Physiologic systems have substantial reserves in younger individuals. The process of aging and intercurrent pathologic processes gradually eliminate these reserves. Changes in endocrine systems, including menopause in women, androgen deficiency in men, loss of skeletal mass, decrease in growth hormone serum concentrations, and increased incidence of type 2 diabetes are all more common or certain in older individuals. This review summarizes the progression of each of these processes with age, the potential outcomes of the untreated process, and the treatment outcomes for these age-related losses. Maintenance of a premenopausal lipid profile presumably protects against cardiovascular events. Maintenance of skeletal mass reduces fracture risk and risk for loss of mobility and independence. Testosterone replacement in hypogonadal older men improves strength and presumably function and independence. Growth hormone therapy is reported to have similar effects. Improvement of long-term outcomes in older type 2 diabetics, however, is more difficult to demonstrate.

Changes in medical care, particularly the advent of antibiotics, public health measures, and vaccinations, have dramatically increased the average life expectancy in the United States in this century (1). With these increases has come the concern not merely that life should be extended, but that useful independent life should be lengthened (1,2). As such, considerable time and effort has been expended in defining risk factors for institutionalization or frailty syndromes. These are described as morbid and premorbid changes in function that either limit or potentially limit free and independent life. Table 1 describes the two such general frailty syndromes, i.e., individuals at risk for or with multiple or prolonged hospitalizations and recoveries. The causes of such syndromes are protean, but they include multiple comorbid conditions. Thus, older frail individuals frequently have multiple problems: for example, congestive heart failure, hypertension, cerebrovascular accidents, peripheral vascular disease, and/or diabetes. The intermediate causes for this frailty syndrome include loss of organ system reserve and polypharmacy. A second proximate cause for prolonged hospitalization and/or recovery are serendipitous events such as falls and fractures. Such events surely limit independent functional living. The intermediate causes for falls and fractures are prolonged reaction time, loss of strength, poor vision, and/or osteoporosis. The initial causes of the intermediate causes of both types of frailty syndromes are also numerous. For the purpose of the review, however, we will be concerned with how age-related changes in endocrine function may lead to these intermediate and proximate causes of frailty. Changes in endocrine systems potentially figure in many of these frailty syndromes. A second issue that we will consider is how pharmacologic intervention may reverse or slow their effects. The purpose of this review is to describe some of the changes in endocrine function, how they relate to the aging, how they might relate to the development of frailty syndromes, and finally, how remedial interventions may alter the changes to prevent the frailty syndromes.

Most individuals enter adulthood with a substantial physiologic reserve in multiple organ systems, including the endocrine function. Aging and intercurrent pathologies will eventually consume this reserve. As these processes continue, function will then be compromised. It should be obvious from this introduction, however, that given the appropriate pathology, virtually any endocrine gland might be subject to the effects of aging. In addition, many endocrine functions are so intertwined that diminution in function of one must adversely affect the remainder.
Table 1. Frailty syndrome.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Prognosis or limited hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximate causes</td>
<td>Prolonged reaction time</td>
</tr>
<tr>
<td>Multiple co-morbid conditions</td>
<td>Loss of strength</td>
</tr>
<tr>
<td>Intermediate causes</td>
<td>Prolonged or limited hospitalizations</td>
</tr>
<tr>
<td>Loss of organ system reserve</td>
<td>Poor vision</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Initial causes</td>
<td>Changes in endocrine function</td>
</tr>
</tbody>
</table>

Table 2. Changes associated with postmenopause.

<table>
<thead>
<tr>
<th></th>
<th>Body fat</th>
<th>Lean body mass</th>
<th>Strength</th>
<th>Skeleton</th>
<th>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen deficiency in</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>otherwise healthy women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone deficiency</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>in otherwise healthy men</td>
<td></td>
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<tr>
<td>GH deficiency in</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>otherwise healthy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>individuals</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*— no effect; ↑, increase; ↓, decrease.

**Gonadal Function in Women**

Menopause is a universal finding in women by the mid sixth decade of life. Interestingly, later menopause (as compared with early) is associated with earlier mortality (3).

