extensive dysfunction of hypothalamus in women with Stein-Leventhal syndrome.

Because the plasma androgens are a substrate for peripheral aromatization (mainly in the cells of fat tissue) their permanently elevated concentration in circulating blood usually results in an increased **formation of extraglandular estrogens**. The increased plasma estrogen concentration, conditioned by the mentioned mechanism, is considered as the cause of inhibition of FSH secretion by a negative feedback, and the cause of stimulation of LH secretion by a positive feedback, giving the characteristic LH/FSH ratio in plasma. In women with Stein-Leventhal syndrome (with or without obesity) insulin resistance has been discovered. The increased plasma insulin concentration is supposed to stimulate androgen secretion in ovarian stroma. Insulin may probably act on the ovary via IGF receptors.

Stein-Leventhal syndrome begins clinically manifest usually in the period of adolescence or in young women (in 2nd or 3rd decennium). Varying degrees of **hirsutism** appear. In adolescent girls it may cause late onset of menarche, but uterine bleeding is dysfunctional and is unpredictable in onset, duration, and amount. **Oligomenorrhea** (prolonged menstrual cycle over 35 days), **hypomenorrhea** (weak menstrual bleeding), and **amenorrhea** ensue after a variable time. About 5–10 % of affected women present with primary amenorrhea. Due to hormonal inbalance ovarian follicles mature insufficiently, and, therefore, multiple atretic follicles are found. These women have persistent anovulation and are infertile. About 40 % of affected women are obese.

Stein-Leventhal syndrome is considered a special type of **polycystic ovarian syndrome**. The term polycystic ovarian syndrome includes those endocrine states which lead to the origin of multiple ovarian cysts associated with similar functional abnormalities to those occuring in the patients with Stein-Leventhal syndrome. Such diseases include: classic and nonclassic virilizing adrenal enzymopathies, virilizing tumors of adrenal cortex, Cushing syndrome, hyperthyroidism, hypothyroidism, and acanthosis nigricans. Heterogenity of polycystic ovarian syndrome points up the fact that polycystic ovaries may also occur in about 20 % of healthy and fertile women.

5.7.3 Secretion of hormones atypical for the ovaries

The ovaries may produce human chorionic gonadotrophin (hCG), thyroid hormone, or serotonin. Thyroxine is secreted by some specialized ovarian teratomas. High level of hCG is caused by ovarian choriocarcinomas, occasionally dysgerminomas, and rare immature malignant teratomas. Serotonin may secrete primary or metastatic intestinal ovarian carcinoids.

Ovarian choriocarcinomas. They are very malignant tumors. Most of them exist in combination with other germ cell tumors, pure ovarian choriocarcinomas are extremely rare. Ovarian choriocarcinoma usually originates in girls before puberty. As hCG itself (also LH itself), without simultaneous presence of FSH, does not stimulate ovarian estrogen production. Therefore, the increased plasma level of hCG does not induce precocious sexual maturation of affected girls. Precocious pseudopuberty cannot originate unless estrogens have been simultaneously produced by ovarian choriocarcinoma.

Specialized ovarian teratomas. The most common of them are struma ovarii and carcinoid. They are unilateral. Teratomas that contain mature thyroid tissue (**struma ovarii**) may secrete thyroxine, although rarely in sufficient quantities to cause thyrotoxicosis. This type of teratomas is usually benign. Primary ovarian and metastatic intestinal **carcinoids** may secrete serotonin (5-hydroxytryptamine) in quantities sufficient to produce the carcinoid syndrome. The primary ovarian carcinoid presumably rises from intestinal epithelium in a teratoma. Metastatic ovarian carcinoid is virtually always bilateral. A combination of struma ovarii and carcinoid in the same ovary is very rare.

