Editorial

Is the Hormonal Fountain of Youth Drying Up?

John E. Morley

Division of Geriatric Medicine, Saint Louis University Health Sciences Center, and Geriatric Research, Education and Clinical Center, VA Medical Center, St. Louis, Missouri.

THE concept of a “Fountain of Youth” was made famous by Ponce de Leon who went in search of the island of Bimini where there was a river that restored youth to those who bathed in it. Of course, while failing to find the fountain of youth, Ponce de Leon did discover Florida, a land to which many elderly people still flock!

However, the concept of a fountain of youth began with the stories in the Old Testament of a River of Immortality that flowed out of the garden of Eden. Alexander the Great searched for a spring that had brought a dried fish back to life while it was being cleaned. In a Hindu story, the priest Cyavanna made a bargain with the two Asvins, who were demigods, to be taken to the Pool of Youth in return for sharing his knowledge.

It was out of these magical beginnings that the concept of a hormonal fountain of youth was born. Simplistically, it was conceived that, as many hormones declined with aging, replacing one or more of these hormones would result in rejuvenation of the older person (1–4). Perhaps the most enduring of these concepts is testosterone replacement for the aging male (5–8) and, more recently, for postmenopausal women (9). This concept was developed when Brown-Sequard injected himself with testicular extracts to rejuvenate himself. This lead to human testicular and “monkey gland” transplants before testosterone was isolated. Estrogen soared to the front of the rejuvenation sweepstakes when the concept of “feminine forever” was introduced in the 1950s; however, its star has fallen with the publication of the results of the Women’s Health Initiative (WHI) (10–14).

Dan Rudman (15) postulated that growth hormone may delay some aspects of the aging process. However, after an original upbeat publication (16), it was reported that growth hormone caused an excess of side-effects (2,17–21). The potential role of growth hormone to reverse undernutrition and frailty remains under scrutiny (22). With the discovery of ghrelin, a peptide hormone released by the fundus of the stomach, which increases food intake and the release of growth hormone from the stomach, there has been a marked increase in the development of ghrelin-like drugs to be used for the treatment of the anorexia of elderly people (23).

Vitamin D levels decline with aging and may reach very low levels, even in persons living in sunny climates (24). Vitamin D and calcium replacement in women in nursing homes decreased hip fracture and deaths (25). The effects of vitamin D on sarcopenia are less clear. Visser and colleagues (26) from the Longitudinal Aging Study Amsterdam found that low vitamin D levels and elevated parahormone levels were highly correlated with muscle mass and muscle strength. Other studies have confirmed this relationship and extended them to low vitamin D being associated with body sway, physical performance, and disability (27–30). However, these findings have not been universal. Some, but not all, vitamin D replacement studies have shown enhanced physical function and strength (31–33). Vitamin D replacement is surprisingly not more effective when given to persons with low circulating levels.

Dehydroepiandrosterone (DHEA) and its precursor pregnenolone have had enormous popular appeal as fountain-of-youth drugs. Much of this was based on studies demonstrating their potency at enhancing memory in mice (34–36). In this issue of the Journal, DHEA-sulfate is demonstrated to be an independent predictor of muscle strength and calf muscle area (37). Unfortunately, replacement with these hormones has so far failed to demonstrate any dramatic effects (38,39). DHEA also failed to improve memory in patients with Alzheimer’s disease (40).

The WHI was stopped prematurely. This led to difficulty in interpreting the effects of estrogen plus progesterone in women (14). The estrogen arm alone continues. Women receiving hormone replacement therapy (HRT) were slightly less likely to die than those receiving placebo. Hip fracture was clearly decreased by HRT (12,13). With a statistical approach different from the preplanned analysis, there was less colon cancer and more breast cancer, pulmonary embolus, and cardiovascular disease in those receiving HRT (12,13,41). There was an increased incidence of Alzheimer’s disease and a decline in cognition in those receiving HRT, though these studies were extraordinarilly flawed (10,11). Previous studies in the Journal have, on the balance, supported the failure of HRT to aid memory (42–47). This may be due to the amnestic effects of progesterone (48). What should the discerning clinician conclude from the WHI? Certainly, there is little or no support to give HRT to women over 60 years of age. In younger women, estrogen should be seen predominantly as a quality-of-life drug to treat menopausal symptoms. Women who undergo a premature menopause (surgical or natural) most probably should continue to take hormone replacement until the time of the natural menopause. Taking HRT for more than 5 years beyond the time of natural menopause cannot be recommended at present. Perhaps the most important lesson...
to be learned from the WHI is that the only criteria for premature halting of large studies should include statistically significant increase in mortality.

Finally, we must return to testosterone. Should we be fueling our engines with testosterone? Sales of testosterone have increased markedly (49), and we now have direct-to-consumer marketing of testosterone products on television, competing with the advertisements for Viagra and Levitra. The Journal has published a number of papers generally demonstrating positive effects of testosterone in relationship to muscle, bone, and cognition (50–57). A number of relatively small-sized replacement studies have supported the concept that testosterone is, at the least, not harmful (5,8,58–60). The Journal has published an important study showing that testosterone promotes the commitment of pluripotent stem cells into the myogenic (satellite cell) lineage and inhibits their differentiation into the adipogenic lineage (61,62).

In this issue of the Journal, we published a consensus paper highlighting the need for a large study to test the efficacy and safety of testosterone (63). The conclusions of the consensus statement are similar to our recent editorial (51). Unfortunately, the Institute of Medicine report commissioned by the National Institute on Aging (NIA) has called for smaller studies before undertaking the large study (64). This means that it will be at least 10 to 15 years before the true safety of long-term testosterone use is determined. The Helsinki Declaration says that studies to determine the safety of drugs are inappropriate. However, in the modern era of designer drugs for enhancing quality of life, safety is of paramount importance. Testosterone is clearly a quality of life drug in need of a major safety study. Historically, it is interesting to note that the Institute of Medicine did not support the WHI as it was felt that HRT was clearly beneficial!

Thus, it would appear that, while the hormonal fountain of youth, like the mythical fountains of youth from bygone eras, remains elusive, it will clearly continue to provide much fodder for scientists. In addition, new hormones such as adiponectin (65), leptin (66), and ghrelin (22) are vying for fodder for scientists. In addition, new hormones such as estrogen plus progesterin and the incidence of dementia and mild cognitive impairment in postmenopausal women—the Women’s Health Initiative Memory Study. A randomized controlled trial. JAMA. 2003;289:2651–2662.


26. Visser M, Deeg DJM, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia). J Clin Endocrinol Metab. 2003;88:5766–5772.
