PUBERTY

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PHYSIOLOGY of PUBERTY

DEFINITION

PHYSICAL CHANGES OF PUBERTY

- Female secondary sex characteristics
- Male secondary sex characteristics

HORMONAL CHANGES OF PUBERTY

- Gonadotropin-Releasing Hormone
- Gonadotropins
- Adrenal steroids
- Ovarian development
- Testis development
- Role of GH, IGF-I and insulin
- Leptin

PHYSIOLOGY OF PUBERTY

DEFINITION

Puberty is the stage of physical maturation in which an individual becomes physiologically capable of sexual reproduction.

PHYSIOLOGY OF PUBERTY

The biological changes include:

- neurosecretory factors and/or hormones
- modulation of somatic growth
- initiation of the development of the sex glands

PHYSIOLOGY OF PUBERTY

- **activation of the hypothalamic-pituitary-gonadal axis:**
  - induces and enhances the progressive ovarian and testicular sex hormone secretion
  - responsible for the profound biological, morphological, and psychological changes to which the adolescent is subjected
- **sex steroid production:**
  - appearance and maintenance of sexual characteristics
  - capacity for reproduction

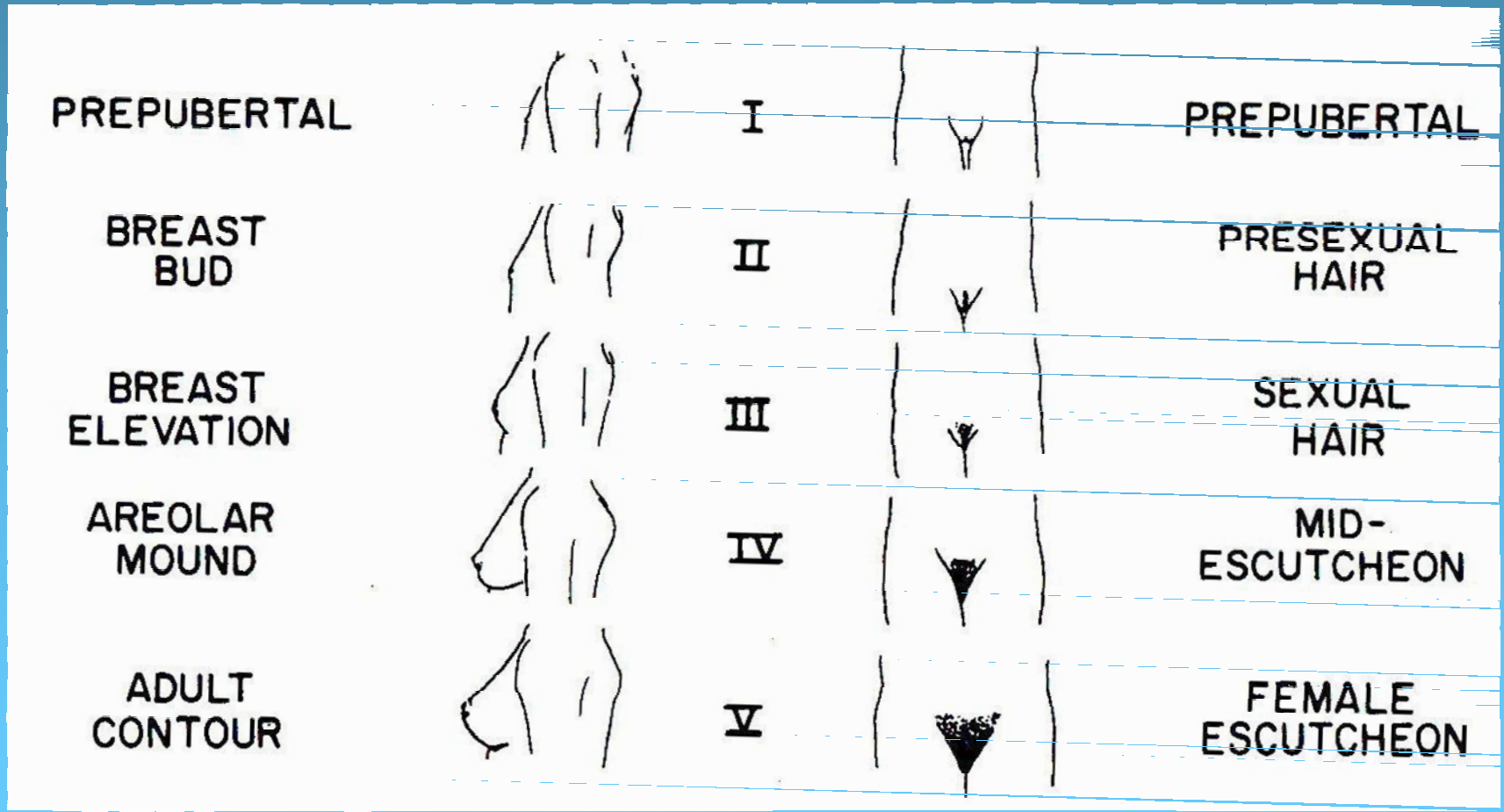
PHYSICAL CHANGES OF PUBERTY

Puberty proceeds through five stages from childhood to full maturity (P1 to P5) as described by Marshall and Tanner. In both sexes, these stages reflect the progressive modifications of the external genitalia and of sexual hair. Secondary sex characteristics appear at a mean age of 10.5 years in girls and 11.5 to 12 years in boys.

PUBERTAL STAGES (TANNER) FEMALE

P1	Prepubertal
P2	Early development of subareolar breast bud +/-small amounts of pubic hair and axillairy hair
P3	Increase in size of palpable breast tissue and areolae, increased amount of dark pubic hair and of axillary hair
P4	Further increase in breast size and areolae that protrude above breast level adult pubic hair
P5	Adult stage, pubic hair with extension to upper thigh

