tive gastritis to the development of other upper gastrointestinal tract diseases.

Clearly, important fundamental and clinically relevant information regarding *H pylori* and its relationship to gastroduodenal diseases will be forthcoming over the next few years. These results will likely have a major effect on our understanding of acid-peptic (or *H pylori*) diseases. At present, it is premature to disregard completely the contribution of acid and pepsin to peptic ulcer diseases.

JON I. ISENBERG, MD
Professor of Medicine
University of California, San Diego, School of Medicine

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'Andropause'—Are Reduced Androgen Levels in Aging Men Physiologically Important?

GONADAL FUNCTION declines with increasing age in both women and men. At the time of menopause in women, there is a relatively abrupt and complete loss of ovarian function that results in markedly reduced estradiol and progesterone production and the cessation of ovulation. This profound reduction in ovarian function has substantial physiologic consequences, including an accelerated loss of bone mass and osteoporosis, hot flushes with accompanying sleep and behavioral changes, vaginal atrophy, and the loss of fertility. In contrast, men experience a more gradual and incomplete loss of testicular function with increasing age, resulting in reduced testosterone and sperm production. Although decreased spermatogenesis may contribute to the age-related reduction in male fertility, other factors such as a loss of interest in fathering children and diminished sexual function are probably the major causes of infertility in healthy elderly men. The physiologic importance of reduced testicular androgen production with aging, referred to by some investigators as "andropause," is unclear.

Numerous cross-sectional and limited longitudinal studies have found that beginning at about 50 years, serum total testosterone levels gradually and progressively decline with age, with lowest concentrations noted in those older than 70 years.[1-5] Because circulating testosterone is mostly bound to serum proteins and the concentration of the major testosterone binding protein, sex hormone-binding globulin, increases as men age, serum-free or bioavailable testosterone concentrations decline to a greater extent than total testosterone levels.[1-5] Furthermore, the normal circadian variation of testosterone levels observed in young men with peak concentrations in the morning is lost in elderly men.[6] As a result of these age-related changes, many elderly men have circulating testosterone levels below the normal range for young men.

Testosterone production by the testes is greatly reduced with aging, both in the basal state and in response to supraphysiologic luteinizing hormone or luteinizing hormone-like (human chorionic gonadotropin) stimulation.[7-10] Histologically, testes from elderly men have a reduced number and volume of Leydig cells.[11] The age-related reduction in the capacity of the testes to produce testosterone may result in a more severe and prolonged reduction of testosterone levels in response to external stresses, such as illness. Despite reduced testicular androgen secretion, serum testosterone levels are not reduced proportionately because testosterone clearance is also reduced with aging.[1]

The decreases in both serum total and free testosterone concentrations with aging are relatively small, and there is considerable variation in testosterone levels in men of all ages. Thus, a substantial number of elderly men have serum testosterone concentrations within the wide range of normal values observed in young men. Despite apparently normal testosterone levels in some elderly men, the pronounced decrease in basal and human chorionic gonadotropin-stimulated testosterone production with aging provides strong evidence for an age-related reduction in testicular Leydig cell function.

Age-related alterations in either active metabolism of testosterone or androgen receptor status may be important in determining androgen action in specific target tissues

and thus, the physiologic significance of reduced testosterone levels in those tissues in aging men. In various peripheral tissues and the testes, testosterone is converted to the active steroid hormone metabolites, estradiol or dihydrotestosterone, by aromatase and 5α-reductase enzymes, respectively. Despite reduced serum testosterone levels with age, most studies have not found notable age-related changes in serum estradiol and dihydrotestosterone concentrations in men.[2,3,5,7,9,10] These findings suggest that the activities of the aromatase and 5α-reductase enzyme may be increased in some tissues (such as fat and prostate, respectively). Age-related alterations in androgen receptor status have not been investigated extensively. Limited studies have suggested that androgen receptors are reduced in skin and increased in hyperplastic prostate of elderly men.[12,13]

