discussion of the risks and benefits (see "Testosterone Replacement," below).

Testicular morphology, semen production, and fertility are maintained up to a very old age in men. Although concern has been expressed about age-related increases in germ cell mutations and impairment of DNA repair mechanisms, there is no clear evidence that the frequency of chromosomal aneuploidy is increased in the sperm of older men. However, the incidence of autosomal dominant diseases, such as achondroplasia, polyposis coli, Marfan's syndrome, and Apert's syndrome, increases in the offspring of men who are advanced in age, consistent with transmission of sporadic missense mutations. Advanced paternal age may be associated with increased rates of de novo mutations, which may contribute to an increased risk of neurodevelopmental diseases such as schizophrenia and autism. The somatic mutations in male germ cells that enhance the proliferation of germ cells could lead to within-testis expansion of mutant clonal lines, thus favoring the propagation of germ cells carrying these pathogenic mutations and increasing the risk of mutations in the offspring of older fathers (the "selfish spermatogonial selection" hypothesis).

APPROACH TO THE PATIENT: Androgen Deficiency

Hypogonadism is often characterized by decreased sex drive, reduced frequency of sexual activity, inability to maintain erections, reduced beard growth, loss of muscle mass, decreased testicular size, and gynecomastia. Erectile dysfunction and androgen deficiency are two distinct clinical disorders that can coexist in middle-aged and older men. Less than 10% of patients with erectile dysfunction have testosterone deficiency. Thus, it is useful to evaluate men presenting with erectile dysfunction for androgen deficiency. Except when extreme, these clinical features of androgen deficiency may be difficult to distinguish from changes that occur with normal aging. Moreover, androgen deficiency may develop gradually. Several epidemiologic studies, such as the Framingham Heart Study, the Massachusetts Male Aging Study, the Baltimore Longitudinal Study of Aging, and the Study of Osteoporotic Fractures in Men, have reported a high prevalence of low testosterone levels in middle-aged and older men. The age-related decline in testosterone should be distinguished from classical hypogonadism due to diseases of the testes, the pituitary, and the hypothalamus.

When symptoms or clinical features suggest possible androgen deficiency, the laboratory evaluation is initiated by the measurement of total testosterone, preferably in the morning using a reliable assay, such as LC-MS/MS that has been calibrated to an international testosterone standard (Fig. 411-6). A consistently low total testosterone level <300 ng/dL measured by a reliable assay, in association with symptoms, is evidence of testosterone deficiency. An early-morning testosterone level >400 ng/dL makes the diagnosis of androgen deficiency unlikely. In men with testosterone levels between 200 and 400 ng/dL, the total testosterone level should be repeated and a free testosterone level should be measured. In older men and in patients with other clinical states that are associated with alterations in SHBG levels, a direct measurement of free testosterone level by equilibrium dialysis can be useful in unmasking testosterone deficiency.

When androgen deficiency has been confirmed by the consistently low testosterone concentrations, LH should be measured to classify the patient as having primary (high LH) or secondary (low or inappropriately normal LH) hypogonadism. An elevated LH level indicates that the defect is at the testicular level. Common causes of primary testicular failure include Klinefelter's syndrome, HIV infection, uncorrected cryptorchidism, cancer chemotherapeutic agents, radiation, surgical orchiectomy, or prior infectious orchitis. Unless causes of primary testicular failure are known, a karyotype should be performed in men with low testosterone and elevated LH to exclude Klinefelter's syndrome. Men who have low testosterone levels but "inappropriately normal" or low LH levels have secondary hypogonadism; their defect resides at the hypothalamic-pituitary level. Common causes of acquired secondary hypogonadism include space-occupying lesions of the sella, hyperprolactinemia, chronic illness, hemochromatosis, excessive exercise, and the use of anabolic-androgenic steroids, opiates, marijuana, glucocorticoids, and alcohol. Measurement of PRL and MRI scan of the hypothalamic-pituitary region can help exclude the presence of a space-occupying lesion. Patients in whom known causes of hypogonadotropic hypogonadism have been excluded are classified as having IHH. It is not unusual for congenital causes of hypogonadotropic hypogonadism, such as Kallmann's syndrome, to be diagnosed in young adults.

TREATMENT ANDROGEN DEFICIENCY

GONADOTROPINS

Gonadotropin therapy is used to establish or restore fertility in patients with gonadotropin deficiency of any cause. Several gonadotropin preparations are available. Human menopausal gonadotropin (hMG; purified from the urine of postmenopausal women) contains 75 IU FSH and 75 IU LH per vial. hCG (purified from the urine of pregnant women) has little FSH activity and resembles LH in its ability to stimulate testosterone production by Leydig cells. Recombinant LH is now available. Because of the expense of hMG, treatment is usually begun with hCG alone, and hMG is added later to promote the FSH-dependent stages of spermatid development. Recombinant human FSH (hFSH) is now available and is indistinguishable from purified urinary hFSH in its biologic activity and pharmacokinetics in vitro and in vivo, although the mature β subunit of recombinant hFSH has seven fewer amino acids. Recombinant hFSH is available in ampoules containing 75 IU (~7.5 μg FSH), which accounts for >99% of protein content. Once spermatogenesis is restored using combined FSH and LH therapy, hCG alone is often sufficient to maintain spermatogenesis.

Although a variety of treatment regimens are used, 1000–2000 IU of hCG or recombinant human LH (rhLH) administered intramuscularly three times weekly is a reasonable starting dose. Testosterone levels should be measured 6–8 weeks later and 48–72 h after the hCG or rhLH injection; the hCG/rhLH dose should be adjusted to achieve testosterone levels in the mid-normal range. Sperm counts should be monitored on a monthly basis. It may take several months for spermatogenesis to be restored; therefore, it is important to forewarn patients about the potential length and expense of the treatment and to provide conservative estimates of success rates. If testosterone levels are in the mid-normal range but the sperm concentrations are low after 6 months of therapy with hCG alone, FSH should be added. This can be done by using hMG, highly purified urinary hFSH, or recombinant hFSH. The selection of FSH dose is empirical. A common practice is to start with the addition of 75 IU FSH three times each week in conjunction with the hCG/rhLH injections. If sperm densities are still low after 3 months of combined treatment, the FSH dose should be increased to 150 IU. Occasionally, it may take ≥18–24 months for spermatogenesis to be restored.

The two best predictors of success using gonadotropin therapy in hypogonadotropic men are testicular volume at presentation and time of onset. In general, men with testicular volumes >8 mL have better response rates than those who have testicular volumes >4 mL. Patients who became hypogonadotropic after puberty experience higher success rates than those who have never undergone pubertal changes. Spermatogenesis can usually be reinitiated by hCG alone, with high rates of success for men with postpubertal onset of hypogonadotropism. The presence of a primary testicular abnormality, such as cryptorchidism, will attenuate testicular response to gonadotropin therapy. Prior androgen therapy does not preclude subsequent response to gonadotropin therapy, although some studies suggest that it may attenuate response to subsequent gonadotropin therapy.