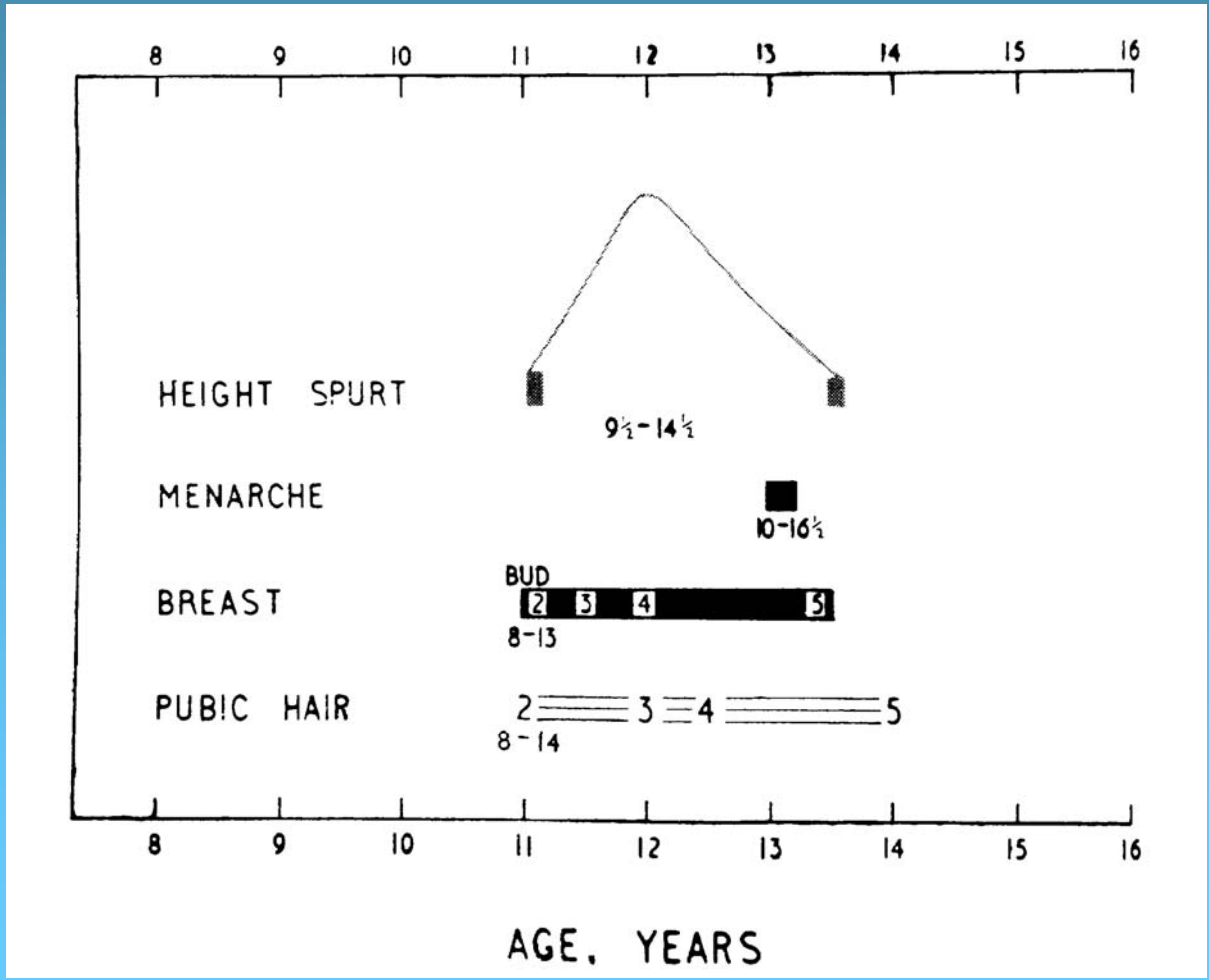
PUBERTAL STAGES (TANNER) FEMALE



From Rosenfield R. Pediatric Endocrinology. Sperling 2nd edition.

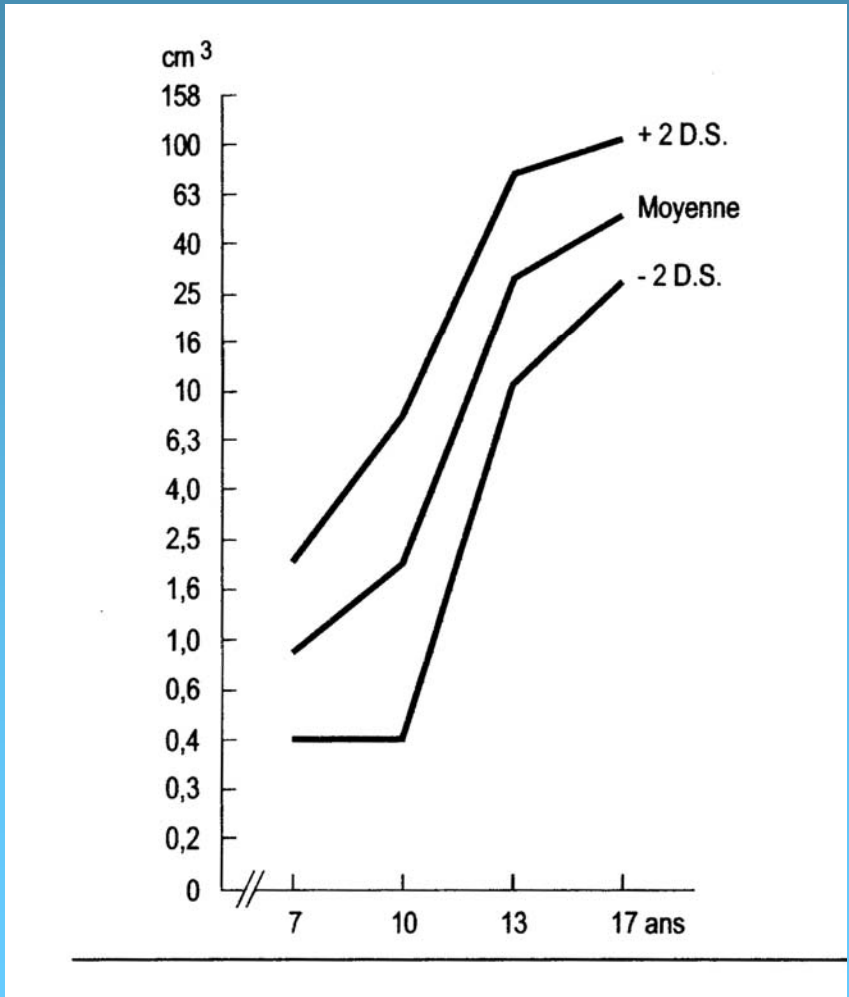
SECONDARY SEX CHARACTERISTICS

Female



From Marshall WA, Tanner JM, ArchDis Child 1969.

GROWTH OF THE UTERUS



From Ivarsson SA et al., Arch Dis Child 1983.

UTERINE DEVELOPMENT

The prepubertal uterus is tear-drop shaped, with the neck and isthmus accounting for up to two-thirds of the uterine volume; then, with the production of estrogens, it becomes pear shaped, with the uterine body increasing in length and thickness proportionately more than the cervix.

OVARIAN DEVELOPMENT: 1

The rising levels of plasma gonadotropins stimulate the ovary to produce increasing amounts of estradiol. Estradiol is responsible for the development of secondary sexual characteristics, that is, growth and development of the breasts and reproductive organs, fat redistribution (hips, breasts), and bone maturation. The maturation of the ovary at adolescence correlates well with estradiol secretion and the stages of puberty.

OVARIAN DEVELOPMENT:2

In prepuberty, the ovarian size volume extends from 0.3 to 0.9cm3. More than 1.0 cm3 indicates that puberty has begun. During puberty, the ovarian size increases rapidly to a mean postpubertal volume of 4.0 cm3 (1.8 to 5.3 cm3).