The frequency of ovulation decreases by age 40, and reproductive ovarian function ceases in the vast majority of women within the next 15 years (4, 5). During this period in most women, ovarian follicles function less well (6). Serum estradiol concentrations are lower than in younger women, and follicle-stimulating hormone concentrations are higher (6). Luteinizing hormone (LH) is reported to be unchanged. Eventually follicular activity ceases, estrogen concentrations fall to postmenopausal values (10–20 ng/L), and LH and follicle-stimulating hormone rise above premenopausal concentrations (5, 7, 8). These altered serum concentrations are clearly associated with a series of changes, including vasomotor instability, psychological symptoms, atrophy of estrogen responsive tissue, rapid loss of skeletal mass, and increased risk of cardiovascular disease (Table 2). Vasomotor instability originates in the hypothalamus, although the mechanism is not completely understood (5, 7, 9, 10). Hormone replacement reduces but does not eliminate such episodes (11, 12). The vaginal mucosa atrophies in postmenopausal women, which may lead to bleeding, and tissue is easily injured. In addition, estrogen deprivation may lead to dysuria, urinary frequency, and/or incontinence because the bladder and urethra are embryologically derived from estrogen-sensitive tissue. These symptoms may respond to systemic or local estrogen replacement therapy. Psychological disturbances associated with menopause include many brought on by sleep disturbances attributable to vasomotor instability (4, 5, 13–15). These can be substantially improved by estrogen therapy. Improving psychosocial support and dietary supplements, particularly phytoestrogen, are also reported to lessen these symptoms and other non-estrogen-responsive postmenopausal symptoms (4, 5, 16).

Rapid loss of bone at the menopause is related to estrogen withdrawal. It takes place within the background of age-related bone loss (see below), which generally begins in the fourth decade of life. It may, therefore, be hard to differentiate between the two. In the perimenopausal period, women lose between 5% and 15% of their bone mass (17). Eighty percent of this rapid loss is primarily trabecular, as opposed to cortical bone. Trabecular bone is more metabolically active than cortical bone (18). During this time, serum parathyroid hormone (PTH), 25-hydroxyvitamin D (25OHD), and 1,25-dihydroxyvitamin D [1,25(OH)2D] reportedly are unchanged. Nonetheless, there is a rapid increase in bone resorption (19, 20). Because bone resorption and formation are closely coupled (21), bone formation also increases (19, 20). The ultimate outcome—loss of bone—suggests that the osteoblastic response might be hindered in some way during this period. It seems more likely, however, that the increased rate of bone loss is attributable to the increased number of resorption cycles. Therefore, each resorption cycle is matched by minimally (constantly) incomplete bone formation (21). Thus, the greater rate of bone loss in early menopause, compared with later menopause, is the result of more resorption cycles being initiated in early menopause compared with later menopause. This explanation does not account for why more resorption cycles should be activated early in menopause than in later menopause, particularly given the lack of change in PTH, the major hormone modulator of bone resorption. This outcome suggests a general alteration in the system that has not yet been described. Although the precise activator(s) of resorption are not completely clear, it seems likely that interleukin-6 (IL-6) plays a role in this activation (22–25). IL-6 increases bone resorption and appears to rise in the peri- and postmenopausal periods. This cytokine, therefore, might account for the increased resorption in the early menopausal period. As described below, IL-6 concentrations increase with age, which should, if IL-6 is an important activator of resorption cycles, increase resorptive activity rather than decrease it. This issue has yet to be resolved. As with other menopausal signs/symptoms, estrogen replacement maintains bone mass during the immediate menopausal period.
when the rate of bone loss is greatest and reduces fracture risk (26–30). Other drugs, including alendronate (31) and raloxifene (32), have been demonstrated to maintain bone mass in postmenopausal women. Alendronate acts by inhibiting bone resorption more than formation (31). Raloxifene (and tamoxifen) belongs to a class of drugs described as selective estrogen receptor modulators, which reportedly act selectively on bone and lipid profiles without increasing the risk of breast or uterine cancer (33).

The risk for cardiovascular disease is lower in premenopausal women than in men (34–36). In the postmenopausal period, this risk increases and becomes comparable to that seen in men (7). Prior to this increase in risk, serum concentrations of atherogenic lipids deteriorate. Premenopausal women generally have higher HDL concentrations than do age-matched men; total cholesterol and LDL concentrations also tend to be lower in premenopausal women than in age-matched men (33–39). Estrogen withdrawal alters the blood lipid concentrations in women to more closely resemble those in men (40–42). Thereafter, cardiovascular risk begins to rise (41, 42). Estrogen replacement in these postmenopausal women is generally, but not always, thought to reduce such risk (43–46). Drugs such as raloxifene also appear to restore a more benevolent lipid profile (32, 33).

