated with nutritional problems than was intentional weight loss in seniors when compared to younger persons.

Overall, these studies support the contention that older, malnourished persons have a high oral control, putting them at increased risk for developing anorexia nervosa (tardive)-like syndrome.

Sociopathy

Older persons are often placed in a situation where they lose their locus of control. We have identified four patterns where anorexia is utilized to regain control of the situation. In the "Strange Case of an Older Woman Who was Cured by Being Allowed to Refuse Therapy" (Morley, 1993), an 85-year-old woman who was threatened with removal from home starved herself to regain control of the situation. She was prepared to accept death as a preferred outcome. When guaranteed the right to stay at home, she regained her lost weight.

Situations may arise where wives, having been controlled by their husbands in the past, now take advantage of their frailty to control their behavior. The husbands in turn may then refuse to eat in attempting to regain control of the situation.

Isolation is a common problem in an institution. An older person who is feeling isolated, recognizes that these residents who are not eating receive assistance with eating, leading to increased interaction with the nurse's aide who feeds them. Anorexia becomes a logical choice to regain companionship.

Residents in institutions will often use refusal to eat as a method to "punish" or "control" staff behaviors. This includes spitting food at staff. Occasionally, we have seen vomiting utilized in the same way.

Excessive Burden of Life

Older persons often decrease their food intake in the few months prior to death. In some people, their lives appear to have become excessively burdensome. In these cases anorexia may provide a comfortable way to exit life. Food refusal is an ethically acceptable method by which some persons choose to die.

Cholesterol Phobia

An intensive campaign has been carried out to get Americans to lower their cholesterol to decrease atherosclerotic disease. Intensive dietary education is often given to older persons following heart attacks to decrease their fat intake. This can lead to marked restriction of food intake with the development of decreased albumin levels.

Globus Hystericus

Some older people develop an imaginary lump in their throat that interferes with their ability to swallow. Globus hystericus is often associated with the presence of a hiatal hernia.

Choking phobia

Choking phobia is associated with the fear of swallowing food (McNally, 1994). This often occurs after an episode of choking on food. It is more common in females and can be treated with antipanic medications.

CONCLUSION

Older persons develop a physiological anorexia of aging that occurs in response to decreased basal energy metabolism and a decrease in voluntary energy expenditure. The physiological anorexia of aging makes older persons highly vulnerable to developing a more severe pathological anorexia. There are numerous psychological causes of weight loss in older persons. Depression is the most common cause of weight loss in old persons.

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CHAPTER 6

The Diagnosis and Management of Protein Energy Undernutrition in Older Persons

MARGARET-MARY G. WILSON AND JOHN E. MORLEY
DIVISION OF GERIATRIC MEDICINE
SAINT LOUIS UNIVERSITY HEALTH SCIENCES CENTER

" . . . thy food shall be thy remedy . . . "
—Hippocrates, 400 BC.

The euphemistic view of aging unjustifiably fosters the concept that humans, like plants, wither away as a manifestation of senescence. Thus, to the uninitiated, advancing age and increasing frailty must of necessity coexist. Anorexia and weight loss in the older person may therefore be acknowledged, but subsequently dismissed as normal accompaniments of aging. The trend toward preventive gerontology is rapidly eroding such myths, highlighting the importance of nutritional status as a major determinant of health, functional status, and medical outcomes in the older segment of the population.

Protein energy undernutrition (PEU) in older persons has been shown to be highly predictive of ensuing morbidity and mortality (Harris, Cook, & Garrison,1988; Tayback, Kumanyika, & Chei,1990; Waaler, 1983). PEU is known to be a strong independent risk factor for in-hospital morbidity and early nonelective hospital readmission (Sullivan, 1992, 1994). This may be attributed to several well-recognized complications of protein calorie undernutrition (see Table 6.1). PEU may result in the development of T-cell defects, alteration in the CD4/CD8 ratio and anergy. A decrease in the number of natural killer cells and a reduction in the blastic response to mitogens have also been demonstrated (Lipschitz, 1986, 1992). The resulting immune dysfunction serves to increase the patients' predisposition to infections by both pathogenic and nonpathogenic organisms. Delayed wound healing, an increased incidence of anemia, and a reduction in cog-

TABLE 6.1 Complications of Protein Energy Undernutrition

- Immune dysfunction
  - Altered CD4/CD8 ratio
  - Decreased natural killer cells
  - Anergy
  - Decreased blastic response to mitogens
- Poor wound healing
- Recurrent falls
- Reduced cognitive function
- Anemia
- Increased drug toxicity
- Muscle weakness

nitive function have also been linked to undernutrition (Bogden, Oleske, & Munres, 1987; Goodwin, Goodwin, & Garry,1983). The risk of adverse effects, particularly from protein-bound drugs, increases with the onset of hypoalbuminemia (Williams, 1990). These factors undoubtedly contribute to the longer duration of hospital stay and the higher mortality rates noted in undernourished patients (Harris et al. 1988; Shaw–Stiffel et al. 1993; Tayback et al.1990).

Undernourished community-dwelling older persons may exhibit reduced performance in the instrumental activities of daily living. It has been suggested that muscle weakness and easy fatiguability resulting from protein energy undernutrition may additionally compromise basic activities of daily living (Morley,1986). These myopathic symptoms have also been offered as a possible explanation for the increased incidence of hip fractures in such patients. Conversely, the presence of untreated protein calorie undernutrition in patients admitted with hip fractures is associated with a greater risk of death (Barstow, Rawlings, & Allison,1983; Foster, Heppenstahl, Friedenberg, & Hozack, 1990; Patterson, Cornell, Carbone, Levine, & Chapman, 1992).

The significant negative impact of protein energy undernutrition on the health and functional status of the older individual mandates early diagnosis and aggressive therapeutic intervention. Unfortunately, despite reported prevalence rates which indicate that protein calorie undernutrition may have attained endemic proportions in the American older population, this condition remains underdiagnosed, reflecting poor nutritional screening (Miller, Morley, Rubenstein, Pietruska, & Strome, 1990; Mowe-Morten & Bohmer, 1991). Inadequate training and a lack of awareness on the part of health professionals regarding the significance, complications, and treat-

ment of undernutrition in the older person have been implicated (Morley,1991).

NUTRITIONAL SCREENING

Developing an effective strategy for productive nutritional assessment of the older person necessitates prior knowledge of the changes in nutritional intake and appetite regulation that occur with advancing age. The National Health and Nutrition Examination survey (NHANES) carried out in 1972 found that 16% of caucasians and 18% of blacks consumed less than 1,000 calories each day (Villa Dresser, Carroll, & Abraham, 1979). Social, financial, psychological and pathological factors were implicated. Physiological anorexia of aging, which has been attributed to several factors, featured as a prominent cause. With increasing age there is a reduction in lean body mass and energy expenditure, resulting in a decreased metabolic rate (Keys, 1973; Morley, Silver, Fiatorone, & Mooradian, 1986). Reduced sensitivity of the gustatory and olfactory receptors may occur, significantly detracting from the hedonic qualities of food and consequently reducing the desire to eat (Bartoshuk, Rifkin, Marks, & Bars,1986; Kamath, 1982). In rodents, aging is associated with a reduction in the opioid feeding drive and an increase in the satiating effect of cholecystokinin, resulting in smaller meals with longer intervals between meals (Gosnell, Levine, & Morley, 1983; Silver, Flood, & Morley, 1988). These factors may contribute to weight loss in the aging individual.

Current research findings suggest the possibility of a discrete entity referred to as *idiopathic senile anorexia.* A significant reduction in cerebrospinal fluid (CSF) levels of alpha tumor necrosis factor (TNF) and beta endorphin have been noted in these patients. An inverse correlation has also been identified between CSF alpha TNF and body weight in such persons (Martinez et al., 1993). The current unavailability of data makes it difficult to ascertain the role of TNF in such subjects.

It cannot be overemphasized that the concept of physiological anorexia does not embrace weight loss of sufficient magnitude to suggest nutritional compromise, as this falls firmly within the realms of a disease entity. The diagnosis of physiological anorexia is of necessity strictly one of exclusion. Its role as a confounding factor in the assessment of undernutrition in the older person can only be countered by an increase in the physician's index of suspicion and broad nutritional screening of the older segment of the population.

An acceptable consensus is yet to be reached regarding the most effective screening tool for undernutrition in older persons. The ideal instrument should be easily applied, cost-effective, and reasonably sensitive and specific. The Nutritional Screening Initiative (NSI) is the result of a national collaborative effort involving family physicians, dietitians, and the National Council of Aging (Posner, Jeffe, Smith, & Miller, 1993). It was formulated to facilitate detection of factors which may compromise the nutritional well-being of the older person and assist in focused direction toward appropriate nutrition services and resources. It utilizes a three-tiered approach initiated by self-screening, carried out by the individual or the primary caregivers. The results of this may justify further assessment by health care or social services personnel. Identification of possible indications for medical intervention leads to assessment by a physician in a clinical setting. The NSI focuses on nutritional status, functional status, and an extensive variety of physical and mental illnesses which may compromise nutritional function. The attempt to screen for numerous factors simultaneously may compromise efficiency, as this tool has been shown to have a relatively low sensitivity and specificity with a low positive predictive value (Posner, Jeffe, Smith, & Miller, 1993). Thus, self-referrals encouraged by the use of this tool include a significant number of false positives, constituting a notable drain on available health resources. Nevertheless, the NSI retains significant value as an epidemiological tool, serving to elevate public awareness regarding the importance of nutritional maintenance in the older person.

In an attempt to further facilitate the detection of older persons at high risk for protein energy malnutrition, Morley has developed a useful screening tool, identified by the acronym SCALES (see Table 6.2). Unlike the NSI, this instrument focuses on risk factors and indices of undernutrition in relative isolation of associated diseases, which should serve to increase its efficiency and predictive value. Indices employed include the individual's mood, as assessed by Yesavage's geriatric depression scale (Yesavage et al., 1983); cognitive function determined by the results of a mini-mental status exam; mobility, eating patterns, and socioeconomic status. Definite parameters are provided for the diagnosis of significant weight loss. Serum cholesterol and albumin levels are also considered (Morley, 1991). This instrument is simple to use, cost-effective, requires limited personnel and is easily adaptable to various clinical settings. These constitute further advantages for its use in clinical assessment of the individual patient with a view to early diagnosis and rapid therapeutic intervention.

TABLE 6.2 SCALES: Assessment Tool for the Early Detection of Patients at High Risk for Protein Calorie Undernutrition

Parameter	1 point	2 points
Sadness	YGDS 10–15	YGDS > 15
Cholesterol	<180	<160
Albumin	<4g/dl	<3.5g/dl
Loss of weight	<2 lbs in 1 mo.	>6 lbs in 6 mos
Eating problems	cognitive impairment or physical limitations	cognitive impairment and physical limitations
Shopping problems	Inability to shop or prepare a meal	

Scores > 3 indicate major risk.

Several similar screening tools have been devised and are currently employed in various clinical settings (Ford & Fairchild, 1990; Frisoni, 1994; Hall, 1990) The multiple determinants of nutritional status prevent accurate validation and standardization of these instruments. This should not detract from their clinical value, as they are intended, primarily, for use as diagnostic aids and are not to be considered substitutes for the routine incorporation of a detailed nutritional assessment into the evaluation of each older person, regardless of state of health or clinical setting.

EVALUATION

The syndrome of undernutrition is not characterized by specific symptoms. The volunteered history may consist of vague complaints such as lethargy, reduced exercise tolerance, and decreased motivation, which are of minimal diagnostic value. Physical examination may provide diagnostic clues such as features of vitamin deficiency, reduced subcutaneous fat, muscle wasting or peripheral edema, although in the overweight patient, these signs may not be readily evident. A systematic approach to the management of undernutrition is greatly enhanced by the utilization of anthropometric measurements and laboratory markers in establishing the initial diagnosis and monitoring response to therapeutic intervention (see Table 6.3).

TABLE 6.3 Anthropometric and Laboratory Indices Utilized in Nutritional Evaluation

Anthropometry:
- Total body weight
- Weight change over time
- Body Mass Index
- Skin-fold thickness
- Arm-muscle circumference

Biochemistry:
- Serum proteins (see Table 6.5)
- Serum cholesterol

Hematology:
- Complete blood count
- Vitamin B_{12}, Folate levels
- Ferritin, iron, and TIBC.

Immunology:
- Total lymphocyte counts
- Skin tests

ANTHROPOMETRY

Weight

Standard reference values utilized in the assessment of weights in Americans are derived from data published by actuaries of the Metropolitan Life Insurance Company. The endpoints utilized in determining "normal" weight ranges are thus more relevant to mortality risk than nutritional well-being. A further drawback is the failure to provide age-adjusted values. It is well recognized that the acceptable weight range increases in older persons. It is suggested that an allowance of 10 lbs be made for each decade over the age of 65 years (Andres, 1994). Using data from the National Health and Nutrition Examination Survey (NHANES) studies, Frisancho established body weight standards for persons up to the age of 74 years (Frisancho, 1984). Elbow breadths were utilized to provide an estimate of frame size (Frisancho, 1983). Several other age-adjusted weight tables are available and accurate nutritional assessment of the older person mandates the use of such tables.

The absolute body weight should not detract from the significance of a trend towards weight loss, as both have proved to be of prognostic significance. A body weight between 55%–60% of ideal has been shown to be barely compatible with life (Heymsfield, Tighe, & Wang, 1994). It has been shown that persons who lose more than 10% of their weight in less than six months have an increased risk of multiorgan dysfunction associated with increased morbidity and mortality (Hill, 1992). However, in older persons lesser degrees of weight loss may be of clinical significance. Stud-

ies have identified an increase in mortality with weight loss of 5kg or more in nursing home patients (Dwyer et al., 1987). For practical clinical purposes, a body weight less than 80% of ideal, using age-adjusted tables, or involuntary weight loss exceeding 10% of baseline body weight over the preceding six months are considered indicative of undernutrition. To facilitate early detection of undernutrition, diagnostic criteria using shorter intervals have been suggested. Thus, weight loss exceeding 1%–2% over a week, 5% over a month or 7.5% within three months should prompt assessment for undernutrition (Henderson, 1990).

Body Mass Index (Quelelet Index)

Interindividual variations in body habitus influence weight. The BMI, calculated by dividing the weight in kilograms by the height in meters squared (Wt/Ht^2), was formulated in an attempt to improve the accuracy of anthropometric data interpretation (Garn, Leonard, & Hawthorne, 1986; James, Ferro, Luzzi, & Waterlow, 1988). This index is based on the concept that the relationship between height and weight remain constant in adults with normal morphology, as weight has been shown to increase proportionately with height squared. The World Health Organization recommended the use of data from the United States National Health Center for Health Statistics as reference values. However, the Gerontology Research Center offers a series of age-adjusted values, as the concept underlying the BMI does not hold true for the older person. In addition to the changes in weight previously mentioned, shortening of the axial skeleton resulting from age-related osteoporosis, kyphoscoliosis, postural changes, and degenerative disc changes may result in a decrease in height with advancing age. An added disadvantage to the use of the BMI is identified in nonambulant patients, in whom standard methods of measuring height may prove impractical (Mcall, Ashcroft, Lovell, & Moore, 1967; Mitchell, 1982; Rossman, 1979; Trotter, 1951). To circumvent this problem, several surrogate parameters of height have been adopted from dimensions of the appendicular skeleton which remain relatively unchanged with advancing age. Supine total arm length, arm span, knee-to-floor height, and erect forearm length have been found to correlate satisfactorily with height. Nomograms enabling conversion are available, however these more cumbersome methodologies have not acheived widespread use (Chumlea & Guo, 1992; Haboubi, Hudson, & Pathy, 1990; Kwok & Whitelaw, 1991).

Body composition analysis

Several common clinical conditions may reduce the predictive value of body weight and BMI readings in undernutrition. These include peripheral edema, ascites, and gross obesity. Excessive tumor growth may mask significant reductions in total body fat and protein in undernourished patients with rapidly progressive malignancies. A sudden increase in caloric and sodium intake in the nutritionally compromised person may lead to significant fluid retention and consequent transient weight gain. Various methods have been devised to provide anthropometric measurements which reflect separate body compartments. For practical purposes the two–compartment model of body composition is utilized, dividing the body into fat mass and fat-free mass. Total body fat stores have been shown to be of prognostic significance, with reduced stores predicting adverse outcomes (Heymsfield et al., 1994).

Several indices may be measured as a reflection of body fat stores, although skin-fold thickness measurements are most often employed. The advantages of this technique include ease of administration, wide availability, and relative cost-effectiveness. However, the accuracy of this technique in nutritional evaluation is hampered by the unpredictable response of subcutaneous fat to undernutrition and the absence of a definite correlation between skin-fold thickness and total body fat. An added disadvantage is the highly variable fat distribution between individuals, although it is suggested that this factor may be overcome by utilizing multiple measurements from varying sites (Heymsfield et al. 1994, Himes, 1991; Lipschitz, 1992; Sjostrom, 1991). In older men, skin-fold thickness over the scapula and iliac crest have been found to correlate more closely with total body fat, while the triceps and the thigh are preferred sites in older women (Durnin & Womersley, 1974; Steen, 1977). The predictive value of this technique is further compromised by aging, which in itself may cause both quantitative and qualitative changes in subcutaneous fat. Altered compressibility of subcutaneous tissue has also been noted in some older persons (Heymsfield et al. 1994; Himes, 1991; Sjostrom, 1991). Significant diurnal variations in skin-fold thickness measurements, which may be partially attributed to observer error, have been noted in some studies.

Arm-muscle circumference has been utilized as a means of assessing total body fat and skeletal muscle mass. Obvious confounding factors are genetics, and pathological and environmental factors such as exercise, which may affect the final determination of muscle bulk. Prediction

equations utilizing skin-fold thickness, weight, age, and sex, have been derived to determine total body fat and fat-free body mass (Steen, 1977). The accuracy of these equations in the older person is unknown.

In spite of the apparent profusion of diagnostic indices in the diagnosis of undernutrition, there is a striking paucity of those which have been validated in the older person. It cannot be overemphasized that the most valuable diagnostic pointer toward undernutrition in older persons remains the exhibition of significant weight loss over a specified time period. Skinfold thickness, arm-muscle circumference, and their various derivatives are unable to detect early undernutrition and are unlikely to prove more sensitive than gross weight changes in detecting more severe stages of undernutrition. The utilization of these indices may, however, assist in objective serial evaluation of undernourished older persons.

More accurate methods of body composition analysis are utilized almost exclusively for research purposes. These include computerized tomography, nuclear magnetic resonance imaging, bioelectrical impedance, in vivo neutron activation analysis, and dual-energy x-ray absorptiometry (Daley & Bistrian,1994; Oldroyd et al., 1993; Prijatmoko et al., 1993). The changes in body water that occur with aging do, however, require that these methods be validated separately for older persons.

BIOCHEMISTRY

Serum biochemical markers are frequently used in the diagnosis and follow-up of undernourished persons. Albumin is most often utilized for this purpose. The precise role of serum albumin levels in the diagnosis of protein calorie undernutrition remains poorly defined, however serum albumin levels less than 3.5g/dl are generally considered to be highly indicative of undernutrition. Definite evidence exists linking hypoalbuminemia to increased patient mortality, prolonged hospital stay, and higher readmission rates (Jhangiani, Agarwal, Holmes, Cayten, & Pitchumoni, 1986; Linn, 1984; Lipschitz, 1982). Studies have demonstrated increased mortality rates in nursing home patients with serum albumin levels less than 4g/dl (Rudman & Feller,1989). In ambulatory older community dwellers, serum albumin levels have been shown to correlate positively with functional status and disease outcomes (Agarwal, Acevedo, Leighton, Cayten, & Pitchumoni, 1988; Constans et al., 1992; Foster, Heppenstahl, Friedenberg, & Hozack, 1990; Hermann, Safran, Levkoff, Kenneth, & Minaker, 1992).

The detrimental effect of hypoalbuminemia on the health status of the

TABLE 6.4 Pathological Causes of Changes in Albumin Metabolism

Reduced albumin synthesis
• Chronic undernutrition
• Hypothyroidism
• Carcinoid syndrome
• Liver disease
• Uremia
• Acute stress
Increased albumin degradation
• Hyperthyroidism
• Nephrotic syndrome
• Malignant disease
• Acute stress
Increased albumin loss
• Nephrotic syndrome
• Protein losing enteropathy
• Glomerular disease
• Peritoneal dialysis
• Severe liver failure
• Thermal injury

older person has been attributed to several factors. Delayed wound healing, immunocompromise, and an increased incidence of adverse reactions from highly protein-bound drugs may all result from a reduction in serum albumin levels. It has been suggested that complications in the older undernourished person may result from a decrease in the available antioxidant and antiinflammatory effects of albumin (Fleck, 1989; Stevens, 1990).

Serum albumin levels are determined by an interplay of several factors. The total body distribution, biosynthetic, and catabolic rates of albumin may be altered in several disease states (see Table 6.4). A compensatory reduction in the catabolism of albumin occurs in undernourished patients associated with an apparent increase in the intravascular albumin content due to intercompartmental redistribution. This may result in falsely elevated serum albumin levels that are not representative of total body albumin (Fleck, 1989; Heymsfield et al., 1994; James & Hay, 1968). As the nutritional status deteriorates further, albumin synthesis declines notably and overt hypoalbuminemia ensues.

Several confounding factors are introduced in the acutely hospitalized patient. Situations of acute stress or injury induce the release of cytokines. This results in an increase in serum acute phase reactants such as

fibrinogen, haptoglobin, alpha 1 glycoprotein and C-reactive protein. Cytokine release during such periods also results in a simultaneous reduction in the synthesis of other serum proteins which include albumin and prealbumin (Pomposelli, Flores, & Bistrian, 1988). The increase in counterregulatory hormones in response to acute stress further influences protein metabolism, by reducing synthesis and increasing catabolism of serum albumin (Boosalis et al., 1989). Direct downregulation of albumin gene expression and transfer also occurs during acute stress and may further contribute to hypoalbuminemia (Perlmutter, Dinarello, Punsal, & Colten, 1986).

Serum albumin levels in the acutely hospitalized patient are therefore poor predictors of nutritional status, prior to treatment of the underlying disease or injury. Review of albumin levels in conjunction with serum levels of acute phase reactants may enhance the validity of nutritional evaluation during the acute phase of illness.

The extent to which serum albumin reflects protein stores and nutritional status remains unclear due to the multitude of confounding factors, which significantly reduce its sensitivity as a diagnostic index of undernutrition. Serum albumin measurements are therefore probably best utilized as markers which identify a high-risk group of persons most likely to benefit from nutritional evaluation and intervention.

Following the institution of nutritional support and management, albumin levels are frequently monitored in an attempt to assess clinical response to treatment. The function of albumin in this regard is significantly compromised by a large body pool and a relatively long half life of about 14–20 days (Heymsfield et al., 1994). Other serum proteins have been used for this purpose, although they are less cost-effective and not readily accessible (see Table 6.5). Serum transferrin levels are unreliable in older persons as the increase in iron stores which occurs with aging may result in transferrin levels which may falsely suggest protein depletion (Lipschitz, 1992). Insulin–like Growth Factor 1(IGF–1) has a half life of 2–6 hours and responds most rapidly to fasting and refeeding. There is evidence to suggest that IGF–1 levels retain positive correlation with nutritional status even during periods of acute stress (Heymsfield et al., 1994). A major drawback common to all protein assays utilized in nutritional evaluation is the lack of diagnostic specificity (Fleck, 1989). Serum albumin assays possess the overriding advantage of being the most cost-effective and readily accessible and it is unlikely that the utilization of other biochemical protein markers will be of additional benefit to the patient.

TABLE 6.5 Serum Biochemical Markers of Nutritional Status

- Albumin
- Prealbumin
- Transferrin
- Retinol–binding protein
- Insulin–like growth factor–1
- Fibronectin

Evidence suggests that hypocholesterolemia, which may result from PEM, may be a marker of increased mortality in older persons. Cholesterol levels below 156mg/dl were shown to be highly predictive of subsequent mortality in a cohort of nursing home residents (Rudman & Feller, 1989). Undernourished persons with hypocholesterolemia should therefore be considered a high risk group, in whom aggressive intervention is warranted. However, low cholesterol levels may also result from an increase in cytokine release.

HEMATOLOGY

Anemia often coexists with protein calorie undernutrition. Iron and folate deficiencies may result from an inadequate diet. There is, however, some evidence to suggest that undernutrition in itself may give rise to a characteristic anemia. Studies suggest that a reduction in erythrocyte requirements, resulting from decreased lean body mass in undernourished persons, may lead to a decrease in erythropoiesis (Finch, 1975). Other studies have identified alterations in erythrocyte function in undernourished patients (Lanzkowsky, 1967).

Total lymphocyte counts (TLC) are not routinely incorporated into the initial diagnostic evaluation of the older person with PEM, although the TLC may assist in stratification of undernutrition according to severity. TLC exceeding 1,200 usually indicate mild PEM while in severe undernutrition, cell counts may be less than 800 (Alpers, Clouse, & Stenson, 1983).

MANAGEMENT

A crucial element in determining the response to therapeutic nutritional intervention is the underlying precipitant or risk factor. Thus, a good working knowledge of factors that may contribute to PEM is essential. Numer-

TABLE 6.6 Causes of Protein Energy Undernutrition

Reduced food intake	Increased nutrient metabolism
Ill-fitting dentures	Hyperthyroidism
Dental/gingival disease	Phaeochromocytoma
Oropharyngeal disease	Behavioral disorders
Cerebrovascular disease	Movement disorders
Parkinsonism	Persistent tremors
Orofacial dyskinesias	Hemiballismus
Gastroesophageal disease	Reduced nutrient utilization
Inflammatory	Malabsorption syndrome
Neoplastic	Chronic inflammatory bowel disease
Dysmotility	Gluten enterpathy
Physical/Mental disability	Multifactorial (see text)
Persistent tremors	Chronic obstructive pulmonary disease
Arthritides	Congestive cardiac failure
Cerebrovascular disease	Malignant disease
Dementia	
Behavioral disorders	

ous causes of protein energy malnutrition are recognized (see Table 6.6).

The most common mechanism underlying malnutrition in older persons is reduced intake, often precipitated by factors which reduce the hedonistic qualities of eating. Difficulty with mastication resulting from ill-fitting dentures, dental, periodontal, or gingival disease may result in dietary modification in an attempt to avoid exacerbation of symptoms. This may notably affect the nutritional quality of the diet, predisposing the person to PEM. Bush and others have developed the Dental Screening Initiative, a self-administered screening tool, developed to identify oral diseases which may interfere with adequate food intake (see Table 6.7). This instrument has been shown to possess both a sensitivity and specificity in excess of 80%. Gastroesophageal disease often presents with dysphagia, odynophagia, regurgitation of previously ingested food, or abdominal pain which may be exacerbated by meals. These symptoms may give rise to a reluctance to eat regularly and thus significantly compromise the patients' nutritional status. Disease of the large bowel with symptoms related to meals may have a similar effect.

Diseases which may affect neuromuscular coordination such as Parkinson's disease, cerebrovascular disease, and arthritides may limit

TABLE 6.7 The Dental Screening Initiative

— Dry Mouth	2 points
— Eating difficulty	1 points
— No recent dental care (within 2 years)	1 points
— Tooth Loss	
— Alternative food selection	1 point
— Lesions/sores/lumps in mouth	1 point

Scores > 2 points indicate the possibility of a dental problem which may affect health and nutritional well-being.

mobility and notably compromise manual dexterity, impacting negatively on food availability and preparation. These diseases may also affect esophageal or pharyngeal motility, further compromising food intake. Older persons with impaired cognitive function are highly susceptible to malnutrition. They often experience difficulty with meal planning and preparation. With progression of the disease, reduced mobility, inability to self-feed, diminished communication skills, and behavioral disorders may further increase the risk of undernutrition (Chenoweth & Spencer, 1986; Silver, 1992).

A significant proportion of older undernourished persons complain of anorexia. This is a nonspecific symptom which may be associated with several diseases. In the older person with anorexia, a detailed evaluation to exclude depression is mandatory. Iatrogenic anorexia should also be considered. Several drugs in common use may cause symptoms of gastrointestinal distress, such as nausea, vomiting, and anorexia. Psychotropic drugs and sedatives can interfere with food availability and preparation by inducing excessive somnolence or psychomotor retardation. Recreational drug use may also be relevant. The link between alcoholism and undernutrition is well established. Older persons may not readily admit to alcohol abuse on initial evaluation. The CAGE screening questionnaire for alcohol abuse has been shown to be fairly sensitive and specific in identifying persons dependent on alcohol, and should be administered routinely during nutritional evaluation (Bush, Shaw, Cleary, Delbanco, & Aronson, 1987) (see Table 6.8). Cigarette smoking may also be detrimental to nutritional status as animal studies suggest that prolonged exposure to nicotine may result in altered taste perception and anorexia. Studies in humans report significant weight gain and an improved appetite following cessation of smoking (Gross & Stitzer, 1989; Millie et al., 1989).

TABLE 6.8 CAGE Questionnaire

A screening tool for problem alcohol drinking.

1. Have you ever considered **C**utting down your alcohol intake?
2. Do you get **A**nnoyed when people refer to your alcohol habits?
3. Do you feel **G**uilty about the amount of alcohol you drink?
4. Do you ever drink alcohol as an **E**ye–opener, first thing in the morning?