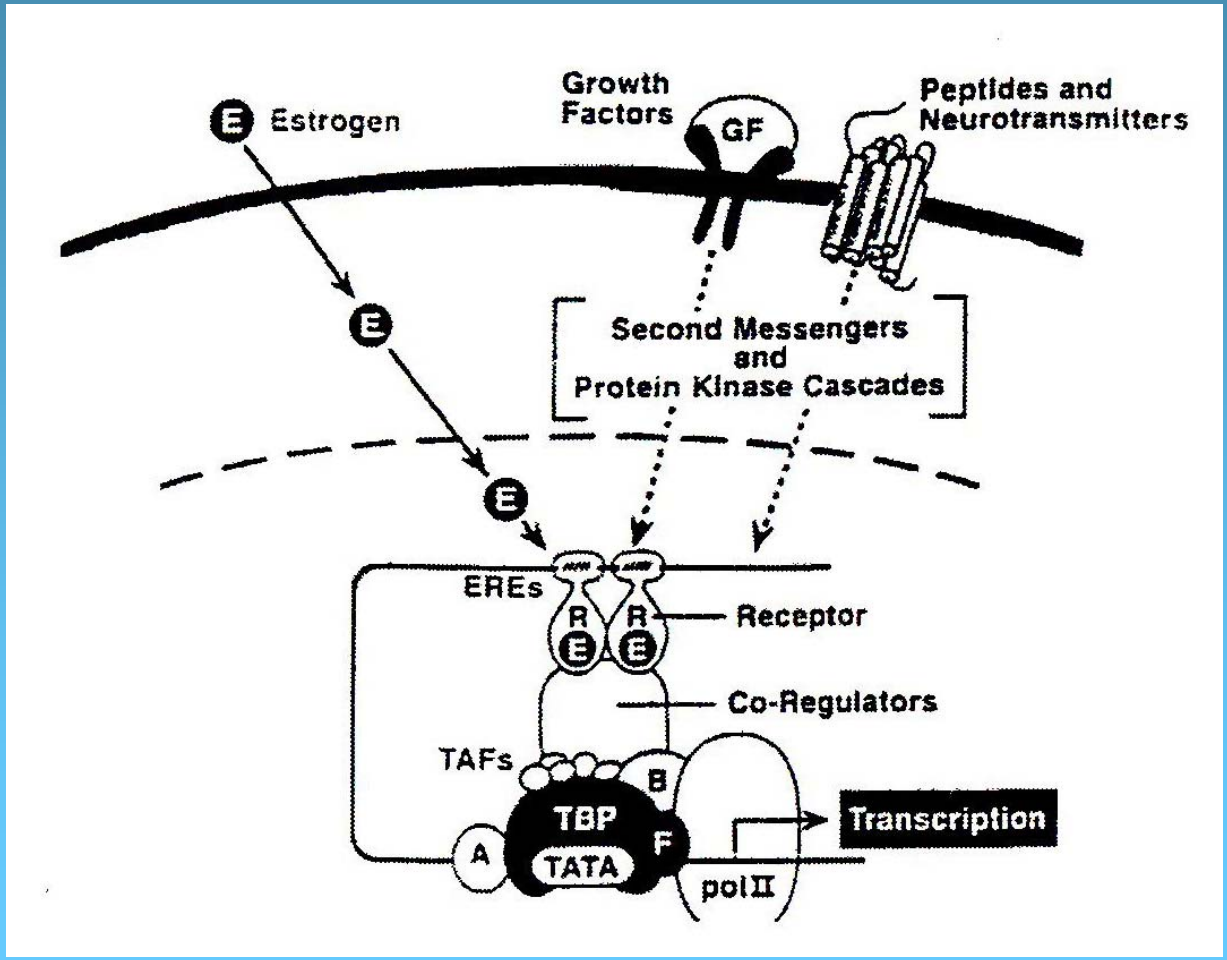
MENARCHE

During puberty, plasma estradiol levels fluctuate widely, probably reflecting successive waves of follicular development that fail to reach the ovulatory stage. The uterine endometrium is affected by these changes and undergoes cycles of proliferation and regression, until a point is reached when substantial growth occurs so that withdrawal of estrogen results in the first menstruation (*menarche*).

OVULATION

Plasma testosterone levels also increase at puberty although not as markedly as in males. Plasma progesterone remains at low levels even if secondary sexual characteristics have appeared. A rise in progesterone after menarche is, in general, indicative that ovulation has occured. The first ovulation does not take place until 6-9 months after menarche because the positive feedback mechanism of estrogen is not developed.

ESTROGEN



From Katzenellenbogen BS. Soc Gynecol Invest 2000.

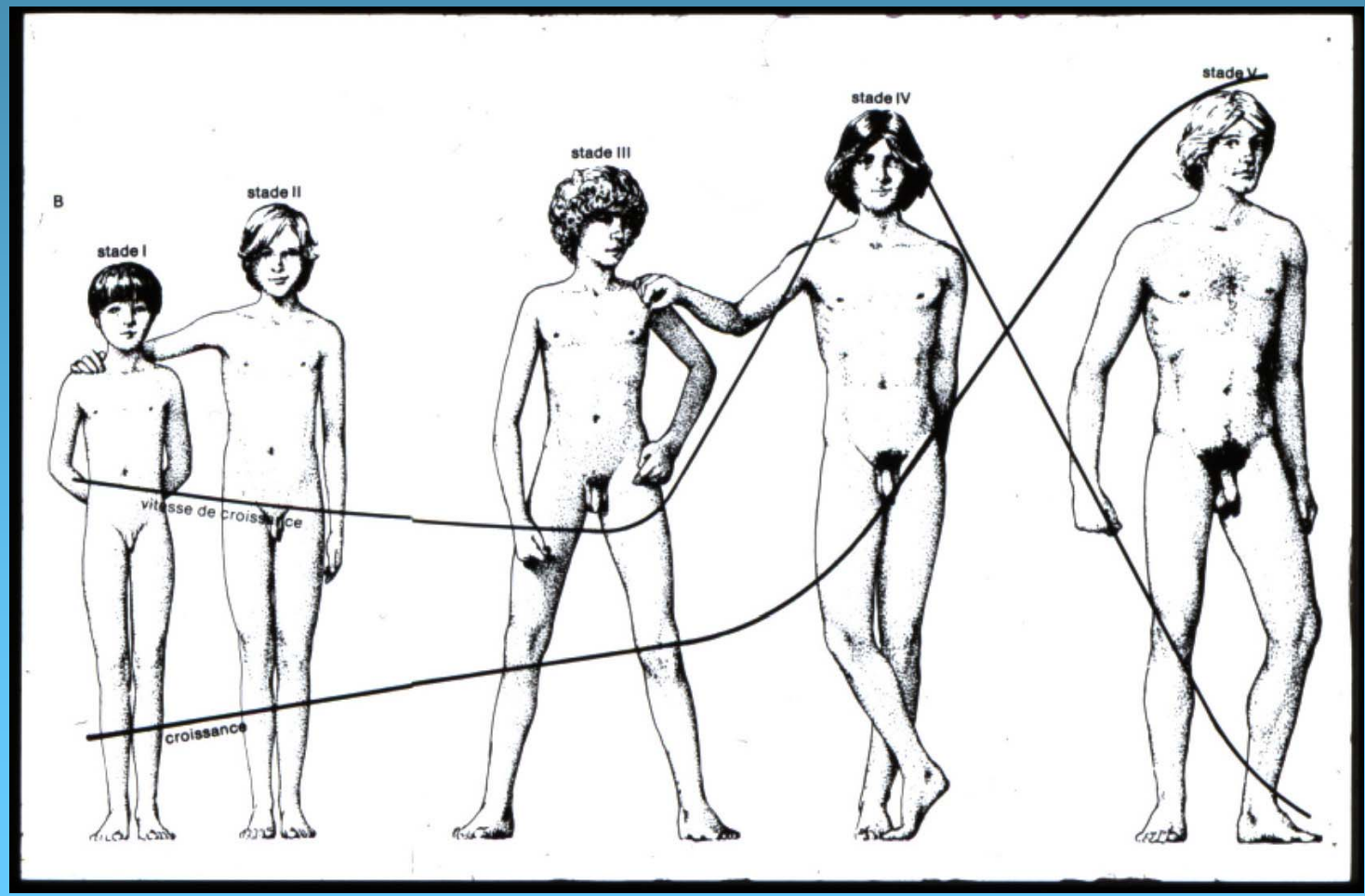
FEMALE SECONDARY SEXUAL CHARACTERISTICS

If breast development, pubic and/or axillary hair, and menses occur earlier than normal variations from the mean, the terms *premature* thelarche, pubarche and/or adrenarche, and menarche are used.

