The aging of the hypothalamic gonadotropin releasing hormone (GnRH) pituitary-testicular axis has been amply documented by a large body of studies of serum total testosterone and free testosterone (FT) (Table 5). The stimulator of testosterone production, luteinizing hormone (LH), increases with advancing age at a rate of 1% per period of 10 years in men 40-70 years old. FSH during the same period increased by 3% yearly. In another study no correlation of LH with testosterone was found, suggesting an alteration in the normal feedback relationship of these hormones. FSH increases at a higher rate of 3% yearly, probably due to a diminished inhibin feedback from the Sertoli cells of the aging testis.

Large-scale cross-sectional and longitudinal studies have documented the great decrease of testosterone despite the increase of LH, indicating an anomaly in the strong forward and feedback relationship of these hormones. In a cross-sectional study of 300 men aged 20 to 100 years grouped in decades, Vermuelen et al. found a decrease of mean serum free testosterone (FT) beginning in the decade of 35-45 years and of testosterone starting in the decade of 45-55 and progressing up to the last 85-100 years. Mean values of T at 75 years were approximately two thirds of those at the age of 20 years, whereas those of FT decreased by 50% during the same period. Sex hormone binding protein (SHBP) binding 45-50% of circulating testosterone started increasing in the decade of 35-45 years and continued to increase up to the last years of life. The proportion of healthy men having subnormal total testosterone (less than 50% of normal) was 33% at age 50-59 years and increased to 53% at age 80-89 years. The decline of DHEA-S was more marked in smokers than in non-smokers, and the same was observed for SHBG. The increase of FSH during the same period increased by 45-50% yearly.