The pronounced variation in serum testosterone levels between men together with the small number of men studied (especially younger than 30 or older than 70 years) may explain why some investigators did not find a major reduction in testosterone concentrations with age. Also, the failure to recognize that the circadian variability of testosterone levels observed in young men with peak levels occurring in the morning is lost in elderly men may explain why investigators who obtained blood specimens during the afternoon did not find a meaningful age-related decline in testosterone concentrations.[10,14]

Testicular function and, in particular, testosterone production are affected by a number of external factors, such as illness (with its associated stress response), medications, psychological state, obesity, exercise, socioeconomic condition (malnutrition associated with poor elderly), and life-style (alcohol or drug abuse). The presence of these factors may contribute to the notable variation in serum testosterone levels in both young and elderly men and a more pronounced age-related decline in testosterone concentrations observed in some studies.[3,5] It is worth emphasizing, however, that substantially decreased testosterone levels have also been reported in carefully screened, exceptionally healthy elderly compared with young men.[7] Because complicating conditions such as illness occur more often in elderly than in young men, serum testosterone levels in the general population of elderly men may be more profoundly suppressed than those in highly selected healthy older men.

Concomitant with the decline in serum testosterone levels, aging is associated with functional changes in a number of androgen-dependent body tissues. These include an age-related decline in sexual interest and function (including diminished libido and erectile function), a reduction in muscle mass and strength, a decrease in bone mass and an increase in fractures (osteoporosis), mood changes (including a decrease in the feeling of well-being and vigor), and alterations in sleep quality (reduced stage 3 and 4 and rapid-eye-movement sleep). These alterations contribute substantially to a functional decline in elderly men and are associated with considerable morbidity and a reduced quality of life. Because these changes occur in androgen target tissues, it is possible that the age-related decline in serum testosterone concentrations may contribute to reduced function.

In this issue of the journal, Swerdloff and Wang present an interesting and timely overview of the potential physiologic importance of reduced serum androgen levels in elderly men.[15] The known effects of severe androgen deficiency on psychosexual function, bone mass, and muscle mass and strength and of testosterone treatment in young hypogonadal men provide a rationale for the hypothesis that declining serum testosterone levels contribute to age-related physiologic alterations and a functional decline in these tissues.

Although severe androgen deficiency in elderly men probably results in physiologic changes similar to those found in young hypogonadal men, formal studies comparing the effects of severe androgen deficiency and responses to testosterone therapy in elderly compared with young hypogonadal men have not been done. Moreover, the physiologic importance of less severe degrees of androgen deficiency as observed in many elderly men remains unclear. In part, this is due to a generally poor understanding of the physiologic effects and mechanisms of the action of androgens on specific body functions and physiologic processes in both young and elderly men. It is likely that the dose-response effects of testosterone therapy will differ for different androgen-dependent physiologic processes. Furthermore, the role of active metabolites of testosterone (estradiol and dihydrotestosterone) and androgen-dependent anabolic hormones (such as growth hormone and insulinlike growth factor-I [IGF-I]) in mediating the actions of testosterone on specific target sites has not been clarified in either young or elderly men.

Although reduced serum androgen levels may contribute to age-related physiologic decline, clinically it is important to consider other factors that may play a role in the age-related functional decline of a particular organ. For example, factors such as reduced activity or immobility, nutritional deficiency, medications, alterations in vitamin D and calcium metabolism, excessive alcohol or cigarette use, diabetes mellitus, reduced growth hormone and IGF-I levels, and falls may all contribute to the reduction in bone mass and increase in the incidence of osteoporotic fractures with aging in men. From the standpoint of clinical management, it is also important to consider the effects of age-related physiologic changes on a patient's function and quality of life before embarking on therapeutic interventions.

To test the hypothesis that the reduction in serum testosterone levels with aging contributes to an age-related physiologic and functional decline, carefully controlled clinical trials to determine whether testosterone replacement therapy in elderly men can improve physiologic indices and function are needed. Initial studies investigating the effects of testosterone replacement therapy in a small number of healthy elderly men have been reported recently.