PUBERTAL STAGES (TANNER) MALE

P1	Prepubertal, testicular length less than 2.5cm
P2	Early increase in testicular size, scrotum slightly pigmented, few long and dark pubic hair
P3	Testicular length 3.3-4 cm, lenghtening of the penis, increase in pubic hair
P4	Testicular length 4.1-4.5cm, increase in length and thickening of the penis, adult amount of pubic hair
P5	Testicular length greater than 4.5cm, full spermatogenesis

PUBERTY: MALE



From Sizonenko PC.

PUBERTY: MALE

Secondary sexual development in boys:

- growth kinetics are enhanced from early puberty on
- maximal velocity is attained only around 14 to 15 years of age
- testis increases in size, mainly at the expense of the seminiferous tubules
- the interstitial (Leydig) cells develop and ensure synthesis and secretion of testosterone

PUBERTY: MALE

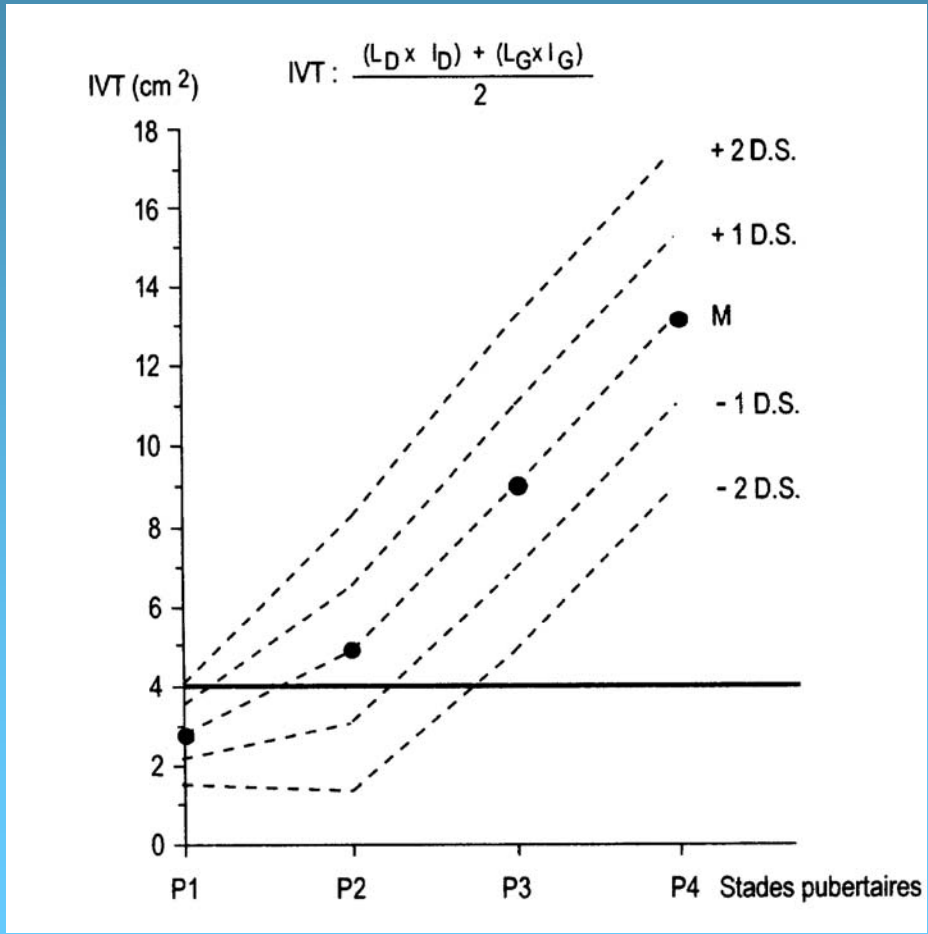
Secondary sexual development in boys:

- a testicular volume of 4 ml or a longitudinal diameter greater than or equal to 2.5 cm and a slight progressive increase in scrotal folds and pigmentation constitute the first signs of puberty

PUBERTY: MALE

Secondary sexual development in boys:

TESTICULAR GROWTH



Index of testicular volume

Burr IM, Sizonenko PC, Pediatr Res 1970.

TESTES DEVELOPMENT:1

The increase in testicular size observed during prepuberty and puberty results essentially from the development of the seminiferous tubules under the stimulating effect of FSH. The testicular volume increases throughout puberty up to Tanner stage P4 when a longitudinal diameter of 5.0 + 0.5 cm or a volume of 17.6 + 4.0 ml is reached.