More than two questions answered in the affirmative is indicative of problem alcohol drinking.

A detailed nutritional history is an essential component of management, as older persons are often on medically prescribed or self-imposed dietary restrictions. In the absence of proper dietary counseling, strict compliance with low salt or low cholesterol diets may compromise the intake of other essential dietary nutrients. The benefits of such diets in the older person remain open to question. Recent studies have shown that a low cholesterol diet in persons over the age of 70 years is ineffective as primary protection against atherosclerotic heart disease (Krumholz, Seeman, & Merrill, 1994)

Defective nutrient utilization resulting from diseases such as diabetes mellitus, chronic liver disease, and malabsorption may precipitate undernutrition in the face of adequate food intake. Hypermetabolic states, as occurs in hyperthyroidism or phaechromocytoma, may result in PEU if nutritional intake is unable to compensate for the increase in energy utilization.

The occurrence of weight loss and undernutrition in several clinical situations is often multifactorial. The term "pink puffer" provides a graphic description of a subgroup of patients with chronic obstructive pulmonary disease who strive to maintain normal arterial oxygen saturation at the expense of a significant increase in respiratory effort. The resultant increase in oxygen consumption and energy expenditure provide a ready explanation for their *asthenic habitus,* traditionally considered to be one of their defining characteristics (Hofford et al., 1990). Indeed, studies have identified a positive correlation between resting energy expenditure, severity of pulmonary hyperinflation, and undernutrition in patients with pulmonary emphysema (Yoneda et al., 1992) Furthermore, the effort of eating has been found to precipitate a reduction in oxygen saturation and exacerbate breathlessness in patients with chronic obstructive pulmonary disease. This may induce a reluctance to indulge in meals and adversely affect nutritional status.

Patients with longstanding cardiac failure constitute another group of patients for whom nutritional evaluation and intervention may be beneficial. Cardiac cachexia describes marked weight loss associated with chronic biventricular cardiac failure. This has been attributed to reduced synthesis and increased degradation of muscle protein (Morrison, Gibson, & Rennie, 1988). Various pathophysiological mechanisms have been proffered as explanations. These include a reduction in skeletal blood flow with resultant cellular hypoxia and disuse atrophy due to immobility (Gibson et al., 1987; Wilson, Martin, Schwartz, & Ferraro, 1984). Elevated circulating concentrations of tumor necrosis factor (TNF) have been found in patients with cardiac cachexia (Bentler & Cerami, 1987). TNF has been shown to induce accelerated catabolism experimentally and may thus play a significant role in the pathogenesis of severe weight loss in cardiac failure. Nutritional intake may be compromised by anorexia related to hepatic congestion, hypoxia, or medication (Ansari, 1987; Berkowitz, Croll, & Likoff, 1963). Protein-losing enteropathy and gut hypomotility are recognized complications of cardiac failure and may lead to increased weight loss by reducing nutrient assimilation (Davidson, 1961; Hakkila, Makala, & Goodman, 1960). The significantly reduced calorie intake in this group of patients is insufficient to match the increased energy requirements resulting from an elevation in myocardial oxygen consumption and an increase in the metabolic cost of respiration (Ansari, 1987). Dietary manipulation directed toward fulfilling the caloric requirements and the provision of adequate essential nutrients contribute notably to reversal of cardiac cachexia (Morrison & Edwards, 1991).

Significant weight loss in the older person justifiably raises the suspicion of an occult malignancy. The etiology of weight loss in neoplastic disease remains uncertain. Zinc deficiency associated with several malignancies has been shown to cause anorexia and ageusia and may result in weight loss. Increased production of potent anorectic agents such as cachectin, bombesin, and interleukins have been noted in patients with cancer (Moody, Pert, Gazdar, Carney, & Minna, 1981; Mordes & Rossini, 1981; Morley & Levine, 1981; Morley, Levine, & Kneip, 1982). Studies have identified neoplastic disease as the etiological factor in fewer than 20% of older persons with significant weight loss (Morley, 1986). The possibility of an underlying malignancy should not, therefore, permit the development of undue pessimism on the part of the physician as this may interfere with aggressive intervention and management.

TABLE 6.9 MEALS ON WHEELS: Common Causes of Undernutrition in Older Persons

Medication (e.g., digoxin, theophylline, psychotropics)
Emotional (depression)
Anorexia/Alcoholism
Late-life paranoia
Swallowing disorders
Oral and dental disease
No money (absolute or relative poverty)
Wandering (dementia/behavioral disorders)
Hyperthyroidism/hyperparathyroidism
Entry problems
Eating problems
Low salt or low cholesterol diets
Shopping and food preparation problems

Proper management of the older person with undernutrition mandates early correction of readily reversible causes of undernutrition. Such factors are often clearly evident following a focused interview with the patient or primary caregivers. As a practical aid to effective history taking, Morley has developed a helpful mnemonic known by the acronym "Meals on Wheels" (see Table 6.9). This provides a quick screen for common causes of PEM which are readily amenable to intervention.

NUTRITIONAL SUPPORT

Justification for the aggressive management of undernutrition is found in several studies which clearly demonstrate an improvement in outcomes, following nutritional therapeutic intervention. Early nutritional support has been shown to improve wound healing, maintain gut integrity, and improve nitrogen balance. Gut bacterial translocation and cytokine release are inhibited, thus reducing the incidence of infections. A reduction in the secretion of hypercatabolic counterregulatory hormones has also been noted with improved nutrition (Collins & McCarthy, 1979; Haydock & Hill, 1987; Nasrallah, 1980; Windsor, Knight, & Hill, 1988). Nutritional repletion has been shown to stimulate gut mucosal growth factors and result in an increase in DNA content (Friedel & Levine, 1992; Kripke, Fox, Berman,

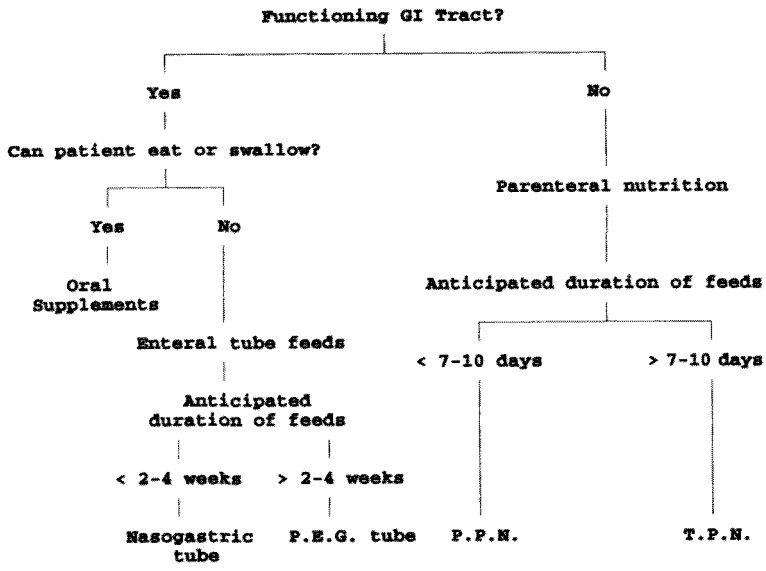

FIGURE 6.1 Dietary supplementation in undernutrition.

Settle, & Rombeau, 1989; Zaloga, Ward, & Priellipp, 1991). These factors may translate into the notable reduction in the length of hospital stay reported in those patients who receive adequate nutritional maintenance. In spite of these findings, nutritional support of the undernourished older patient remains inadequate, as therapy is often restricted to medical management of the underlying cause. Specific indications for various nutritional intervention strategies, relevant to the older person, remain unclear and poorly defined (see Figure 6.1). Regardless of the underlying state of health, nutritional evaluation and support should be routinely included in the overall management plan of the older person.

Oral nutritional supplementation

For patients who are able to eat the required daily allowances of all nutrients, appropriate meals comprising normal food items are preferred. The recommended daily intake of macronutrients in older persons has not been established. The U.S. Food, Drug, and Nutrition Board (FDNB), The Food and Agriculture Organization (FAO), and the World Health Organization

(WHO) all have failed to provide age-adjusted values (Joint FAO/WHO expert committee report,1973).

Predictive equations, which adjust for age, sex, body mass, and level of activity, may be used in estimating daily caloric requirements (Alpers, Clouse, & Stenson, 1983). However, the accuracy of such equations in older persons is unknown. For practical clinical purposes, a caloric intake of 35kcal/kg of ideal body weight should fulfill the energy requirements of most undernourished older persons (Lipschitz, 1982). Starvation and hypercatabolic states may necessitate the consumption of two to three times the recommended daily allowance of essential nutrients (Heymsfield, Bethel, Ansley, Nixon, & Rudman, 1979).

Difficulty with mastication or deglutition may warrant alteration of the consistency of meals and in some cases pureed meals may be necessary. Dietary compliance may be encouraged in anorectic persons by incorporating individual dietary preferences into meals. Socialization during meals and attempts to enhance the aesthetic qualities and palatability of meals may also increase food intake. For patients who are unable to eat the required amount of food, oral nutritional supplements are indicated. A wide variety of preparations are available for use in isolated or multiple nutrient deficiencies. Specific preparations also exist to cope with patients who may have special nutritional needs such as undernourished patients with diabetes mellitus, chronic renal failure, or severe chronic pulmonary disease. Ideally, the use of oral nutritional supplements should be temporary, as sensory-specific satiety may develop rapidly with these preparations and interfere with subsequent compliance (Bernard, Jacobs, & Rombeau, 1986).

Enteral tube feeding

Alternative methods of nutrient delivery are required for persons who are unable to eat or swallow. In the presence of a functioning gastrointestinal tract, enteral feeding is preferred to parenteral feeding. Advantages of enteral tube feeding include a lower incidence of infections and metabolic complications, increased cost-effectiveness, ease of administration and more efficient nutrient utilization (Adams et al.,1986; Kudsk et al., 1992; Moore, Moore, Jones, McCroskey, & Peterson, 1989; Peterson et al., 1988). Furthermore, prolonged total parenteral nutrition has been shown to result in small bowel hypoplasia and alterations in gastrointestinal secretion.

Nasogastric (NG) or nasoenteric (NE) tubes are best utilized for short–term nutritional support only, as significant morbidity is associated with

TABLE 6.10 Complications of Nutritional Intervention

Enteral tube placement
- Nasal/pharyngeal trauma
- Malposition/dislodgement of tube
- Gastroesophageal erosions
- Aspiration pneumonia
- Pneumothorax
- Viscus perforation
- Gastroesophageal reflux

Enteral/Parenteral supplementation
- Fluid overload
- Dehydration
- Respiratory/Circulatory failure
- Disordered glucose metabolism
- Electrolyte imbalance—Na, K, Mg, Ca, P
- Elevated liver enzymes

Parenteral nutrient delivery
- Hemorrhage from intravenous placement site
- Local infection/septicemia
- Air embolism
- Hepatic disease
- Metabolic bone disease
- Fatty acids deficiencies
- Trace element deficiencies

prolonged use of NG or NE tubes (see Table 6.10). Reported complication rates range from 7.6%–19%. Studies have demonstrated a one-year mortality rate as high as 40% among tube-fed older nursing home residents (Ciocon, Silverstone, Graver, & Foley, 1988). Advancing age has been shown to be a major risk factor for pulmonary aspiration among tube-fed patients (Mullan, Roubenoff, & Roubenoff, 1992). When nasal feeding tubes are inserted in older persons, thin flexible tubes are preferred, as these are often more comfortable and cause less distortion of the gastroesophageal sphincter. The risk of significant reflux and subsequent aspiration is thus notably reduced (Forlaw & Guenter, 1990). In most persons, nasogastric tube placement is considered more appropriate as physiological gastric emptying mechanisms and subsequent gastrointestinal nutrient transit are undisturbed. In persons with gastric atony, proximal intestinal fistulas, or severe gastric reflux and a high attendant risk of aspiration, NE tube placement should be utilized. Nasoenteric placement is also preferred in patients in whom pancreatobiliary stimulation would be undesirable, as gastrin and cholecystokinin secretion is notably reduced by avoiding nutrient passage through the stomach (Bodoky, Horsanyi, Pap, Tihanyi, & Flauther, 1991; Kellum, Holland, & McNeill, 1988). The postpyloric position of NE tubes mandates slow, continuous infusion of feeds

to allow for efficient digestion and absorption of nutrients. Contraindications to the use of NG or NE tubes include intestinal obstruction, paralytic ileus, recurrent gastrointestinal hemorrhage and severe gastrointestinal obstruction.

In persons in whom it is anticipated that oral intake of food may not be possible over a prolonged period, placement of gastrostomy or jejunostomy tubes may be indicated. Currently, endoscopic percutaneous techniques are employed, eliminating or minimizing the need for anesthesia.

Enteral formulas

Several enteral nutritional formulas of varying composition are available. The underlying disease state and the digestive and absorptive capacity of the gastrointestinal tract are crucial factors in selection of the appropriate formula. In patients who retain normal gastrointestinal function, pureed meals may be delivered through large bore tubes. Polymeric formulas are available, composed of macronutrients, but of lower viscosity and thus suitable for delivery through smaller bore tubes which are more comfortable. In persons with malabsorption associated with chronic intestinal inflammation or pancreatobiliary disease, formulas containing predigested macronutrients are better tolerated. Specific formulations exist for patients who may have special nutritional requirements as a result of underlying disease.

Enteral formulas may also be categorized on the basis of protein content. Standard formulas containing 11%–15% of protein will suffice for patients with normal protein requirements. For patients who require protein restriction, low protein formulas which contain less than 10% of protein may be used.

Acutely stressed patients are often in a hypercatabolic state, thus high protein formulas (15% protein) should be utilized in such patients. A further consideration in such patients is the precipitous reduction in the synthesis of certain amino acids, notably glutamine and arginine. This effectively transforms them into essential amino acids (Daly et al., 1992; Lacy & Wilmore, 1990). Studies have highlighted the importance of glutamine in the maintenance of normal gastrointestinal function and the prevention of bacterial translocation (Souba et al., 1990). Arginine is important in the preservation of cellular immunity and collagen synthesis (Barbul, 1986). Branched chain amino acids, which play a central role in acheiving positive nitrogen balance, are also depleted during acute stress (Cerra,

Blackburn, Hirsch, Mullen, & Luther, 1987). Adequate repletion of these amino acids should constitute a goal of nutritional therapy.

Mode of feeding

In older persons bolus tube feedings may increase the risk of aspiration, as a result of the large volume of gastric residue which may be associated with this method. Continuous infusions are therefore preferred. This may be maintained over 24 hours or administered as cycled continuous infusions, over 14–18 hours only, providing a feed-free break within each 24–hour period. The relative superiority of either method has not been ascertained, however continuous cyclic feeding appears to mimic normal feeding patterns more closely. Furthermore, failure to provide a nocturnal feed-free period has been shown to obliterate the normal physiological variations in cortisol, insulin, and glucagon secretion (Saito, Nishimura, & Kato, 1989). This may adversely affect subsequent metabolic processes. As gastric emptying has been shown to exhibit a circadian rhythm, with an increased rate during the day, maximal nutrient utilization will be encouraged by feeding during this period (Goo, Moore, Greenberg, & Alazraki, 1987). In addition to these physiological benefits, cyclic continuous infusion of feeds during the day may reduce the risk of nocturnal aspiration and is also more easily integrated into the overall schedule of patient care.

Infusion of feeds is usually initiated at a rate of 50 ml/hour. This may be increased by 25 ml every 8–12 hours, if tolerated by the patient, until the recommended daily caloric intake is achieved. However, there is little evidence to suggest that this initiation regimen is mandatory, and in several cases infusion of feeds may be commenced at the maximal rate. Following prolonged starvation, however, initiation and progression of tube feedings should be gradual, to allow for mucosal regeneration.

Parenteral nutrition

In persons with severely compromised enteric absorptive capacity anticipated to exceed 1–2 weeks, intravenous infusion of nutrients may be necessary. Parenteral nutrition should be avoided in the presence of a functioning gastrointestinal tract. Ideally, infusion should be through a large central vein. Standard Total Parenteral Nutrition (TPN) formulations, made

up of 25% dextrose and 5% amino acids, electrolytes, and various trace elements, may be utilized for the vast majority of persons. Lipid emulsion supplements may be added to prevent deficiency of essential fatty acids during prolonged parenteral nutrition. For persons with special nutritional needs, appropriate modifications may be made.

For short-term administration of parenteral feeds, peripheral venous access may be employed. Low osmolality solutions which are less irritant are available for peripheral infusion. In hospitalized older persons undergoing several investigations which may necessitate withholding oral feeds, our experience suggests that peripheral parenteral nutrition may be necessary to ensure adequate nutritional maintenance, especially if their baseline serum albumin level is below 3.5g/dl.

Pharmacological adjuncts in the treatment of PCU (see Table 6.11)

Several studies have explored the role of a variety of anabolic growth factors in the treatment of undernourished patients. Theoretically these factors should promote nitrogen retention and increase lean body mass. A reduction in serum growth hormone, a recognized potent anabolic agent, has been shown to occur with aging. This has been proffered as a possible cause of age–related muscle wasting and osteopenia. Animal studies also suggest that anorexia may result from growth hormone deficiency. Short–term growth hormone administration has been shown to improve nitrogen retention in healthy older persons, with a demonstrable increase in lean body mass and skin thickness. Rudman, Feller, and Nagraj (1990) studied the effect of the administration of human growth hormone to healthy older men over the age of 60 years, with subnormal baseline plasma IGF–1 levels reflecting declining activity of endogenous growth hormone. They identified a significant increase in lean body mass, adipose tissue, and lumbar vertebral bone density (Rudman, Teller, & Nagraj, 1990). No adverse effects were recorded during the first six months of therapy. However, continuous therapy over an 18-month period resulted in a notable incidence of adverse reactions, the most common of which were carpal tunnel syndrome, gynecomastia, and hyperglycemia (Cohn, Feller, Draper, Rudman, & Rudman, 1993).

In contrast to earlier studies, Kaiser, Silver, and Morley (1991) examined the effect of short-term growth hormone therapy in older persons with involuntary weight loss of undetermined etiology. They demonstrated a sig-

TABLE 6.11 Pharmacological Adjuncts in the Treatment of Undernutrition

- Growth hormone
- Insulin–like growth factor
- Anabolic steroids
- Megesterol acetate
- Prednisolone
- Cyproheptadine
- Cannabinoids
- Epidermal growth factor

nificant reduction in urinary nitrogen excretion during a 3-week course of growth hormone therapy. There was also a significant increase in weight, mid-arm muscle circumference, and a nonsignificant trend to suggest an improved appetite in treated persons. There were no adverse effects noted during the course of the study. These findings suggest that short-term growth hormone therapy may be of therapeutic value in the management of older undernourished persons, especially in the absence of clearly defined underlying cause. However, in the absence of data pertaining to the safety and efficacy of long-term administration of growth hormone, this cannot be recommended for routine use.

The anabolic properties of androgenic steroids and related compounds are well recognized. However, their therapeutic potential and clinical utility in undernutrition remains ill-defined despite the results of numerous trials. The most consistent finding would appear to be an improvement in serum or urine nitrogen parameters. Further interpretation of the available literature as regards to clinical parameters and positive patient outcomes is confounded by the variety of steroids and nutritional supplements used as treatment modalities. Furthermore, only a few studies involved adequate patient numbers. These, however, suggest that steroids such as nandrolone decanoate and stanozol may be beneficial only in undernourished persons on an inadequate diet. The clinical applicability of androgenic and other anabolic steroids remains questionable, as the significant adverse effect profile of steroid therapy may significantly outweigh any benefits derived from its use in undernutrition.

A relative deficiency of Insulin Growth Factor–1 is thought to contribute to the muscle wasting which occurs in several catabolic states, such as severe sepsis and undernutrition. Animal studies suggest that in such cases, the administration of exogenous IGF–1 may enhance nitrogen re-

tention and gluconeogenesis. Further studies also indicate that IGF–1 may play a significant role in restoring and maintaining normal gastrointestinal mucosal function.

Several other pharmacological strategies have been utilized in the treatment of undernutrition. These include corticosteroids, cannabinoids, cyproheptadine, and megesterol acetate. Only the latter has consistently proved to be relatively effective and well tolerated. Megesterol acetate has been shown to be a strong appetite stimulant, increasing the palatability and the hedonic qualities of meals. Objective results of megesterol therapy include a significant increase in caloric intake and an increase in lean body mass (Loprinzi, Schaid, Dose, Burnham, & Jensen, 1993; Skarlos et al.,1993). The clinical use of megesterol acetate is currently restricted to younger persons with the acquired immune deficiency syndrome (AIDS) or malignant disease. The effects in older persons remain unknown.

It is strikingly apparent that an impressive array of therapeutic options exists for the treatment of PEU. Improved methods of nutrient delivery and the availability of a wide variety of nutritional supplements have made a positive impact on the treatment of PEU. Currently, there is limited data to confirm that these therapeutic interventional strategies translate into improved outcomes. Further research is required in this area. In the interim, it may prove equally beneficial and definitely more cost-effective to develop preventive interventional strategies aimed at improving physician and patient awareness of PEU and emphasizing the importance of optimal nutritional maintenance in the older person.

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CHAPTER 7

Vitamins and Aging

LARRY E. JOHNSON
DEPARTMENT OF FAMILY MEDICINE
UNIVERSITY OF CINCINNATI MEDICAL CENTER

Vitamin requirements in older persons have traditionally been considered to be the same or less than those of younger adults. Data now suggests, however, that many vitamin needs increase with advancing age (Russell & Suter, 1993). The controversy is confounded by the fact that there are few large studies of vitamin requirements in the elderly.

The elderly comprise a heterogeneous group, in which chronological and biological age are often disparate; whether it is possible to incorporate this variability into broadly useful recommendations for vitamin requirements remains unclear. The latest Recommended Dietary Allowances (RDAs), published in 1989, include, as have earlier editions, all persons above 51 years of age as one category (Table 7.1) (Food and Nutrition Board, 1989). In addition, certain medical problems become more common with age. If vitamin needs are affected by these common problems, perhaps recommendations regarding vitamin requirements should be tailored to individual risk factors and disease states rather than to age categories alone.

A number of countries have made recommendations for vitamin intakes for people as old as 90 years (Wahlqvist & Flint-Richter, 1989). These tend to be extrapolations from what is known about younger persons and are educated estimates rather than based on scientific measurements.

It is also difficult to apply the RDAs in clinical practice. The RDAs are the amounts of essential nutrients, including vitamins, considered adequate to meet the known needs of most healthy persons (Food and Nutrition Board, 1989). The RDAs are designed as guides, not goals, since many of the estimates for nutrient requirements, particularly for the elderly, are based on limited data. In addition, many factors influence vitamin requirements for any specific individual.

The purpose of defining "nutrient needs" should go beyond preventing

TABLE 7.1 Recommended Dietary Allowances (RDAs) for Vitamin Intake in the Elderly (Over Age 51) (Food and Nutrition Board, 1989).

	RDA	
	Men	**Women**
Fat-soluble vitamins		
Vitamin A (retinol)	1,000 mcg[a]	800 mcg[a]
Vitamin D	5 mcg[b]	5 mcg[b]
Vitamin E (tocopherol)	10 mg[c]	8 mg[c]
Vitamin K	80 mcg	65 mcg
Water-soluble vitamins		
Vitamin B_1 (thiamin)	1.2 mg	1.0 mg
Vitamin B_2 (riboflavin)	1.4 mg	1.2 mg
Vitamin B_6 (pyridoxine)	2.0 mg	1.6 mg
Vitamin B_{12} (cobalamin)	2.0 mcg	2.0 mcg
Folic acid (folacin)	200 mcg	180 mcg
Niacin	15 mg[d]	13 mg[d]
Biotin	30–100 mcg	30–100 mcg
Pantothenic acid	4–7 mg	4–7 mg
Vitamin C (ascorbic acid)	60 mg	60 mg

[a]As retinol equivalents (1 RE = 1 mcg retinol or 6 mcg beta-carotene or 3.33 IU).
[b]As cholecalciferol (5 mcg cholecalciferol = 200 IU vitamin D).
[c]As alpha-tocopherol equivalents (1 alpha-TE = 1 mg d-alpha-tocopherol).
[d]As niacin equivalents (1 NE = 1 mg niacin = 60 mg dietary tryptophan).

classic deficiency states like scurvy, pellagra, and beriberi, and include the goal of maximizing health. As one example, the vitamin C requirements to prevent scurvy are about 10 mg a day, and the RDA is set at 60 mg. However, epidemiologic data suggest that intakes eight times the RDA are associated with least risk for cataract formation (Robertson, Donner, & Trevithick, 1991). While future RDAs may address the issue that some vitamins have beneficial functions at intakes far above the current RDAs, one cannot be constrained by the current RDAs when addressing health promotion and disease prevention (Schneider, Vining, Hadley, & Farnham, 1986).

Vitamin deficiency is common in the frail elderly. Yet why are vitamin deficiencies poorly recognized? First, industrialized societies have successfully reduced classic deficiency diseases. Many of these severe deficiencies were characterized by easily recognized histories and physical findings, and they occurred at all ages. These severe deficiency states are now relatively uncommon in the United States, and both physicians and lay per-

sons no longer think of their possibility. In addition, nutritional deficiencies mimic or are masked by common age-associated comorbidity. Weakness, bone pain, skin disorders, cheilosis, frequent infections, weight loss, and failure to thrive are manifestations of both vitamin undernutrition and many common disease states. Finally, except for vitamin B_{12} and folate, current laboratory tests are generally expensive, unavailable, or insensitive in detecting vitamin deficiencies. A high degree of suspicion is necessary to detect and treat vitamin deficiencies before the damage becomes irreversible.

VITAMIN DISORDERS ASSOCIATED WITH GENERAL UNDERNUTRITION: THE B-VITAMINS—THIAMIN (B_1), RIBOFLAVIN (B_2), PYRIDOXINE (B_6), AND NIACIN

Undernutrition is common in many high-risk elderly populations (O'Hanlon & Kohrs, 1978). Characteristics that increase the likelihood of deficiency are listed in Table 7.2. Mnemonics such as MEALS ON WHEELS (see chapter 6) can be helpful in remembering risk factors. Inadequate intake of the water-soluble vitamins is commonly found in many nutrition surveys, particularly in the poor, institutionalized, or alcoholic elderly. In addition, thyroid disease and diabetes mellitus increase the risk of certain vitamin deficiencies (Cooperman & Lopez, 1991). Healthy, community-dwelling, middle-class Americans should be least likely to develop a water-soluble vitamin deficiency, but even 5%–10% of this low-risk group consume deficient amounts of the B-vitamins (Garry, Goodwin, Hunt, Hooper, & Leonard, 1982). Unfortunately, simple, readily available blood tests for most vitamins are not available, and *serum* vitamin levels may not reflect the more clinically relevant *tissue* stores. Abnormal levels can also be nonspecific (e.g., elevated homocysteine can reflect pyridoxine deficiency but more commonly is caused by vitamin B_{12} or folate deficiency). As better metabolic markers for subclinical deficiency become more widely available and cheaper, new risk categories may become apparent and more deficiencies detected.

General undernutrition will eventually affect all vitamins, though water-soluble vitamins and those with reduced reserves will become deficient first. In general, vitamin C and the B vitamins (including folic acid) can become deficient over weeks to months, while the fat-soluble vitamins (A, D, E, and K) and those with an efficient enterohepatic circulation and

TABLE 7.2 Common Factors Causing Vitamin Deficiencies in the Elderly

Social/Psychologic
Social isolation and loss of conjugate meals
Depression
Unable to drive or walk to the market
Hidden alcoholism
"Instant bachelors" who have never learned to buy, store, or cook food
Finicky eaters
Elder abuse and neglect
Inadequate assistance with eating
Poverty
Physical
Decreased calorie requirements and food intake
Decreased taste or olfactory sensation
Dentures: poorly fitting, painful; decreased taste and swallowing
Poor dental hygiene
Physical handicaps and decreased mobility
Neurologic impairments of chewing and swallowing (e.g., stroke, Parkinson's disease)
Memory and attention disorders (e.g., dementia, psychosis)
Chronic disease (e.g., chronic lung disease, congestive heart failure)
Atrophic gastritis
Intestinal motility disorders (e.g., constipation, gastroparesis)
Negative reinforcers of food intake: hiatal hernia, reflux, lactose intolerance, exertional hypoxia, intestinal angina
Medications (prescription and nonprescription): digoxin, fluoxetine, laxatives, antacids, diuretics, chemotherapy, anticonvulsants, antibiotics
Increased requirements (e.g., hypermetabolic states, smoking)

Source: From Johnson, L.E. (1995).

stores, such as vitamin B_{12}, require longer periods of deprivation to become affected.

Classic deficiencies of thiamin (beriberi) and niacin (pellagra) are rare in the United States. This rarity contributes to their common misdiagnosis when they do occur because most physicians have never seen them. Subtle riboflavin, pyridoxine, and niacin deficiencies can be associated with oral signs and symptoms, such as sore mouth (stomatitis), cracking

at the corners of the mouth (angular cheilosis), and dermatitis, as well as peripheral neuropathy, vague mental status changes, and a superficial ocular keratitis. These nonspecific signs and symptoms are also commonly associated with aging comorbidities and it is unknown what proportion are primarily due to vitamin deficiencies. Vitamin deficiencies are associated with impaired immunocompetence, perhaps contributing to infections that are common in the frail elderly (Chandra, 1991). Deficiency of one B-vitamin can also affect others. For example, severe riboflavin deficiency reduces both the metabolism of pyridoxine and the conversion of tryptophan to niacin (McCormick, 1989).