5.8 Endocrine disorders of the testes

Classification of endocrine disorders of the testes, similarly as classification of endocrine disorders of the ovaries, has not been yet sufficiently transparent

and uniform. At present **pathogenetic classification** has been considered most convenient. It is based on the following three criteria:

1. The type of intensity of hormonal secretion, i.e., hyposecretion or hypersecretion of testicular steroid hormones.
2. The place of origin of an endocrine disorder, i.e., primary, secondary, or tertiary disorder of hormonal secretion.
3. The basic cause of endocrine disorder, i.e., inborn or acquired endocrine disorder.

5.8.1 Hyposecretion of testicular hormones

Deficiency of testicular androgens is also denoted as **male hypogonadism** (hypogonadismus masculinus). It is almost always accompanied also by insufficient spermatogenesis, however, in most adult men with insufficient spermatogenesis regulated by FSH, the deficiency of testicular androgens regulated by LH is not present. Hyposecretion of testicular androgens occurs more often than their hypersecretion.

Pathogenesis of hyposecretion of testicular hormones is variable. Principally, the male hypogonadism may be divided into peripheral and central hypogonadism. Hypogonadism conditioned by the disorder on the level of peripheral tissues (resistance of target tissues to androgens or the disorder of their degradation by cells of peripheral tissues) is a separate form of hypogonadism.

5.8.1.1 Primary male hypogonadism

The cause of its origin is within the testes themselves, therefore, it is also denoted as peripheral or testicular hypogonadism. It may be **inborn** (congenital) or **acquired**. Primary male hypogonadism is characterized by the increased concentration of gonadotropins (mainly LH) and decreased plasma testosterone level. It is, therefore, also denoted as **hypergonadotropic male hypogonadism**.

A. Inborn primary male hypogonadism

Its most common cause are gonosomal anomalies. Occasionally it may originate due to testicular agenesis, gonadal dysgenesis, anorchia (the "vanishing testes syndrome"), bilateral cryptorchidism, testicular biosynthetic defect (enzymopathy), and agenesis of Leydig cells.

The most common form of inborn primary male hypogonadism is Klinefelter syndrome. Other forms of gonosomal anomalies are rare.

Klinefelter syndrome

Klinefelter syndrome (**syndrome of seminiferous tubular dysgenesis**) is the most common form of primary male hypogonadism. Its incidence is approximately 0.1–0.2 % of male population. It originates due to gonosomal anomaly. From the cytogenetic point of view it is **a simple trisomy XXY** manifested by the 47,XXY karyotype of all cells of the patient (**the classic form** of Klinefelter syndrome). **The mosaic form** of Klinefelter syndrome has been also found. There are several variants of the mosaic form. The most common of them being the one with the 47,XXY/46,XY karyotype. Other mosaic patterns, e.g., 47,XXY/48,XXXY or 47,XXY/48,XXYY, are rarer. The classic form accounts for about 80–90 % and the mosaic form for about 10–20 % of all cases of Klinefelter syndrome.

Pathogenesis. The classic form of the 47,XXY trisomy results from nondisjunction of the chromosomes during either the first or second meiotic divisions in the course of gametogenesis in one of the parents. About 40 % of the responsible **meiotic nondisjunctions** occur in the father during spermatogenesis, and 60 % occur in the mother during oogenesis. The result of meiotic nondisjunction of XX chromosomes during oogenesis is the origin of one ovum with XX chromosomes (its karyotype is 24,XX) and the other ovum has no X chromosome (its karyotype is 22,O). After fertilization of an ovum with the 24,XX karyotype by a sperm with the 23,Y karyotype, the zygote with the 47,XXY karyotype originates. The result of meiotic nondisjunction of XY chromosomes during spermatogenesis is the origin of one sperm with the 24,XY karyotype and the other sperm with the 22,O karyotype. After fertilization of a 23,X ovum by a 24,XY sperm the 47,XXY zygote originates. The 47,XXY zygote may also originate after fertilization of a 24,XX ovum by a 23,Y sperm. There is no phenotypic difference between those who receive the extra X chromosome from their father and those who receive it from their mother. The cause of meiotic nondisjunction of XX chromosomes during oogenesis may be advanced maternal age. The influ-

ence of age on paternal nondisjunction of XY chromosomes is not assumed. Some authors consider also the existence of genetic predisposition to the origin of meiotic nondisjunctions. The participation of irradiation or viral infection as predisposing factors of meiotic nondisjunctions has not been found for the present.