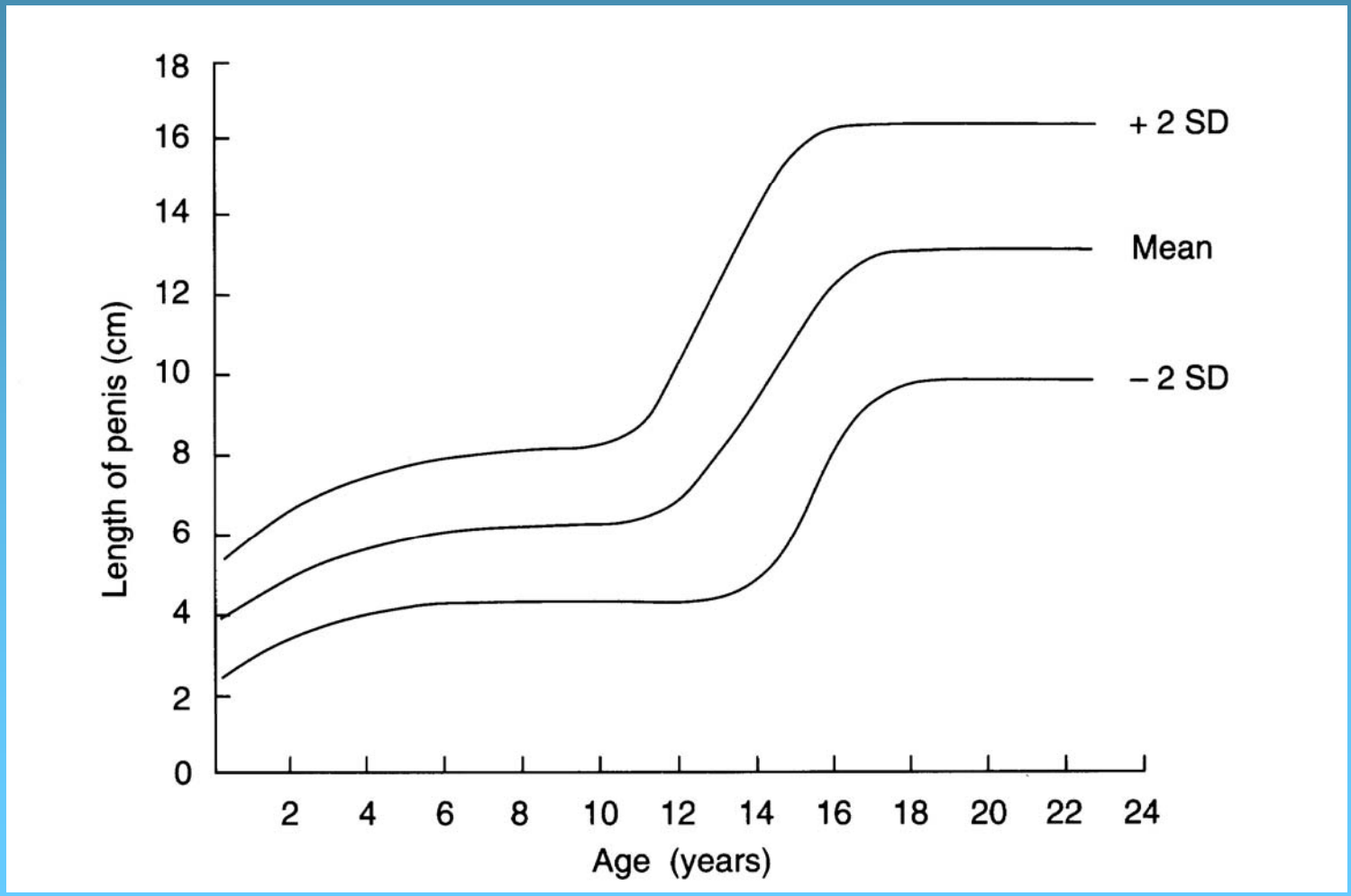
TESTES DEVELOPMENT:2

Long-standing pulsatile LH secretion induces the differentiation of interstitial cells into testosterone-secreting Leydig cells, which, in turn, exert a negative feedback control on LH secretion. As puberty progresses, spermatogenesis is initiated and then sustained by FSH and by testosterone produced by the Leydig cells under LH control.

TESTES DEVELOPMENT:3

A significant increase of plasma testosterone is found only between Tanner pubertal stages P3 and P4. Dihydrotestosterone shows a pattern similar to that of testosterone, and the proportion of dihydrotestosterone to testosterone decreases gradually until adulthood, when dihydrotestosterone levels are approximately 10% of those of testosterone.

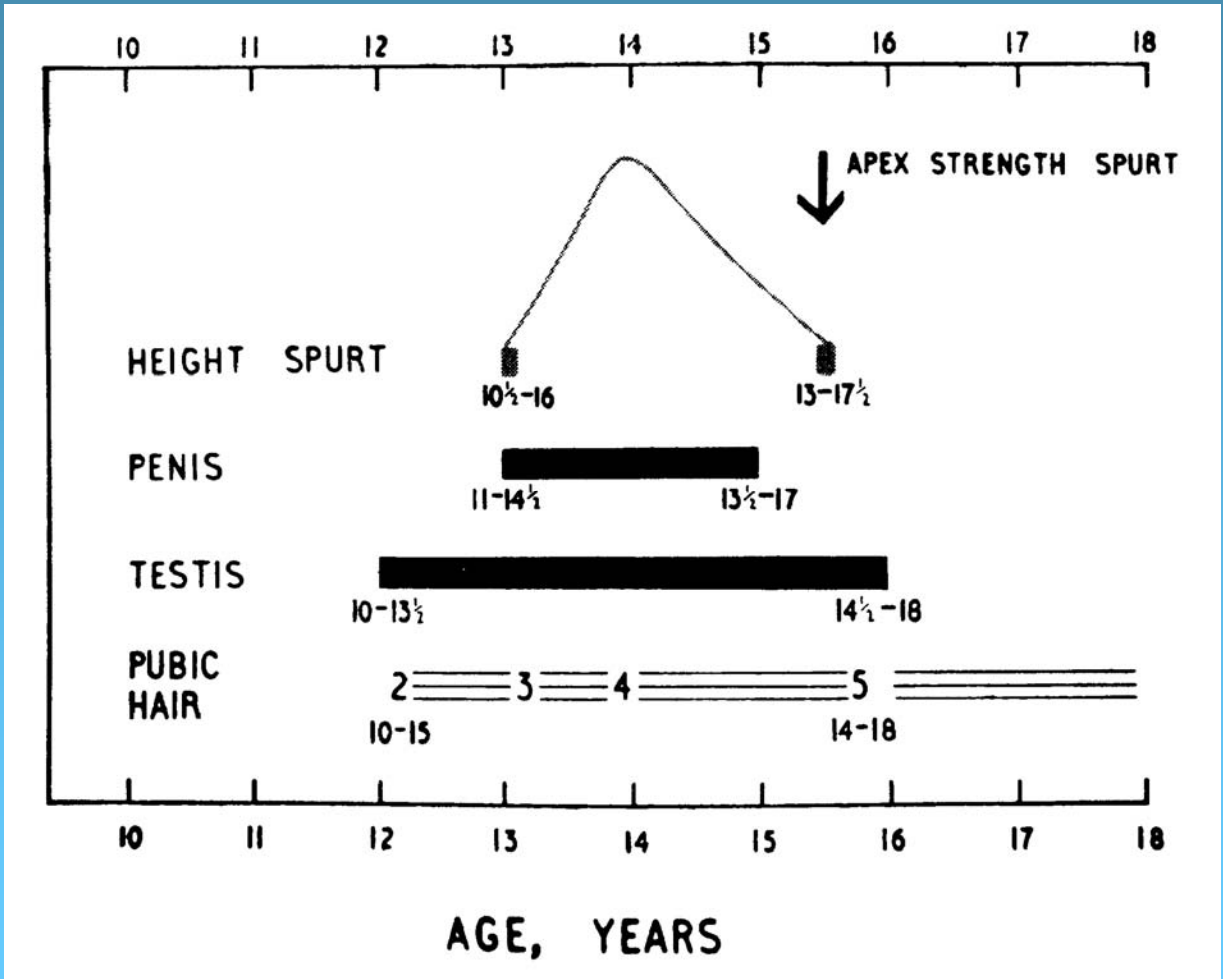
PENILE GROWTH



From Schonfeld WA. Am J Dis Child 1943.

