the other hand, low-normal basal gonadotropin levels or a normal response to exogenous GnRH is consistent with an early stage of puberty, which is often heralded by nocturnal GnRH secretion. Thus, constitutional delay is a diagnosis of exclusion that requires ongoing evaluation until the onset of puberty and the growth spurt.

TREATMENT DELAYED PUBERTY

If therapy is considered appropriate, it can begin with 25–50 mg testosterone enanthate or testosterone cypionate every 2 weeks, or by using a 2.5-mg testosterone patch or 25-mg testosterone gel. Because aromatization of testosterone to estrogen is obligatory for mediating androgen effects on epiphyseal fusion, concomitant treatment with aromatase inhibitors may allow attainment of greater final adult height. Testosterone treatment should be interrupted after 6 months to determine if endogenous LH and FSH secretion have ensued. Other causes of delayed puberty should be considered when there are associated clinical features or when boys do not enter puberty spontaneously after a year of observation or treatment.

Reassurance without hormonal treatment is appropriate for many individuals with presumed constitutional delay of puberty. However, the impact of delayed growth and pubertal progression on a child's social relationships and school performance should be weighed. Also, boys with constitutional delay of puberty are less likely to achieve their full genetic height potential and have reduced total-body bone mass as adults, mainly due to narrow limb bones and vertebrae as a result of impaired periosteal expansion during puberty. Administration of androgen therapy to boys with constitutional delay does not affect final height, and when administered with an aromatase inhibitor, it may improve final height.

DISORDERS OF THE MALE REPRODUCTIVE AXIS DURING ADULTHOOD

HYPOGONADOTROPIC HYPOGONADISM

Because LH and FSH are trophic hormones for the testes, impaired secretion of these pituitary gonadotropins results in secondary hypogonadism, which is characterized by low testosterone in the setting of low LH and FSH. Those with the most severe deficiency have complete absence of pubertal development, sexual infantilism, and, in some cases, hypospadias and undescended testes. Patients with partial gonadotropin deficiency have delayed or arrested sex development. The 24-h LH secretory profiles are heterogeneous in patients with hypogonadotropic hypogonadism, reflecting variable abnormalities of LH pulse frequency or amplitude. In severe cases, basal LH is low and there are no LH pulses. A smaller subset of patients has low-amplitude LH pulses or markedly reduced pulse frequency. Occasionally, only sleep-entrained LH pulses occur, reminiscent of the pattern seen in the early stages of puberty. Hypogonadotropic hypogonadism can be classified into congenital and acquired disorders. Congenital disorders most commonly involve GnRH deficiency, which leads to gonadotropin deficiency. Acquired disorders are much more common than congenital disorders and may result from a variety of sellar mass lesions or infiltrative diseases of the hypothalamus or pituitary.

Congenital Disorders Associated with Gonadotropin Deficiency Congenital hypogonadotropic hypogonadism is a heterogeneous group of disorders characterized by decreased gonadotropin secretion and testicular dysfunction either due to impaired function of the GnRH pulse generator or the gonadotrope. The disorders characterized by GnRH deficiency represent a family of oligogenic disorders whose phenotype spans a wide spectrum. Some individuals with GnRH deficiency may suffer from complete absence of pubertal development, while others may manifest varying degrees of gonadotropin deficiency and pubertal delay, and a subset that carries the same mutations as their affected family members may even have normal reproductive function. In approximately 10% of men with idiopathic hypogonadotropic hypogonadism, reversal of gonadotropin deficiency may occur in adult life after sex steroid therapy. Also, a small fraction of men with idiopathic hypogonadotropic hypogonadism may present with androgen deficiency and infertility in adult life after having gone through apparently normal pubertal development. Nutritional, emotional, or metabolic stress may unmask gonadotropin deficiency and reproductive dysfunction (analogous to hypothalamic amenorrhea) in some patients who harbor mutations in the candidate genes but who previously had normal reproductive function. The clinical phenotype may include isolated anosmia or hyposmia. These striking variations in phenotypic presentation of GnRH deficiency have highlighted the important role of oligogenicity and gene-gene and gene-environment interactions in shaping the clinical phenotype.

Mutations in a number of genes involved in the development and migration of GnRH neurons or in the regulation of GnRH secretion have been linked to GnRH deficiency, although the genetic defect remains elusive in nearly two-thirds of cases. Familial hypogonadotropic hypogonadism can be transmitted as an X-linked (20%), autosomal recessive (30%), or autosomal dominant (50%) trait. Some individuals with idiopathic hypogonadotropic hypogonadism (IHH) have sporadic mutations in the same genes that cause inherited forms of the disorder. The genetic defects associated with GnRH deficiency can be conveniently classified as anosmic (Kallmann's syndrome) or normosmic (Table 411-2), although the occurrence of both anosmic and normosmic forms of GnRH deficiency in the same families suggests commonality of pathophysiologic mechanisms. *Kallmann's syndrome*, the anosmic form of GnRH deficiency, can result from mutations in one or more genes associated with olfactory bulb morphogenesis and the migration of GnRH neurons from their origin in the region of the olfactory placode, along the scaffold established by the olfactory nerves, through the cribriform plate into their final location into the preoptic region of the hypothalamus. Thus, mutations in *KAL1, FGF8, FGFR1, NELF, PROK2, PROK2R,* and *CHD7* have been described in patients with Kallmann's syndrome. An X-linked form of IHH is caused by mutations in the *KAL1* gene, which encodes anosmin, a protein that mediates the migration of neural progenitors of the olfactory bulb and GnRH-producing neurons. These individuals have GnRH deficiency and variable combinations of anosmia or hyposmia, renal defects, and neurologic abnormalities including mirror movements. Mutations in the *FGFR1* gene cause an autosomal dominant form of hypogonadotropic hypogonadism that clinically resembles Kallmann's syndrome; mutations in its putative ligand, *FGF8* gene product, have also been associated with IHH. Prokineticin 2 (*PROK2*) also encodes a protein involved in migration and development of olfactory and GnRH neurons. Recessive mutations in *PROK2* or in its receptor, *PROKR2*, have been associated with both anosmic and normosmic forms of hypogonadotropic hypogonadism.

Normosmic GnRH deficiency results from defects in pulsatile GnRH secretion, its regulation, or its action on the gonadotrope and has been associated with mutations in *GnRHR*, *GNRH1*, *KISS1R*, *TAC3*, *TACR3*, and *NROB1* (*DAX1*). Some mutations, such as those in *PROK2*, *PROKR2*, and *CHD7*, have been associated with both the anosmic and normosmic forms of IHH. *GnRHR* mutations, the most frequent identifiable cause of normosmic IHH, account for ~40% of autosomal recessive and 10% of sporadic cases of hypogonadotropic hypogonadism. These patients have decreased LH response to exogenous GnRH. Some receptor mutations alter GnRH binding affinity, allowing apparently normal responses to pharmacologic doses of exogenous GnRH, whereas other mutations may alter signal transduction downstream of hormone binding. Mutations of the *GnRH1* gene have also been reported in patients with hypogonadotropic hypogonadism, although they are rare. G protein–coupled receptor *KISS1R* (*GPR54*) and its cognate ligand, kisspeptin (*KISS1*), are important regulators of sexual maturation in primates. Recessive mutations in *GPR54* cause gonadotropin deficiency without anosmia. Patients retain responsiveness to exogenous GnRH, suggesting an abnormality in the neural pathways controlling GnRH release. The genes encoding neurokinin B (*TAC3*), which is involved in preferential activation of GnRH release in early development, and its receptor (*TAC3R*) have been implicated