Aging and the Thyroid

As a result of the medical advances that have occurred since the 2nd World War, we are living longer; 11% of the US population or approximately 25,000,000 people are aged 65 years or older. Moreover, this group represents the most rapidly growing segment of the population. This phenomenon, the potential impact of which was only recently appreciated, has brought about the current explosion of interest in the effects of the aging process, from middle life through senescence, on organ physiology and cell function and on the clinical and laboratory presentation of disease. As a result, a rapidly expanding information base is emerging and nowhere is this more evident than in the case of the endocrine system.

The aging process may affect hormone physiology in one or more of several ways depending upon the specific endocrine organ in question. First, it could lead to a primary alteration in the metabolic disposition of hormone which through regulatory mechanisms would lead to a secondary parallel alteration in production; if the setpoint for feedback regulatory control were not altered, plasma hormone concentration would remain unchanged. Second, the aging process could be associated with a primary alteration in hormone production rate, with the expected parallel alteration in plasma hormone concentration. Finally, it could be associated with alterations in tissue responsiveness to hormone. In the case of the thyroid hormones, some of these alterations appear to be operative in elderly persons. Several studies have shown a decrease in the metabolic clearance rate of L-thyroxine (T_4).[1,2] This is in all likelihood due to a primary reduction in the metabolic disposition of hormone which parallels the age-related reduction in lean body mass, rather than to an increase in plasma binding since thyroxine-binding globulin is essentially unchanged. Because plasma T_4 concentration remains unchanged,[3-5] the production rate of T_4, which is due entirely to glandular secretion, must be reduced. In the case of L-triiodothyronine (T_3), the situation is complicated by the fact that this hormone is derived in large part from the outer ring (5′-)monodeiodination of T_4 in the peripheral tissues and from glandular secretion.

The plasma concentration of T_3 in elderly persons has been a subject of some controversy. Early studies had suggested a substantial decrease with aging. In these early studies, however, the effects of concurrent illness, reduced caloric intake and medication—factors that are now known to profoundly influence T_3 production or disposition—were not considered. More recent studies conducted in healthy, ambulant elderly persons have shown a small decline in plasma T_3 concentration, but not of the magnitude that was initially suggested.[3-5] Since the metabolic clearance rate of T_3 is not increased in the elderly, this decline must reflect a decrease in the production rate of T_3. Because about 80% of T_3 production is derived from the peripheral monodeiodination of T_4, the decreased production rate may merely reflect the reduction in the overall metabolic disposition of T_4 cited above. If this were the case, the concentration of reverse triiodothyronine (rT_3), the alternate metabolically inert product generated through inner ring (5-)monodeiodination of T_4, would be expected to be reduced to a proportionately equivalent extent. This, however, is not the case; plasma rT_3 concentration does not decline as a function of age.[4,5] This observation suggests

ABBREVIATIONS USED IN TEXT

rT_3 = reverse triiodothyronine
T_3 = L-triiodothyronine
T_4 = L-thyroxine

that in addition to the quantitative alterations described above, there may also exist an age-related qualitative alteration in which iodothyronine outer ring deiodination (5′-deiodination) is selectively depressed. This would result in both reduced generation of T_3 from T_4 and reduced degradation of rT_3. On the other hand, the small decrease in plasma T_3 concentration could be due, at least in part, to a decrease in the contribution of glandular secretion to T_3 production. Although thyroid radioiodine uptake values fall within the normal range in elderly persons, the thyroid iodide clearance rate is reduced. However, to my knowledge, there are no data concerning the influence of the aging process on T_4-T_3 concentration ratios in thyroglobulin or in the thyroid venous effluent.

The acquisition of information concerning the influence of the aging process on neuroendocrine regulatory mechanisms has not kept pace with that dealing with peripheral hormone metabolism. With the advent of ultrasensitive radioimmunoassays for pituitary hormones and the development of releasing-factor stimulation tests, however, information in this area is emerging rapidly. Basal values of plasma thyroid-stimulating hormone in elderly persons are within the normal range for young adults, although in some cross-sectional studies the mean values tend to be somewhat higher than those in younger persons.[3,5] Responsiveness of the thyroid-stimulating hormone secretory mechanism to thyrotropin-releasing hormone, however, may be dampened, and this appears to be more prominent in elderly men.[6,7]

From the foregoing, it is evident that the aging process is accompanied by only subtle changes in the values of the standard thyroid function tests. Moreover, so far as is known, the values deviate from the norm in the expected manner when thyroid dysfunction supervenes. Thus, on purely theoretical grounds, thyroid diagnosis ought not to pose a problem in elderly persons. Unfortunately, in the clinical setting, this is not necessarily the case.

In this issue of the journal, Rosenthal and Sanchez survey the problem of thyroid diagnosis in the elderly. Two phenomena, in the main, contribute to this problem. First, the clinical presentation of thyroid dysfunction in elderly persons frequently differs from that in younger patients. For example, thyrotoxicosis may masquerade as proximal myopathy, as cardiac insufficiency, supraventricular tachydysrhythmia, or a worsening of anginal pattern, or as unexplained weight loss; often, the usual clinical manifestations that one associates with thyrotoxicosis in a younger patient are lacking, and goiter may be absent. Moreover, when some other severe illness coexists, the serum T_3 and T_4 concentrations may not display their expected increases. Consequently, the correct diagnosis is often delayed and presumably on occasion never made. In my experience, this is by far the commonest type of "missed thyroid diagnosis." The other phenomenon that may contribute to the problem of thyroid diagnosis is the presence of a systemic nonthyroid illness. An elderly patient may superficially resemble a patient with hypothyroidism in dis-

playing some hair loss, dryness of the skin and general slowing. When these changes are associated with the laboratory abnormalities of the "euthyroid sick syndrome," a mistaken diagnosis of hypothyroidism could be made and treatment instituted with potentially disastrous consequences. This represents the commonest form of thyroid "overdiagnosis." Rosenthal and Sanchez address this aspect in some detail and provide some guidelines for the laboratory diagnosis of hypothyroidism in a case of nonthyroid illness.

As alluded to above, aging is accompanied by some physical changes that are reminiscent of those of hypothyroidism. Accordingly, it has been suggested that the aging process after middle life may be due in part to reduced responsiveness of the tissues to thyroid hormones. In keeping with this suggestion is a recent observation that nuclear T_3 receptor affinity and density are reduced in mononuclear cells harvested from elderly persons.[8] However, it is difficult to reconcile this observation with the finding that the basal metabolic rate, the only index of thyroid hormone action that has been assessed in relation to age in humans, is appropriate for the mass of metabolically active tissue in elderly persons.[9] Moreover, lean body mass has been a more accurate predictor of thyroid hormone requirements than age.[10] Thus, the balance of evidence in humans to date would not support a role for reduced tissue responsiveness to thyroid hormones in the aging process.

KENNETH A. WOEBER, MD
Chief of Medicine
Mount Zion Hospital and Medical Center
Professor and Vice-Chair
Department of Medicine
University of California, San Francisco
School of Medicine
San Francisco

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