The mosaic form of Klinefelter syndrome results from chromosomal **mitotic nondisjunctions** after fertilization of the zygote (mainly during the first cell divisions) and can arise either in a 46,XY zygote or a 47,XXY zygote. The latter situation, i.e., double nondisjunction (meiotic and mitotic), may be the usual of the mosaic form and thus explain why the mosaic form is less common than the classic form of Klinefelter syndrome.

Chromosomal aberration is usually **manifested** at the time of expected puberty, when plasma FSH concentration is physiologically increased. However, its effect on primary dysgenetically changed germinal epithelium of seminiferous tubules of the testes does not lead to their enlargement, but cause their progressive fibrotization and hyalinization. **With the onset of puberty**, progressive histological changes also originate in Leydig cells, but their number is normal or more often increased (pseudoadenomatous changes of the Leydig cells). The ability of impaired Leydig cells to synthetize testosterone is, therefore, gradually reduced. Plasma testosterone concentration gradually decreases resulting in the origin of primary male hypogonadism. Plasma LH level is gradually increasing by feedback mechanism (**hypergonadotropic male hypogonadism**).

The increased plasma LH concentration initially stimulates production of estradiol in Leydig cells. Later, due to progressive impairment of testes, evident decrease not only of testicular testosterone secretion, but also of testicular estradiol secretion develops. Extraglandular production of estrogens, however, continues. They are formed by aromatization of adrenal androgens in extraglandular tissues. Though plasma estrogen level is low, with regard to very low plasma testosterone concentration it is relatively high. Due to the increased ratio of circulating estrogen to androgen various degrees of **feminization** of the patients, including gynecomastia, have been developed. Besides that, relative predominance of plasma estradiol over plasma testosterone increases production of testosterone-binding globulin (TeBG) in the liver. The increased plasma concentration of TeBG is the cause of even greater decrease of free testosterone in circulating blood.

The clinical picture of Klinefelter syndrome is characterized mainly by signs and symptoms resulting from seminiferous tubular dysgenesis and hypergonadotropic hypogonadism. Though it is congenital gonosomal anomaly, the boys usually develop normally before puberty. However, most prepubertal patients have a distinctive body habitus with an increase in length between the soles and the pubic bone, which creates the appearance of an elongated body. The disorder begins clinically manifested already in the time of expected puberty. Classic manifestation of this disease is the origin of **sexual infantilism**. However, such severe degree of the disorder is not frequent. The intensity of the disorder of sexual development in the patients is usually variable. In some affected boys only **delayed puberty** may originate. It is also possible that the onset of puberty is not delayed, but impaired Leydig cell reserve and low testosterone levels may lead to slow progression or arrest of pubertal development. In other patients puberty may be normal, spermatogenesis is, however, missing.

The classic form is characterized by small, firm testes, impaired spermatogenesis, a male phenotype, insufficient androgenization, and later by a variable degree of feminization. The **reduced spermatogenesis** is related to the degree of morphologic changes in the testes. Most of affected men are infertile. The small atrophic testes are often associated with a small penis, and the lack of such secondary male characteristics as deep voice, beard, and male distribution of pubic hair. **Gynecomastia** occurs in about 90 % of patients, and is probably secondary to an increased ratio of serum estradiol to testosterone. **The eunuchoid body habitus** with abnormally long legs is also characteristic. Most individuals have a male psychosexual orientation and function sexually as men. Potency may be initially normal, but due to progressive decrease of plasma testosterone concentration it may decrease. The mean IQ is somewhat lower than normal, but mental retardation is uncommon. Plasma gonadotropin concentrations, particularly FSH, are consistently elevated, whereas testosterone levels are variably reduced. Mean plasma estradiol levels are relatively elevated. The ratio of

circulating estrogen to testosterone determines the degree of feminization in individual cases.