The role of endogenous gonadal steroid hormones in postmenopausal women has received notice recently. Postmenopausal women with higher estradiol concentrations appear to have greater bone density (47). Endogenous (and perhaps exogenous) androgen appears to protect against bone loss or to restore lost bone (48). A second study has suggested that postmenopausal women with greater bone density (perhaps related to higher gonadal steroids) have a greater risk for breast cancer (49). A third area of study has involved the controversial hypothesis that estrogen replacement may prevent the development of Alzheimer disease (50–55). Several studies have supported this result (50–52), but several do not (53–55). The area is difficult to interpret for several reasons. First, relatively prolonged estrogen replacement seems necessary to provide protection against Alzheimer disease. Well-educated women are overrepresented in the group of women taking estrogen long term (4, 56). Because neuropsychiatric function in most studies is dependent on educational status, it is difficult to be certain that the baseline cognitive state of a group of women not taking estrogen was really equivalent to the baseline cognitive state of the women taking estrogen. In this circumstance, the current status of cognitive function of either group in a study may not be directly comparable. Similarly, it seems likely that there might be a certain self-selection in women who take estrogen. Such women may be a little more determined to remain active as they age. There remains a certain amount of “use it or lose it” in cognitive function. Older individuals who play bridge or do crossword puzzles appear to be cognitively more adept than individuals who are otherwise as healthy but less mentally active (4, 56–59). Finally, although Alzheimer disease is common, so is multi-infarct dementia; a combination of the two is also common. It is within the realm of possibility that estrogen therapy might help retain cognitive function in postmenopausal women by decreasing the incidence of arteriosclerosis, thus decreasing the incidence of dementia (60). Clearly, estrogen therapy decreases the risk for fractures and improves the risk for cardiovascular effects. All of these outcomes should reduce the risk for frailty syndromes in older women.

### Gonadal Function in Men

Serum testosterone decreases with aging in cross-sectional (61, 62) as well as longitudinal studies (63). Free and bioavailable testosterone also decline with age. Sex hormone-binding globulin is reported to increase with age. There is an associated mild increase in serum LH, particularly in the very old (61–63). This increase is inappropriately small. The decrease in serum testosterone may be caused primarily by the pituitary alterations. Unlike women, however, men have no universally recognized syndrome of “andropause” nor any time by which they will have testosterone deficiency. Decreased serum testosterone is associated with lower libido but probably not erectile dysfunction in older men (64). In addition, the decrease in serum testosterone may be associated with decreases in hemoglobin, lean body mass, and bone mass, and perhaps some memory changes (61–63). Such changes are also frequently seen with decreasing serum concentrations of growth hormone (GH) (65). To an extent, they are similar to changes observed in women after the menopause (Table 2). These changes approximate those seen with “normal” aging. Several studies of replacement testosterone in hypogonadal older men have been reported. Although the experience with men is not as extensive as with estrogen replacement in postmenopausal women, short-term studies have demonstrated that testosterone replacement therapy improves hemoglobin, decreases fat mass, and improves strength and bone mass (66–68). Such outcomes should decrease the risk for developing frailty syndromes in older men.

### Adrenal Function

Adrenal medullary function and baseline serum epinephrine and norepinephrine concentrations apparently increase with advancing age. Stimulable increases in serum epinephrine and norepinephrine (as percentages of the basal concentrations) decrease with age (69, 70). Such findings may explain several clinical observations. For example, monotherapy for hypertension that uses a peripheral vasodilator is frequently more successful in older individuals than younger individuals. Older individuals have less reflex tachycardia than younger individuals, presumably because the former cannot mount as much sympathetic response as the latter. Similarly, the increas-
ing incidence of type 2 diabetes and peripheral insulin resistance undoubtedly is exacerbated by the constant increased basal concentrations of epinephrine and norepinephrine.

Adrenal cortical function also appears to increase with age (71). Thus, mean glucocorticoid and mineralocorticoid serum concentrations are higher in older compared with younger individuals. The target organ for mineralocorticoid activity (kidney), however, becomes less responsive as age progresses (72), and sodium losses become more fixed as age progresses. Thus, the effect of increasing mineralocorticoid activity is apparently blunted by end organ resistance. Generally, the response to antidiuretic hormones appears to be better preserved. Individuals can clear free water better than they can conserve sodium. Therefore, when stressed, most older individuals become hyponatremic. Increased glucocorticoid activity may also play a role in the increasing incidence of type 2 diabetes and insulin resistance seen in older individuals (see below).

Increased basal adrenal medullary and cortical activity reduces the functional reserve for either epinephrine/norepinephrine or steroid hormones. This circumstance provides less ability to respond to stress, corresponding to an initial frailty syndrome.