Pyridoxine metabolism and bioavailabilty are affected by over 40 drugs, including estrogen, isoniazid, carbidopa, hydralazine, cycloserine, and penicillamine; patients on these drugs may benefit from supplementation. Pyridoxine deficiency can interfere with immunocompetence by impairing interleukin-2 production and lymphocyte proliferation (Meydani et al., 1991). High doses of pyridoxine (50–200 mg) may have an anti-emetic effect as well as a role in treating carpal tunnel syndrome, depression, and narcotic addiction (Bender, 1992). A sensory neuropathy and ataxia can occur at prolonged daily doses of 100 mg although most reports of toxicity occur at 2–7 g/d. In addition, pyridoxine can increase the peripheral decarboxylation of levodopa and thus reduce its effectiveness as a treatment for Parkinson's disease. It may also decrease the anticonvulsant effect of phenytoin.

High doses of nicotinic acid (but not nicotinamide) can produce uncomfortable facial flushing. Nicotinic acid may also raise uric acid (aggravating gout), elevate blood sugar (diabetes mellitus), or cause liver toxicity. Large doses, however, have been successfully used to reduce serum lipids. There is little toxicity associated with high-dose thiamin or riboflavin intakes.

Absorption or metabolism of most water-soluble vitamins does not change markedly with age. Atrophic gastritis with hypochlorhydria, occurring in 15%–45% of persons over the age of 65 years, can impair the release of pyridoxine and folate from food, but this malabsorption may be balanced by increased bacterial synthesis of these vitamins following overgrowth of bacteria in the upper gastrointestinal tract that takes place when stomach juices are less acidic. Hypochlorhydria also decreases vitamin B_{12} bioavailability, as well as calcium and iron absorption.

Isolated B-vitamin deficiencies are uncommon in the elderly, except for thiamin deficiency in alcoholics and pyridoxine deficiency resulting from

specific antagonists, and generally the B-vitamins should be replaced together. Effectiveness of simple multivitamin supplementation in the frail elderly remains unknown (Baker, Frank, & Jaslow, 1980; Mann, Garry, Hunt, Owen, & Goodwin, 1987). Aggressively attacking the underlying causes of undernutrition must be a priority (Table 7.2), often requiring social service intervention as well as diligently searching for depression and alcohol abuse. Patients must be followed closely for noncompliance, and a heightened awareness maintained because of the poor specificity of physical signs and symptoms.

VITAMIN B_{12} AND FOLIC ACID METABOLISM

Vitamin B_{12}

Vitamin B_{12} (or cobalamin) is bound to animal protein such as meat, fish, shellfish, and eggs, as well as associated with some plant products due to microorganism contamination. It is released from food by the action of acid and digestive enzymes, and attaches to R-binding proteins found in gastric juices and saliva. Pancreatic enzymes degrade the R-proteins to allow intrinsic factor (IF), made by the stomach's parietal cells, to bind to vitamin B_{12}.

The vitamin B_{12}-IF complex continues down the intestine and attaches to receptors in the terminal small bowel. Vitamin B_{12} passes through the bowel wall, and then throughout the body, attached to the transport protein, transcobalamin II (the combined vitamin B_{12}-transport molecule is called holotranscobalamin II). The liver is the major storage site for vitamin B_{12}.

Causes of Deficiency

Vitamin B_{12} lost in the bile is efficiently recovered via the enterohepatic cycle. This recycling is so efficient that the half-life of vitamin B_{12} is approximately four years in the presence of a normal gastrointestinal tract and large liver reserves. Thus, vitamin B_{12} deficiency secondary to inadequate intake takes from 2–6 years to develop. Vegetarians who consume little or no animal proteins should be monitored periodically for deficiency and counselled appropriately (Lowik, Schrijver, Odink, van den Berg, &

Wedel, 1990; Miller, Specker, Ho, & Norman, 1991). Interfering with the enterohepatic cycle or distal absorption will increase the rate that deficiency develops.

Estimates of the true prevalence of cobalamin deficiency in the elderly range from 3%–44% (Lindenbaum, Rosenberg, Wilson, Stabler, & Allen, 1994). Most vitamin B_{12} deficiency in elderly persons is probably due to atrophic gastritis rather than pernicious anemia (Pennypacker et al., 1992).

Prolonged use of gastric antacids, histamine (H_2)-receptor antagonists, and omeprazole can decrease absorption of protein-bound vitamin B_{12}, particularly in those marginally nourished, due to a decrease in stomach acidity as well as IF inhibition (Festen, 1991). Other causes of vitamin B_{12} malabsorption include pancreatic insufficiency, bacterial overgrowth (which can also result from hypoacidity), parasitic infections within the intestine, and any disease affecting the distal small bowel. Elderly persons with AIDS may have vitamin B_{12} deficiency due to gastritis or small bowel enteropathy, decreased holotranscobalamin II receptors on certain tissues, or as a result of AZT (Zidovudine) toxicity (Herbert, Fong, Gulle, & Stopler, 1990; Kieburtz, Giang, Schiffer, & Vakil, 1991).

The Schilling test may be used to detect malabsorption of vitamin B_{12} (but not to diagnose deficiency). Errors are common in performing or interpreting the Schilling test in the frail elderly (Fairbanks, Wahner, & Phyliky, 1983). Free vitamin B_{12}, as given in the classic Schilling test, may be easily absorbed, but vitamin B_{12} bound to protein, as it is normally consumed in the diet, may not be available due to inadequate stomach acidity. A modified Schilling test (food Schilling test) using protein-bound cobalamin has been used to more closely mimic normal vitamin B_{12} ingestion (Doscherholmen & Swaim, 1973). Because the Schilling test includes an injection of vitamin B_{12}, all baseline tests should be complete before it is given.

Pathophysiology of Vitamin B_{12} Deficiency

The earliest serum marker of decreased vitamin B_{12} absorption is low holotranscobalamin II (Herzlich & Herbert, 1988). This can precede a decrease in serum vitamin B_{12} by weeks or months. As vitamin B_{12} deficiency progresses, DNA synthesis slows. This is reflected in the dU suppression test (Carmel & Karnaze, 1985) and the presence of hypersegmented nuclei in polymorphonuclear leukocytes (Thompson et al.,

1989). Erythrocyte (RBC) folate and serum vitamin B_{12} levels also begin to fall at this stage, and serum and urine homocysteine and methylmalonic acid (MMA) levels rise (see Figure 7.1, p. 152).

Depletion of vitamin B_{12} may occur more rapidly in one tissue than another, and neurologic damage may not be synchronized with the hematologic changes (Herbert et al., 1990). It is well established that macrocytosis (elevated MCV) and megaloblastic anemia are insensitive and late manifestations of vitamin B_{12} deficiency; they may be absent even in frank pernicious anemia (Allen, Stabler, Savage, & Lindenbaum, 1990; Carmel, Sinow, Siegel, & Samloff, 1988). Neurologic and neuropsychiatric damage may occur before or after hematologic disease because the enzymes that become dysfunctional are not affected at the same rate (Lindenbaum, Savage, Stabler, & Allen, 1990; O Broin, Kelleher, McCann, Ryder, & Scott, 1990).

Severe iron deficiency may mask co-existing vitamin B_{12} and/or folate deficiency, and a combined deficiency may present with *only* a microcytic, hypochromic anemia. Iron deficiency and vitamin B_{12} deficiency often coexist, perhaps due to atrophic gastritis or intravascular hemolysis.

Signs and Symptoms of Vitamin B_{12} Deficiency

The signs and symptoms of vitamin B_{12} deficiency are difficult to distinguish from age-associated comorbidities. Lassitude, exertional dyspnea, and general vague complaints may be present (Pruthi & Tefferi, 1994). A pale, smooth tongue may be more common than a painful, red beefy one. The most common peripheral neurologic symptoms of cobalamin deficiency are paraesthesias (tingling, numbness, pins and needles sensation), usually bilaterally in the feet and/or hands. Some patients also have a gait ataxia and extremity weakness due to corticospinal tract involvement (Healton, Savage, Brust, Garrett, & Lindenbaum, 1991). The combination of peripheral neuropathy with corticospinal tract signs (ataxia) is called subacute combined degeneration (i.e., both dorsal and lateral columns in the spinal cord are affected). Neurologic findings include diminished or absent vibration and/or proprioception sense in the lower extremities. Touch and pain sensation may also be reduced. Patients with the most profound anemias usually have the least neurologic damage, and vice versa. Rarely, the only manifestation of vitamin B_{12} deficiency may be orthostatic hypotension (Lossos & Argov, 1991).

Biochemical Indicators of Vitamin B_{12} Deficiency

While serum radioassays have improved the detection of vitamin B_{12} deficiency, there are troublesome problems with sensitivity and specificity (Carmel, 1990; Joosten et al., 1993; Lindenbaum et al., 1990). Serum vitamin B_{12} is also not a sensitive measure of total body cobalamin, and may be a poor measure of more biologically significant tissue levels (i.e., serum levels can remain normal as tissue levels become depleted). It is estimated that 5%–33% of cobalamin deficient patients have cobalamin levels between 200–300 pg/mL, and that 0.1%–1.0% have cobalamin serum levels above 300 pg/mL, normally considered replete (Lindenbaum et al., 1990; Yao, Yao, Yao, Yao, & Lou, 1992).

Serum vitamin B_{12} levels are currently the most practical and widely available screening tool for cobalamin deficiency. It remains controversial whether advanced age alone should be the sole reason to screen. Vitamin B_{12} deficiency should also be considered in patients being treated for iron deficiency, and for any older patient with peripheral neuropathy, psychopathology, or difficulty ambulating; that is, the threshold for screening should be low (Stabler, Allen, Savage, & Lindenbaum, 1990).

Measurement of MMA or homocysteine may improve the detection of vitamin B_{12} deficiency, and these metabolites may be more sensitive markers for tissue stores, rising before serum cobalamin levels fall. Deficiency of methionine synthetase, due to vitamin B_{12}, folate, or vitamin B_6 (pyridoxine) deficiency, raises homocysteine levels. Deficiency of methylmalonyl CoA mutase, due to vitamin B_{12} deficiency, increases MMA in both serum and urine.

A simplified algorithm is to consider persons with a serum vitamin B_{12} level <200 pg/mL deficient. In deficient persons with a long life expectancy and good quality of life, a "food Schilling test" may be done to determine if the cause is pernicious anemia. Pernicious anemia is specifically associated with an increased risk of gastrointestinal cancers, and an accurate diagnosis would target patients who would need to be followed more closely in the future.

MMA should be measured in persons whose serum cobalamin levels are in the intermediate range of 200–350 pg/mL, as well as *anyone* with compatible neurologic or neuropsychiatric signs or symptoms regardless of his or her cobalamin levels. Assessment of transcobalamin II, perhaps the earliest indicator of deficiency, is not yet readily available. A trial of therapy (parenterally initially) while monitoring MMA or homocysteine

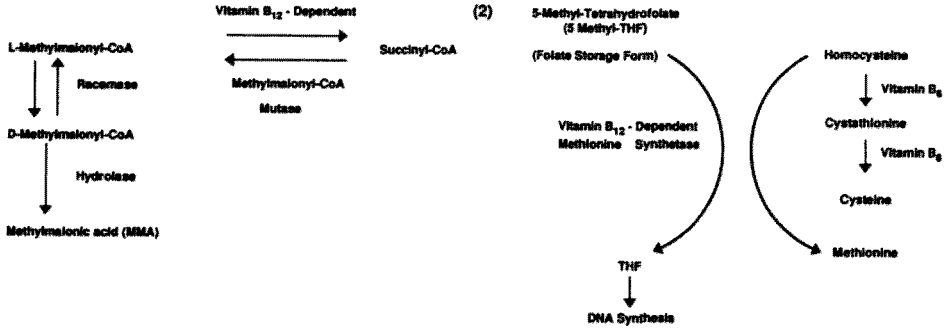

FIGURE 7.1 Metabolic pathways dependent upon vitamin B_{12}, vitamin B_6, and folic acid. Methylmalonic acid (MMA), 5-methyl-THF, and homocysteine accumulate in vitamin B_{12} deficiency. Homocysteine levels also rise in folate and vitamin B_6 deficiencies (see text for details). From Johnson (1995).

metabolic levels in enigmatic cases, is appropriate; elevated levels should fall following therapy in true deficiency states (Allen et al., 1990).

Dementia

The similarities and differences between the neuropsychiatric symptoms associated with vitamin B_{12} deficiency and dementias common in elderly persons can be confusing. Folate deficiency alone probably does not cause a neuropathy or myelopathy despite the fact that the methionine synthetase enzyme is affected. It can, however, induce or worsen neurologic abnormalities in a cobalamin-deficient patient, including those who have recently started cobalamin replacement. Low folate is more commonly a co-existing problem in dementia (Larson, Reifler, Sumi, Canfield, & Chinn, 1986). Any association between vitamin B_{12} deficiency and Alzheimer's disease remains uncertain (Basun, Fratiglioni, & Winblad, 1994; Ikeda et al., 1992).

Delirium, not dementia, may be the mental status change most commonly associated with vitamin B_{12} deficiency (Hector & Burton, 1988). Mental impairment as the *sole* manifestation of cobalamin deficiency is

rare. However, confusion, memory loss, disorientation and bradyphrenia have been shown to improve in patients known to be vitamin B_{12} deficient and these symptoms are hard to distinguish from dementia (Martin, Francis, Protetch, & Huff, 1992; O'Neill & Barber, 1993). Overall, dementia in the elderly is rarely caused by cobalamin deficiency alone (Barry & Moskowitz, 1988; Siu, 1991). Evaluating a dementia patient for vitamin B_{12} deficiency should be based on individual risk factors, the presence of suspicious neurologic or hematologic findings, or the likelihood that the dementia is due to a reversible cause. Persons with low cobalamin levels and cognitive changes suggestive of dementia may show improvement with cobalamin replacement, especially if treatment is begun early (Martin et al., 1992).

The hematologic findings of vitamin B_{12} deficiency and folate deficiency are identical, and folate replacement may improve the hematologic parameters in cobalamin deficiency without reversing the neurologic deterioration. Therefore, it is important to differentiate cobalamin deficiency from folate deficiency. If the two diseases cannot be easily distinguished by serum vitamin levels (remember that vitamin B_{12} deficiency can erroneously increase serum folate and decrease RBC folate), MMA or total homocysteine levels can be helpful. A trial of therapy replacement watching only for improvement in macrocytosis or anemia often is *not* diagnostic and may delay the correct diagnosis.

Treating Vitamin B_{12} Deficiency

Dosing schedules for vitamin B_{12} replacement in cobalamin deficiency are anecdotal. A dietary history should be done on all vitamin B_{12}-deficient patients; the RDA for vitamin B_{12} is 2 micrograms (mcg). Once inadequate intake is ruled out, uncomplicated patients with inadequate absorption should achieve complete remission following a single injection of 100 mcg vitamin B_{12}. Patients with continuing absorption problems will need monthly injections of 100 mcg for life. Patients with multiple or severe coexisting medical problems, evidence of more severe deficiency such as neurologic findings, or those whose symptoms do not completely resolve should have higher initial and/or monthly injections (1000 mcg). Oral vitamin B_{12}, given in large doses (1000–2000 mcg daily), is also usually effective even in the absence of intrinsic factor (Hathcock & Troendle, 1991). There is insufficient experience at this time to determine the role of sub-

lingual or intranasal vitamin B_{12} replacement. Vitamin B_{12} is generally nontoxic even in large doses. This low toxicity, however, does not justify its use as a placebo.

Reticulocytosis, a decrease in nuclear hypersegmentation, or a fall in MMA or homocysteine should occur within 10 days of replacement. Neurologic evidence of response to treatment should be seen within several months (Healton et al., 1991). Nonresponders should be reevaluated for evidence of continued vitamin B_{12} tissue deficiency (reevaluating MMA or homocysteine levels), or for other causes of neuropathy. Recovery depends on the extent and location of the neuropathy and myelopathy. Rapid recovery is most suggestive of remyelination. Axonal recovery can take years with peripheral injury, or may never occur with central nervous system disease. The more severe the neurologic symptoms, or the longer the duration of symptoms and the less anemic the patient, the less complete the response to treatment (Healton et al., 1991). Advanced age itself may also decrease likelihood of complete recovery (Fine & Soria, 1991).

Folate

Folic acid (or folate) is derived from the Latin word for leaf (*folium*). The reason we have the number "12" in vitamin B_{12}, but are missing the lower numbers, is that some of the lower numbers were different forms of folate (Rosenberg, 1990). Folate is present in many foods, and is especially concentrated in spinach, liver, and kidney. About 10% of persons 45–74 years of age in the NHANES II survey had low serum folate levels (Senti & Pilch, 1985). Food folate is degraded by heat and storage, and leached and lost into cooking water.

Pathophysiology of Folate Deficiency

Like most water-soluble vitamins, folate deficiency is commonly linked to general malnutrition and alcohol abuse. Folate, like vitamin B_{12}, is excreted into bile and reabsorbed from the gut in an enterohepatic cycle. Decreased small bowel mucosal transport can reduce folate absorption; this can be caused by various inflammatory diseases in the gut as well as general sepsis, uremia, and the mucosal edema that accompanies congestive heart failure. Alcohol decreases enterohepatic circulation of folate, while

phenytoin both decreases absorption and increases excretion. Zinc deficiency may impair absorption of some forms of folate because an enzyme needed for hydrolysis is zinc-dependent. Folate requirements increase in hereditary spherocytosis and chronic hemolytic anemia, multiple myeloma and other malignancies, renal dialysis, and iron deficiency.

High small bowel pH secondary to stomach hypochlorhydria decreases folate absorption, but this may be compensated for clinically by increased bacterial folate synthesis due to the resulting bacterial overgrowth. Overall, aging has little effect on folate absorption. Folate deficiency may also be due to various drug-nutrient interactions, including nitrous oxide, pyrimethamine, sulfasalazine, cotrimazole, phenytoin, phenobarbital, alcohol, methotrexate, zinc, and pentamidine.

Detection of Folate Deficiency

Low *serum* folate represents negative folate balance, catabolism exceeding absorption, but does not diagnose tissue folate deficiency (Herbert, 1987). An early sign of tissue depletion is a decreasing erythrocyte (RBC) folate and decreasing liver stores, followed by an abnormal dU suppression test (indicating a slowing of DNA synthesis) and hypersegmentation of neutrophil nuclei. Macrocytosis and anemia, as in vitamin B_{12} deficiency, appear late.

Serum folate decreases rapidly when folate intake or absorption decreases. However, because folate accumulates within the RBC during its formation and remains relatively stable for the life of the cell, RBC folate decreases more slowly than serum folate as folate-deficient erythrocytes replace those made prior to deficiency. It therefore may take 2–3 months before RBC folate becomes deficient. Serum folate increases and RBC folate decreases in the presence of coexisting vitamin B_{12} deficiency. RBC folate also increases in the presence of anemia not due to either vitamin B_{12} or folate deficiency. As a screening tool, when diet has not changed dramatically, serum folate is generally sufficient.

Vitamins B_{12}, B_6, and folate each play a role as either coenzymes or substrates in the metabolism of homocysteine (Selhub, Jacques, Wilson, Rush, & Rosenberg, 1993; Stampfer & Willett, 1993). It has been demonstrated from epidemiologic studies that elevated homocysteine is an independent risk factor for vascular disease (Pancharuniti et al., 1994; Stampfer et al., 1992). In fact, the relative risk for cardiovascular disease

associated with hyperhomocysteinemia may be greater than that of smoking or elevated LDL cholesterol (Mason & Miller, 1992). Homocysteine has been postulated to contribute to vascular disease by inhibiting cross-linking during synthesis of elastin and collagen, increasing prostaglandin formation in platelets and blood vessels, activating coagulation factors that may initiate clotting, having a direct cytotoxic effect on blood vessels, and/or participating in the oxidizing damage associated with LDL cholesterol (Ueland & Refsum, 1989).

Vitamin supplementation can reduce moderate hyperhomocysteinemia. Folic acid may have the greatest potential for reducing elevated homocysteine regardless of etiology, perhaps because it serves as a substrate and not merely a coenzyme in remethylation. High doses of folic acid (5 mg daily) decrease plasma homocysteine levels even in patients without obvious folate deficiency (Ueland & Refsum, 1989). Vitamin B_{12} administration appears to reduce homocysteine levels that are elevated only secondary to vitamin B_{12} deficiency, and vitamin B_6 may reduce levels only following eating. It does not appear that serum homocysteine rises *before* serum vitamin B_{12} declines, and an elevated homocysteine level may occur only after moderately advanced vitamin B_{12} deficiency (Hall & Chu, 1990).

In patients with both iron and folate deficiency, the earliest sign that folate is deficient is a subtle increase in hypersegmentation. Otherwise, the signs of iron deficiency may predominate. The dU suppression test will also be abnormal in this mixed deficiency.

Treating Folate Deficiency

The RDA for folate is 200 mcg for men and 180 mcg for women. Folate can be replaced orally from a good diet or by supplementation, usually in combination with other B-vitamins. Folate is generally safe, though in high doses it may mask coexisting vitamin B_{12} deficiency, antagonize anticonvulsant therapy, and interfere with zinc metabolism.

VITAMINS AND BONE METABOLISM

Healthy bone development and maintenance require a correct balance of vitamin D or sunlight exposure; vitamin K; calcium; phosphorus; estrogen, adrenal, parathyroid, and thyroid hormones; fiber; protein; acid-base

status; and life style (physical activity, as well as caffeine, tobacco, and alcohol intake) (Toss, 1992). Healthy kidneys, liver, and gastrointestinal tract are also required.

The most important vitamin in bone metabolism is vitamin D (Parfitt et al., 1982; Reichel, Koeffler, & Norman, 1989). It enables normal bone mineralization, facilitates intestinal calcium and phosphorus absorption, regulates renal reabsorption and homeostasis of amino acids and phosphate, and influences the activity of parathyroid hormone (PTH) on bone and in the kidney. Vitamin D also stimulates both osteoblastic and osteoclastic activity in bone.

Vitamin D has many other roles, and receptors for vitamin D are found in a wide variety of tissues and cells (Reichel et al., 1989). Vitamin D may directly influence beta-cell function in the pancreas and thyroid hormone synthesis, affect cellular proliferation and differentiation of skin (e.g., it may have a role in treatment for psoriasis), participate in a paracrine system affecting macrophage and cytokine and immunoglobulin synthesis by lymphocytes, and modulate muscle function (Collins & Norman, 1991).

Vitamin D Sources

Vitamin D is not plentiful in food: major sources are *fortified* dairy products, fatty fish, eggs, and liver (Haddad, 1992). Dietary intake of these often falls in the aging population; lactose intolerance in some ethnic groups may also play a role. The current RDA for vitamin D in older persons is 200 IU (or 5 mcg) (refer to Table 7.1). Vitamin D may be ingested as ergocalciferol (D_2) or cholecalciferol (D_3), both found in foods and nutritional supplements, or synthesized from 7-dehydrocholesterol to vitamin D_3 in the skin after sun exposure. To become physiologically active, vitamin D must undergo 25-hydroxylation in the liver (calcidiol; 25[OH]D), followed by 1-hydroxylation in the kidneys (calcitriol; $1,25[OH]_2D$).

As intake decreases, endogenous skin production becomes more important (Reid, Gallagher, & Bosworth, 1986; Webb, Pilbeam, Hanafin, & Holick, 1990; Webb & Holick, 1988). The concentration of 7-dehydrocholesterol decreases in the aging epidermis, associated with a decrease in vitamin D synthetic capacity (MacLaughlin & Holick, 1985). Darkly pigmented skin and the use of sunscreens further reduce skin capacity to synthesize vitamin D (Matsuoka, Wortsman, Hanafin, & Holick, 1988). Sunlight exposure may decrease with age, especially in the homebound and institutionalized elderly.

Age-related Bone Loss

Osteopenia is a general term for bone loss, which has many causes. Vitamin D deficiency causes osteomalacia in adults (and rickets in children), manifested as soft and easily deformed bone. The resulting clinical picture is characterized by proximal bone pain, backache, difficulty rising from a chair or climbing stairs, a waddling gait, and decreased mobility because of pain. These are nonspecific signs and symptoms, common in many geriatric syndromes, and often attributed to "rheumatism." There may also be muscle tenderness and weakness as well as anorexia and weight loss. Deficient mineralization is not a direct effect of the lack of vitamin D or its metabolites on bone cells, but rather of a decreased supply of calcium and phosphorus. A deficiency of calcium or phosphate can cause changes identical to those seen in osteomalacia due to vitamin D deficiency.

In contrast to osteomalacia, osteoporosis is associated with a reduction in bony tissue (thinning of the bones), but the bone that remains has a normal mineral content, unlike the soft and poorly mineralized bone in osteomalacia. Osteoporosis and osteomalacia are both common and frequently coexist because of age-associated risk factors. A common feature in both type I (postmenopausal) and type II (senile or old age) osteoporosis is calcium malabsorption, attributable to both decreased vitamin D levels and intestinal unresponsiveness to calcitriol (Lamberg-Allardt, 1991). Type II osteoporosis is associated with (a) decreasing calcidiol levels secondary to decreased sunlight exposure, decreased synthesis when exposed to sunlight, and decreased vitamin D intake; (b) secondary hyperparathyroidism as decreased serum vitamin D levels lead to decreased calcium absorption; (c) age-related decreased production of calcitriol in response to PTH (Slovik, Adams, Neer, Holick, & Potts, 1981); and (d) possibly a decreased number of calcitriol receptors in bone and intestine (Ebeling, Sandgren, DiMagno, DeLuca, & Riggs, 1990; Morris, Need, Horowitz, O'Loughlin, & Nordin, 1991).

Vitamin D Physiology

Vitamin D has different effects depending on whether it is given in vitamin D-depleted (promoting bone mineralization) or replete states (stimulating demineralization) (Lamberg-Allardt, 1991). This contributes to some

of the confusion and contradictions among studies. Much bone metabolism research involves osteoporosis in postmenopausal women who are *not* elderly (i.e., type I osteoporosis). In addition, type II osteoporosis in elderly women may or may not be identical to senile osteoporosis found in elderly men (Drinka & Bauwens, 1987). Trabecular and cortical bone also respond differently to therapy designed to prevent or treat osteoporosis.

The ability to absorb vitamin D from the gastrointestinal tract probably decreases with advanced age (Morris et al., 1991). There is little evidence of an age-related decline in liver 25-hydroxylation, although it is well known that anticonvulsant therapy decreases liver hydroxylation. There is, however, a marked *decrease* in 1-hydroxylation by the aging kidney (Clemens, Zhou, Myles, Endres, & Lindsay, 1986). This reduction may be caused by a decreased responsiveness of the 1-alpha-hydroxylase enzyme to PTH, as well as an overall decline in renal function with age.

Vitamin D also facilitates the action of parathyroid hormone to maintain ionized calcium concentration in its proper and narrow range. The loss of this calcemic action is responsible for the hypocalcemia and secondary hyperparathyroidism associated with vitamin D deficiency. Both calcitriol and calcium repress parathyroid hormone gene expression. Calcium malabsorption may precede hyperparathyroidism in early vitamin D deficiency, and it appears to respond to small doses of calcitriol (0.25–0.5 mcg daily) (Nordin & Morris, 1992).

Calcitriol is the active form of vitamin D. However, serum levels of calcitriol correlate poorly with body stores, clinical disease, parathyroid hormone (PTH) levels, or calcidiol levels. Serum calcitriol levels are unchanged even in advanced age. The most reliable indicator of vitamin D status is the calcidiol (25[OH]D) serum level. Calcidiol levels are often but not always lower in older individuals (Clemens et al., 1986; Holick, 1986). In the future, new serum PTH assays may be the most sensitive markers of vitamin D deficiency (Ashby, Newman, & Rinsler, 1989).

Low calcium intake is common in American women; more than 75% of women over 35 years of age consume less than the RDA of 800 mg. A negative calcium balance causes bone demineralization to maintain proper serum calcium levels. Calcium absorption varies inversely with calcium intake.

Calcium absorption decreases with advancing age for several reasons (Bullamore, Gallagher, Wilkinson, & Nordin, 1970; Heaney et al., 1982). Vitamin D is the main regulator of calcium absorption, and vitamin D receptor concentration in the intestine appears to decrease with age (Ebeling

et al., 1990). The atrophic gastritis and hypochlorhydria common in aging (as well as the use of antacids and histamine (H_2) blockers) decrease solubility of calcium and hence its absorption. The dietary form of calcium is also important (Reid, Ames, Evans, Gamble, & Sharpe, 1993). Soluble calcium sources, such as calcium citrate or calcium from milk, are absorbed normally even if elderly subjects have atrophic gastritis (Wood & Serfaty-Lacrosniere, 1992). Calcium carbonate and calcium phosphate absorption will improve if administered with a meal, even in the presence of atrophic gastritis; calcium citrate absorption improves when taken on an empty stomach. Absorption also improves if not more than 500–600 mg elemental calcium is consumed at one time.