The mosaic form is present in about 10–15 % of the patients with Klinefelter syndrome. The most common of mosaic patterns is the one with the 47,XXY/46,XY karyotype. The presence of a normal XY cell line in these patients can modify the clinical expression of the 47,XXY cell line. Thus, in general, these patients manifest **a lesser degree of testicular pathology**, testosterone deficiency, and gynecomastia. The testes may be normal in size. The decreased libido and potency may not appear until the fourth or fifth decade. Secondary sexual characteristics are less impaired than those of patients with the classic form. In many patients with the mosaic form seminiferous tubules exhibit spermatogenesis being usually insufficient (oligospermia), however, some of them may be even fertile.

Many other variants of Klinefelter syndrome have been described, including those with uniform cell lines (such as 48,XXYY, 48,XXXY, 49,XXXYY, and 49,XXXXY) and various mosaic patterns. All these forms are rare. With an increase in the number of X chromosome, the severity and frequency of various somatic anomalies also increase. The presence of three or more X chromosomes in genotype is usually associated with a severer degree of mental retardation of the patients. The presence of two or more Y chromosomes in genotype is usually associated with antisocial, deliquent behavior. In general, the greater the degree of chromosomal abnormality (and in mosaic forms the more cell lines that are abnormal), the severer are the clinical manifestations.

B. **Acquired primary male hypogonadism**

It is a rare disorder, because the organic factors damaging the testes most frequently affect only seminiferous tubules (germinal epithelium). Rarely, only due to severe form of damage also Leydig cells are affected leading to hyposecretion of testosterone and thus to peripheral male hypogonadism. Due to lowered plasma testosterone level hypothalamic-pituitary system is stimulated to an increased secretion of GTHs by positive feedback mechanism. Their plasma concentration is, therefore, increased (**hypergonadotropic male hypogonadism**).

One of the most common causes of acquired peripheral male hypogonadism is **viral orchitis**. It occurs in childhood and adulthood. The best known of them is mumps orchitis. Other viral agents may act in a similar fashion, including echovirus, lymphocytic choriomeningitis virus, and group B arboviruses. Primary hypogonadism may originate also secondary to extensive impairment of testes in patients with **autoimmune orchitis**, and also with gonorrheal or syphilitic orchitis. The testes can also be damaged after long-lasting therapy by antineoplastic and chemotherapeutic drugs, after radiotherapy, or after trauma. The cause of its origin may be also castration of the patients with malignant tumors of the testes. Certain signs of peripheral hypogonadism may originate due to chronic alcohol ingestion. Large doses of ethanol damage not only germinal epithelium, but also Leydig cells.

The clinical picture of acquired primary male hypogonadism depends on the age at which the testicular hormone deficiency develops (before or after puberty). The consequences of extensive impairment of the testes in childhood begin manifested clinically as late as in the time of expected onset of puberty.

1. **Prepubertal testicular hypogonadism**. It is manifested by the disorder of spontaneous onset of puberty or it may result in the origin of sexual infantilism. A degree of the disorder depends on the extent of Leydig cell damage, and thereby on the degree of testicular androgen deficiency. It is manifested by hypogenitalism and by the disorders in the development of secondary sexual characteristics which may be sometimes completely absent. In an affected subject breaking the voice does not occur, libido is absent, female fat distribution and sometimes also gynecomastia originate.