**Skeletal/Mineral Metabolism**

Bone mineral density (skeletal mass) increases in most individuals until about age 20. It remains stable thereafter until about age 35, depending on the site measured. This peak bone mass may determine much of the risk for osteoporosis in later life. The determinants of peak bone mass appear to be almost evenly divided between genetic and environmental (acquired) factors. Bone mass declines after age 35 at a relatively steady rate throughout the remainder of life. In women, the perimenopausal/postmenopausal time period is associated with a sudden increase in the rate of skeletal loss (17). This increase gradually subsides over 5–10 years back to the baseline rate of loss (see above) (17). Decreased bone mineral density is associated with increased incidence of fragility fractures, including compression fractures and femoral fractures, of which femoral fractures are the most studied. In women, femoral fracture incidence is ~15–20 per hundred thousand per year until about age 45; the incidence then begins to increase exponentially, doubling every 6–7 year and reaches ~3% per year at ages 85 to 90. In men, the pattern is similar. The baseline rate in men is ~20–30 femoral fractures per hundred thousand per year until age 55; the rate of femoral fractures then begins to increase exponentially, again doubling every 6–7 years. The rate in men reaches ~1.5% per year at ages 85 to 90 (73, 74). Femoral fractures reduce mobility and impair independence. Prevention of this outcome, therefore, is prevention of a frailty syndrome. Studies in women have suggested that hormone replacement therapy (26–28) and alendronate (31) can reduce the incidence of hip (and other) fractures. In some (75) but not all (76) reports, vitamin D and calcium supplementation reduced hip (and other) fractures. No studies have examined fracture prevention in men.

Decreased skeletal mass associated with increasing age is the result of a series of changes associated with aging. Calcium absorption/transport in the intestinal mucosa decreases with age (77); calcium intake also generally decreases with age (78). Renal function, including 1-α-hydroxylase activity, decreases with age (72, 79). 1-α-Hydroxylase catalyzes the conversion of 25OHD to 1,25(OH)2D, the active metabolite of vitamin D. Decreased 1,25(OH)2D leads to further diminution of vitamin D-sensitive calcium absorption. Thus, at least three factors potentially play a role in decreasing calcium absorption from the gut: (a) decreased calcium intake, (b) decreased (native) calcium absorption, and (c) decreased vitamin D-dependent calcium absorption. The result of decreased calcium absorption is increased dependence on skeletal calcium as a source of needed calcium.

Other changes related to age occur in mineral metabolism. As renal function declines with age, PTH increases (80, 81). In addition, serum 25OHD declines with age, in both cross-sectional (82) and longitudinal (83) studies. At a minimum, this decline in older individuals appears associated with age-related reductions in vitamin D synthesis in the skin (84) as well as a reduction in physical activity, which in turn reduces exposure to the sun (83). Serum 25OHD and PTH are inversely related when serum 25OHD is <20–30 μg/L (85). Increasing PTH is associated with increased osteoclastic and osteoblastic activity. Such increased activity is probably associated with more rapid loss of bone. Both hypothyroid and hypoparathyroid individuals (with decreased cellular activity of the skeleton) have increased bone mineral density (86, 87).

Osteoclastic and osteoblastic activity are closely coupled. In younger individuals (~20–40 years of age), bone resorption and formation are generally identical. Although calcium absorption declines with age, it is not clear whether there is a primary defect in osteoblastic function associated with increasing age, such that after the age of ~40, every resorptive cycle that is initiated is associated with an incomplete osteoblastic response and the loss of a small unit of bone. It has been suggested that older osteoblasts do not respond as well to insulin-like growth factor 1 as younger osteoblasts (88). To date, therapeutic intervention to maintain bone mass, prevent fractures, and potentially maintain independence or prevent frailty has been reported only in women (27–33).

**Thyroid Function**

Changes in the thyroid gland with aging are not constant and probably depend on endemic iodine intake and rates of goiter (89). The prevalence of thyroidal disease increases with age. In those older individuals who are free of thyroidal disease, however, thyroid function remains relatively normal. Thyroidal uptake of iodine is reported
resistance in older individuals. This change appears to be concomitant with decreased rate of triiodothyronine degradation. Thus, the overall concentrations of thyroxine and triiodothyronine do not appear to change with age (89).

