pituitary dysplasia. Acquired pituitary failure in the newborn also can be caused by birth trauma, including cranial hemorrhage, asphyxia, and breech delivery.

SEPTO-OPTIC DYSPLASIA Hypothalamic dysfunction and hypopituitarism may result from dysgenesis of the septum pellucidum or corpus callosum. Affected children have mutations in the *HESX1* gene, which is involved in early development of the ventral prosencephalon. These children exhibit variable combinations of cleft palate, syndactyly, ear deformities, hypertelorism, optic nerve hypoplasia, micropenis, and anosmia. Pituitary dysfunction leads to diabetes insipidus, growth hormone (GH) deficiency and short stature, and, occasionally, thyroid-stimulating hormone (TSH) deficiency.

Tissue-Specific Factor Mutations Several pituitary cell–specific transcription factors, such as Pit-1 and Prop-1, are critical for determining the development and committed function of differentiated anterior pituitary cell lineages. Autosomal dominant or recessive Pit-1 mutations cause combined GH, prolactin (PRL), and TSH deficiencies. These patients usually present with growth failure and varying degrees of hypothyroidism. The pituitary may appear hypoplastic on magnetic resonance imaging (MRI).

Prop-1 is expressed early in pituitary development and appears to be required for Pit-1 function. Familial and sporadic *PROP1* mutations result in combined GH, PRL, TSH, and gonadotropin deficiency. Over 80% of these patients have growth retardation; by adulthood, all are deficient in TSH and gonadotropins, and a small minority later develop adrenocorticotropic hormone (ACTH) deficiency. Because of gonadotropin deficiency, these individuals do not enter puberty spontaneously. In some cases, the pituitary gland appears enlarged on MRI. *TPIT* mutations result in ACTH deficiency associated with hypocortisolism.

Developmental Hypothalamic Dysfunction • ***KALLMANN SYNDROME*** Kallmann syndrome results from defective hypothalamic gonadotropin-releasing hormone (GnRH) synthesis and is associated with anosmia or hyposmia due to olfactory bulb agenesis or hypoplasia (Chap. 411). Classically, the syndrome may also be associated with color blindness, optic atrophy, nerve deafness, cleft palate, renal abnormalities, cryptorchidism, and neurologic abnormalities such as mirror movements. The initial genetic cause was identified in the X-linked *KAL* gene, mutations of which impair embryonic migration of GnRH neurons from the hypothalamic olfactory placode to the hypothalamus. Based on further studies, at least a dozen other genetic abnormalities, in addition to KAL mutations, have been found to cause isolated GnRH deficiency. Autosomal recessive (i.e., *GPR54, KISS1*) and dominant (i.e., *FGFR1*) modes of transmission have been described, and there is a growing list of genes associated with GnRH deficiency (*GNRH1, PROK2, PROKR2, CH7, PCSK1, FGF8, NELF, WDR11, TAC3, TACR3*). A fraction of patients have digenic mutations. Associated clinical features, in addition to GnRH deficiency, vary depending on the genetic cause. GnRH deficiency prevents progression through puberty. Males present with delayed puberty and pronounced hypogonadal features, including micropenis, probably the result of low testosterone levels during infancy. Females present with primary amenorrhea and failure of secondary sexual development.

Kallmann syndrome and other causes of congenital GnRH deficiency are characterized by low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels and low concentrations of sex steroids (testosterone or estradiol). In sporadic cases of isolated gonadotropin deficiency, the diagnosis is often one of exclusion after other known causes of hypothalamic-pituitary dysfunction have been eliminated. Repetitive GnRH administration restores normal pituitary gonadotropin responses, pointing to a hypothalamic defect in these patients.

Long-term treatment of males with human chorionic gonadotropin (hCG) or testosterone restores pubertal development and secondary sex characteristics; women can be treated with cyclic estrogen and progestin. Fertility also may be restored by the administration of gonadotropins or by using a portable infusion pump to deliver subcutaneous, pulsatile GnRH.