2. **Postpubertal testicular hypogonadism**. It need not evidently influence a masculine look of the patient. Pubic hair may be thinned. Moustache and beard growth is slowed. Sometimes also partial regression of genitalia, though imperceptible at the first sight, may occur. In some patients libido and potence may be decreased, in others may be preserved (due to psychic conditional nature of sexuality). Possible change of behavior may be manifested by the loss of aggressiveness. Anemia, osteoporosis, and muscle weakeness may originate. Obesity also develops. The change of fat distribution may be associated with the loss of typical masculine figure.

5.8.1.2 Central male hypogonadism

In the patients with central male hypogonadism plasma concentrations of gonadotropins are low, and, therefore, it is also denoted as **hypogonadotropic male hypogonadism**. The causes and consequences of the origin of adenohypophyseal and hypothalamic male hypogonadism have been partially mentioned in the chapter on pathophysiology of hypothalamic-adenohypophyseal system.

Central male hypogonadism originates due to:

1. **organic lesion** in hypothalamic-pituitary area (tumors, aneurysms, hemorrhages, inflammatory processes, surgical interventions, irradiation, head trauma, and others);

2. various **inborn syndromes** (Laurence-Moon-Biedl-Bardet syndrome, Kallmann syndrome, Babinski-Fröehlich syndrome);

3. **hyperprolactinemia** (hypothalamic or adenohypophyseal);

4. **fertile eunuch syndrome** being a special form of central prepubertal male hypogonadism. This syndrome is conditioned by a selective resistance of gonadotrope cells of adenohypophysis to LHRH. FSH secretion is normal, LH secretion is, however, missing. LH deficiency is the cause of disorder of Leydig cell development and subsequent testosterone deficiency. Due to normal concentration of FSH in circulating blood seminiferous tubules and testes are of normal size after puberty and spermatogenesis is usually preserved, therefore, the term fertile eunuch is used. However, as a consequence of testosterone deficiency, spermatogenesis is often insufficient. The clinical picture is characterized by the contrast between the well developed testes and decreased length of penis and by the presence of eunuchoid habitus;

5. **combinated disorder** of pituitary hormone production, mainly deficiency of gonadotropins with deficiency of growth hormone;

6. **constitutional delay** in growth and puberty;

7. prepubertal or postpubertal **panhypopituitarism**;

8. **severe chronic systemic disease** (renal failure and cirrhosis of the liver) altering the overall health state of a patient;

9. long-term **starvation**.

The clinical picture of central male hypogonadism is essentially the same as that of in the patients with primary hypogonadism. It depends on the age of a patient at the time of the origin of testicular androgen deficiency. It is quite often only a part of more complex clinical picture determined by the cause of its origin. **In boys** either true delayed puberty or sexual infantilism originate. **In adult men** hypogonadism is manifested by a decrease even loss of libido and potence, regression of secondary sexual charateristics, and muscle weakness.

5.8.2 Hypersecretion of testicular hormones

Hypersecretion of testicular androgens is denoted as **male hypergonadism** (hypergonadismus masculinus). The cause of its origin may be within the testes themselves (primary male hypergonadism) or is localized in the hypothalamic-pituitary area (central male hypergonadism). Male hypergonadism occurs much more rarely than male hypogonadism. The clinical picture of hypersecretion of testicular androgens depends on the age at which the hypersecretion appears. The clinical features are similar to those originated in male individuals with oversecretion of adrenal androgens.

5.8.2.1 Primary male hypergonadism

Peripheral male hypergonadism originates due to hormonally active testicular tumors autonomously producing testosterone and sometimes also estradiol. It occurs very rarely. Excess testosterone is secreted mainly by Leydig cell tumors and rarely by Sertoli cell tumors (androblastomas). **Leydig cell tumors** may elaborate androgens, or sometimes androgens and estrogens (estradiol). They are usually unilateral. **Sertoli cell tumors** may elaborate estradiol (more commonly) or androgens, but only infrequently in sufficient quantity to cause masculinization or feminization. They are frequently bilateral. Both kinds of these testicular tumors may arise at any age, although the majority of the reported causes of Leydig cell tumors have been noted between 20–40

years of age and those of Sertoli cell tumors have been found in childhood. Leydig cell tumors and Sertoli cell tumors account for about 2 % of all testicular tumors. Approximately 10 % of these both kinds of testicular tumors are malignant, the great majority of them are benign. In some patients the mixed tumors containing cells of germinal (germ cells) and stromal (Leydig and Sertoli cells) origin may occur. Most distinctive of them is the **gonadoblastoma** which prevailingly synthesize androgens.