In a double-blind, placebo-controlled, crossover study, Tenover found that administering testosterone enanthate, 100 mg a week, for three months to 13 healthy elderly

men with low serum total and non–sex hormone-binding globulin bound testosterone levels (< 350 ng per dl and < 46 ng per dl, respectively) substantially increased lean body mass, reduced urinary hydroxyproline excretion, increased hematocrit, and decreased the total and low-density lipoprotein-cholesterol without changing high-density lipoprotein (HDL)-cholesterol levels.[16] Furthermore, 12 of the 13 men experienced behavioral changes (such as increased libido and feelings of well-being) that permited them to determine correctly whether they were receiving testosterone or placebo, despite the double-blind design of the study. No adverse effects or changes in prostate volume or postvoiding residual urine volumes were noted, but serum prostate-specific antigen levels increased slightly during testosterone treatment.

In a preliminary study, Morley and co-workers found that administering testosterone enanthate, 200 mg every two weeks, for three months to eight elderly hypertensive men with low serum bioavailable testosterone levels (<70 ng per dl) substantially increased hand-grip strength, serum osteocalcin levels, and hematocrit and decreased total cholesterol without changing HDL-cholesterol levels, compared with six untreated control subjects.[17]

Despite the short-term nature of these studies, testosterone treatment of mildly androgen-deficient elderly men had notable beneficial effects on lean body mass, muscle, and hematocrit and possibly on bone turnover and mood. No significant adverse clinical effects were noted.

As discussed by Swerdloff and Wang, when contemplating the use of testosterone replacement therapy in elderly men with mild androgen deficiency, the possible risks as well as benefits must be considered.[15] Of particular concern is the potential for testosterone treatment to stimulate benign or malignant prostate growth—benign prostatic hyperplasia and prostate carcinoma, respectively—and to reduce HDL-cholesterol levels that may result in an increased risk of coronary artery disease.

Larger and longer term studies are needed to determine both the risks and benefits of androgen replacement therapy in elderly men. To avoid the adverse effects of pharmacologic levels of androgens, a reasonable initial goal of therapy in elderly men is to restore normal testosterone levels. If the late evening to morning rise in serum testosterone levels is found to be physiologically important (for example, in maintaining normal sleep quality), it may also be useful to restore a normal circadian variation of serum testosterone levels. Such truly physiologic testosterone replacement is now possible and practical using recently developed transdermal testosterone delivery systems.[18] Recent evidence suggests an important role for dihydrotestosterone in stimulating benign prostatic hyperplasia. Because of concerns regarding the stimulation of prostate growth and the suppression of HDL levels during testosterone therapy, it may be useful to explore combining testosterone with a 5α-reductase inhibitor or to use an androgen preparation, such as 7α-methyl-19-nortestosterone that is aromatized but not 5α-reduced.[19]

In summary, aging in men is associated with a gradual and progressive decrease in serum testosterone levels and a decline in various physiologic functions. The physiologic importance of lower androgen levels in elderly men and their relationship to age-related decreases in sexual interest and function, muscle mass and strength, and bone mass and alterations in mood and sleep quality remain unclear. Clarification of the functional significance of reduced testosterone levels with aging ("andropause") awaits carefully designed, long-term, placebo-controlled trials to determine the possible risks and benefits of androgen replacement therapy in selected elderly men.

ALVIN M. MATSUMOTO, MD
Associate Professor of Medicine
Division of Gerontology and Geriatric Medicine
University of Washington School of Medicine
Chief of Gerontology
Associate Director, Gerontology Research, Education and Clinical Center
Department of Veterans Affairs Medical Center
Seattle

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Lessons From Hypersensitivity Pneumonitis

THE RESPIRATORY TRACT is one of three sites of interaction of humans with the environment (the other two being the skin and gastrointestinal tract). The 7,200 liters of air