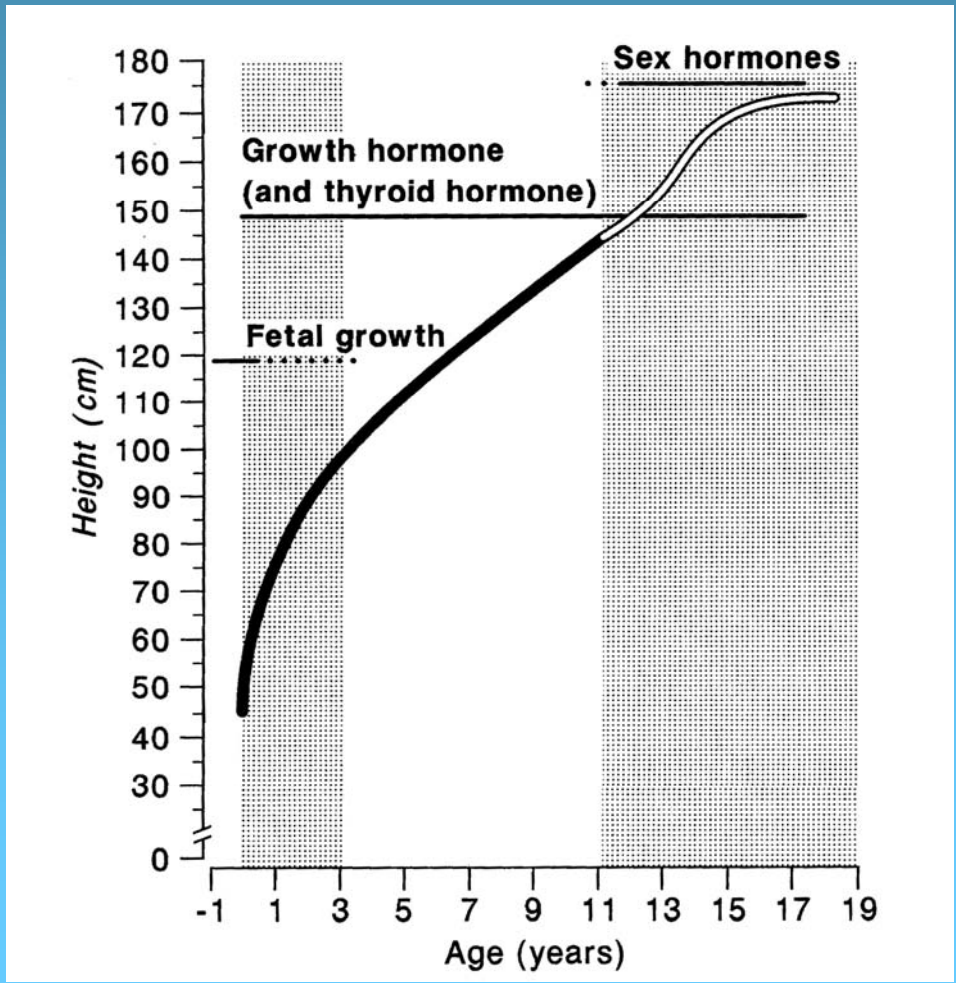
SECONDARY SEX CHARACTERISTICS

Male



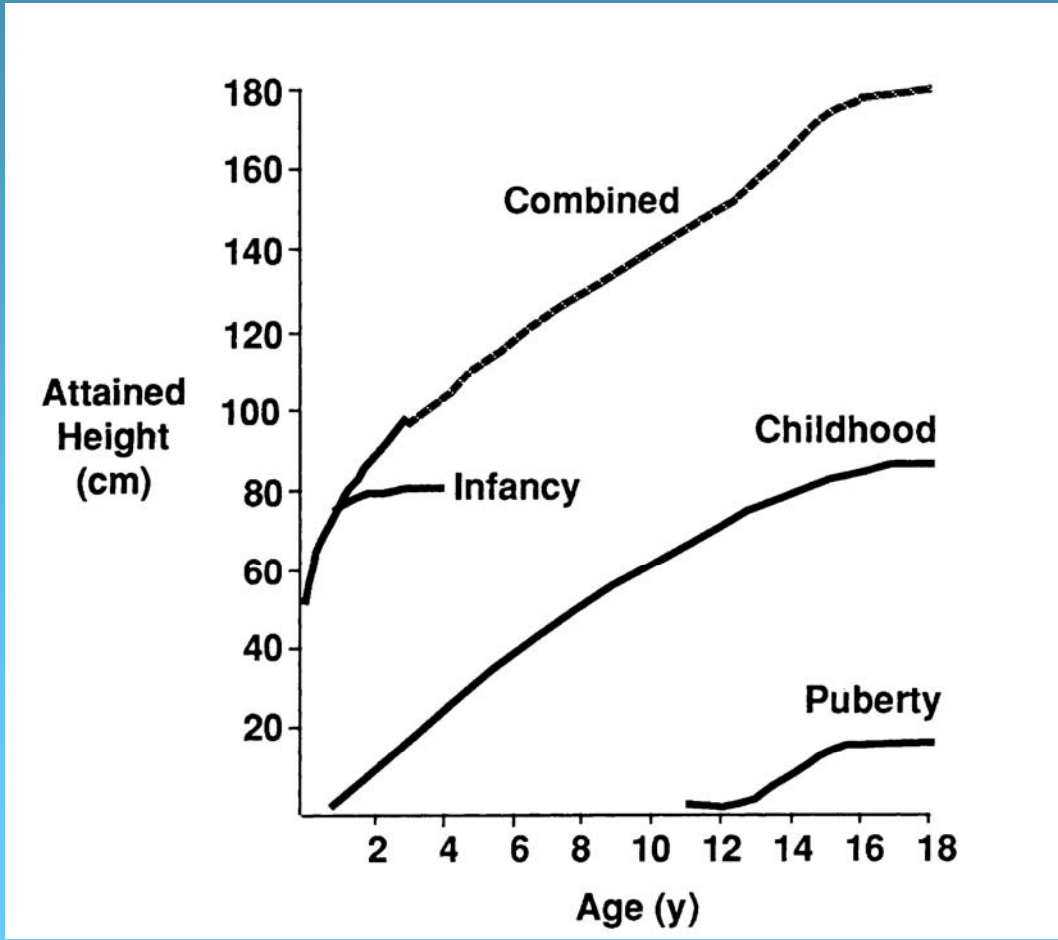
From Marshall WA, Tanner JM, ArchDis Child 1970.

PUBERTAL GROWTH SPURT



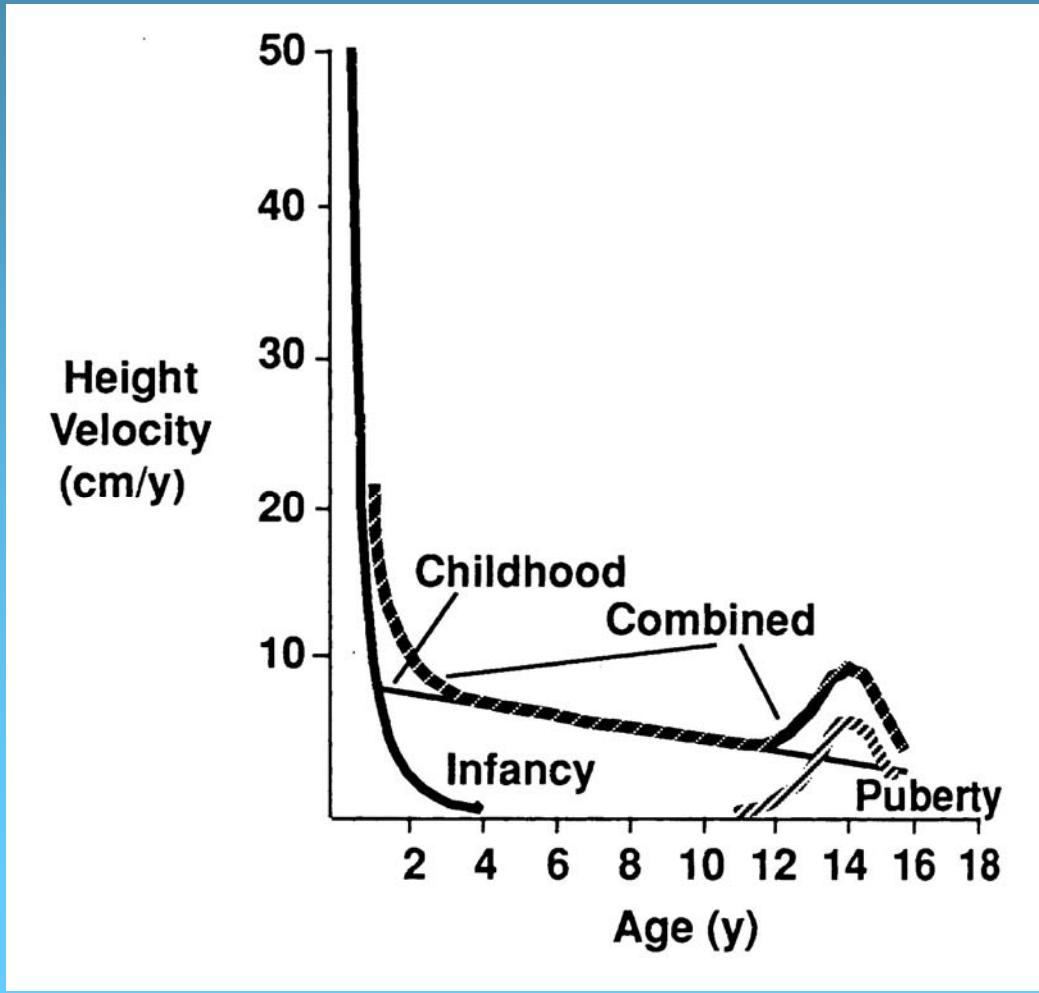
From Grumbach MM et al. Williams Textbook of Endocrinology 10th edition.