Enhanced formation of testosterone and estradiol by Leydig cells may be also present in patients with **germ cell tumors** secreting endocrinologically active hCG. The hCG acts to increase testosterone and estradiol production in unaffected areas of the testes. This secretion of testosterone and estradiol is independent of the hypothalamic LHRH. The testicular germ cell tumors include seminoma, embryonal carcinoma, choriocarcinoma, and benign or malignant teratomas. They account approximately for 95 % of all testicular neoplasms. Germ cell tumors of all types can also originate in extragonadal sites, most commonly in the brain or in the mediastinum. These extragonadal germ cell tumors presumed to arise either from aberrant migration of germ cells early in embryogenesis or, alternatively, from some common precursor stem cell line that normally gives rise to germ cells and to cells of the thymus and the pineal. A primary germ cell tumor localized in the pineal or in the suprasellar regions is denoted as **germinoma**.

Increased plasma testosterone and estradiol concentrations cause suppression of the production of endogenous adenohypophyseal gonadotropins by feedback mechanism. Plasma gonadotropin levels are, therefore, low (**hypogonadotropic male hypogonadism**). When production of testosterone and estradiol by testicular tumor is autonomous, testosterone secretion by uninvolved portions of the testes is depressed (due to low plasma LH level), and azoospermia and decreased size of the contralateral testis are common (due to low plasma FSH level). The clinical picture of hormonally active testicular tumors depends on the age of patients at which the neoplasms originate. It also depends on the fact whether the testicular tumor secretes only testosterone or testosterone and estradiol as well. Similar clinical features can result from endocrinologically active hCG-secreting testicular and extratesticular tumors.

If excess testosterone occurs **in childhood**, a clinical picture of isosexual precocious pseudopuberty (incomplete isosexual precocity) originates. It is manifested by precocious development of genitalia and secondary sexual characteristics. Spermatogenesis is absent, indicating that androgen formation is not the result of premature activation of the hypothalamic-pituitary system. If hypersecretion of testosterone originates **in adulthood**, it need not be evidently clinically manifested.

When the cells of a testicular tumor produce also estradiol, in the clinical picture the symptoms of **feminization** are simultaneously also present. Enhanced formation of estradiol by testicular tumors is more common in adult men than in boys. Feminization is manifested by the origin of gynecomastia, thinning of pubic hair, decrease even loss of potence, and diminishing of prostate.

5.8.2.2 Central male hypergonadism

In the patients with central male hypergonadism plasma concentrations of gonadotropins (mainly LH concentration) are primarily increased. Therefore, it is also denoted as **hypergonadotropic male hypergonadism**. The causes and consequences of its origin have been partially mentioned in the chapter on the pathophysiology of hypothalamic-adenohypophyseal system.

The cause of central male hypergonadism may be various organic (mainly CNS tumors) or functional disorders of the hypothalamic-pituitary area. The functional disorders are usually of unknown etiology (idiopathic form of central male hypogonadism). The best known organic causes of central male hypergonadism include hypothalamic hamartoma, pineal tumors, other tumors of the pineal region, and gonadotrope adenomas of hypophysis. Gonadotrope adenomas most often occur in the middle age, mainly between the ages 35 and 45. Less common causes of central male hypergonadism include hydrocephalus, intracranial aneurysms, encephalitis, sarcoid or tuberculous granulomas of the hypothalamus, arachnoid cysts, or brain abscess.