Foods rich in fiber and phytate, healthful in many ways, inhibit calcium absorption, as well as the absorption of zinc and iron. Other lifestyle factors may also affect calcium and bone metabolism (Arnaud & Sanchez, 1990). Immobilization and inactivity can cause rapid bone loss, elevations of serum and urinary calcium, and decreases in PTH, calcitriol, and intestinal calcium absorption. Lifestyle factors often interfere with bone health; for example, smoking, alcohol intake, and caffeine consumption are higher in persons with poor calcium intake (Toss, 1992).

Vitamin D Deficiency

Average vitamin D intake in non-institutionalized elderly in North America and Europe is about 100 IU daily, and rarely exceeds 200 IU (Krall, Sahyoun, Tannenbaum, Dallal, & Dawson-Hughes, 1989). Subclinical vitamin D deficiency may be quite common (Villareal, Civitilli, Chines, & Avioli, 1991). Studies of free-living elderly have found that between 9%–43% have low calcidiol serum levels; prevalence of deficiency ranges from 35% to 90% in hospitalized or institutionalized elderly (Egsmose et al., 1987; Russell & Suter, 1993; Webb et al., 1990). Intake of 220–800 IU vitamin D daily is necessary to prevent elevated production of PTH (Krall et al., 1989; Lips et al., 1987; Parfitt et al., 1982; Webb et al., 1990). However, institutionalized men receiving calcium and vitamin D above the RDA may still develop secondary hyperparathyroidism (McMurtry, Young, Downs, & Adler, 1992). Based on these data, it is felt by many that the current RDA for vitamin D (200 IU) is too low. It has been recommended that elderly persons not regularly exposed to sunlight receive a daily vitamin D supplement of 400 IU *in addition to* their regular diet (Dawson-Hughes, Dallal, Krall, & Harris, 1991; Gloth, Tobin,

Sherman, & Hollis, 1991; Russell & Suter, 1993; O'Dowd, Clemens, Kelsey, & Lindsay, 1993). Biochemical screening with calcium and alkaline phosphatase alone is associated with a high error rate in detecting occult osteomalacia.

Seasonal variation in serum PTH and calcidiol is inversely related in people living in northern latitudes, with decreased vitamin D status in winter months. Wintertime spinal bone loss is found to be reduced, but not eliminated, in postmenopausal women consuming (with supplements) at least 12.5 mcg (500 IU) vitamin D along with enough calcium to assure 800 mg a day (Dawson-Hughes et al., 1991). Persons who appear most responsive to supplementation are those who have been consuming less than 400 mg calcium daily.

A study of very old women (averaging 84 years of age) found that supplementation with 800 IU of vitamin D and 1.2 g of calcium for 18 months slowed bone loss and reduced the incidence of non-vertebral fractures by 30% and hip fractures by 41% (Chapuy et al., 1992). This suggests that even very old women may benefit from supplementation. It is controversial whether increased calcium intake alone can reduce bone loss in postmenopausal women, but older women may benefit, particularly those whose calcium intake is low (Aloia et al., 1994; Barrett-Connor, Chun Chang, & Edelstein, 1994; Elders, et al. 1991; Reid, Ames, Evans, Gamble, & Sharpe, 1993). Support is building for recommending increased intake of calcium (to 1.2–1.5 g daily–significantly higher than the current RDA of 800 mg in postmenopausal women not on estrogen replacement).

The use of vitamin D in osteoporosis focuses on the use of calcitriol in mediating calcium metabolism in doses that do not increase bone resorption (by its calcemic action) but rather reduce it (Nordin & Morris, 1992). Studies comparing 0.5 mcg calcitriol daily versus placebo have shown small increases in spinal density (Gallagher & Goldgar, 1990), not seen with slightly smaller doses (0.4 mcg/d) (Ott & Chesnut, 1989). Calcitriol, and perhaps other vitamin D analogues, can also decrease vertebral fracture rate better than calcium supplementation alone (Orimo, Shiraki, Hayashi, & Nakamura, 1987; Tilyard, Spears, Thomson, & Dovey, 1992). Administration of estrogens to osteoporotic individuals increases calcium absorption by increasing serum calcitriol levels, mediated indirectly through stimulation of renal 1-hydroxylase by PTH (Lamberg-Allardt, 1991). However, a lower calcitriol concentration has been shown to be associated with less bone loss from the spine and wrist in postmenopausal women supplemented with calcium. This suggests that a low serum

calcitriol concentration may be protective in postmenopausal bone loss, at least when calcium is adequate (Lamberg-Allardt, 1991).

Aging and lack of estrogen may also cause peripheral end-organ resistance to calcitriol in intestine and bone. Estrogen therapy, but not short-term use of calcitriol, can correct this abnormality (Gennari, Agnusdei, Nardi, & Civitelli, 1990). Increased serum PTH in the elderly may be necessary for adequate production of calcitriol by aging kidneys, and a reduction in PTH may not always be an appropriate goal in managing type II osteoporosis (Kochersberger, Westlund, & Lyles, 1991).

Vitamin D-fortified milk appears to be a safe and effective method to supply vitamin D to elderly populations (Keane et al., 1992) although there has been some concern that milk fat contributes disproportionately to hyperlipidemia. Coffee-associated osteoporosis may be minimized by drinking at least one cup of milk a day (Barrett-Connor et al., 1994). Vitamin D deficiency can be prevented in high-risk persons (those institutionalized or homebound on marginal diets) by once or twice yearly oral doses of 10,000 to 100,000 IU vitamin D (Weisman et al., 1986) or annual intramuscular injections of 150,000 IU ergocalciferol (Heikinheimo et al., 1991). Thirty minutes of daily sun exposure with head, neck, forearms, and lower legs exposed can significantly increase calcidiol levels in elderly persons (Reid et al., 1986). Direct sunshine is not absolutely essential as UV-B radiation can penetrate light cloud cover fairly well.

Vitamin D Toxicity

Chronic vitamin D ingestion of over 25,000 to 50,000 IU a day may be extremely toxic. Excessive intake causes increased calcium absorption from the intestines and increased calcium mobilization from bone. The resultant hypercalcemia can cause anorexia, weakness, constipation, and soft tissue calcification of the heart (aortic stenosis), blood vessels, lungs, joints, and kidney (leading to renal insufficiency). Elderly persons do face some risk in unmonitored supplementation, especially in the sunny months. Persons with hypercalcemia, parathyroid disorders, and chronic renal insufficiency are at greatest risk. All supplemented persons should have periodic renal and serum calcium assessments made. In general though, careful supplementation is associated with little toxicity (Chapuy, Chapuy, & Meunier, 1987; Freaney, McBrinn, & McKenna, 1993; Honkanen, Alhava, Parviainen, Talasniemi, & Mönkkönen, 1990).

Vitamin K and Bone Metabolism

Vitamin K (from the word "Koagulation") is a cofactor for modifying, by carboxylation, glutamic acid residues to form the calcium-binding amino acid, gamma-carboxyglutamate, often abbreviated to Gla. The best known proteins with Gla-residues are prothrombin and other coagulation factors (Vermeer, Knapen, Jie, & Grobbee, 1992). However, vitamin K depletion that has no effect on blood coagulation (involving hepatic Gla-proteins) can still reduce the Gla-containing extrahepatic protein, osteocalcin (OC) (bone Gla-protein) (Ferland, Sadowski, & O'Brien, 1993; Hauschka, Lian, Cole, & Gundberg, 1989). The RDAs for vitamin K (80 mcg for men and 65 mcg for women) were derived from its role in blood coagulation, not with respect to any role in bone metabolism.

Osteocalcin (OC) is a bone-specific noncollagenous protein containing two or three Gla residues (Vermeer et al., 1992). It is synthesized by osteoblasts, and synthesis is stimulated by calcitriol. After synthesis, osteocalcin moves to the bone matrix and binds to hydroxyapatite. Serum concentrations generally reflect bone turnover rates except in renal failure.

The function of osteocalcin is currently unknown. Serum levels of undercarboxylated osteocalcin (ucOC) increase markedly in women over 70 years of age and correlate strongly with hip fracture risk in frail institutionalized women (unlike other biochemical indices of bone metabolism that have poor predictive value for hip fracture risk) (Szulc, Chapuy, Meunier, & Delmas, 1993). Vitamin K (1 mg/d) can decrease serum ucOC and reduce urinary calcium loss in postmenopausal women (Vermeer et al., 1992). Vitamin K increases calcium absorption—perhaps the vitamin D receptor is a vitamin K-dependent protein. Serum ucOC has a circannual rhythm the opposite of calcidiol (i.e., higher in winter than summer) (Szulc et al., 1993). Vitamin D may be important, directly or indirectly, for achieving normal carboxylation of OC. Low doses of vitamin D and calcium can decrease elevated ucOC levels. In addition, administration of vitamin K to postmenopausal women has been shown to increase bone mass (Orimo et al., 1992).

Subtypes and Sources of Vitamin K

There are different forms of vitamin K. Vitamin K_1 is phylloquinone and is found in green plants. Vitamin K_2 (menaquinones of various chain

lengths) is made by microbes in fermented foods as well in the intestine; it may have different effects on bone metabolism than vitamin K_1 and be more sensitive to age (Hodges, Pilkington, Shearer, Bitensky, & Chayen, 1990).

Vitamin K is absorbed from both the small and large intestines. The various subtypes of vitamin K are absorbed at varying intestinal sites and by differing active and passive mechanisms (Suttie, 1991). Diseases that impair fat absorption such as obstructive jaundice, pancreatic insufficiency, or celiac disease can markedly decrease vitamin K absorption. Vitamin K is transported from the intestine via the lymphatic system, and subsequently to tissues throughout the body.

Drug Interactions with Vitamin K

Long-term use of vitamin K antagonists as oral anticoagulants appears to inhibit *both* hepatic and bone Gla-enzyme systems and may increase urinary calcium loss and eventually reduce bone mineral content (Vermeer et al., 1992). Persons on long-term anticoagulants may therefore be at risk of osteopenia. Certain antibiotics in malnourished patients inhibit hepatic vitamin K metabolism and may cause both hypoprothrombinemia and impaired bone metabolism (Lipsky, 1994; Shearer et al., 1988). The role for intestinal bacteria in producing significant amounts of vitamin K for absorption appears less than earlier believed (Lipsky, 1994). Vitamin E may also potentiate warfarin anticoagulants and borderline vitamin K deficiency. Vitamin E use should be specifically discussed with all persons on any anticoagulant. There are no known hazards of ingestion of natural forms of vitamin K except when taking oral anticoagulants, and even this is probably minimal (Karlson, Leijd, & Hellstrom, 1986).

VITAMINS AS ANTIOXIDANTS

Potentially toxic intermediate compounds are generated from oxygen during normal metabolism. As electrons are added to oxygen, known as oxygen reduction, free radicals (possessing unpaired electrons that are highly reactive to other molecules) and other unstable compounds are generated (Bulkley, 1993; Rice-Evans & Diplock, 1993; Stogner & Payne, 1992). Cigarette smoke, ozone, and ionizing radiation appear to be toxic in part

because of free radical generation (Schiller, Reilly, & Bulkley, 1993). Free radicals impair generation of ATP, damage DNA, depolymerize mucopolysaccharides, and inactivate enzymes. Free radicals may play a role in cancer or immune disorders, and have been implicated in over 50 diseases.

Oxidation and Atherogenesis

Observational and epidemiologic studies strongly suggest, but do not conclusively prove, that antioxidant vitamin intake is inversely associated with cardiovascular disease and mortality (Gey et al., 1993; Hennekens & Gaziano, 1993). Population studies suggest that alpha tocopherol (vitamin E) serum levels are correlated more strongly with ischemic heart disease than either cholesterol or diastolic blood pressure (Gey et al., 1993). A cohort study of 11,000 people found a substantial reduction in cardiovascular deaths and total deaths in persons with higher intakes of vitamin C, primarily as supplements (Enstrom, Kanim, & Klein, 1992). A 12-year follow-up of the Prospective Basel (Switzerland) Study found that either low plasma carotene or vitamin C levels are associated with a significant increase in ischemic heart disease risk, and if *both* are low, for increased cerebrovascular stroke risk (Eichholzer, Stahelin, & Gey, 1992).

Large epidemiologic studies, including 90,000 women in the Nurses' Health Study (Stampfer et al., 1993) and 40,000 men in the Health Professionals Follow-up Study (Rimm et al., 1993), found that 60 to 200 IU of supplemental vitamin E daily for two years decreased the relative risk of major coronary artery disease by one third. There were also trends toward a reduction in risk for mortality from cardiovascular causes and ischemic stroke. These studies, however, did not find a protective effect for vitamin C on coronary disease.

Preliminary analysis of 333 physicians participating in the Physicians' Health Study who had clinical evidence of coronary artery disease (chronic stable angina or coronary revascularization, but no prior myocardial infarction or stroke) has found that the group taking beta carotene (50 mg every other day) had 40% fewer coronary events than the control group (Hennekens & Gaziano, 1993).

Age-associated Eye Disease

Studies have shown that persons who consume more than 300 mg ascorbate or 400 IU tocopherol daily have about one-third the risk for developing cataracts (Robertson, Donner, & Trevithick, 1989). Persons who consumed less than 125 mg of vitamin C daily over the previous year had a four-fold greater probability of having any cataract and an 11 times greater risk for having a posterior subcapsular cataract than those who consumed more than 490 mg vitamin C (Jacques & Chylack, 1991). Low serum concentrations of alpha tocopherol and beta carotene are also associated with increased incidence of senile cataract (Knekt, Heliövaara, Rissanen, Aromaa, & Aaran, 1992). Similar associations have been found with vitamin A and carotenoids (Hankinson et al., 1992), multivitamins (Leske, Chylack, & Wu, 1991; Seddon et al., 1994), and with consumption of fewer than 3-1/2 servings of fruits and vegetables daily (Jacques & Chylack, 1991).

A study of patients with neovascular age-related macular degeneration (AMD) found that persons with higher carotenoid levels had 1/2–1/3 the risk of macular degeneration compared to control patients (Eye Disease Case-Control Study Group, 1993). While no statistically significant protective effect was found for vitamins C, E, or selenium individually, an antioxidant index combining these micronutrients showed significant reductions in risk with increasing levels of the index. In addition, persons with AMD have much lower levels of several antioxidant enzymes in their cells compared with age-matched subjects (Prashar, Pandav, Gupta, & Nath, 1993).

Carcinogenesis

Free radicals and oxidant damage appear to play a major role in some forms of cancer (Schwartz, Antoniades, & Zhao, 1993). Epidemiologic studies on population groups (but not specifically elderly populations) have generally shown a protective effect of fruit and vegetable consumption, foods rich in vitamin C and beta carotene, on many kinds of cancers (Block, 1992; Faivre, Boutron, & Quipourt, 1993; Weisburger, 1991). To what degree the antioxidant properties of vitamins are specifically responsible for these effects is unclear. For example, ascorbic acid, unrelated to its antioxidant capabilities, may inhibit stomach cancer by reducing nitrous acid

and the formation of carcinogenic N-nitroso compounds in the gastrointestinal tract. Because carotenoids, folic acid, vitamin C, soluble and insoluble fiber, and many phytochemicals are frequently in the same foods, it is difficult to determine which dietary factor is most responsible or how synergetic the interactions are (Marchand, Yoshizawa, Kolonel, Hankin, & Goodman, 1989; Steinmetz & Potter, 1991a, 1991b; Ziegler, 1991). Phytochemicals such as isothiocyanates in broccoli and brussel sprouts, ellagic acid in fruits, isoflavonoids in legumes, polyphenols in wine and olive oil, protease inhibitors in soybeans and potatoes, and diallyl sulfide in garlic, as well as many others may also be protective. In addition, persons who consume this type of diet may have other lifestyle behaviors that also lower their risk (Freeland-Graves, Greninger, Graves, & Young, 1986).

Beta carotene and/or preformed vitamin A intake have been most strongly associated with a decreased risk for lung cancer and upper gastrointestinal tract cancers (Steinmetz & Potter, 1991a; Ziegler, 1991). The association is less consistent with hormonally related cancer. A 12-year follow-up of almost 3,000 men in Basel, Switzerland revealed a significant inverse relationship between carotene levels on entering the study and subsequent cancer, particularly lung and stomach cancers (Eichholzer, Stahelin & Gey, 1992). A prospective study of nearly 90,000 female registered nurses found that large intakes of vitamin C or E did not protect women from breast cancer, but a low intake of all forms of vitamin A (<6,630 IU daily) was associated with an increased risk for the disease (Hunter et al., 1993). Women who consumed little vitamin A from food, but who took at least 10,000 IU from supplements had about half the risk for breast cancer compared to women who did not take supplements.

Antioxidant vitamin and mineral supplementation (beta carotene = 50 mg, vitamin E = 30 mg, and selenium = 50 mcg) in 15,000 people with one of the world's highest rates of upper gastrointestinal tract cancer in rural China (ages 40–69), over a 6-year period, was associated with a reduction in total mortality, primarily due to a decrease in stomach cancer (Blot et al., 1993). There was also a nonsignificant trend toward decreased cerebrovascular disease mortality. Vitamin C has also been associated with decreased risk for many gastrointestinal tract cancers and lung cancer (Block, 1991a). An analysis combining the data of 12 case-control studies of diet and breast cancer found a significant inverse association between vitamin C intake and breast cancer (Howe et al., 1990). There is also an inverse relationship between vegetable consumption and the risk for breast cancer (Howe et al., 1990).

Not all studies are positive, indicating that much remains to be learned about vitamins and cancer. A recent randomized, double-blind, placebo-controlled primary prevention trial of young white male smokers (ages 50–69) followed for five to eight years showed no protective effect of daily 20 mg beta carotene and 50 IU alpha tocopherol (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994). Surprisingly, this study showed a higher incidence of lung cancer and ischemic heart disease among the men who received beta carotene, but fewer cases of prostate cancer in those who received vitamin E. Another study using daily supplements of beta carotene (25 mg), vitamin C (1 g), and vitamin E (400 mg) for 4 years did not find a decrease in colorectal adenoma incidence compared to the placebo group (Greenberg et al., 1994).

Vitamin A and Carotene

Although vitamin A intake decreases with age, hypovitaminosis A in adults is uncommon, even in the very old. There is evidence that vitamin E and vitamin C status decline in many older individuals, while retinol status usually does not (Panemangalore & Lee, 1992; Porrini, Simonetti, Ciappellano, & Testolin, 1987).

Vitamin A may refer to two different groups of substances, and this can cause considerable confusion. One is retinol, or preformed vitamin A. It is found in dairy products, animal and fish meats, and synthetic vitamin A analogues. Vitamin A is necessary for maintaining the integrity of epithelial tissues (e.g., skin, cornea, gastrointestinal tract, and lungs). It is also required for proper retinal function, immune function, and growth (Sklan, 1987).

Vitamin A activity in foods is currently expressed as retinol equivalents (RE); 1 RE is defined as 1 mcg all-trans retinol, and roughly estimated to be equivalent, due to poorer absorption, to 6 mcg all-trans beta carotene or 12 mcg of other provitamin A carotenoids (Food and Nutrition Board, 1989; Olson, 1987). International units (IU) are often used for both vitamin A and the carotenoids, and are frequently confusing and inaccurate. One RE equals 3.33 IU (or IU_a) of preformed vitamin A (retinol) and 10 IU (or IU_c) of provitamin A carotenoids. Despite this, food composition tables often assume that 1 IU_a = 1 IU_c. Therefore, the consumer and physician should use food composition tables only as rough guides to approximate vitamin A and carotenoid quantities in specific foods.

Using REs to determine the antioxidant activity of foods is also misleading, since retinol is generally *not* an antioxidant. The current RDA for vitamin A is 1,000 mcg RE in men and 800 mcg RE in women (as seen in Table 7.1). However, it has been proposed that this is too high and could be safely reduced to 700 mcg RE and 600 mcg RE for elderly men and women, respectively (Olson, 1987; Russell & Suter, 1993). Except at the extreme ranges, serum retinol levels correlate poorly with vitamin A status and are affected by many non-nutritional diseases.

The other form of vitamin A is carotene (provitamin A), found primarily in plants, especially carrots and dark green leafy vegetables. It includes alpha, beta, and gamma carotene, lutein, lycopene, zeaxanthin, and cryptoxanthin. The color intensity of a fruit or vegetable does not reliably indicate its provitamin A content (Food and Nutrition Board, 1989). Beta carotene usually makes up the largest fraction of provitamin A in foods. Carotene is also found in yellow animal fat and dairy products. Of the approximately 600 or so carotenoids, only 50–60 are known to be precursors to vitamin A, but many more may act as antioxidants and be protective independent of any provitamin A role (Olson, 1987). There are no RDAs for the carotenoids. It is difficult to interpret tables of carotenoid contents of foods since neither retinol equivalency nor beta carotene content may fully reflect the significant biologic antioxidant activity (Erdman, Bierer, & Gugger, 1993).

Only about 15% of beta carotene is absorbed by the body. Absorption is reduced further in extremely low fat or high fiber diets, and in the presence of bile acid sequestrants, and only 20% of that absorbed is ultimately converted to retinol. Bioavailability is affected by many factors (Erdman et al., 1993). Pureed or finely chopped vegetables yield higher beta carotene absorption than whole or sliced whole vegetables; absorption can be as low as 1%–2% from raw carrots; mild heating, such as steaming, improves absorption by denaturing pigment-protein complexes (for example, the carotenoid lycopene is poorly absorbed from tomato juice unless the juice is heated first). Except for reversible carotenodermia, an orange-yellow skin discoloration most prominent in palms and soles but not sclera, which may be seen with a daily ingestion of 30 mg beta carotene (Micozzi, Brown, Taylor, & Wolfe, 1988); side effects of beta carotene ingestion are rare. Most of the beta carotene in the blood is associated with LDL cholesterol and stored primarily in fat rather than the liver.

Vitamin C

About 10 mg daily of vitamin C will prevent scurvy, believed to be derived from the Italian word *scorbutico*—an irritable, whining, cranky person (perhaps the result of impaired catecholamine synthesis) (Bender, 1992). The current RDA for vitamin C in adults is 60 mg (Table 7.1). Like other vitamins, the RDA for vitamin C was not formulated with respect to its antioxidant properties. Vitamin C deficiency is common in general malnutrition and in many frail elderly populations (Mandal & Ray, 1987; McClean, Dodds, Steward, Beaven, & Riley, 1976). Early clinical evidence of deficiency is dermatitis and petechial hemorrhages, gum bleeding, and poor wound healing. The absorption and pharmacokinetics of ascorbic acid do not appear to change with age, although higher intakes of vitamin C are needed in older men than in older women to attain the same plasma concentrations, probably due to higher renal tubular reabsorption in women.

Vegetables and fruits contain the highest concentrations of vitamin C; meats, fish, poultry, eggs, and dairy products contain some; and grains contain none. In the United States, most ascorbate is supplied by citrus fruits, potatoes, and other vegetables (Food and Nutrition Board, 1989). Vitamin C is easily destroyed by heat and oxygen, or lost in cooking water.

Bioavailability of vitamin C is inversely related to the amount ingested as well as on its form. Sustained release capsules allow higher absorption than standard pills (Garry, Vanderjagt, & Hunt, 1987). Smoking lowers ascorbic acid levels and smokers require a higher intake to achieve comparable plasma levels to those of nonsmokers, perhaps because of increased metabolism (Gerster, 1987).

Vitamin E

Vitamin E is the generic term for a group of chemicals (tocopherols and tocotrienols) originally discovered to affect reproduction in the rat (Machlin, 1991). It was given the letter "E" to follow vitamin D, and given the name tocopherol from the Greek *tokos,* for childbirth, and *pherin,* to bring forth. Alpha tocopherol is considered the most active compound, but other forms may also have significant biologic function. The RDA for vitamin E is 10 mg (natural alpha tocopherol equivalents) for men and 8 mg for women (see Table 7.1). Although the synthetic form of alpha to-

copherol has 74% of the activity of naturally occurring alpha tocopherol (Food and Nutrition Board, 1989), both the natural and synthetic forms provide equal antioxidant protection to LDL (Reaven & Witztum, 1993). The bioavailability of the various stereoisomers in synthetic vitamin E may differ, however (Acuff, Thedford, Hidiroglou, Papas, & Odom, 1994). International units (IU) are still frequently used; 1 mg *natural* alpha tocopherol (one alpha tocopherol equivalent) equals about 1.1–1.5 IU, while 1 mg *synthetic* alpha tocopherol equals 1 IU. Beta tocopherol has one-half the activity of natural alpha tocopherol; gamma tocopherol has one-tenth the activity (Food and Nutrition Board, 1989).

Large losses of tocopherols can occur during processing, storage, and preparation of food. The richest sources in the American diet are common vegetable oils and products made from them (e.g., margarine and shortening). Western diets contain 2 to 4 times the amounts of gamma tocopherol, but alpha tocopherol appears to be much better absorbed and accounts for most of the total serum tocopherol concentration (Ferns, Konneh, & Anggard, 1993). Meats, fish, animal fats, and fruits and vegetables have little vitamin E.

Vitamin E decreases platelet adhesion, which does not depend on its antioxidant properties, and may be protective in thromboembolic disease (Steiner, 1993). It also enhances cell-mediated immunity in healthy elderly persons, and may retard some of the age-related changes in the immune system (Meydani et al., 1990). The role of vitamin E in intermittent claudication syndromes remains unclear.

Clinical vitamin E deficiency syndromes are not well recognized in adults, although peripheral neuropathy, hand myopathy, and cardiomyopathy may occur in association with severe fat malabsorption (Ferns et al., 1993; Meydani et al., 1990).

Toxicity of Antioxidant Vitamins

Vitamin A is easily the most dangerous of the antioxidant vitamins. Hypervitaminosis A can occur both acutely and after chronic ingestion. Acute toxicity presents as headaches, drowsiness, lethargy, papilledema, nausea, vomiting, and skin dryness and scaling (Leo & Lieber, 1988). Elderly people with normal kidney and liver function may tolerate a daily dose of 50,000 RE for up to 6 months, while younger adults have taken 300,000 RE (as retinyl palmitate) daily for 12 months with few adverse effects

(Bendich & Langseth, 1989; Pastorino et al., 1991). However, toxicity has been seen on daily intakes of as little as 15,000 RE (Korner & Vollm, 1975). Chronic toxicity may classically, and non-specifically, present as desquamation and redness of the skin and mucous membranes, alopecia, headaches, anorexia, fatigue, irritability, thyroid suppression, hypercalcemia, cerebrospinal fluid pressure elevation (producing symptoms similar to pseudotumor cerebri), and hepatosplenomegaly (Leo & Lieber, 1988). Hypercalcemia and a negative calcium balance similar to that seen with hypervitaminosis D may occur.

Vitamin E toxicity may present as diarrhea or fatigue, but even huge intakes are usually well tolerated (Bendich & Machlin, 1988). The major side effect may be that vitamin E potentiates warfarin (coumadin) and increases bleeding risk in persons on this anticoagulant. Under certain circumstances, vitamin E acts to promote skin tumors in animals (Mitchel & McCann, 1993). Therefore, prolonged topical exposure to antioxidants such as vitamin E should be discouraged until more is known.

Vitamin C can increase the absorption of iron. Thus, supplementation may be hazardous in persons at risk of iron overload (e.g., anemia of chronic disease, thalassemia, hemochromatosis) without close supervision. It is possible that in the presence of appropriate levels of copper or iron, ascorbic acid can act as a prooxidant (Garland, 1991); whether this is clinically significant is unknown. Periodic blood donations would decrease the risk of increased iron absorption associated with vitamin C intake. Some persons with recurrent renal oxalate stones may increase their risk with high intakes of vitamin C. However, in general, supplement use of ascorbic acid causes no problems, even in older persons (Jacob et al., 1988; Rivers, 1987). Vitamin C may also affect fecal occult blood tests as well as some urinary and blood sugar tests. Abruptly discontinuing high vitamin C intake may make some persons deficient but this is probably rare (Bender, 1992). There is little acute toxicity to high dose vitamin C ingestion; occasionally diarrhea can occur.

Supplementation

Evidence supporting the benefits of fruit and vegetable consumption, major sources of vitamins, is extensive. However, vitamins are not the only healthful qualities of fruits and vegetables—they also contain fiber and other chemicals (known and unknown) that likely are beneficial. Because

of this, most vitamin intake should ideally come from the consumption of a balanced diet. A *minimum* intake of 5 servings of fruits and vegetables daily has been recommended.

The RDA for most vitamins can be obtained from a diet rich in fruits and vegetables. Vitamin D can come from adequate sunshine exposure or fortified foods; vitamin B_{12} is primarily in meats; vitamin E is found naturally only in vegetable oils. However, the current RDA for certain vitamins may be inadequate for older adults (Russell & Suter, 1993). In addition, the RDAs, designed to prevent severe deficiencies, may not be sufficient for optimum health.

Supplementation should not be considered a substitute for a balanced diet. However, supplementation may improve the nutritional status of persons who cannot or will not consume a diet rich in fruits and vegetables, or who receive inadequate exposure to sunlight, or who smoke. Few adults consume even the minimum recommended amounts of fruits and vegetables daily (Block, 1991b). Supplementation will also increase intake of vitamin E without consuming a high fat diet. Furthermore, supplementation will allow the intake of vitamins in quantities that currently appear to be associated with maximum antioxidant effect. There is evidence that even healthy elderly persons may benefit from simple multiple vitamin supplementation (Bogden et al., 1994; Chandra, 1992).