PUBERTAL GROWTH SPURT



From Grumbach MM et al. Williams Textbook of Endocrinology 10th edition.

HEIGHT VELOCITY



From Grumbach MM et al. Williams Textbook of Endocrinology 10th edition.

BONE AGE

Puberty is completed usually within 3 to 4 years of its onset, and the final height resulting from complete fusion of the epiphyses occurs within approximately 2 years after menarche.

PRECOCIOUS/DELAYED PUBERTY

Puberty is considered precocious if these changes are noted prior to 8 years of age in girls and 9 years of age in boys and is considered delayed when such changes do not occur prior to 13 years of age in girls and 14 years of age in boys (Europe).

CHRONOLOGICAL ASPECT

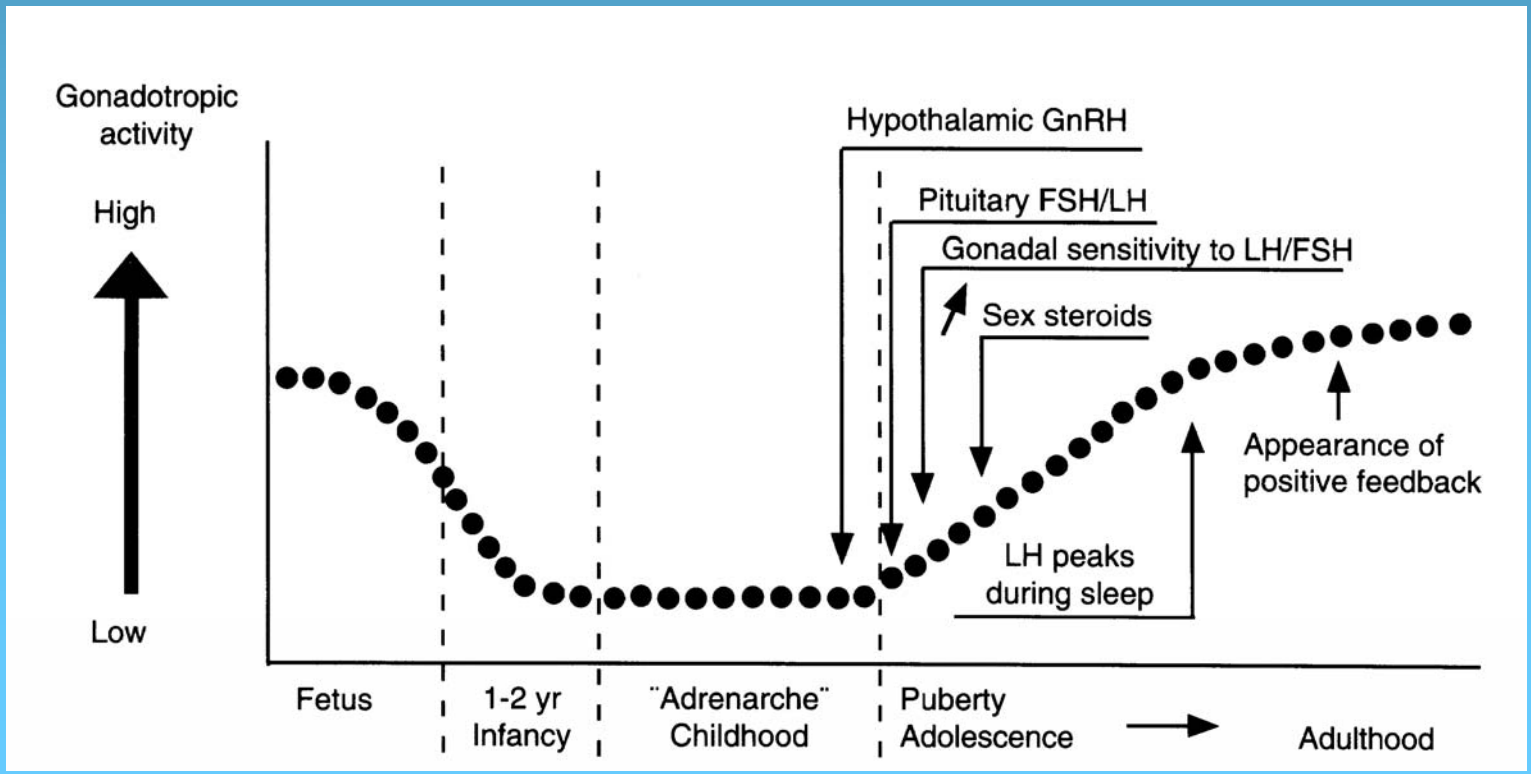
- **GIRLS**
  - acceleration of growth rate
  - development of breasts and pubic hair
  - axillary hair
  - menarche
- **BOYS**
  - increase of testicular volume
  - increase of penile length
  - pubic hair
  - increased growth rate
  - axillary hair
  - deepening of the voice

SUMMARY

	GIRLS	BOYS
Beginning of puberty	10.9 years (8.5-13.3)	11.2 years (9.2-14.2)
Growth spurt	12.2 years (pic)	13.9 years (pic)
Years of puberty	2-3 years	3-5 years
Menarche/ Voice deepening	12.9 years (10-15)	14.6 years (12-17)

PHYSIOLOGY OF PUBERTY

Activation of the hypothalamo-pituitary-gonadal axis



From Forest MG et al., 1973.

HORMONAL CHANGES:

Gonadotropin-Releasing Hormone 1

In prepubertal children, no significant luteinizing hormone (LH) or follicle-stimulating hormone (FSH) response to intravenous or subcutaneous administration of GnRH is observed. During adolescence, the LH response to GnRH increases progressively in both sexes. The increase of FSH is much less marked than that of LH. The primary triggering mechanism that initiates the activation of the hypothalamic-pituitary-gonadal axis at puberty is still hypothetical.

HORMONAL CHANGES:

Gonadotropin-Releasing Hormone 2

One of the important neuroendocrine mechanisms that control the onset of puberty is probably an increase in the frequency of GnRH pulse stimulation of the pituitary. Whatever the mechanism, the process is not abrupt but develops over several years, as evidenced by slowly rising plasma concentrations of the gonadotropins and testosterone or estrogens.

HORMONAL CHANGES:

Gonadotropin-Releasing Hormone 3

1. One of the factors involved in « triggering » GnRH secretion is the GPR54 gene, encoding a G protein-coupled receptor.
2. Human mutations found in hypogonadotropic hypogonadism.
3. Defect in migration and/or final differentiation of the neurons in the hypothalamus.
4. Modulate the activity of GnRH.
5. GPR54 regulates the releas of GnRH at hypothalamic level.

Seminara SB,et al. NEJM, 2003.

HORMONAL CHANGES:

Gonadotropins 1

The first demonstrable biological change of puberty is the appearance of pulsatile LH release during sleep. As puberty progresses, the frequency and amplitude of LH secretory peaks increase, although peaks are also found during the wake period. At the end of puberty, the difference between sleep and wake LH secretory patterns disappears.