The above mentioned organic or functional disorders of the hypothalamic-hypophyseal area most commonly cause increased secretion of LHRH and subsequently increased secretion of gonadotropins. Primary increase of production of GTHs (without preceding increase of LHRH) is rare.

The clinical picture of central male hypergonadism

depends on the age at which the cause of increased secretion of LHRH or GTHs originates. If the centrally conditined hyperfunction of the testes occurs **prepubertaly in boys**, isosexual true precocious puberty originates. Its occurrence in boys is, however, rarer than in girls. In affected boys spermatogenesis is present and possible fertility may also occur. If the oversecretion of gonadotropins originates **in adult men** (rare occurrence) its clinical consequence may be low plasma testosterone concentration and the origin of impotence. It is apparently paradoxical origin of testicular hypogonadism in the affected adult men with increased plasma concentration of GTHs. The pathogenesis of this testicular hypogonadism in adult men with overproduction of gonadotropic hormones is not exactly known. It is supposed that long-lasting increased concentration of gonadotropins in circulating blood leads to down-regulation of receptor number, i.e., to reduction of LH receptors on the Leydig cell membrane.

In the clinical picture of central male hypergonadism, which is caused by expansive growth of cerebral tumors, some local symptoms induced by compression of intracranial structures may be also present.

In about 40 % of boys with true precocious puberty the cause of origin of precocious LHRH production is not known (**idiopathic true precocious puberty**).

Tumors and other organic cerebral causes of true precocious puberty probably activate precocious releasing of LHRH by their effect on hypothalamus, However, hypothalamic hamartomas associated with true precocious puberty may secrete LHRH themselves, because they are composed of disordered but mature neural elements. LHRH secretion by these **ectopicly placed LHRH peptidergic neurons** is probably not subject to the normal restraining influences of the anterior hypothalamus, and early pubertal development is likely the consequence of unrestrained LHRH secretion. Precocious puberty is believed to occur when the cells of the hamartoma make connections with the median eminence and thus serve as an "accessory hypothalamus". About 10 % of hypothalamic hamartomas are not associated with true precocious puberty.

Hamartomas of the tuber cinereum are most frequently associated with true precocious puberty. They are congenital tumors composed of heterotopic mass of neurosecretory mature neurons, fiber bundles, and glial cells. These neurosecretory cells are similar to the LHRH-containing neurons in the medial basal hypothalamus. LHRH neurosecretory cells of the tumor are unrestrained by the intrinsic CNS mechanism that inhibits the normal LHRH pulse generator and act as an ectopic LHRH pulse generator independently on the LHRH neurosecretory neurons in the medial basal hypothalamus to produce intermittent secretory bursts of LHRH. It seems, that many causes previously thought to be idiopathic true precocious puberty are due to hamartomas of the tuber cinereum (sometimes miniature). Hamartomas grow slowly, if in fact they do enlarge.

The relationship between the origin of true precocious puberty and the presence of tumors of the pineal gland has been known for a longer time. A tumor of the pineal parenchymal cells is termed **pinealoma**. According to its degree of differentiation it can be a pineocytoma or pineoblastoma. Other tumors localized in the pineal region include mainly astrocytoma, glioma, glioblastoma, germinoma, and ependymoma. True precocious puberty in boys with a pineal tumor or with other tumor of the pineal region is probably due to the effect of this tumor on function of the adjacent hypothalamus. In the hypothalamus precocious production of LHRH occurs. The hypothesis, that pineal tumors and tumors of the pineal region influence the function of the hypothalamus, is supported also by frequent simultaneous occurrence of insipidus diabetes, polyphagia, obesity, somnolence, or behavioral disturbance. It is likely, therefore, that tumors of the pineal gland and tumors of the pineal region cause true precocious puberty by mechanism similar to that of other types of cerebral tumors or other types of brain organic lesions.