Supplementary vitamins are drugs and, like other drugs, more is not necessarily better. Fortunately, toxicity for many vitamins, with the exception of vitamins A, D, niacin, and pyridoxine, is remarkably low. The long-term consequences of high dose vitamins is unknown, however, and should not be underestimated. High doses of vitamins can have adverse interactions with foods, other vitamins, and drugs. It is well known that high doses of folic acid may mask vitamin B_{12} deficiency, and high intakes of vitamin C increase iron absorption in persons at risk for iron toxicity. Therefore, all patients who take multiple vitamins or doses in excess of the RDA should deliberately mention them when asked about *any* medication intake, or when consulting with *any* physician. Supplements almost certainly do not fully compensate for adverse risk behaviors. Supplements should be tailored as interventions in the context of an individual's other health risks, including genetic susceptibility to certain diseases, expected life span, and personal philosophy.

Vitamin misuse is common, and there is considerable misinformation in lay literature and advertisements. While intakes of vitamins in excess of the RDA may be supported by scientific data with respect to antioxi-

dant activity or bone metabolism, there is no credible evidence to encourage megavitamin use for treating cancer or other chronic/fatal/painful diseases. Patients in these categories are vulnerable to false hope and exploitation, and their use of potentially toxic vitamin combinations must always be considered. Other patients who may take inappropriate or harmful amounts of vitamins are health food advocates or persons distrustful of the medical establishment. Obtaining a thorough dietary and medication history and maintaining a trusting and open dialogue with patients is the best way to counsel them on appropriate vitamin use and to detect either vitamin deficiency or toxicity.

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CHAPTER 8

Exercise and Aging

ROGER J.M. MCCARTER
DEPARTMENT OF PHYSIOLOGY
UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER

There is widespread current interest in the use of exercise as a strategy to combat the diseases and frailty of old age (Åstrand, 1992; Lowenthal, Kirschner, Scarpace, Pollock, & Gravis, 1994; Rogers & Evans, 1993). Habitual exercise is also believed to promote psychological and functional well-being (McAuley, Cournea, & Lettunich, 1991). Because many of the adaptations to exercise are in a direction opposite to changes associated with advancing age, there is interest in the possibility that exercise may slow the rate of aging (Quinn, Sprague, Van Hus, & Olson, 1990).

This contemporary focus on the benefits of exercise is in marked contrast to early predictions that strenuous exercise would shorten the lifespan and exacerbate effects of disease. Indeed, in the last century, the Reverend C. Wordsworth, organizer of the Oxford–Cambridge boatrace, stated public concern that participants in competitive rowing would not reach the age of 30 (Hartley & Lewellyn, 1939). Such views were in agreement with the "rate-of-living" theory of aging (Pearl, 1928), which predicted decreased lifespan with increased metabolic rate and were supported by early studies showing decreased survival of rats undergoing daily exercise (Benedict & Sherman, 1937).

Consistent with these views, current studies indicate that strenuous exercise constitutes an "oxidative stress" in which activities of antioxidant enzymes are observed to increase (Ji, 1993). More recently, Åstrand (1992) pointed out that men and women have survived over millions of years of evolution as a consequence of a physically active lifestyle, as successful hunters and gatherers of food. It is only in the most recent few decades that technological progress in industrialized nations has led to physical inactivity, a lifestyle in which the most successful individuals are the most sedentary. Holloszy and Khort (1995) note that this lifestyle is in fact characterized by a state of "exercise deficiency," in which a sedentary status

is the norm and in which, remarkably, regular physical activity is viewed as an intervention.

The purpose of this review is to focus on the interaction of exercise and aging: to consider evidence that exercise modulates aging processes; and to evaluate the use of exercise for improving the quality of life in the elderly. An important point in this evaluation is the critical role of the type of the exercise involved. Habitual physical activity involving endurance exercise is associated with adaptations different from those of resistance, or strength training. Also, for a given type of exercise, threshold levels of intensity may be required to achieve physiological adaptation. Intensity of endurance exercise is measured relative to the individual's maximum aerobic capacity ($\dot{V}o_{2max}$), whereas intensity of resistance exercise is determined as a percentage of the maximum load the individual is capable of lifting once only (the one repetition maximum, or 1RM). Comparison of results of different studies, therefore, must include evaluation of the intensity and nature of particular training protocols. Central also to these considerations is the role of skeletal muscle. Particular types of exercise result in activity of individual muscles and muscle groups. Usually only those muscles specifically involved in the activity will exhibit a training effect, although broad systemic effects are also brought about as a consequence of the body's integrated response to exercise training. The ability of skeletal muscles of aged individuals to adapt to activity thus becomes of importance, especially since loss of skeletal muscle is a characteristic feature of advancing age.

The discussion commences with age-related changes in whole-body activity levels, in skeletal muscle, and in the ability of muscles of aged individuals or laboratory animals to adapt to increased activity. Evidence for protective effects of habitual exercise against functional deterioration is then evaluated. Since aging is characterized by increased vulnerability with time, the latter consideration leads to discussion of evidence for and against the role of exercise as an anti-aging agent. Several excellent reviews provide additional information in this area (Booth, Weeder, & Tsing, 1994; Carmeli & Reznick, 1994; Holloszy & Kohrt, 1995; Lakatta, 1993; Rogers & Evans, 1993).

PHYSICAL ACTIVITY AND AGING

Physical activity declines with advancing age in humans and in laboratory rodents. In a cross-sectional study McGandy et al. (1966) measured

nutrient intakes and energy expenditure in 250 men aged 22–99 years. Physical activity patterns were assessed on the basis of extensive interviews and total daily energy expenditure was estimated from dietary records. The authors estimated an approximately linear decrease in physical activity and in daily energy expenditure associated with physical activity (amounting to about 25%) over an age range of 28–80 years. A 1985 survey found that less than 10% of Americans over 65 years of age engage in programs of aerobic or strength-type exercise (Teague & Hunnicutt, 1989). Overall, there is a decrease with age in time devoted to active leisure pursuits and also a decrease with age in the intensity of these activities (Cunningham, Montoye, Metzer, & Keller, 1968). In laboratory rats, Yu et al. (1985) found decreased spontaneous activity with age of male Fischer 344 rats maintained under barrier conditions and fed ad libitum. Similar observations have also been noted for running wheel activity in rats provided with running wheels in their cages. Holloszy et al. (1985) found decreased running activity of male Long-Evans rats between 6 and 10 months of age, but this was counteracted by a slight decrease (<10%) of daily food allotment. In contrast, female Long-Evans rats exhibited sustained wheel running over most of their lifespan, although the intensity declined from about 8 km/day to 2 km/day from 4–34 months of age. This is shown in Figure 8.1 (Holloszy, 1993). Decreased physical activity with age has also been noted in insects (Sohal & Buchan, 1981). It seems, therefore, that decline in physical activity with advancing age is a characteristic feature of many different animals.

This relative inactivity has a broad range of adverse physiological consequences. Decreased appetite, slowed bowel function, and constipation are associated with decreased physical activity (Altman, 1990). Atrophy of skeletal muscle is a major consequence, related to decreased fiber size, increased rates of protein degradation and inhibition of protein synthesis (Musacchia, Steffen, & Fell, 1988). Such disuse atrophy is associated with exaggerated loss of contractile proteins in comparison with other cellular proteins, leading to loss of specific active tension (force per unit area), as well as loss of absolute muscle tension (Evans, 1992). Changes in muscle metabolism also occur. For example, significant glucose intolerance was found after only 3 weeks of bed rest in healthy adults (Lutwak & Whedon, 1959), and decreased responsiveness to insulin has been noted in muscles of untrained individuals (Åstrand, 1992). Indeed, there are many similarities between effects of disuse and aging on skeletal muscle, as noted by Bortz (1982). In addition to effects on skeletal muscle per se, inactivity

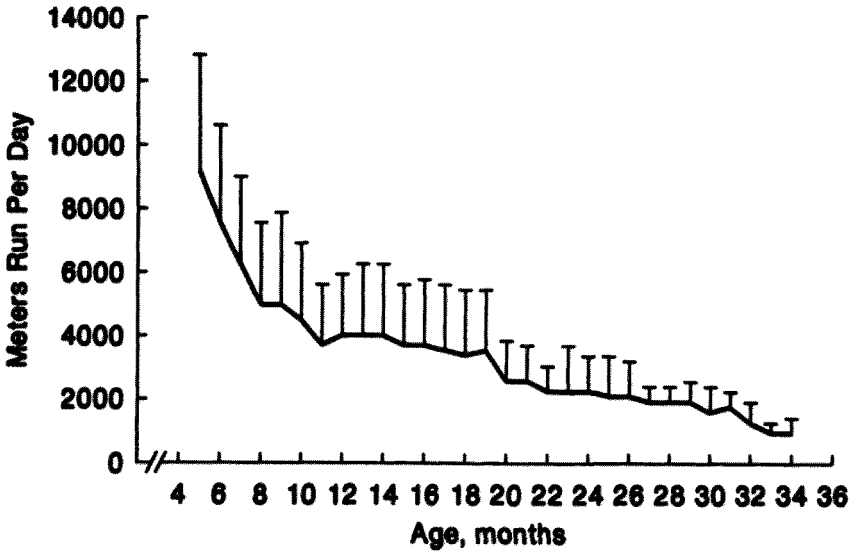

FIGURE 8.1 Voluntary wheel running as a function of age of female Long-Evans rats fed *ad libitum*. (*Source:* From Holloszy, J.O., Exercise increases average longevity of female rats despite increased food intake and no growth retardation. *Journal of Gerontology, 48;* B99, copyright © 1993, the Gerontological Society of America, used with permission.)

leads to decreased psychomotor performance, or the ability to process and react to specific information (Graves, Pollock, & Carroll, 1994). Active individuals participating in regular vigorous physical activity have consistently faster psychomotor responses. For example, Baylor and Spirduso (1988) found middle-aged women participating in vigorous aerobic activity exhibited significantly shorter total reaction times and times required to move from one position to another than women who were sedentary.

Perhaps the major consequence of physical inactivity is, however, greatly increased risk of cardiovascular disease. During 1987, more than 500,000 deaths in the United States were attributable to coronary heart disease (Åstrand, 1992). Data from several studies indicate that the most prevalent modifiable risk factor in this regard is a sedentary lifestyle. As shown in Figure 8.2, this risk factor far exceeds those associated with elevated serum cholesterol, smoking, and hypertension. Indeed, the data of Paffenbarger, Hyde, Wing, and Hsieh (1986) indicate that male Harvard

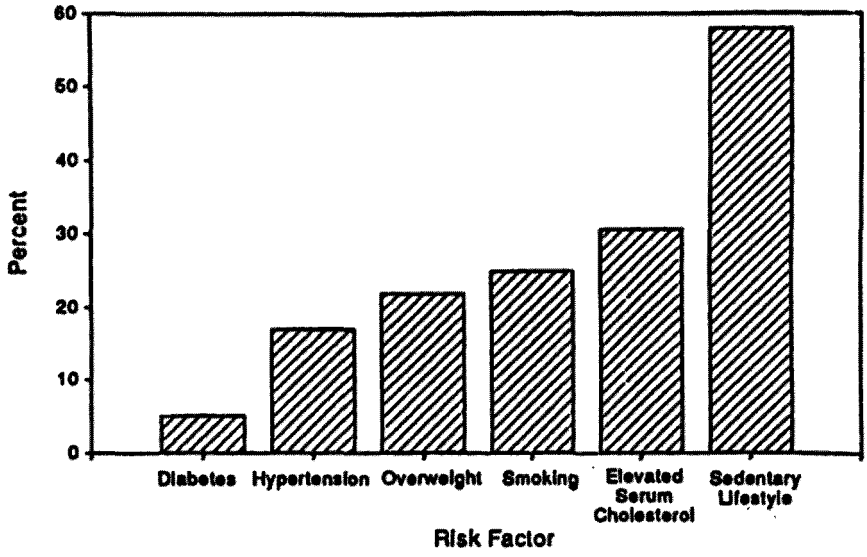

FIGURE 8.2 Analysis of most prevalent modifiable risk factors for coronary heart disease, based on data of the 1988 Behavioral Risk Factor Surveillance System and the 1976-1980 Second National Health and Nutrition Examination Survey. (*Source:* From JAMA, 264; 1392, copyright © 1990, used with permission.)

alumni expending between 2000 and 3500 kcal/week on exercise activities had a significantly lower risk of developing coronary heart disease than less active alumni.

The characteristic decline of physical activity with advancing age may be a consequence of several factors. Altered behavior, presence of disease, declining functional capacity or increased energy requirements of movement (Martin, Rothstein, & Larish, 1992) may play a role in this effect. However, a major factor in this decline is certainly altered function of skeletal muscle. The extent to which age-related changes in contractile properties of skeletal muscle influence levels of physical activity and vice versa is the subject of current interest (Evans, 1992). An important issue is whether or not inherent age changes in skeletal muscle limit physical performance in the elderly or, indeed, if decreased physical activity is a major factor in the deterioration of skeletal muscle function with age.

AGING OF SKELETAL MUSCLE

Bodily movements ultimately depend on appropriate functioning of skeletal muscle. Activities of normal daily living and the increased performance of exercise can only be executed if appropriate amounts of skeletal muscle are available and if properties of the muscle are suited to these activities. For example, if aging leads to loss of mass of skeletal muscle and to preferential loss of rapidly contracting muscle fibers, then only physical activity involving decreased intensity and slower movement would be possible in the elderly. Such a behavioral change would impact whole body energetics, tissue composition, and potentially induce a cycle of positive feedback leading to increasing adiposity and a more sedentary lifestyle. In this section, the goal is to examine current findings with a view to separating those changes of skeletal muscle which are inevitable consequences of aging from those changes which may be modulated by interventions such as exercise.

Contraction of muscle is the end result of many events occurring in series, all of which must operate appropriately in order to bring about movement. The series of events consists of activity of motor neurons, transmission of activity across nerve-muscle junctions, the process of excitation-contraction coupling within muscle fibers, development of active tension by the contractile proteins, and finally movement of limbs depending on loading conditions. Muscle fibers are activated in groups, or motor units. Each motor unit consists of a single alpha motor neuron and all of the muscle fibers innervated by this motor neuron. Innervation ratios range from tens to thousands of muscle fibers and contractile properties of all fibers are similar in a given motor unit. There is little information regarding effects of age on patterns of innervation of these α-motor neurons. The patterns are determined by activity of the central nervous system via pyramidal and extra-pyramidal tracts and nuclei located in the cortex and midbrain, respectively. Activity of α-motor neurons is also modulated by proprioceptive feedback from stretch and load sensors located in the muscles. More research is needed in this area, since declining input with age from higher centers and from sensory neurons would be expected to exert significant effects on muscle mass and function.

The likelihood that changes occur in central and sensory input to motor units is suggested by evidence that motor units are indeed affected by aging. Results in aging laboratory animals and humans suggest decreased numbers of motor neurons, decreased numbers of motor units, preferential loss of fast units, increased size of remaining units, and decreased con-

duction velocity of action potentials along axons of remaining units (Brown, 1972; Campbell, McComas, & Petito, 1973; Kanda & Hashizume, 1989; Stålberg & Fawcett, 1982). The remarkable similarity in age-related change of motor neurons and motor units recorded in two separate cross-sectional studies of aging humans is shown in Figures 8.3 and 8.4. In Figure 8.3 (Tomlinson & Irving, 1977) the relative constancy up to about 60 years of age of limb motor neuron number in ventral horns of the lumbosacral region of the spinal column is shown. Significantly decreased numbers of motor neurons were found in these areas for individuals 70 years and older. The work of Campbell et al. (1973), shown in Figure 8.4, demonstrates the relative constancy of motor unit number in *extensor digitorum brevis* muscles of individuals up to 60 years of age. Thereafter, motor unit number decreased rapidly with age. Consistent with the idea that motor units are lost in late middle age is the finding that fiber-type grouping occurs in muscles at this stage of life. For example, Lexell and Downham (1992) found a mosaic pattern of different types of muscle fibers in *vastus lateralis* muscles of young and adult men. However, from 60 years of age onward there was grouping of particular types of muscle fibers, suggesting that fibers that lost their motor innervation were incorporated into neighboring motor units, presumably as a consequence of terminal sprouting of nearby motor axons. Accelerated loss with age of fast motor units has been reported in humans and in laboratory animals (Baker, 1989; Kanda, Hashizume, Nmoto, & Asaki, 1986). However, the work of Kanda and Hashizume (1989) suggests caution should be exercised in interpreting differential rates of loss of fast and slow units in different muscles. These authors found no difference in distribution of fast and slow motor units in gastrocnemius muscles of SPF barrier-raised Fischer 344/Du Cri rats with age (10–14 months vs 23–30 months old), but did find significantly reduced conduction velocity in all motor units with age. These authors stressed the need to identify age-related changes of slow and fast motor units in the same muscle, since such changes might be muscle-specific. Such specificity of change is suggested by the early work of Corbin and Gardiner (1937), who determined loss of motor axons innervating muscles of the torso from as early as 30 years of age.

Differential changes with age have also been identified in junctions of nerve and muscle. Rosenheimer and Smith (1985) investigated these junctions in *extensor digitorum longus* (EDL), diaphragm (DPH), and *soleus* (SOL) muscles of barrier-raised Fischer 344 rats 10–30 months old. They found decreased proliferation of nerve terminal branches with age in EDL

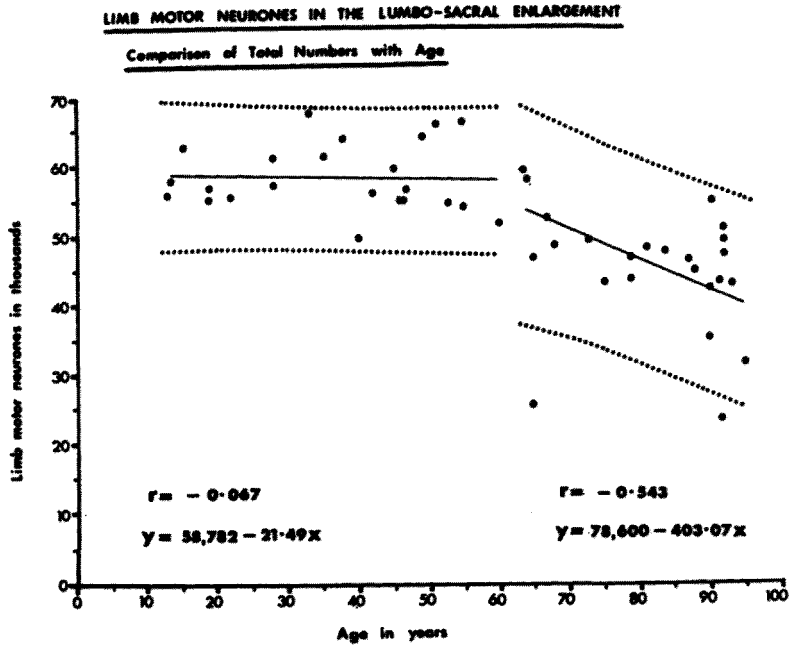

FIGURE 8.3 Number of motor neurons versus age in lumbosacral sections of individuals aged 13–95 years. Solid lines are regressions less than and greater than 60 years. Broken lines represent 95% confidence interval. (*Source:* From Tomlinson, B.E., & Irving, D. J., The numbers of limb motor neurons in the human lumbrosacral cord throughout life. *Journal of the Neurological Sciences, 34;* 214, copyright © 1977, used with permission of Elsevier Science Publishers.)

and SOL muscles, whereas those in DPH muscles increased with age. Major changes in end-plate morphology were found at 28 months of age in all 3 muscles. Cardassis and LaFontaine (1987) found gradual loss of synaptic contact between nerve and muscle in SOL muscles of CD-Crl: COBS rats with age, whereas in DPH muscles there was ongoing structural remodelling of neuromuscular junctions. The authors also noted abrupt changes in junction morphology after 20 months of age for both muscles, with loss of entire junctions in SOL but not DPH muscles. Oda (1984) found gradual accumulation with age of altered numbers of preterminal branches and post-junctional receptors in intercostal muscles of human volunteers ranging in age from 32–76 years. All of these studies demonstrate that changes do occur with age in structure and function of motor neurons and nerve-muscle junctions. The changes may occur at different

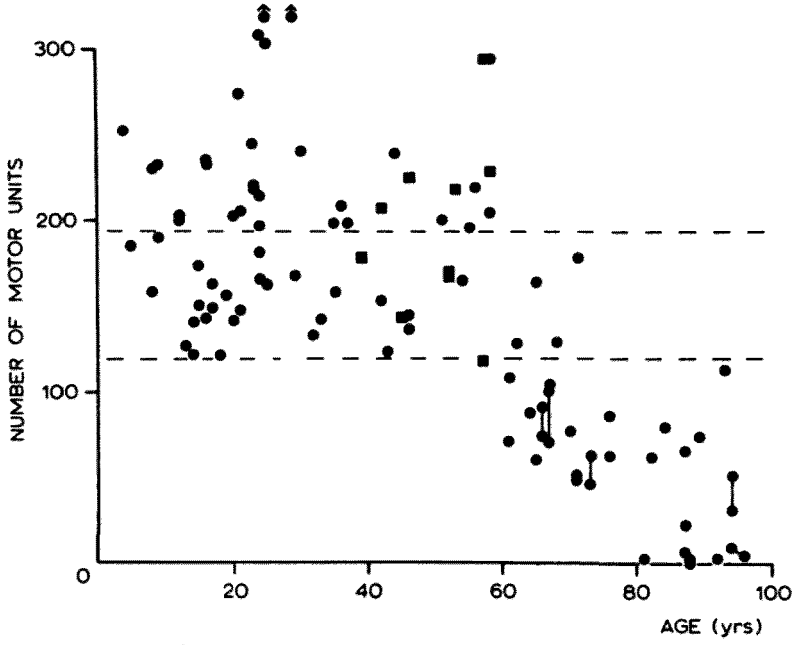

FIGURE 8.4 Number of functioning motor units versus age in extensor digitorum brevis muscles of 94 individuals aged 3–96 years. Upper broken line represents mean number of motor units from 3 to 58 years. Lower broken line indicates lowest number in same age range. (*Source:* From Campbell, M.J.A., McComas, A.J., & Petito, F. Physiological changes in ageing muscles. *Journal of Neurology, Neurosurgery and Psychiatry, 36;* 174,copyright © 1973, used with permission of BMJ Publishing Group.)

rates for different muscles. Evidence to date strongly suggests an ongoing dynamic interaction between muscle fibers and the nerves which innervate them, with a continuous process of structural remodelling of nerve-muscle contact. It seems likely that aging modulates the balance between nerve terminal branching and withdrawal of nerve-muscle contact. An important point to note also is that several studies indicate abrupt changes in junction structure at particular ages. Such changes may not be identified in studies using only "young" and "old" subjects, emphasizing the need to investigate a range of ages in conducting aging research.

Activity of motor nerves and nerve-muscle junctions is followed by propagation of action potentials along muscle cell membranes and activation of the contractile proteins via the process of excitation–contraction (E–C) coupling. There is little information regarding effects of aging on

this process. However, the importance of gathering such information is emphasized by the fact that defects in this process are known to occur (such as in the clinical condition of malignant hyperpyrexia), and by recent findings that muscle performance of the elderly can be greatly increased without concomitant increase in muscle size (Evans, 1992). The results of Gafni and Yuh (1989) suggest marked decline with age in concentration of proteins of the sarcoplasmic reticulum (SR), an essential component of E–C coupling, in limb muscles of Sprague-Dawley rats. They also found decreased capacity of SR vesicles of old rats (17–28 months) to accumulate Ca^{++} ions and decreased numbers of Ca^{++} ions accumulated by these vesicles per molecule of ATP hydrolyzed. These results are important, since such changes in muscles of the elderly would lead to increased energy cost of movement and decreased ability to induce relaxation of active muscles. The results are, however, in contrast to findings of Bertrand, Yu, and Masoro (1975), who demonstrated increase with age in coupling of Ca^{++} transport to ATP hydrolysis in vesicles isolated from muscles of SPF barrier-raised Fischer 344 rats. The divergent results of these studies emphasize the need for additional information in this area. It should be noted, however, that studies indicate at least some elderly individuals are able to fully recruit motor units at frequencies required for maximum performance, indicating intact pathways of excitation (MacDonaugh, White, & Davies, 1984; Vandervoort & McComas, 1986).

Movement of limbs is dependent on development of sufficient force by muscles to overcome external loads followed by shortening of muscles over appropriate distances and at appropriate speeds. Capacity for generating active tension is a function of the number of force-generators in parallel, that is, the cross-sectional area of the motor unit or muscle. Capacity for shortening is determined by the number of contractile units (sarcomeres) in series (i.e., the length of the muscle fiber) as well as by the external load. Speed of shortening is determined not only by the numbers of sarcomeres in series and external load, but also by characteristics of the force generators, such as the rate of ATP-hydrolysis. The most obvious limitation to mobility of the elderly is loss of muscle mass with age. This is due primarily to loss of cross-sectional area of muscle, since there is little indication of significantly decreased length of muscle fibers with age. Indeed, age-related loss of muscle mass is the most commonly encountered form of muscle atrophy. The loss of cross-sectional area and therefore of force generators in parallel limits development of appropriate active tension, thereby decreasing not only ability to execute normal daily activi-

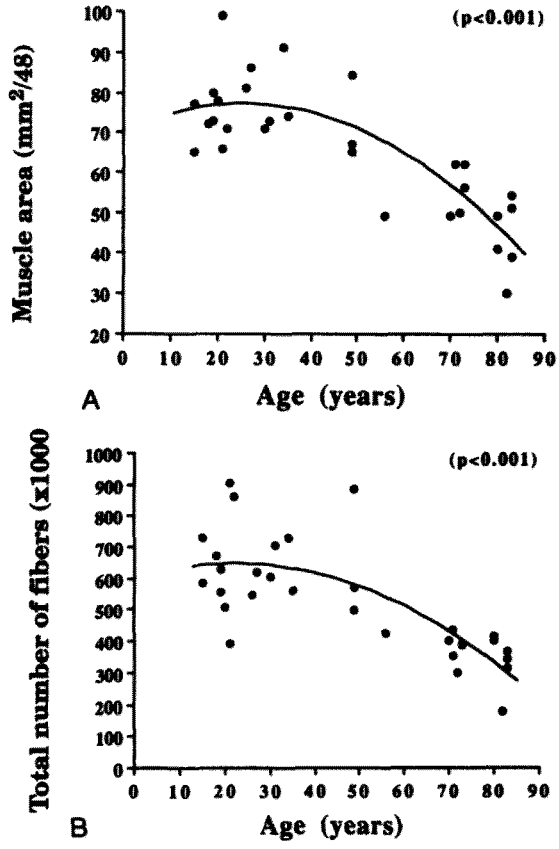

FIGURE 8.5 Cross-sectional area (A) and number of fibers (B) of *vastus lateralis* muscles versus age in men aged 15–83 years. (*Source:* From Lexell, Taylor, & Sjostrom, What is the cause of ageing atrophy? *Journal Neurological Sciences, 72*; 284–285, copyright © 1988, Elsevier Science Publishers, used with permission.)

ties, but also ability to exercise. Loss of muscle cross-sectional area in humans was measured in a definitive study by Lexell and colleagues (Lexell, Taylor, & Sjöström, 1988), as shown in Figure 8.5. These authors measured cross-sectional area of entire *vastus lateralis* muscles from cadavers of 43 males aged 15–83 years. The authors noted a small decline (10%) in muscle area for individuals from about 25 to 50 years of age. As can be seen in Figure 8.5(A), there was a marked decrease in area of muscles from age 50 years onwards. This decrease in area was due in part to a loss of muscle fibers, as shown in Figure 8.5(B). However, there was also a decrease in mean area of rapidly contracting type II fibers, but no change

in mean fiber area of slow type I fibers. The results demonstrate a loss of about 40% in mass of this muscle from 20 to 80 years of age, and indicate the loss is a consequence of both decreased fiber number and area.

Not only is there decreased mass of muscle with age, but a change in composition occurs, with increasing accumulation of noncontractile connective tissue and fat (Borkan, Hutts, Gerzol, Robbins, & Silbert, 1983; Lexell, Henriksen-Larsen, Winblad, & Sjöström, 1983). These changes clearly decrease the capacity for generating active tension in the elderly, and would be expected to limit performance. Many reports document such a decrease in maximum isometric strength with age, as reviewed by Vandervoort (1992). Rogers and Evans (1993) concluded that available evidence indicates relative constancy of muscle strength up to 50 years of age in humans, with progressively increasing loss of strength thereafter. In comparison with strength at age 30, there appears to be a decrease of about 40% in muscle strength by age 80, but extent of loss varies widely for different muscle groups. Decrease in strength has also been noted in some, but not all, studies of muscles of laboratory rodents (Brooks & Faulkner, 1988; Larsson & Edstrom, 1986; McCarter & McGee, 1987; Walters, Sweeney, & Farrar, 1990). The issue of whether or not decreased muscle strength with age can be fully accounted for by loss of cross-sectional area is controversial. In an extensive review of data available for men and women, Rogers and Evans (1993) concluded that "decrease in muscle size with aging can account for much of the reduction in muscle strength" (p. 71), indicating little loss of intrinsic strength in muscles of the elderly. This conclusion is also supported by many studies in muscles of rodents, particularly those using healthy, barrier-protected animals (Eddinger, Cassens, & Moss, 1986; Florini, 1987; McCarter & McGee, 1987; Walters et al., 1990). However, it is apparent that loss of specific force, that is, active tension per unit area, is present in some muscles of elderly rodents and humans (Brooks & Faulkner, 1988; Bruce, Newton, & Woledge, 1989), a consequence of either loss of intrinsic strength, altered composition of muscles, presence of disease and/or other factors.