BARDET-BIEDL SYNDROME This very rare genetically heterogeneous disorder is characterized by mental retardation, renal abnormalities, obesity, and hexadactyly, brachydactyly, or syndactyly. Central diabetes insipidus may or may not be associated. GnRH deficiency occurs in 75% of males and half of affected females. Retinal degeneration begins in early childhood, and most patients are blind by age 30. Numerous subtypes of Bardet-Biedl syndrome (BBS) have been identified, with genetic linkage to at least nine different loci. Several of the loci encode genes involved in basal body cilia function, and this may account for the diverse clinical manifestations.

LEPTIN AND LEPTIN RECEPTOR MUTATIONS Deficiencies of leptin or its receptor cause a broad spectrum of hypothalamic abnormalities, including hyperphagia, obesity, and central hypogonadism (Chap. 415e). Decreased GnRH production in these patients results in attenuated pituitary FSH and LH synthesis and release.

PRADER-WILLI SYNDROME This is a contiguous gene syndrome that results from deletion of the paternal copies of the imprinted *SNRPN* gene, the *NECDIN* gene, and possibly other genes on chromosome 15q. Prader-Willi syndrome is associated with hypogonadotropic hypogonadism, hyperphagia-obesity, chronic muscle hypotonia, mental retardation, and adult-onset diabetes mellitus (Chap. 83e). Multiple somatic defects also involve the skull, eyes, ears, hands, and feet. Diminished hypothalamic oxytocin- and vasopressin-producing nuclei have been reported. Deficient GnRH synthesis is suggested by the observation that chronic GnRH treatment restores pituitary LH and FSH release.

ACQUIRED HYPOPITUITARISM

Hypopituitarism may be caused by accidental or neurosurgical trauma; vascular events such as apoplexy; pituitary or hypothalamic neoplasms, craniopharyngioma, lymphoma, or metastatic tumors; inflammatory disease such as lymphocytic hypophysitis; infiltrative disorders such as sarcoidosis, hemochromatosis (Chap. 428), and tuberculosis; or irradiation.

Increasing evidence suggests that patients with brain injury, including contact sports trauma, subarachnoid hemorrhage, and irradiation, have transient hypopituitarism and require intermittent long-term endocrine follow-up, because permanent hypothalamic or pituitary dysfunction will develop in 25–40% of these patients.

Hypothalamic Infiltration Disorders These disorders—including sarcoidosis, histiocytosis X, amyloidosis, and hemochromatosis—frequently involve both hypothalamic and pituitary neuronal and neurochemical tracts. Consequently, diabetes insipidus occurs in half of patients with these disorders. Growth retardation is seen if attenuated GH secretion occurs before puberty. Hypogonadotropic hypogonadism and hyperprolactinemia are also common.

Inflammatory Lesions Pituitary damage and subsequent secretory dysfunction can be seen with chronic site infections such as tuberculosis, with opportunistic fungal infections associated with AIDS, and in tertiary syphilis. Other inflammatory processes, such as granulomas and sarcoidosis, may mimic the features of a pituitary adenoma. These lesions may cause extensive hypothalamic and pituitary damage, leading to trophic hormone deficiencies.

Cranial Irradiation Cranial irradiation may result in long-term hypothalamic and pituitary dysfunction, especially in children and adolescents, as they are more susceptible to damage after whole-brain or head and neck therapeutic irradiation. The development of hormonal abnormalities correlates strongly with irradiation dosage and the time interval after completion of radiotherapy. Up to two-thirds of patients ultimately develop hormone insufficiency after a median dose of 50 Gy (5000 rad) directed at the skull base. The development of hypopituitarism occurs over 5–15 years and usually reflects hypothalamic damage rather than primary destruction of pituitary cells. Although the pattern of hormone loss is variable, GH deficiency is most common, followed by gonadotropin and ACTH deficiency. When deficiency of one or more hormones is documented, the possibility of diminished reserve of other hormones is likely. Accordingly, anterior pituitary function should be continually