**Growth Hormone**

Pituitary function, LH, follicle-stimulating hormone, and thyroid-stimulating hormone decline with age. It is not surprising, therefore, that GH also has been reported to decline with age beginning in the third decade (92). This decrease is associated with decreased insulin-like growth factor concentrations (64, 92, 93). Pathologically decreased GH is associated with many of the changes seen with aging (Table 2) and with decreased concentrations of gonadal steroids in serum. Thus, pathologically decreased GH is associated with increasing fat, decreasing muscle mass, and decreasing bone mass (94), all of which are seen as age increases. It is not clear (as with testosterone) whether these changes are in part or in toto the sequelae of decreased GH function. Small studies have reported GH replacement in GH-deficient older subjects (95–97). These studies have demonstrated small increases in skeletal mass and lean body mass as well as a decrease in body fat (93). There are frequent side effects, however, including carpal tunnel syndrome, hypertension, and arthralgias (96, 97). Thus, GH replacement therapy has potential benefits but a greater risk of side effects than some other therapies described.

**Diabetes (Type 2)**

The prevalence of type 2 diabetes is age-related (98–100). Approximately 20% of individuals over the age of 65 have type 2 diabetes. Older type 2 diabetics tend to be leaner than younger type 2 diabetics. Individuals with diabetes are more prone to a series of cardiovascular and peripheral vascular complications than unaffected older individuals. Type 2 diabetics on average have a poorer prognosis with these complications than do nondiabetics (99).

Most studies demonstrate an age-related increase in fasting glucose of 10–20 mg/L per decade. Postprandial glucose concentrations are reported to rise at a rate of ~150 mg/L per decade (98, 101). As age increases, on average, a small increase in fasting hepatic glucose output is reported, with impairment of non-insulin-dependent glucose disposal (101, 102). In addition, insulin secretion is impaired with age, with less insulin being released in the early and late phase after challenges (102). The distribution of insulin moieties also appears to be shifted with age (103), and insulin resistance increases with age. Other endocrine changes, particularly in adrenal function with age, may also play a role in this process (98). In addition, dietary intake, activity, and body composition alter with age and may play a role in increasing insulin resistance in older individuals.

**Other Changes Associated with Aging**

IL-6 is an inflammatory and postinflammatory cytokine with multiple effects (22). It activates the hypothalamic-pituitary-adrenal axis, increasing adrenocorticotropin and plasma cortisol (104, 105). In addition, IL-6 increases plasma concentrations of vasopressin, suggesting a role in the production of the syndrome of inappropriate antidiuretic hormone (22, 106). IL-6 has postulated effects on lipid metabolism, the thyroid axis, and skeletal metabolism (see above). IL-6 concentrations have been reported to increase with age and to increase with increasing frailty (107, 108).

Body composition also alters with age. Generally, fat mass increases until about age 65, when it begins to decrease (109, 110). Lean body mass is reported to decrease steadily from the fifth or sixth decade onward. To what extent, if any, such changes cause decreased strength or function (increased frailty) and to what extent they are caused by this decrease in strength and function remains problematic. It seems likely that each contributes to the other in a circular fashion. In such a system, increasing fat mass would marginally reduce exercise tolerance. Reduced exercise tolerance would reduce exertion. It seems likely that other endocrine changes also play a role in these changes. Thus, increased glucocorticoids might increase central obesity and may induce some proximal myopathy, again further decreasing exercise tolerance and exercise. Decreased testosterone in men plays much the same role. It would marginally decrease lean body mass, decreasing strength and exercise tolerance. Exercise would decrease marginally as a result. Relative GH deficiency with age may also play a role in decreasing lean body mass, thereby causing loss of strength and function. It seems likely that in the vast majority of older individuals, no single deficiency or change drives all of the others. The question remains, however, whether replacing or improving function in one might not then improve function in all.

In summary, many endocrine systems change with aging. In the most extensively studied of these, menopausal women develop a series of changes in skeletal mass, lipid metabolism, and perhaps cognitive function that are reported to benefit from but not resolve with estrogen supplementation. Such therapy preserves function and delays the onset of frailty syndromes. Similarly, declines in gonadal function in men are associated with changes in strength, function, and loss of bone mass. Small studies have suggested that testosterone replacement improves but does not eliminate these changes. These studies are not as extensive as those examining estrogen replacement in women. Adrenal activity increases with aging. Although this may change the approach to treatment of diabetes or hypertension, no direct therapy for this change has been examined. Skeletal metabolism also changes with age, leading to a loss of bone mass and a predisposition to fracture, with a subsequent loss of
independence. Vitamin D supplementation and pharmacologic interventions have been demonstrated to reduce fracture incidence in older women and presumably prolong independence. The effects of these therapies on fracture incidence in older men have not been examined. Lastly, glucose metabolism changes in older individuals. Therapy for older type 2 diabetics should generally recognize these changes. Obesity will generally be less of a problem in older type 2 diabetes. Other causes of insulin resistance are generally more important.

References


76. Lips P, Graafmans WC, Ooms ME, Bezemer D, Bouter LM.