Most studies utilizing muscles of laboratory rodents indicate no change in the maximum speed of shortening (Vmax) with age, consistent with studies showing no age-related change in fiber composition and characteristics of myosin ATP-ase, particularly in muscles of SPF barrier animals (Eddinger et al., 1986; Fitts, Troup, Witzman, & Holloszy, 1984; Florini & Ewton, 1989; McCarter & McGee, 1987; Walters et al., 1990). Little information is available also on changes in elasticity with age of

muscles at rest. This is surprising, since passive elastic properties play an important role in regulating muscle performance in the body (Kovanen, Suominen, & Keikkinen, 1984). Energy is stored in nonactivated muscles that are stretched during movement of limbs. Passive elasticity may limit range of movement as well as the energy cost of movement. Since several reports show decreased economy of movement in the elderly (Martin et al., 1992; Pearce et al., 1983), the role of passive elastic changes of muscles with age warrants further study. An especially important case in point relates to the respiratory muscles. Significant increases in the energy costs of ventilation have been found in elderly humans, with stiffening of respiratory structures, including muscles being implicated in this occurrence (Keddan, 1980). Studies of McCarter and Kelly (1993) in Fischer 344 rats demonstrate increased stiffness of different skeletal muscles with age but the extent of increase is muscle dependent, as shown in Figure 8.6. Change in tensile strength with age has been found also in muscles of human cadavers (Yamada, 1970). Available evidence indicates increased collagen content of skeletal muscles with age, with slow-twitch muscles exhibiting higher collagen content than fast-twitch muscles (Kovanen, Suominen, Ristelli, & Ristelli, 1988).

Surprisingly few studies have examined changes with age in endurance or energy cost of contraction of skeletal muscle. Early studies by Ermini (1976) and others indicate lower levels of ATP, creatine phosphate (CrP), and glycogen in muscles of old versus young laboratory rodents. Fitts et al. (1984) found muscles of old rats had lower levels of CrP and glycogen and elevated lactate following activity. However, studies of muscles in the human forearm using noninvasive NMR techniques indicate similar levels of CrP and ATP before and after activity in adult (20–45 years) and elderly (70–80 years) individuals (Taylor et al., 1984). Consistent with these findings, several studies in rodents show no change in fatigability of skeletal muscles with advancing age (Fitts et al., 1984; McCarter & McGee, 1987; Walters et al., 1990). Endurance might be limited also by vascular supply and/or metabolic capacity of muscles of the elderly. Several studies indicate similar density of capillaries (about 350/mm^2) and similar capillary-to-muscle fiber ratio (about 1.5:1) in muscles of old and young individuals (Aniansson, Grimby, & Nygaard, 1980; Grimby, Danneskiold-Samsoe, Hvid, & Saltin, 1982). However, when selection criteria for subjects included sedentary status, reduction in capillary density was found in muscles of 25- versus 65-year-old men and women (Coggan et al., 1992A). These and earlier results suggest that physical inactivity, rather

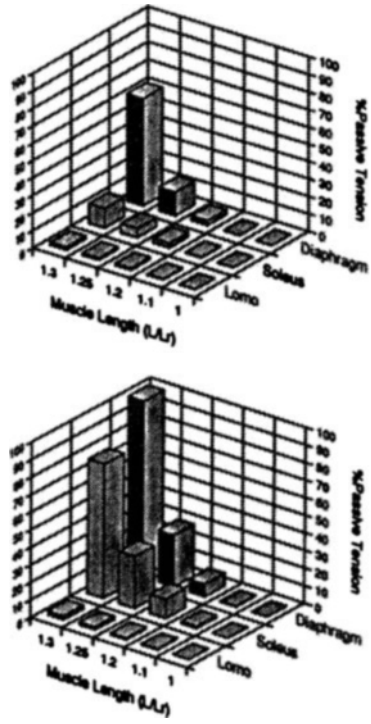

FIGURE 8.6 Resting tension versus muscle length for diaphragm, soleus and lateral omohyoideus muscles of male Fischer 344 rats of age 6 months (A) and 24 months (B). Tensions expressed as percentage of maximum tension recorded (diaphragm muscles of 24-month-old rats). (*Source:* From McCarter & Kelly, in J. Morley & R. Coe (Eds.), *Aging and Musculoskeletal Disorders* (p. 52), copyright © 1993 Springer Publishing Company, Inc., NY, 10012, used with permission.)

than inherent aging processes, limit vascular supply in muscles of the elderly. A very large number of studies have reported activities of enzymes related to glycolytic and aerobic capacity of skeletal muscles of young and old individuals. These have been recently reviewed by Rogers and Evans (1992, p. 79) who concluded that " . . . glycolytic enzyme activities . . . are not adversely affected by aging . . . " Similarly, a large number of Scandinavian studies demonstrate no loss of oxidative capacity in skeletal muscles of young versus old subjects. However, when selection criteria of subjects ensured the sedentary status of individuals (Coggan et al., 1992a), a decrease of about 25% in oxidative enzyme activity was noted in muscles

of old versus young individuals. Physical inactivity thus also appears to play a role in decreased aerobic capacity rather than aging processes in muscles of the elderly. In addition, studies in animal models show that changes in enzyme activities with age are also muscle-specific, depending upon the fiber-type distribution of muscles sampled (Holloszy, Chen, Cartee, & Young, 1991).

The capacity of aged skeletal muscle to repair damage and/or to regenerate following injury might also be a limiting factor. An important component in this process is the presence of satellite cells, which provide new myogenic cells for repair and regeneration. Gibson and Schultz (1983) reported age-related decline in the ratio of satellite cells to muscle cell nuclei in *soleus* (SOL) and *extensor digitorum longus* (EDL) muscles of Sprague-Dawley rats 1, 12, and 24 months old. Over this age range, the ratio decreased two-fold for SOL muscles and about three-fold for EDL muscles. Consistent with these results, Gutmann and Carlson (1976) reported decreased regeneration of old transplanted muscles in comparison with those transplantations associated with young rats and muscles of young rats. Similarly, lengthening contractions produced more damage in muscles of old mice than in muscles of adult or young mice (Zerba, Komorowski, & Faulkner, 1990).

In summary, reports of changes with age in skeletal muscle demonstrate great diversity of outcome. Loss of mass of some skeletal muscles appears to be an inevitable consequence of advancing age. This may be related to aging of the central nervous system, decreased loading of muscles, decreased sensory input with age, and/or loss of motor neurons (Lexell, 1993). Much more information is needed in this area, particularly relating to load-bearing versus non-load-bearing muscles in different anatomical locations, and to effects of altered hormonal status (Florini, 1987). Decreased muscle mass is due in part to loss of fibers and/or to losses in mean fiber area, particularly of fast-twitch Type II fibers. It is important to note that loss of fibers is probably irreversible and may constitute a fundamental component of aging processes. In this regard, there is evidence that the regenerative ability of muscles of the aged is impaired. On the other hand, loss of fiber area may be reversed by strategies which increase net synthesis of contractile proteins, such as exercise. The extent to which increased area of remaining fibers may fully compensate for loss of other fibers emerges as an important issue for future research. It is also not clear to what degree remaining muscle fibers are fully activated during contraction of muscles in the elderly, that is, the extent to which processes of excitation–contraction coupling may be impaired in muscles of the elderly.

A source of optimism that interventions may be effective in restoring function is that several studies show little decrease in muscle performance in healthy old individuals and laboratory animals. Performance in vivo may yet be limited by inevitable age-related changes such as increased collagen content and increased stiffness of muscles. However, such diversity of change has been identified in muscles of the aged that few changes may be inevitable consequences of inherent aging. Given the remarkable ability of skeletal muscle to adapt to altered functional needs, increased physical activity seems a promising strategy to retard age-related deterioration of muscle function.

EFFECTS OF EXERCISE ON SKELETAL MUSCLE IN THE ELDERLY

Early reports suggested the existence of a "threshold age" beyond which exercise might be detrimental to skeletal muscle (McCafferty & Edington, 1974; Steinhagen-Thiesen, Reznick, & Hilz, 1980). These studies reported atrophy of muscles and increased mortality of rats or mice forced to run on treadmills commencing at 20 months of age or older. In contrast, increased mass and survival were found for muscles of younger animals subjected to similar training protocols. More recent work in rodents and in humans demonstrates enhancement of muscle structure and function in response to both endurance and resistance-type training (reviewed by Rogers & Evans, 1993). A significant aspect of these later studies is the use of healthy laboratory animals and individuals, suggesting the earlier studies might have been compromised by training exacerbating effects of existing disease. Consistent with the ability of muscles of old animals to respond positively to rigorous exercise is the interesting report of McCormick and Thomas (1992). These authors found proliferation of satellite cells in soleus muscles of 26-month-old rats in response to 10 weeks of forced treadmill running. The more recent work also demonstrates the specificity of exercise: usually only those muscles participating in the training exhibit changes, and changes are dependent on the type of exercise involved, endurance or strength training.

There is now considerable evidence indicating advancing age does not diminish the ability of skeletal muscle to adapt to endurance training in healthy individuals. This has been demonstrated for muscles of elderly men and women and for muscles of old laboratory rodents, provided the inten-

sity and duration of the exercise are of sufficient magnitude. For example, the early work of Suominen, Heikkinen, and Parkatti (1977a) demonstrated only modest increase (10%–15%) in aerobic capacity of skeletal muscle in men and women 69 years of age. This was in response to 8 weeks of low-intensity aerobic training. Increasing the intensity of exercise resulted in marked increase (45%) in aerobic capacity in muscles of 56–70-year-old sedentary men (Suominen, Heikkinen, Liesen, Michel, & Hollmann, 1977b). Intensity of exercise has been assessed in terms of the percentage of maximum oxygen consumption ($\dot{V}o_{2max}$), percentage of maximum heart rate (%HRmax) and percentage of maximum heart rate reserve (%HRR) of the individual measured during the exercise (Rogers & Evans, 1993). On this basis, for example, Meredith et al., (1989) compared effects of vigorous endurance training in 24-year-old and 65-year-old men and women. All subjects exercised for 12 weeks (3 days/week) at 70% of heart rate reserve. Increase in oxidative capacity of muscles was significant for both groups and was almost five-fold greater for muscles of older individuals (128% vs. 27%, old vs. young, respectively). Örlander and Aniansson (1980) exercised elderly men (about 71 years old) 45 minutes per day, 3 times per week, for 12 weeks at 70% of $\dot{V}o_{2max}$. They found significantly increased activity of muscle cytochrome C oxidase but surprisingly no change in other oxidative enzyme activities. Coggan et al., (1992b) conducted an extensive investigation of the effects of 10 months of endurance training on muscle function in healthy 65-year-old men and women. Subjects exercised 45 minutes per day, 4 days per week at an intensity of 80% of maximal heart rate. Activities of enzymes related to oxidative metabolism were significantly increased following training, whereas those related to glycolytic capacity were not affected (with the exception of lactate dehydrogenase which was decreased by training). Capillary density and capillary-to-fiber ratio were increased by the exercise. Increased mean fiber area of Type I fibers and conversion of Type IIb to Type IIa fibers was also noted. These results are similar to adaptations to endurance exercise found in young adults (Gollnick et al., 1973). In a previous study, Coggan et al. (1990) also demonstrated significantly higher oxidative enzyme activity, Type I fiber area, and capillary-to-fiber ratio in muscles of master athletes (average age 63 years) than those of young runners (average age 26 years). Thus, the enhanced performance benefits of endurance training appear to be cumulative and may be sustained regardless of advancing age in men and women.

Results obtained in laboratory animals are consistent with and extend these observations. For example, Daw, Starnes, and White (1988) and Brown, Ross, and Holloszy (1992) found that long-term endurance training in rats resulted in prevention of age-related atrophy in soleus muscles but not in *extensor digitorum longus* (EDL) muscles. Similarly, Fitts et al. (1984) found that voluntary wheel running in rats from 6 to 28 months of age resulted in significant increase in mass of soleus muscles but did not prevent age-related decrease in mass of EDL muscles. Farrar, Martin, and Ardies (1981) reported increased respiratory capacity (27%–54%) of intermyofibrillar and subsarcolemmal mitochondria of 24-month-old Sprague-Dawley rats following 6 months of endurance training. Young, Chen, and Holloszy (1983) demonstrated that swimming activity from 6–24 months of age in Long-Evans rats increased oxidative enzyme activity significantly (20%–40%). Not all age-related characteristics are retarded by endurance exercise. In an interesting series of experiments, Kovanen and colleagues (Kovanen et al., 1988; Kovanen & Suominen, 1989) found that lifelong (1–24 months) endurance training enhanced the age-related increase in Type IV collagen of soleus muscles of male Wistar rats, but there was no such effect of training in *rectus femoris* muscles of these rats.

Effects on skeletal muscle of resistance or strength training have been investigated extensively in elderly men and women. Relatively few studies have been reported in old laboratory animals, probably because of technical problems of implementing the regimen. This type of exercise has been particularly effective for maintaining or increasing muscle function in men and women throughout life, but especially in those 70 years of age and older. It should be noted, however, that most studies in this area have involved muscles of the thigh, particularly the quadriceps. Animal studies showing diversity of muscle responses to age and training indicate caution should be exercised in generalizing these results.

Early studies indicated only modest effects of strength-type exercise on muscle mass and function in the elderly. For example, Aniansson, Ljungberg, Rundgren, and Weltequist (1984) reported that 26 weeks of concentric/eccentric exercise, 3 times per week, resulted in a 9% increase in strength of quadriceps muscles in women of average age 73 years. More recent studies especially in the very old, (reviewed by Rogers & Evans, 1993), have demonstrated massive increase (up to 200%!) of muscle strength, together with modest increases of total muscle and mean type I and type II fiber areas. A feature of recent studies, by Evans and colleagues in particular, is the use of high-intensity regimens in which subjects exer-

cise at 80% of their one repetition maximum load (1RM). The load is progressively increased as muscle strength increases, with rapid and dramatic improvement of muscle function, as shown in Figure 8.7. In this example, Frontera and colleagues (1988) exercised knee flexors and extensors of elderly men (average age 66 years) for 12 weeks at 80% of 1RM. Muscle strength increased by about 5% per day, so that at the termination of training flexor strength was 200% greater than at the start of the study. Cross-sectional area of quadriceps increased by 11% and mean areas of type I and type II fibers increased by 34% and 28%, respectively. This training regimen also resulted in increased muscle oxidative enzyme activity, capillary density and increased excretion of 3-methyl-L-histidine, indicative of increased myofibrillar protein turnover (Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988). Similarly, Brown, McCartney, and Sale (1990) found increased area of type I, type II fibers and 48% increase in strength of biceps brachii muscles following 12 weeks of weightlifting in older men of average age 63 years. In this interesting study, strength of the control untrained arm also increased by 12% and there was increased endurance of the trained arm. Grimby et al. (1992) demonstrated increased strength and electromyographic activity in quadriceps muscles of healthy men aged 78–84 years in response to dynamometer training. The specifity of training was demonstrated by the results of Klitgaard et al. (1990). These authors found that muscle cross-sectional area in 70-year-old men who participated in regular resistance exercise was similar to that of 28-year-old sedentary men. However, cross-sectional area of muscles in 70-year-old men who were sedentary, or who undertook regular swimming or running activity was 20%–24% less than the control group.

Perhaps the most persuasive demonstration of the remarkable ability of skeletal muscles of the elderly to respond to resistance training is the series of studies by Fiatarone and colleagues. In these studies, hip and knee extensors of old, institutionalized men and women (age range 72–98 years) were strength-trained for 8–10 weeks, 3 days per week, 45 minutes per day, at an intensity of 80% of 1RM. Results were impressive. In an initial, uncontrolled study involving 3 men and 6 women of average age 90 years, quadriceps strength increased by 174% and muscle cross-sectional area increased by 15% after 8 weeks of progressively increasing resistance training (Fiatarone et al., 1990). The men and women of this study exhibited significant improvement in mobility also. A subsequent recent study (Fiatarone et al., 1994) utilized 100 frail nursing home residents of average age 87 years. Training extended over 10 weeks, 3 days/week, 45 min-

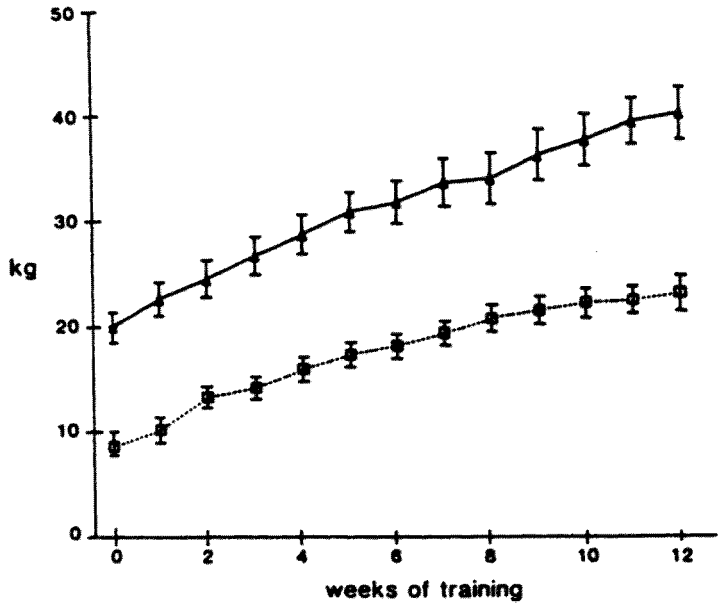

FIGURE 8.7 Dynamic strength (1RM) of knee extensors (solid symbols) and flexors (open symbols) versus weeks of resistance training in 12 men of average age 66 years. (*Source:* From W.R. Frontera, C.N. Meredith, K.P. O'Reilly, H.G. Knuttgen, & W.J. Evans, strength conditioning in older men: skeletal muscle hypertrophy and improved function. *Journal of Applied Physiology, 64;* 1041, copyright © 1988, used with permission of the American Physiological Society.)

utes/day at 80% of 1RM. Knee extensor muscle strength increased by 113%, gait speed increased by 12%, and spontaneous activity increased by 28%. This effect of strength training on physical activity is illustrated in Figure 8.8. Muscle cross-sectional area of these individuals increased by 2.7%, whereas in control sedentary subjects cross-sectional area decreased by 1.8%. Nutritional supplementation (360 kcals/day) in a second group of resistance-trained individuals did not produce any significant improvement in muscle function over that induced by training alone. The few studies available involving resistance-training of old laboratory animals have produced data consistent with the human trials. Klitgaard, Marc, Brunet, Vandewalle, and Monod (1989) found age-related decline in mass and active tension development of hindlimb muscles (*soleus* and *plantaris*) of Wistar rats was offset by 20 weeks of strength training. The training also

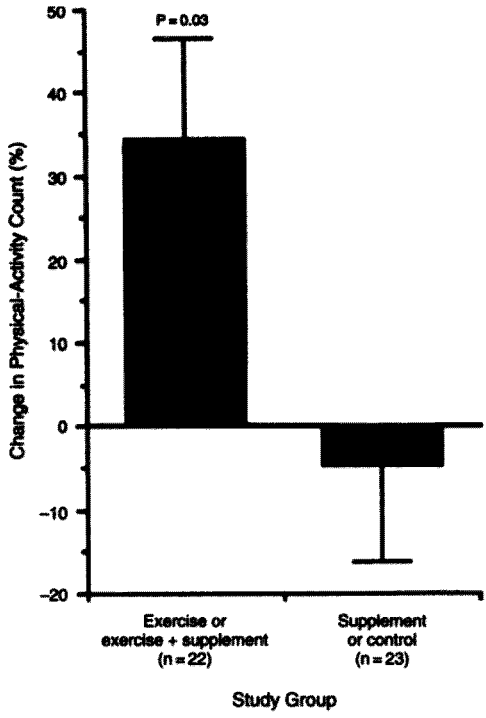

FIGURE 8.8 Change in daily spontaneous activity following 10 weeks of resistance training, training plus supplemental nutrition, no training or supplemental nutrition alone in 100 men and women of average age 87 years. (*Source:* From A.M. Fiatarone et al., Exercise training and nutritional suplementation for physical frailty in very elderly people. Reprinted by permission of the *New England Journal of Medicine, 30;* 1774, copyright © 1994.)

led to increased muscle glycogen concentration. In contrast, swim training of similar rats did not counteract the aging effects. Brown (1989) found that strength training of old Sprague-Dawley rats (21, 24, 27 months old) resulted in hypertrophy of *palmaris longus* (wrist flexor) muscles.

In summary, it seems unlikely that there exists a "threshold age" beyond which exercise may be detrimental in healthy older individuals. Current evidence suggests age-related decline in muscle mass, fiber area, and especially strength may be retarded by high-intensity strength training. Moreover, decreased aerobic capacity and capillary density of muscles with

age may be counteracted by vigorous endurance training. Studies of strength training also suggest that activation of existing muscle fibers may be a significant problem in the elderly, since major improvements of strength were accompanied by only modest increases of muscle cross-sectional area following training. Thus, although loss of some motor units and muscle fibers may be inevitable components of aging, available evidence indicates a combination of high-intensity strength and endurance training may significantly improve muscle function in the elderly. There is some evidence to suggest such improvement may also enhance mobility and therefore quality of life of the elderly.

SYSTEMIC EFFECTS OF EXERCISE IN THE ELDERLY

Increased physical activity directly impacts skeletal muscle but also modulates other physiologic systems. Aging and related diseases are associated with altered states of many of these systems. The impact of exercise on selected functions will be considered briefly since detailed reviews of these areas are available elsewhere (e.g., Borst, Millard, & Lowenthal, 1994; Holloszy & Khort, 1995; Lakatta, 1993; McCarter, 1995; Tipton & Vailas, 1990).

A characteristic feature of advancing age is decreased capacity for aerobic activity or decreased rate of maximum oxygen consumption ($\dot{V}o_{2max}$). The $\dot{V}o_{2max}$ represents the greatest rate at which oxygen may be consumed during increasingly intense exercise that utilizes large muscle masses, such as during strenuous running. Many studies (reviewed by Hagberg, 1987) indicate this quantity decreases linearly (about 1% per year) with advancing age in healthy men and women. $\dot{V}o_{2max}$ provides an upper limit to the amount of aerobic activity that an individual can undertake. When this falls to the level of the basal metabolic rate (BMR) presumably even minor activities of normal daily living are not possible. Several factors such as disease, genetic background, muscle mass, etc., are thought to influence the $\dot{V}o_{2max}$. However, regular intense physical activity, such as endurance training, exerts a major effect. The $\dot{V}o_{2max}$ of highly trained athletes is about 50% higher than that of untrained individuals (Grimby & Saltin, 1966). Several studies indicate the ability of elderly men and women to increase $\dot{V}o_{2max}$ by training (increase of about 25%) is similar to that achieved by young adults (e.g., Hagberg et al., 1989; Kohrt et al., 1991). The increased $\dot{V}o_{2max}$ produced by exercise in elderly men, (as in young individuals) is a

consequence of increased maximal cardiac output and increased arteriovenous oxygen difference. In contrast, evidence in elderly women suggests the increased $\dot{V}o_{2max}$ of exercise training may be accomplished entirely by increased extraction of oxygen (Spina et al., 1993a,b). Decreased $\dot{V}o_{2max}$ with age is associated with diminished maximal cardiac output, or Qmax (Tate, Hyek, & Taffet, 1994). This quantity is in turn the product of maximal heart rate (HRmax) and maximal stroke volume (SVmax). Both HRmax and SVmax diminish with advancing age. HRmax decreases at the rate of about 1 beat per minute per year and this decline is not affected by exercise training (Ehsani, Ogawa, Miller, Spina, & Jilka, 1991). Decreased SVmax with age is associated with diastolic dysfunction, slower filling of the heart during diastole, and this function is modulated by endurance exercise, even in the elderly (e.g., Levy, Cerqueira, Abrass, Schwartz, & Stratton, 1993). Mechanisms responsible for the exercise-induced change of contractile properties of the heart are not known, but are associated with altered gene expression (Tate et al., 1994). There is also evidence for the involvement of the autonomic nervous system in these effects. In young adults the principal mechanism responsible for increasing heart rate during exercise is withdrawal of parasympathetic (vagal) input to the sinoatrial node, followed by increased sympathetic activity and the release and binding of norepinephrine to ß-adrenergic receptors. With advancing age the exercise-induced increase in heart rate is blunted, due in part to less withdrawal of vagal tone and also to decreased ß-adrenergic responsiveness (Taylor, Hand, Johnson, & Seals, 1991). Although tissue content of catecholamines increases with advancing age in humans, there are increased levels of circulating plasma catecholamines in the elderly (Roberts & Tumer, 1987), leading possibly to blunted ß-adrenergic responsiveness. The combination of impaired chronotropic and inotropic responses to ß-adrenergic stimulation are thought to contribute to age-associated decline of aerobic capacity and $\dot{V}o_{2max}$ (Seals, Taylor, Ng, & Esler, 1994).

Decreased bone density is another characteristic feature of advancing age in men and women. Loss of bone commences from about 25 years of age onwards in women and from about 35 years of age in men. It is accelerated in post-menopausal women and in conditions associated with inactivity of skeletal muscle, such as limb immobilization (Thomas, 1994). Weight-bearing exercise and strength-training have been demonstrated to retard the age-associated loss of bone mass (American College of Sports Medicine, 1990). This has been dramatically confirmed in the elderly by

the recent results of Nelson, Fiatarone, Morgani, Tice, and Evans (1994). These authors found 12 months of strength training (40 minutes per day, 2 times per week at 80% of 1RM) prevented age-related bone loss in women aged 50–70 years. There appears to be a good correlation between muscle mass and bone mass, with athletes and more muscular individuals having greater bone density (Doyle, Brown, & Lachance, 1970; Nilsson & Westlin, 1971). An endocrine link exists for bone and muscle mass in the circulating levels of growth hormone (GH) and insulin-like growth factor (IGF-1). The pulsatile release of GH from the anterior pituitary is age related, with secretion integrated over 24 hours being 29%–70% less in elderly than in young men (Corpas, Harman, & Pineyro, 1992; Iranmanesh, Lisarralde, Veldhuis, 1992). GH stimulates production of IGF-1 in muscle, bone and other tissues, and IGF-1 mediates many of the trophic functions of GH. Several studies have established the effectiveness of GH administration for increasing lean mass and reducing adipose mass in the elderly. Rudman et al. (1990) found that replacement doses of GH in elderly men (60–81 years of age) who had low levels of circulating IGF-1 resulted in an average gain of 3.7 kg of lean mass and loss of 2.4 kg of adipose tissue over a 6-month period. Marcus et al. (1990) found that acute administration (7 days) of higher than replacement doses of growth hormone to elderly men and women resulted in increased bone turnover, increased levels of circulating IGF-1 and a positive nitrogen balance. The potential importance of GH replacement therapy for retarding age-related loss of skeletal muscle and bone is tempered by significant side effects. These include carpal tunnel syndrome, insulin resistance, and gynecomastia (Marcus et al., 1990; Rudman et al., 1990). On the other hand, several studies have demonstrated the effectiveness of moderate-to-high-intensity exercise in stimulating GH secretion. In young adults, acute aerobic exercise (at 40%–70% $\dot{V}o_{2max}$) and resistance exercise (at 70%–85% of 1RM) stimulates GH secretion (reviewed by Borst et al., 1994). Pyka, Wiswell, and Manus (1992) found a threshold intensity for GH secretion during resistance exercise of about 70% 1RM in young individuals (average 27 years old). However, there was no significant GH secretion in healthy elderly subjects at the same intensity. Similarly, Hagberg, Seals, and Yerg (1988) found higher levels of IGF-1 in young men undergoing endurance training, but not in elderly men.

Altered carbohydrate metabolism may also limit performance of the elderly. For example, the onset of muscle fatigue and ability to sustain endurance exercise at 50% $\dot{V}o_{2max}$ are determined by levels of glycogen in

skeletal muscle (Hultman, 1967) and there is decreased glycogen content in muscles of the elderly (Meredith et al., 1989). Studies in laboratory rats indicate that endurance training of both young and old rats leads to similar "glycogen sparing," that is, trained animals deplete muscle glycogen stores by smaller amounts following a given bout of exercise (Cartee & Farrar, 1988). However, muscle activity leads to greater loss of glycogen in muscles of old (28-month-old) than adult (9-month-old) rats (Fitts et al., 1984). There is also considerable evidence for age-related development of insulin resistance and glucose intolerance (reviewed by Jackson, 1990). Holloszy and Kohrt (1995) argue that this development may be related to central adiposity, specifically to increased abdominal fat, rather than to aging per se. For instance, Kohrt et al. (1993) examined insulin resistance in young and old men and women who ranged from insulin-sensitive to insulin-resistant. Age accounted for less than 2% of the variance in insulin resistance when waist girth was taken into account, with centrally-located body fat emerging as the major factor in this effect.

Since exercise training leads to maintenance of lean mass and reduced adiposity, regular intense physical activity may retard the development of age-related insulin resistance via its effect on body composition (Holloszy & Khort, 1995). Indeed, evidence indicates preferential loss of abdominal fat following endurance exercise training in elderly individuals who were previously sedentary (Kohrt, Robert, & Holloszy, 1992; Schwartz et al., 1991). Also, several studies show body fat contents of older athletes are significantly less than those of sedentary age-matched controls and comparable to those of young, untrained individuals (Coggan et al., 1990; Meredith et al., 1989). Exercise training may be effective in treating non-insulin-dependent diabetes mellitus (NIDDM) if this is related to insulin resistance rather than to insulin deficiency, for reasons outlined before: insulin resistance due to increased abdominal adiposity may be counteracted in the long-term by the effect of vigorous exercise in reducing central fat stores. Another acute effect of exercise is the stimulation of glucose transport across cell membranes of skeletal muscle (Holloszy & Narahara, 1965). This insulin-like action of exercise persists for only a short time after the bout of activity, but there is a significant and long-lasting increase in muscle responsiveness to insulin following exercise (Garetto, Richter, Goodman, & Ruderman, 1984; Gulve, Cartee, Zierath, Corpus, & Holloszy, 1990). These effects of exercise provide enhanced ability to maintain carbohydrate homeostasis in individuals who are insulin-resistant. These benefits were demonstrated by the work of Reitman, Vasquez,

Klimes, and Nanglesparan (1984), who found significant improvement in glucose tolerance in Pima Indians having NIDDM following eight weeks of vigorous activity, exercising 5–6 days per week. Vigorous exercise training, however, also results in decreased secretion of insulin (Le Blanc et al., 1981). This effect would be counterproductive in individuals having NIDDM associated with insulin deficiency.

Mechanisms by which exercise modulates glucose metabolism in adipose and muscle tissue have been examined in considerable detail. These studies mostly have involved tissues of laboratory rodents, although similar results have been found using muscle and fat cells of men and women (Cartee, 1994). Exercise and insulin stimulate glucose transport in skeletal muscle at least in part as a consequence of recruiting additional carrier proteins (GLUT-4) from intracellular storage sites to the surface membrane (Birnbaum, 1992). There is also evidence suggesting the possibility of increased intrinsic activity of transporter proteins (King, Hirschman, Hertan, & Horton, 1989). Since effects of muscle activity and insulin are additive, it is possible that different intracellular storage sites are mobilized in response to these two stimuli (Nesher, Karl, & Kipnis, 1985). With development (rather than aging) there is decreased concentration of GLUT-4 transporter protein in many, but not all, skeletal muscles. Transporter concentration in a wide variety of muscles appears to be unchanging between adulthood and old age (reviewed by Cartee, 1994). Studies in middle-aged to older men and women show that both acute and long-term exercise lead to significant increase (almost two-fold) in levels of GLUT-4 in muscle. For example, Hughes et al. (1993) demonstrated that 122 weeks of cycling at only 50% of HRR in glucose-intolerant older men and women (average age 64 years) resulted in a 1.6-fold increase in GLUT-4 concentration of *vastus lateralis* muscles and improved whole-body insulin sensitivity. These effects provide further illustration of exercise modulating deleterious consequences of advancing age or enabling adaptation to these consequences.

Another example in this regard concerns the effects of exercise on the well-known decline of metabolic rate with age. Total Daily Energy Expenditure (24EE) has been estimated from studies of daily caloric intake and by indirect calorimetry in humans and laboratory rodents (reviewed by McCarter, 1995). McGandy et al. (1966), in a cross-sectional study of 252 healthy men ranging in age from 20 to 99 years, concluded that 24EE decreases with age. Vaughan, Zurlo, and Ravussin (1991) studied 24EE of men and women aged 18 to 85 years in a large respiratory chamber. Total daily energy expenditure was significantly lower in older (average

71 years) than in younger (average 24 years) individuals. However, when results were normalized to fat-free mass, age was not a major determinant of 24EE. Basal metabolic rate (BMR) is by far the major component of 24EE, accounting for 60–75% of 24EE. A large number of studies, using both cross-sectional and longitudinal designs, shows decreased BMR with advancing age (reviewed by Poehlman & Horton, 1990). Interpretation of these data is complicated by the many different normalization procedures used to compare rates of metabolism of individuals of varying body composition and size (reviewed by McCarter, 1995). There is agreement that much of the decline in BMR with age is a consequence of decreased skeletal muscle mass (Tzankoff & Norris, 1977). However, several reports indicate decreased BMR, or resting metabolic rate (RMR) in elderly versus young individuals, independent of differences in fat-free mass (Fukagawa, Bandani, & Young, 1990; Vaughan et al., 1991). These results suggest that altered tissue composition and/or decreased intensity of cellular energy metabolism may also play a role in the age-related decrease of BMR.

The contribution of physical activity to total daily energy expenditure is large and variable (15%–30% of 24EE). Results of Ravussin, Lillioja, Anderson, Christin, and Bogaardus (1986) demonstrate that differences in spontaneous activity account for much of the variation of 24EE between individuals regardless of differences in body size. Age-related decline of 24EE and BMR have potentially deleterious consequences: decreased energy output in the face of unaltered energy intake may lead to increased adiposity, as is commonly encountered with advancing age. Alternatively, decreased energy intake to offset the decreased energy output involves the possibility of malnutrition. This could occur if intake of essential vitamins and minerals falls below daily requirements as a consequence of reduced food intake. Habitual physical activity, therefore, offers a promising strategy to maintain 24EE with advancing age and to avoid the complications of increasing adiposity or malnourishment. Stimulation of skeletal muscle produces a massive increase in energy expenditure. The metabolic rate of active muscle fibers may increase 100-fold above resting levels, and, if large muscle groups are activated, whole body metabolic rate may increase ten-fold during exercise. The nature and intensity of the exercise (e.g., strength-training versus endurance training) determines the level to which metabolism is increased. The use of resistance training to counter effects of declining 24EE with age is illustrated by the recent study of Campbell, Chim, Young, and Evans (1994). These authors measured body composi-

tion, muscle strength, and energy metabolism in 8 men and 4 women aged 56–80 years, before and after 12 weeks of resistance training (upper and lower body exercises at 80% of 1RM, 3 days/week). Muscle strength increased by 24%–92% as a consequence of training. Initial body weights were maintained during training and this required increased energy intake of about 15% over initial values. The mean RMR increased by 6.8% after training, as shown in Figure 8.9. This increase was significant when normalized to body weight and protein plus mineral mass, but not significant when expressed relative to FFM or body cell mass. There was a significant decrease in fat mass (1.8 kg) and significant increase in FFM (1.4 kg), although the latter appeared due to increased body water rather than to increase in metabolic mass. These results demonstrate the effectiveness of resistance training in healthy older individuals for increasing RMR and nutrient intake, while decreasing fat mass. Studies of the effects of endurance exercise on BMR have produced equivocal results, with evidence for both increase and no change in BMR following training. In reviewing these results, Poehlman and Horton (1990) suggest that differences in outcome may be related to the intensity of exercise involved in the various studies. There is evidence that endurance training does not result in less physical activity at other times of the day (Goran & Poehlman, 1992); however, the same study found that endurance training, in contrast to resistance training, does not increase total energy expenditure in healthy, elderly individuals.

A final example of the broadly protective effects of exercise in old age comes from a study of thermo regulation in rodents by McDonald, Horowitz, and Stern (1988). These authors trained 24-month-old male Fischer 344 rats on treadmills for 6 months (20 m/minute on a level surface, 60 minutes/day, 5 days/week). When subjected to a cold challenge (6 hours at 6°C) the core temperature of elderly sedentary rats decreased from 36.3°C to 31.2°C, whereas that of trained rats decreased only 1.1°C, from 36.4 to 35.3°C.

EFFECTS OF EXERCISE ON LONGEVITY

Aging is characterized by declining function and decreased ability to maintain homeostasis in the face of challenge. It is not surprising therefore, that habitual exercise is widely viewed as a potential strategy to slow the rate of aging. The previous discussion demonstrates the effectiveness of

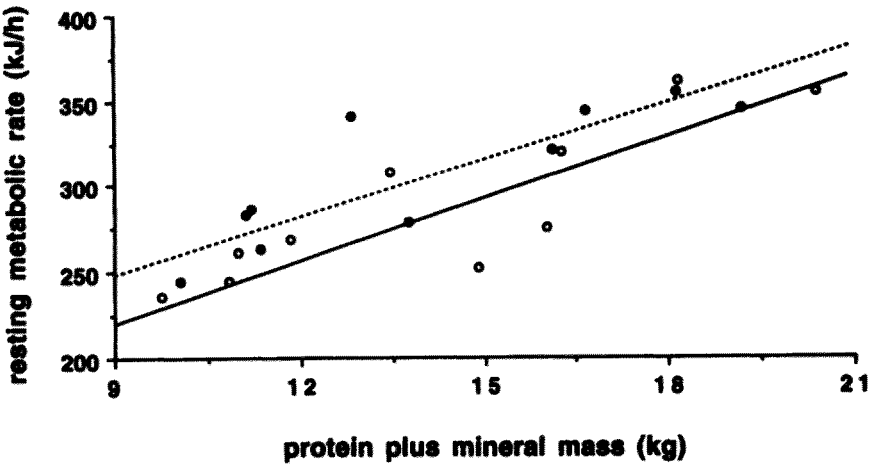

FIGURE 8.9 Resting metabolic rate versus protein plus mineral mass of 10 men and women (average age about 65 years) before (open symbols) and after (solid symbols) 12 weeks of resistance training. (*Source:* From Campbell, W.W., Crim, M.C., Young, V.R., & Evans, W.J. Increased energy requirements and changes in body composition with resistance training in older adults, *American Journal of Clinical Nutrition, 60;* 172, copyright © 1994, used with permission of the American Society for Clinical Nutrition.)

regular exercise in counteracting many of the deleterious consequences of advancing age. Also, several epidemiological studies in men and women indicate increased life expectancy associated with regular physical activity. One of the first such studies was that of Paffenbarger et al. (1986). These authors determined levels of physical activity and mortality in a longitudinal study extending over 16 years in about 17,000 male Harvard alumni. At every age there was decreased mortality in those individuals devoting 2,000 to 3,500 kcal/week to physical activity when compared with those individuals expending more or less weekly energy on exercise. Life expectancy was estimated to be increased by about 1.5 years as a consequence of this activity. Such extension of life expectancy, or 50% mortality, does not however, provide evidence of decreased rate of aging. Although there is considerable debate regarding definitions of aging, many gerontologists regard evidence of increase in mortality rate doubling time (MRDT), increase in age of 10th percentile survivors (maximum lifespan), delayed functional decline, and altered pathology, as prerequisites to establish retardation of aging processes (Finch, 1990).

To date only caloric restriction in laboratory rodents has been demonstrated to meet all of these criteria (Masoro, 1988). This author is aware

of no studies examining effects of lifelong resistance exercise on mortality. However, many studies have examined effects of endurance exercise on survival in laboratory rodents (reviewed by McCarter, 1994). It seems likely that early work showing decreased survival with endurance exercise (e.g., Benedict & Sherman, 1937) may have been compromised by the stress of exercise exacerbating effects of disease in non-barrier-maintained rats. Later studies indicate increased longevity with endurance-type exercise. Goodrick (1980) found that in male and female Wistar rats 50% survival and maximum lifespan were increased by about 4 months when voluntary wheel running was initiated at 1.5 months of age. Since increased maximum lifespan is an important criterion for determining slowing of aging processes, these data suggest lifelong endurance-type exercise might retard the rate of aging. In contrast, Holloszy and colleagues found no effect of voluntary wheel running on maximum lifespan in male or female Long-Evans rats, as shown in Figure 8.10 (Holloszy et al., 1985; Holloszy, 1993). The Long-Evans rats used by this group were known to be free of specific pathogens, whereas the Wistar rats of the earlier study were housed under conventional (non-barrier) conditions. It is possible therefore, that the increased maximum lifespan found by Goodrick (1980) might have been a consequence of exercise providing protection from infectious disease, rather than due to retarded aging (Holloszy, Smith, Vining, & Adams, 1985). Results found by McCarter and Palmer (1991) demonstrate similar effects in specific-pathogen-free male Fischer 344 rats; lifelong voluntary wheel running resulted in significant increase in age of 50% survival but no increase in maximum lifespan. Available data using laboratory rodents known to be free of infectious disease thus indicate that sustained endurance-type exercise increases longevity but does not increase maximum lifespan. Such exercise may prolong the average lifespan by enhancing the ability to deal with the challenges of disease. However, available data do not support a role for exercise in slowing the rate of aging. Moreover, it is possible that beneficial effects of exercise on aging processes might be offset by deleterious effects, such as increased generation of damaging free radicals, as suggested by the data of Ji (1993). It should be noted also that some recent studies (such as by Beauchenne, Dellwo, Darabian, Haley-Zitlin, & Wright, 1990) indicate no effect of lifelong exercise on survival. These data suggest a threshold level of intensity of exercise may exist for realizing longevity effects as noted previously for functional effects.

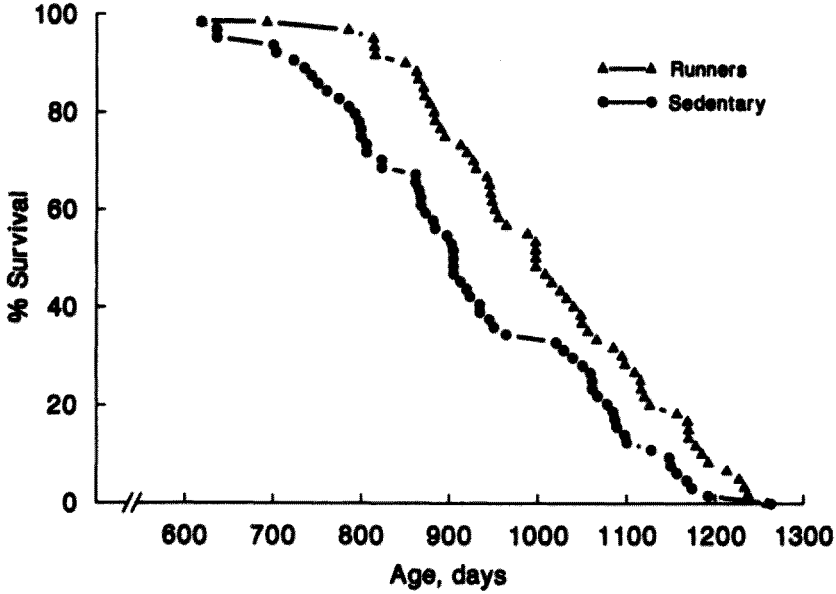

FIGURE 8.10 Survival with age of female Long-Evans rats with and without voluntary wheel running. (*Source:* From Holloszy, J.O., *Journal of Gerontology, 48;* B99, copyright © 1993, used with permission.)

CONCLUSIONS

The preceding discussion demonstrates the important emerging role of regular exercise in counteracting deleterious aspects of aging. It seems likely that many of these deleterious aspects are the result of an increasingly sedentary lifestyle, rather than inevitable consequences of aging processes. In this view, habitual physical activity is protective against changes in body composition and functional deterioration caused by too little exercise. This is consistent with an evolutionary view of the intensity of human activity required for successful adaptation, with the necessary intensity decreasing markedly only during the immediate past in industrialized nations (Åstrand, 1992; Holloszy & Kohrt, 1995). The view is also consistent with survival data in laboratory rodents which suggest beneficial effects of exercise are not related to primary aging processes. An important insight from current research is that threshold levels of intensity may be required to induce changes in body composition and function. However, present results demonstrate dramatically that given appropriate intensity beneficial effects of exercise may be realized at any age, even in

nonagenarians. Some effects of aging may be inevitable, such as the loss of muscle fibers secondary to loss of motor neurons in the central nervous system or increased stiffness of muscles due to accumulation and crosslinking of collagen. Available evidence suggests the frailty of old age may be related to ineffective use of fibers remaining in muscles of the elderly rather than to catastrophic decrease in muscle fiber number. Also, the role of age-related changes of proprioceptive reflexes in physical activity remains to be established. However, the ability of remaining muscle fibers to respond to increased demands appears remarkably intact with age. Regular, intense physical activity of both resistance and endurance type thus offers considerable promise for improving the quality of life of the elderly.

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CHAPTER 9

Cholesterol and the Healthy Senior

RAHMAWATI SIH
DIVISION OF GERIATRIC MEDICINE
SAINT LOUIS UNIVERSITY HEALTH SCIENCES CENTER

Cholesterol has become of increasing interest to the American public, as it is well recognized that an elevated level of cholesterol is a risk factor for coronary artery disease, particularly in the young and middle-aged population. With aging, there is an increasing prevalence of and mortality from coronary artery disease (Agner, 1984–85; Elveback & Lie, 1984; White, Edwards, & Dry, 1950). Hyperlipidemia is not a clear predictor of the risk of atherosclerosis in the older population, and the benefit of lowering cholesterol in seniors to quality of life, morbidity, and mortality is questionable.

CHANGES OF LIPID LEVELS WITH AGE

The lipoproteins are particles that function to transport lipids, primarily the cholesteryl esters and triglycerides, through the bloodstream. The lipoproteins are composed of a core composed of varying amounts of triglycerides and cholesteryl esters, surrounded by phospholipids, unesterified cholesterol, and specific proteins termed *apoproteins*. The apoproteins function as binding sites for enzymes, transport proteins and thus guide the lipoproteins to various sites for further metabolism. The composition of the lipid core, the types of apoproteins, the density, and the size of the lipoprotein determine its class. The five major classes of lipoproteins include the chylomicrons, VLDL (very low density lipoproteins), IDL (intermediate density lipoprotein), LDL (low density lipoprotein) and HDL (high density lipoprotein).

In most industrialized societies, serum cholesterol and serum triglyceride levels increase through middle age. The rise in serum cholesterol is

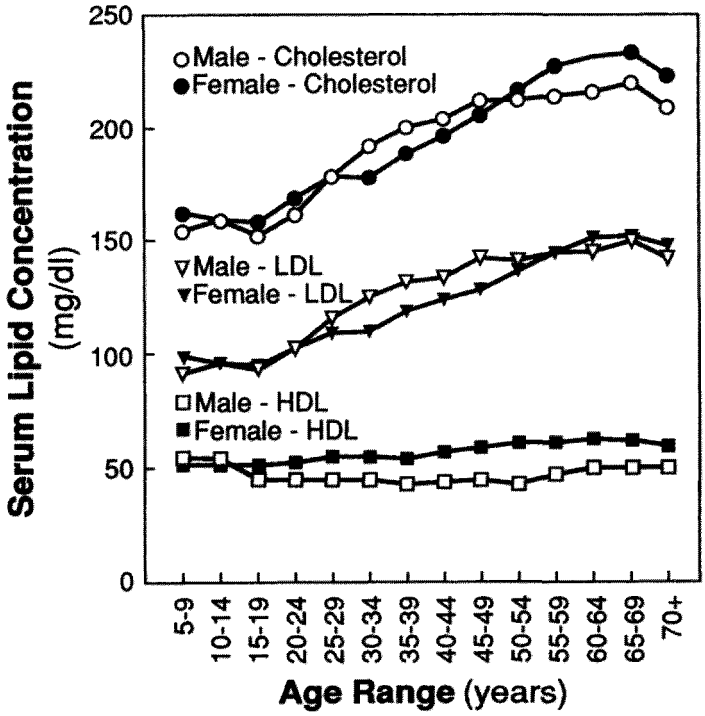

FIGURE 9.1 Changes in serum lipid profile with aging. Median serum total cholesterol, low density lipoprotei, and high density lipoprotein concentrations for men and women in the United States at 5-year intervals. (*Source:* Adapted from *The Lipid Research Clinics Population Studies Data Book* [1980]. Bethesda, MD: U.S. Department of Health and Human Services/PHS/NIH, Vol. I: 52–53, 70–77. Used with permission.)

due, primarily, to the increase in LDL while the rise in triglyceride levels reflect an increase in VLDL. Data from the Lipid Research Clinics show that cholesterol levels increase in men up to about 50 years of age, then plateau and finally decline at about age 70. In women, cholesterol levels increase with age up to ages 65 to 69 prior to falling. These same changes are also seen in LDL levels (Figure 9.1)

Cholesterol makes up about 45% of LDL by weight. The role of LDL is to carry cholesterol to nerve tissue, cell membranes, and cells that

require cholesterol for metabolic function including synthesis of steroid hormones. The age-associated rise in LDL may be due to an increase in LDL production and/or a decrease in its breakdown. Studies however, are conflicting. Data analyzed from 27 prior studies found a decline in the breakdown or fractional catabolic rate of LDL apoprotein B but no change in the rate of LDL production with age (Miller, 1984). The decrease in the fractional catabolic rate of LDL apoprotein B has been confirmed by other studies (Ericsson, Eriksson, Berglund, Einarsson, & Angelin, 1986; Grundy, Vega, Bilheimer, 1985; Kesianiemi, 1987), but Grundy et al. (1985) also described an increase in LDL production. These data may reflect more obese older subjects in the study.

The actual mechanism of the age-related decline in LDL breakdown is not known. Some of the current hypotheses include an increase in LDL autoantibodies and immune complexes, a decrease in LDL receptor activity in hepatic tissues, a decline in LDL receptor affinity due to age-related changes in the apo B portion of the LDL molecule, a decrease in LDL receptor expression, and the suppression of LDL receptor synthesis due to accumulation of tissue cholesterol with advancing age (Miller & Nanjee, 1992).

HDL levels are similar between the sexes during childhood, but at puberty HDL declines in boys and remains stable until the middle of the fifth decade when it slowly rises. HDL levels slowly climb in women throughout adult life until late in the fifth decade after which it falls. Figure 9.1 summarizes the population studies in North America of changes of serum cholesterol concentrations with age.

HDL is produced by the liver and intestines, and by the peripheral catabolism of chylomicrons and VLDL. Gonadal steroids may influence the decrease of HDL at puberty and the increase in the mid-50s in men. A positive correlation is generally found between plasma testosterone and HDL concentrations in adult men, and the higher levels of HDL in prepubertal and aged men (when testosterone levels are lower) may reflect the interaction between testosterone, estrogen, and adiposity (Laskarzewski et al., 1983). The higher plasma HDL levels observed in premenopausal women compared to men may be explained by lower hepatic lipase activity. Hepatic lipase is involved in HDL catabolism. A greater rate of apoprotein AI production, the major protein of HDL, and higher lipoprotein lipase activity are other factors which may also account for the differences in the HDL levels of women and men. Lipoprotein lipase influences HDL levels through the breakdown of triglyceride-rich lipoproteins.

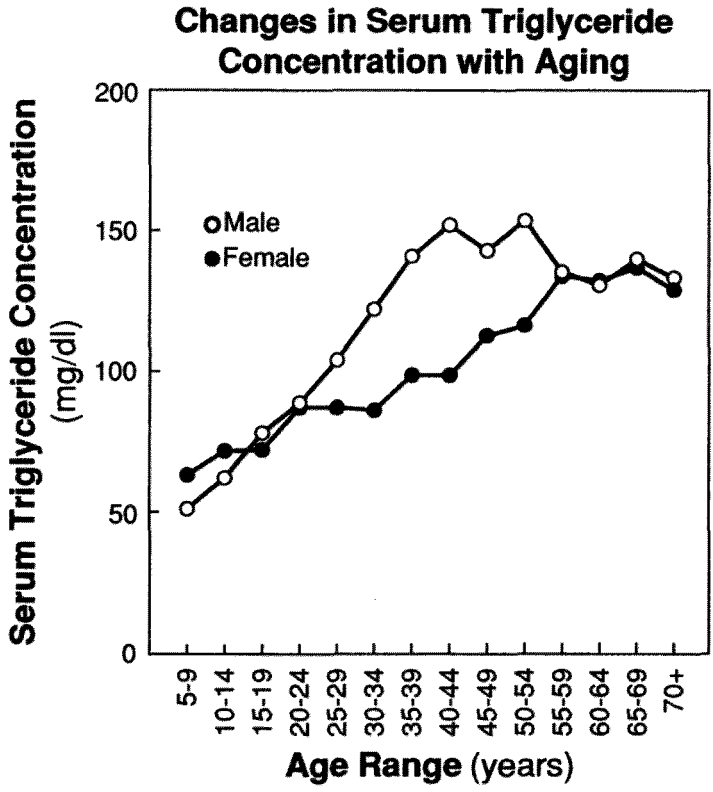

FIGURE 9.2 Median serum triglyceride concentrations for men and women in the United States at 5-year intervals. (*Source:* Adapted from *The Lipid Research Clinics Population Studies Data Book* (1980). Bethesda, MD: U.S. Department Health and Human Services/PHS/NIH, Vol. I: pp. 58–59.

There is a progressive increase from birth through adulthood in triglyceride levels. The rate of rise is greater in men than in women. In men, triglycerides continue to rise until the mid-50s when a gradual drop occurs. Plasma triglyceride levels continue to rise in women until about 70 years of age prior to their decline (Figure 9.2).

The rise in triglyceride levels reflects an increase in the plasma VLDL concentration, but there are few data regarding the metabolism of VLDL and aging. There may be a decrease in triglyceride clearance with age. In one study, there was a noted decline in the rate of triglyceride clearance after parenteral lipid infusion in women with increasing age from 31 to

TABLE 9.1 Proposed Mechanisms of Changes in Lipid Metabolism in Old Age

LDL[a]	decreased FCR[b] of LDL apo B[c]
	? decreased LDL receptor activity
	? change in LDL receptor affinity due to age-related changes in apo B
	? increase in LDL autoantibodies
	? decrease in LDL receptor expression with age
	? decrease in LDL receptor synthesis from accumulated tissue cholesterol
	? increase in LDL production
HDL[d]	Men; interaction between testosterone, estrogen, and adiposity
	Women (premenopausal);
	increase in apo AI production
	decrease in HL[f] activity
	increase in LPL[g] activity
VLDL[h]	? decrease in TG[i] clearance
	? decrease in LPL activity

[a]low density lipoprotein; [b]fractional catabolic rate; [c]apolipoprotein B; [d]high density lipoprotein; [e]apolipoprotein AI; [f]hepatic lipase; [g]lipoprotein lipase; [h]very low density lipoprtoein; [i]triglycerides; ? = possibility of.

70 years, without any significant changes in men (Tollin, Ericsson, & Backman, 1985). In another study, higher postprandial triglyceride concentrations after a fat-rich meal were noted in older subjects when compared to younger subjects (Cohn, McNamara, Cohn, Ordovas, & Schaefer, 1988). Several studies have demonstrated a decline in LPL activity with age which, in turn, may result in an increase in VLDL–triglyceride concentrations (Bradows & Campbell, 1972; Nikkila & Niemer, 1957). The mechanisms of changes in lipid metabolism in old age are summarized in Table 9.1.

HYPERLIPIDEMIAS

Hyperlipidemia is the accumulation, in excess, of one or more of the lipids present in plasma. This suggests abnormalities of lipid transport and/or metabolism resulting in defective removal or lipoproteins from plasma, excessive endogenous production of lipoproteins, or both. Much of the variability in serum lipids can be attributed to polygenic factors, but environmental factors are the probable cause of hyperlipidemia in most of the

TABLE 9.2 World Health Organization Classification of Lipid Phenotypes

	TC[a]	TG[b]	LDL[c]	VLDL[d]	Chylomicrons
Type I	–	++	–	–	++
Type IIa	++	–	++	–	–
Type IIb	++	+	++	+	–
Type III	++	++	–	++	–
Type IV	+	++	–	++	–
Type V	–	+++	–	++	++

[a]total cholesterol, [b]triglycerides, [c]lowdensity lipoproteins, [d]very low density lipoproteins

population. For practical purposes, hyperlipidemia can be manifested as hypercholesterolemia and/or hypertriglyceridemia. The World Health Organization classifies lipoprotein phenotypes into six types, based on the specific electrophoretic patterns of the various lipoproteins in plasma (Table 9.2). This classification does not differentiate primary from secondary hyperlipidemia nor does this account for the expression of high or low HDL phenotypes. Plasma lipoprotein patterns may change with time, a single disorder may have several different phenotypes, and a variety of diseases or mechanisms may share the same phenotype.

An increase in plasma triglycerides is a normal response to alcohol consumption and excessive intake of calories, and is often noted in the third trimester of pregnancy. Obesity, estrogens, corticosteroids, hypothyroidism, uremia, multiple myeloma, macroglobulinemia, lymphoma, systemic lupus erythematosis, and diabetes mellitus can all aggravate hypertriglyceridemia.

Familial hypertriglyceridemia presents as Types IV and V. In familial Type IV, there is a mild to moderate increase in total cholesterol and an increase in triglycerides secondary to an increase in VLDL synthesis. Present in 0.2% to 0.3% of the population (Goldstein, Schrott, Hazzard, Bierman, & Motulsky, 1973), those with this type of hyperlipidemia have larger VLDL particles, an increase in the triglyceride to apo B ratio, and a decrease in HDL. Type V familial hypertriglyceridemia is characterized by a marked increase in triglycerides secondary to elevated chylomicrons and VLDL.

Familial hypercholesterolemia or Type II hyperlipoproteinemia is seen in approximately 0.2% of the population and 3% of coronary prone families (Williams, et al., 1990). The defect in familial hypercholesterolemia is a mutation affecting the LDL receptor resulting in decreased LDL removal. In Type IIb there is an elevation of LDL with mild to moderate

hypertriglyceridemia secondary to high VLDL. Those who are homozygous for this mutation suffer from extreme hypercholesterolemia due to an absence of receptor mediated catabolism of LDL–apo B and a decreased breakdown of IDL and LDL. Anorexia nervosa and hypothyroidism can similarly increase LDL by decreasing LDL removal.

Type III hyperlipoproteinemia or familial dysbetalipoproteinemia is a combined elevation of total cholesterol and triglycerides secondary to an accumulation of VLDL and chylomicron remnants. This is due to a defect in apo E such that it loses its affinity for the LDL/apo B, E receptor.

Familial combined hyperlipidemia is a combined elevation of both cholesterol and triglycerides and may present as phenotypes IIa and b, IV and V. Inheritance is believed to be autosomal dominant and affects approximately 0.5% of the population. Its prevalence ranges from 14% to 48% of those prone to premature coronary artery disease (Goldstein et al., 1973; Williams et al., 1990). Hypothyroidism, nephrotic syndrome, and glucocorticoids can similarly increase LDL and/or VLDL and apo B.

The two genetic lipoprotein abnormalities that have been associated with longevity include familial hypobetalipoproteinemia and familial hyperalphalipoproteinemia. (Glueck, Gartside, Fallat, Sielski, & Steiner, 1976) Familial hypobetalipoproteinemia is characterized by very low concentrations of VLDL and LDL. It must be differentiated from hypobetalipoproteinemia due to gammopathies, malnutrition and liver disease as these secondary causes do not carry the same favorable prognosis. Familial hyperalphalipoproteinemia is characterized by very high HDL levels, greater than 90th percentile. Secondary causes of hyperalphalipoproteinemia include alcoholism, use of phenobarbital, phenytoin and carbemazepine, and insulin use in diabetes mellitus.

There are few data regarding lipid phenotypes and the older population. Two studies that have examined the lipoprotein profiles of healthy older people include the Framingham Heart study and a study by Thieszen, Hixson, Nagengast, Wilson, and McManus (1990). The Framingham Heart study assessed subjects who eventually became healthy octogenarians without clinical evidence of atherosclerosis. The cohort of 55- to 64-year-olds who did not develop cardiovascular disease had normal lipoprotein levels and were very unlikely to have low HDL cholesterol concentrations compared with similar aged subjects who developed vascular disease or died. Thieszen found that the broad diversity of lipid phenotypes in the general population persisted in 41 nonagenarians studied. A low total cholesterol, low LDL and high HDL were not more commonly seen in those living

into their nineties. Thus, a low-risk lipid profile may confer longevity but is not its sole determinant.

CHOLESTEROL AND MORTALITY

Multiple studies demonstrate that serum cholesterol is directly related to the risk of development of atherosclerosis. The National Cholesterol Education Program has recommended that the desirable plasma cholesterol concentration for adults older than 20 years is below 200 mg/dl (5.17 mmol/l). This recommendation, however, does not take into consideration the rise in serum lipids with age, thus classifies 60% of those over the age of 65 years as candidates for the treatment of hypercholesterolemia. Additionally, the National Cholesterol Education Program Expert Panel has suggested that data from the clinical trials of middle-aged patients should be extrapolated to the older population (Anonymous.; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 1993) Whether cholesterol lowering in this population actually improves morbidity and mortality is not certain, and recent studies have suggested this is a highly questionable premise.

Some studies have found that total serum cholesterol remains an important risk factor for cardiovascular disease in the older person, others have noted that the risk decreases with advancing age and yet other studies suggest an increase in illness and mortality associated with low serum cholesterol. Whether cholesterol is a risk factor for coronary heart disease and mortality in persons older than 70 years is not known.

Results of the Kaiser Permanente and Honolulu studies suggest that cholesterol may remain a risk factor in older men. In the Kaiser Permanente study, it was found that in men aged 60 to 79 years, the relative risk of coronary mortality did not change with age, but an additional risk of coronary heart disease was correlated with increasing cholesterol levels (Rubin, Sidney, Black, Browner, Hulley, & Cummings, 1990)

The Honolulu Heart Program followed 1,480 men and demonstrated that cholesterol continues to be a predictor of atherosclerotic events in those older than 65 years; however, cholesterol was a lesser risk factor for development of coronary artery disease than systolic hypertension or diabetes mellitus. The relative risks of coronary heart disease in men age 65 and older for total serum cholesterol was 1.64 compared to 2.15 and 1.86 for systolic hypertension and diabetes mellitus, respectively (Benfante & Reed, 1990).

The Framingham Heart study followed a cohort of 5,209 men and women who were enrolled from 1948 to 1980. In an age-specific analysis, it was found that the relationship of total cholesterol and all-cause mortality was positive at age 40, negative at age 80, and not significant for ages 50 to 70 years. In other words, higher total cholesterol level was associated with higher overall mortality at age 40, but at age 80, higher cholesterol was associated with lower overall mortality. Coronary heart disease mortality at ages 40, 50, and 60 was significantly lower when cholesterol levels were lower. At age 70, the relationship lost its significance, and at age 80 years, the mortality decreased 0.5% for each 1 mg/dl (0.026 mmol/l) of serum total cholesterol (Kronmal, Cain, Ye, & Omenn, 1993).

Similarly, the Established Population for the Epidemiologic Study of the Elderly (EPESE), a prospective, community-based cohort study of men and women 70 years and older found that hypercholesterolemia and low HDL cholesterol are not important risk factors in the incidence of overall mortality, mortality from coronary heart disease or hospitalization for coronary heart disease (Krumholz et al., 1994). In fact, in this study, the highest rates of myocardial infarction or unstable angina were in those with the lowest serum cholesterol levels. After adjustment for cardiovascular risk factors, the odds ratios for all-cause mortality were not significant in the group with total cholesterol levels ≥240 mg/dl (6.2 mmol/l) versus total cholesterol levels <200 mg/dl (5.2 mmol/l); the group with HDL cholesterol levels in the highest versus the lowest tertile; or the group with the highest versus lowest tertile of total cholesterol:HDL cholesterol ratios.

Many studies have demonstrated a U- or J- shaped mortality curve when examining serum cholesterol levels. In a nursing home study of 92 women over 60 years of age, Forette and colleagues found that mortality was lowest at a serum cholesterol of 7.0 mmol/l (270 mg/dl). The relative death rate was 5.2 times greater and 1.8 times greater in those with a cholesterol of 4.0 mmol/l (150 mg/dl) and 8.8 mmol/l (340 mg/dl), respectively (Forette, Tortrat, & Wolmark, 1989). In Renfrew and Paisley, a survey of 15,000 men and women found that the lowest mortality occurred with a cholesterol level of 215 mg/dl (5.56 mmol/l) in men and 280 mg/dl (7.24 mmol/l) in women (Isles, Holes, Gillis, Hawthorne, & Lever, 1989).

Data from both the Whitehall Study of 17,718 men aged 40 to 64 years (Rose & Shipley, 1980), and a cohort study of 11,121 Yugoslav men aged 35 to 62 years exhibited a J-shaped, negative relationship between serum cholesterol and mortality. In the Yugoslavian study, death from cor pulmonale and tuberculosis was significantly associated with low levels

of cholesterol although death from cancer was not (Kozarevic, et al., 1981).

The Cardiovascular Health Study was a population based, longitudinal study of 5,201 people older than 65 years that found low cholesterol concentrations of ≤160 mg/dl (4.14 mmol/l) were associated with number of bed days, prolonged measured walk, and cognitive deficits in women; and diabetes mellitus and poor self-rated health in both men and women (Manolio, et al., 1993).

Low cholesterol levels were found to be an antecedent of death independent of age and functional impairment in a VA nursing home study (Rudman, Mattson, Nagraj, Caindee, Rudman, & Jackson, 1987). In the setting of low cholesterol, a prospective study of 224 nursing home residents found the relative risk of mortality was increased ten-fold. Low cholesterol levels were also significantly associated with use of enteral feeding, pressure sores, and an elevated white blood cell count, reflecting poor nutritional status and infection (Verdery & Goldman, 1991).

In a Swedish study of over 54,000 adults aged 45 to 74 years of age, a strong negative correlation was noted between cholesterol concentration and mortality from injuries and suicide in men even after adjustment for cancer. In the first 6 years of the study the relative risk of death from suicide was 4.2 in the lowest quartile of cholesterol distribution compared with the top quartile (Lindberg, Rastam, Gullbus, & Eklund, 1992).

Reduction in mortality is not always found in interventional studies, most of which have been performed in middle-aged men. The MRFIT (Multiple Risk Factor Intervention Trial) study randomized 12,866 high-risk men aged 35 to 57 years to receive special intervention of stepped care hypertension control and cigarette and dietary education versus usual care. The 6-year overall mortality and the mortality from coronary heart disease was not significantly different in the two groups (Anonymous. Multiple Risk Factor Intervention Trial Research Group, 1982). An earlier dietary intervention trial of veterans aged 55 to 89 years, demonstrated no difference in total or cardiac mortality despite reductions in serum cholesterol (Dayton, Pearce, Hashimoto, Dixon, & Tomiyasu, 1969).

Lipid lowering medications can effectively modify serum lipid profiles in the hyperlipidemic older patient (Bach, Cooper, O'Brien, Jerums, 1990; Morisaki, et al., 1990; Santinga, et al. 1994), but a significant impact on overall mortality has not been demonstrated in nearly all coronary risk modification trials. Additionally, many of these trials have not included older individuals, and much of the data supporting lipid-lowering agents are from secondary prevention trials.

The Helsinki Heart Study, a randomized, placebo-controlled study of

The Helsinki Heart Study, a randomized, placebo-controlled study of gemfibrozil in over 4,000 middle-aged men with cholesterol levels >200 mg/dl (5.17 mmol/l), found a 34% reduction in atherosclerotic events, but no difference in either total death rate or death from coronary artery disease (Frick et al., 1987). Findings were similar from the Lipid Research Clinics Coronary Primary Prevention Trial and the use of cholestyramine (The Lipid Research Clinics Coronary Primary Prevention Trial Results, 1984).

In the World Health Organization trial examining the effects of clofibrate and coronary artery disease, patients with hypercholesterolemia were randomized into treatment and placebo groups. While clofibrate use resulted in a significant reduction in new onset coronary artery disease, total mortality was actually increased (Oliver, 1971).

Most recently, the Scandinavian Simvastatin Survival Study (Scandinavian Simvastatin Survival Study Group, 1994) examined the use of simvastatin, a HMG Co A reductase inhibitor, in patients aged 35 to 70 years with a history of myocardial infarction or angina. This study found a reduction in coronary events of 34%, coronary death of 42% and, quite significantly, a reduction in overall death of 30% with the use of simvastatin. Again, this study did not specifically examine the older patient, and the study was confined to use in secondary prevention.

Ravnskov examined the outcomes of 22 controlled primary and secondary coronary prevention trials. This meta-analysis revealed no effect on total mortality even after correction for excess mortality induced by the intervention. There was only a 0.32% reduction in nonfatal coronary heart disease which was unrelated to the degree of cholesterol lowering (Ravnskov, 1992).

Similar to examinations of cardiovascular disease, there is a U-shaped relationship between serum cholesterol and stroke death. Although there is a positive association of elevated serum cholesterol levels with death from nonhemorrhagic stroke, low cholesterol levels have been associated with hemorrhagic strokes (Iso, Jacobs, Wentworth, Neaton, & Cohen, 1989). In a retrospective study of over 350,000 middle-aged men screened for the MRFIT, the 6-year risk of death by hemorrhagic stroke was three times higher in hypertensive men with serum cholesterol levels under 4.14 mmol/l (160 mg/dl). The pathogenesis of this association is speculative. There is evidence to suggest that low serum cholesterol levels can weaken the endothelium of intracerebral arteries, may alter the integrity of cell membranes, and may affect platelet aggregability.

Certainly, serum cholesterol levels are less predictive of mortality in the older population thus have little utility in screening. Given the strong association between low cholesterol, and poor health and mortality as well as the unconvincing evidence of overall benefit of cholesterol manipulation in the older person, there should be safety concerns regarding cholesterol lowering interventions in this patient population. There appears to be little role for lipid lowering as primary prevention in the older patient.

ANTIOXIDANTS AND LIPID PEROXIDES

One of the current hypotheses of the pathogenesis of atherosclerosis is that "toxic LDL" can cause the development of the fatty streak. This "toxic LDL" is formed by oxidation of the lipid component of the lipoprotein via a free radical mechanism involving superoxide anion and/or hydrogen peroxide. *In vitro* studies have demonstrated that endothelial cells and vascular smooth muscle cells can oxidize human LDL. The oxidized LDL was found to be toxic to human fibroblasts. In the presence of free radical scavengers, the LDL was no longer toxic to the fibroblasts. This suggests that endothelial cells and vascular smooth muscle cells oxidize human LDL by cellular generation of free radicals (Morel, DiCorleto, & Chisholm, 1984).

Oxidized LDL further contributes to atherosclerosis by functioning as a chemotactic agent for monocytes by producing granulocyte/macrophage-colony stimulating factor (CSF), granulocyte-CSF and monocyte-CSF (Cushing et al., 1990; Rajavashisth, et al., 1990) and by transforming monocytes to macrophages which via a scavenger receptor pathway stimulates cholesterol esterification and formation of foam cells (Fogelman et al., 1980). Oxidized LDL is also directly cytotoxic to endothelial cells in vitro (Evensen, Galdal, & Nilsen, 1983).

In vivo, patients with coronary artery disease or peripheral vascular disease, plasma lipid peroxide concentrations were found to be significantly higher than in patients without occlusive arterial disease (Stringer, Gorog, Freeman, & Kakar, 1989). There has also been demonstrated a strong correlation between the severity of aortic atherosclerosis and the concentration of lipid peroxides in the aortic wall (Harland, Gilbert, Steel, & Brooks, 1971).

In vitro experiments have found that alpha tocopherol (vitamin E) inhibited oxidation of LDL; thus multiple studies have examined the use of

antioxidants to prevent peroxidative lipoprotein modification and, in turn, prevent atherosclerosis. In a placebo-controlled trial of alpha tocopherol in men, there was an increase in plasma and LDL alpha tocopherol and decrease susceptibility of LDL to oxidation. There were no effects seen on lipoprotein profiles (Jialal & Grundy, 1992).

Vitamin E may also have an impact on ischemic heart disease. In a study comparing European populations, there was a strong inverse correlation between vitamin E consumption and mortality from coronary artery disease. Vitamin E was a more important factor than either blood pressure or cholesterol (Gey, 1990). Recently, two large cohort studies of 87,245 women and 39,910 men observed a lower risk of coronary disease after adjustment for age and smoking in those with higher vitamin E intake. Vitamin E supplementation for short periods did not show any benefit, but intake for at least two years was associated with a relative risk of major coronary disease of 0.59 in women and 0.63 in men. (Rimm, Stampfer, Ascherio, Giovannucci, Colditz, & Willett, 1993; Stampfer, Hennekens, Manson, Colditz, Rosner, & Willett, 1993).

Probucol has also been shown to inhibit oxidation of LDL in both animals and humans. The reduction of plasma lipid peroxides may occur through a free radical scavenging action (Paterson, et al., 1992). In Watanabe heritable hyperlipemic and cholesterol-fed rabbits, probucol retards progression of atherosclerosis (Carew, Schwenke, & Steinberg, 1987; Daugherty, Zweifel, & Schonfeld, 1989; Kita et al., 1987). Probucol can lower LDL and HDL cholesterol levels in humans in doses of 1.0 gm/day. Lower doses of 250 mg/day continue to have antioxidant effects and may have a less detrimental effect on HDL (Cristol, Jialal, & Grundy, 1992; Reaven, Parthasarathy, Beltz, Witztum, 1992). The effect of probucol on the development and progression of atherosclerosis in humans is currently under investigation (Walldius, et al., 1993)

APOLIPOPROTEIN E AND DISORDERS OF LIPOPROTEINS

Apolipoprotein E (apo E) has received recent attention because of its association with Alzheimer's disease. Apo E is an integral part of the metabolism of lipoproteins and cholesterol. It makes up the protein portion of VLDL, chylomicron remnants, and subpopulations of HDL, and functions as the ligand of these lipoproteins for certain receptors including the LDL receptor.

Apo E2, apo E3, and apo E4 are the common isoforms that correspond to the three major alleles at the apo E gene locus: epsilon 2, epsilon 3, and epsilon 4. In the general population the estimated frequency of the epsilon 2, epsilon 3, and epsilon 4 alleles is 8%, 77% and 15%, respectively (Rall, Jr., & Mahley, 1992). Genetic variability with the possibility of 6 common phenotypes (E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4) and posttranslational glycosylation (Zannis & Breslow, 1981) contribute to the polymorphism of apo E. This polymorphism appears to have a large influence on the variability of lipid levels seen in the population as well as the presence of atherosclerotic disease and the response to the treatment of hyperlipidemia.

The epsilon 2 allele is associated with a low total cholesterol, low LDL, low LDL apo B, mild triglyceride elevation, and marked elevation of apo E levels in comparison to the epsilon 3 allele. The epsilon 4 allele has the opposite association with lipoprotein profiles (Davignon, Gregg, & Sing, 1988).

From cohort studies of young women and old women, there was a lower allele frequency of epsilon 4 and a higher frequency of epsilon 2 with age suggesting a selection against the epsilon 4 genotype (Cauley, Eichner, Kamboh, Ferrell, & Kuller, 1993). Several studies have noted an increased incidence of atherosclerotic disease in those with the apo E4 phenotype (Miida, 1990; Kuusi et al., 1989). Postmortem studies of young men found the apo E2/3 phenotype was associated with the lowest levels of LDL, total cholesterol and atherosclerosis. The apo E3/4 phenotype was associated with the highest levels (Hixson 1991). The presence of the epsilon 4 allele was also associated with an increased risk of atherosclerotic heart disease in the Multiple Risk Factor Intervention Trial. The E4/4 phenotype was also more common in men aged 30 to 50 years with known coronary artery disease than in age matched controls. In the 40 and under age group the E4/4 phenotype was 16 times more common and in the 40 to 50 age group 60% greater among the disease group when compared with controls (van Bockxmeer & Mamotte, 1992). The epsilon 4 allele was also more prevalent in a study of 100 men with cerebrovascular disease when compared with healthy age-matched controls (Pedro–Botet et al., 1992). In a study of Japanese patients with multi-infarct dementia, the prevalence of the epsilon 4 allele was approximately twice that of their controls (Shimano et al., 1989).

Apo E4 is immunochemically localized to senile plaques, vascular amyloid and neurofibrillary tangles present in Alzheimer's disease. Strittmatter and colleagues examined 30 people with late-onset Alzheimer's disease

and found the E4 frequency in the affected group was 0.50 compared with 0.16 in the 91 age-matched controls (Strittmatter et al., 1993). The known correlation between myocardial infarction and dementia may be related to the inheritance of the E4/4 phenotype.

Several studies have examined the relationship between apo E phenotype and response to lipid-lowering medications. The hypolipidemic responses to lovastatin (O'Malley & Illingworth, 1990), pravastatin, cholestyramine (Berglund et al., 1993), and gemfibrozil (Manttari, Koskiner, Ehnholm, Huttenen, & Manniene, 1991) are independent of apo E phenotype. In a study of patients with familial hypercholesterolemia, probucol decreased total cholesterol, LDL, VLDL, and triglycerides more in those who carried the apo E4 phenotype than in those who did not (Eto, Sato, Watanabe, Iwashima, & Nakinu, 1990).

The effects of dietary manipulation on lipoprotein profiles have been studied with respect to apo E phenotype. The Helsinki Heart study followed lipid profiles of 230 middle-aged patients and found that those with the epsilon 4 allele experienced a greater reduction in LDL and total cholesterol with dietary counseling than those who did not. A high cholesterol diet resulted in a two-fold greater increase in total cholesterol LDL and apo B in young healthy students with the apo E4/4 phenotype when compared with other phenotypes (Lehtimaki, Moilanen, Solakivi, Laippala, & Ehnholm, 1992). In a study of LDL metabolism, and cholesterol absorption, elimination and synthesis on a low fat/low cholesterol diet, there was a decrease in LDL and a decline in cholesterol absorption but an increase in cholesterol synthesis. The rate of cholesterol synthesis increase was proportionate to the apo E subscript such that cholesterol synthesis was highest in the apo E4/4 phenotype and lowest in the apo E2/2 phenotype (Miettinen, Gylling, Vanhanen, & Ollus, 1992). In a study of 67 men and women given a diet with a high polyunsaturated fat to saturated fat ratio (P:S) versus a low P:S diet, women with the E3/E2 phenotype experienced a decline in HDL on the high ratio diet thus did not benefit from this dietary intervention. Men with the E4/E3 phenotype appeared to benefit the most from the high P:S diet with respect to the lipoprotein profile (Cobb, Teitlebaum, Risch, Jedel, & Ostfeed, 1992).

No recommendations exist regarding the use of apo E phenotypes as a screening tool in the approach to the treatment of hypercholesterolemia. Based on current studies, probucol and dietary interventions appear to be most effective in carriers of the epsilon 4 allele. Knowledge of apo E phenotypes may help to target young and middle-aged adults for which select means of risk modification will be effective, but once a patient has

reached old age, apo E loses its clinical significance. The lack of sensitivity and specificty of apo E4/4 in identifying individuals who may have a higher risk of developing late onset Alzheimer's disease makes it a poor screening tool.

MANAGEMENT OF HYPERLIPIDEMIA IN THE OLDER PATIENT

In the assessment of the hyperlipidemic patient, other cardiac risk factors such as smoking and hypertension, diet, exercise, and secondary causes such as diabetes mellitus and medications need to be determined (Table 9.3). Treatment guidelines suggest a 6-month trial of a low saturated fat, low cholesterol diet and weight loss in the obese patient prior to instituting drug therapy. Dietary cholesterol contributes significantly to the cholesterol pool and bile acids in the enterohepatic circulation. Most of this cholesterol is in the form of cholesteryl ester which, when hydrolyzed by pancreatic enzymes, forms free fatty acids, and unesterified cholesterol. Approximately 30% to 60% of the unesterified cholesterol present in the intestinal lumen enters body pools (Grundy, 1978). While diet may be effective in the older person, aggressive lipid lowering diets may exacerbate problems with malnutrition, and the unappetizing nature of low fat diets can cause anorexia. The potential morbidity from protein calorie malnutrition probably outweighs that of moderate hypercholesterolemia.

A rational approach to healthful eating may be more easily achieved rather than radically changing lifelong eating habits. Patients can be advised to trim fat from cuts of meat, increase intake of fish and beans, avoid fried foods, and use monounsaturated fats such as olive oil. In a study comparing olive oil and butter, olive oil increased excretion of cholesterol from the small bowel (Bosaeus, Belfrage, Lindgren, & Andersson, 1992). Consumption of foods rich in soluble fiber such as oat bran may also reduce serum lipids (Jenkins et al., 1993).

Epidemiological studies suggest that a low level of HDL-cholesterol is an important predictor of coronary artery disease (Jacobs, Mebane, Bagdiwala, Criqui, & Tyroler, 1990; Wilson 1990). In addition to a genetic predisposition, common causes of low HDL include cigarette smoking, obesity, lack of exercise, beta blockers, hypertriglyceridemia and androgenic steroids. Raising HDL-cholesterol as recommended by the National Cholesterol Education Program starts with hygienic measures such

Table 9.3 Potential Secondary Causes of Hyperlipidemia in Older Persons

Endocrinologic Disease
Diabetes Mellitus
Thyroid Disease
Nutrition
Alcoholism
Obesity
Renal Disease
Nephrotic Syndrome
Chronic Renal Failure
Immunologic Disease
Gammopathies
Systemic Lupus Erythematosis
Liver Disease
Cholestasis
Hepatocellular disease
Medications
Beta blockers
Thiazide diuretics
Steroids
Microsomal enzyme-inducing agents

as smoking cessation, loss of excess weight, discontinuation of medications that lower HDL, and aerobic exercise. Exercise has been associated with an increase in HDL levels which may occur through increased delivery of chylomicrons to lipoprotein lipase in muscle capillary beds during muscle activity (Ruys et al., 1989). Endurance exercise training has also been demonstrated to increase total HDL by 14% in a young group of healthy men and by 15% in an old group of healthy men (Schwartz et al., 1992). Because of the unknown efficacy and possible adverse effects of HDL-raising agents, niacin and gemfibrozil are not recommended for the purposes of raising HDL.

There is also a body of evidence to support the consumption of moderate amounts of alcohol to raise HDL cholesterol levels. Moderate alcohol intake has been associated with higher concentrations of HDL cholesterol but is dependent on normal hepatic synthetic function (Rosenson, 1993). Alcohol intake greater than one drink daily increased HDL cholesterol levels in men but even smaller quantities have been correlated with increases in HDL in women (Weidner et al., 1991). Reduction in levels of HDL can

occur with chronic alcohol induced liver damage due to impaired hepatic synthetic function (Okamoto, Fijimoro, Nakano, & Tsujii, 1988).

The incidence of atherosclerotic heart disease in postmenopausal women approaches that of men (Eaker, Packard, & Weiner, 1987). Those women who have received estrogen replacement have a reduced risk of coronary artery disease (Bush et al., 1987). Estrogen replacement therapy lowers LDL cholesterol concentrations and raises HDL cholesterol. Ethinyl estradiol administered on a daily basis elevates HDL cholesterol levels by 21% and lowers total cholesterol and LDL cholesterol concentrations by 11% and 25%, respectively (Applebaum-Bowden et al., 1989). Conjugated equine estrogens in doses of 0.625 mg daily given with medroxyprogesterone acetate 10 mg daily for 10 days of the 28-day cycle have increased HDL cholesterol levels by 16% and lowered LDL by 15% (Walsh et al., 1991).

Multiple pharmacological agents are available for lowering serum cholesterol levels. Cholestyramine and colestipol are bile acid sequestrants. This class of medication functions by removing bile acids from the intestinal tract. This causes the conversion of hepatic cholesterol to bile acids and, in turn, increases synthesis of LDL receptors to decrease circulating LDL levels. Constipation, abdominal bloating, malabsorption and drug-drug interactions are common side effects.

Clofibrate and gemfibrozil are fibric acids. These agents increase lipoprotein lipase activity causing a decrease in triglycerides, an increase in HDL, but also an increase in LDL in those with high triglycerides. Side effects of the fibric acids include development of cholesterol gallstones, myopathies, and skin rash.

Nicotinic acid inhibits production of VLDL which results in a reduction of triglycerides and LDL, and an increase in HDL. The dose determines the degree of change in lipoprotein profiles. Unfortunately, adequate dosages up to 1,500 mg 3 times daily can be limited by development of side effects of flushing, pruritus, hepatotoxicity, and glucose intolerance. The sustained release formulation is often symptomatically better tolerated but is more frequently associated with liver damage. Flushing may be mitigated by taking an aspirin.

Lovastatin, pravastatin and simvastatin, HMG CoA reductase inhibitors, inhibit the synthesis of cholesterol in the liver, increasing LDL receptor and decreasing serum LDL. This class of agents is expensive but effective and generally well tolerated. Development of myopathies, hepatotoxicity and diarrhea are among the known side effects. In combination with

erythromycin these agents can produce severe myositis, myoglobinuria, renal failure and death (Suki, 1991).

Combinations of certain lipid lowering agents appear to have beneficial effects. In the Stockholm Ischemic Heart Disease Secondary Prevention Study, a combination of clofibrate and niacin improved both overall mortality from 29.7% in the control group to 21.8% in the treatment group. Coronary mortality was reduced by 36.4% in the treatment group when compared with control (Carlson & Rosenhamer, 1988). A combination of niacin and colestipol was examined in the Cholesterol Lowering Atherosclerosis Study and demonstrated a decrease in progression of atherosclerosis and in some cases, a regression in coronary atherosclerosis in men with established coronary artery disease (Blankenhorn et al., 1987). It should be stressed that this approach was in secondary prevention and has not been studied in older persons. The hazards of polypharmacy may outweigh any potential benefits in this age group.

A recent meta-analysis of 35 randomized controlled single-factor trials examined the risk of death from coronary events above which cholesterol reduction demonstrated any net benefits. Total mortality from cholesterol lowering was seen only for trials including patients at very high initial risk of coronary heart disease. No benefit was noted in the medium risk group, and the low-risk group suffered adverse treatment effects. As well, drug intervention increased mortality from causes other than coronary heart disease when compared with non-drug treatments (Smith, Song, & Sheldon, 1993). While much of these data are from a middle-aged population, this analysis can be prudently extrapolated to the older individual.

At present there are no data to support treating hypercholesterolemia in women over the age of 70 with a cholesterol less than 300 mg/dl and no history of vascular disease. Similarly, a cutoff of 260 mg/dl would seem reasonable in men of this age group. As HDL cholesterol appears to be protective, it would be advisable to avoid treatment in those older persons with levels greater than 60 mg/dl. The issue of which older patient should receive treatment for hypercholesterolemia, methods of treatment and which parameters should be considered therapeutic goals is not straightforward. More prospective studies that specifically examine the older population are needed to resolve some of these questions.

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