HORMONAL CHANGES:

Gonadotropins 2

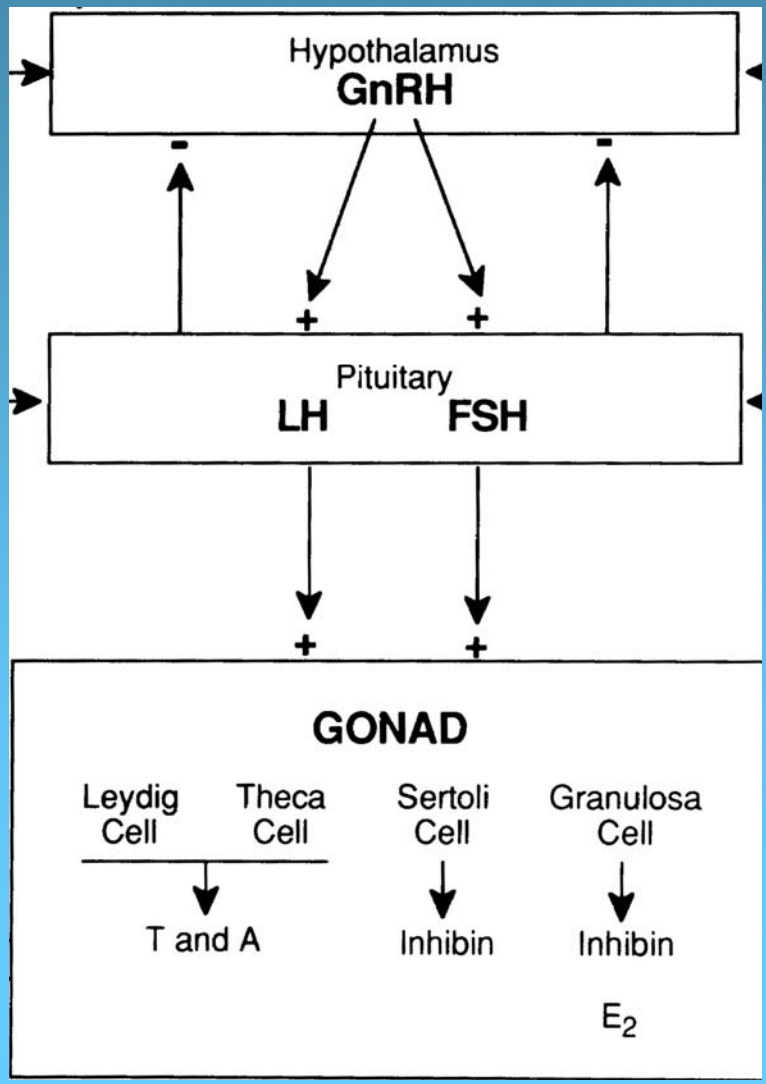
In girls, circulating FSH levels increase progressively from 10 to 11 years of age (stage P2), approximately 1 year prior to those of LH. Thereafter, gonadotropins continue to increase throughout puberty, but important fluctuations are observed in relation to the menstrual cycle.

HORMONAL CHANGES:

Gonadotropins 3

In boys, a significant increase in both plasma FSH and LH is also found from the onset of puberty (stage P2), closely linked to the rapid increase in testicular size characteristic of this pubertal stage. A further significant increase in circulating gonadotropins is also observed at late puberty (stages P4 and P5).

HYPOTHALAMO-PITUITARY-GONADAL AXIS

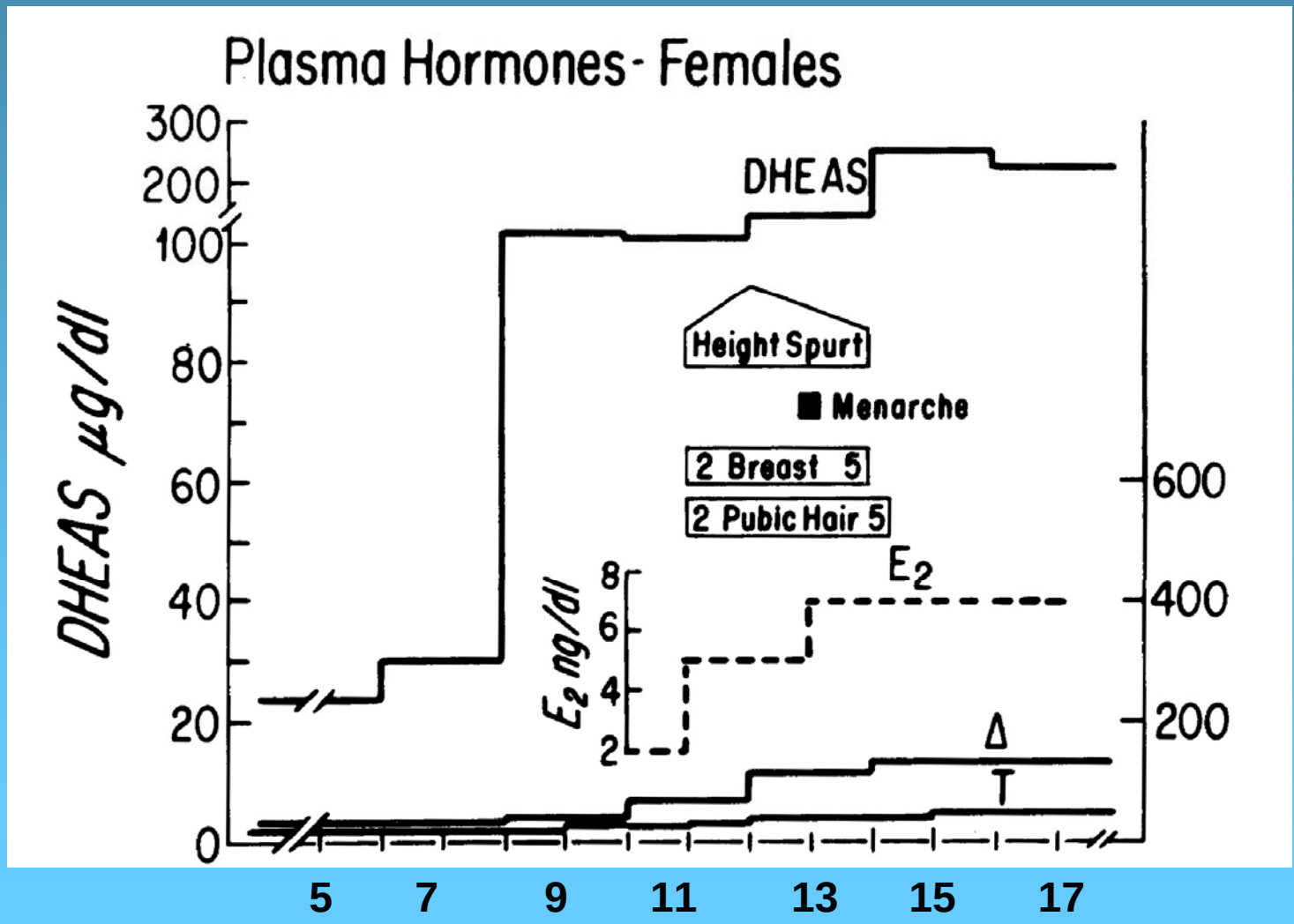


HORMONAL CHANGES:

Adrenal Steroids 1

Adrenal androgens vary from infancy through adolescence. This phenomenon is called *adrenarche*. In girls, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) increase as early as 6 to 7 years of age, followed within 1 to 2 years by a concomitant increase in androstenedione.

HORMONAL CHANGES

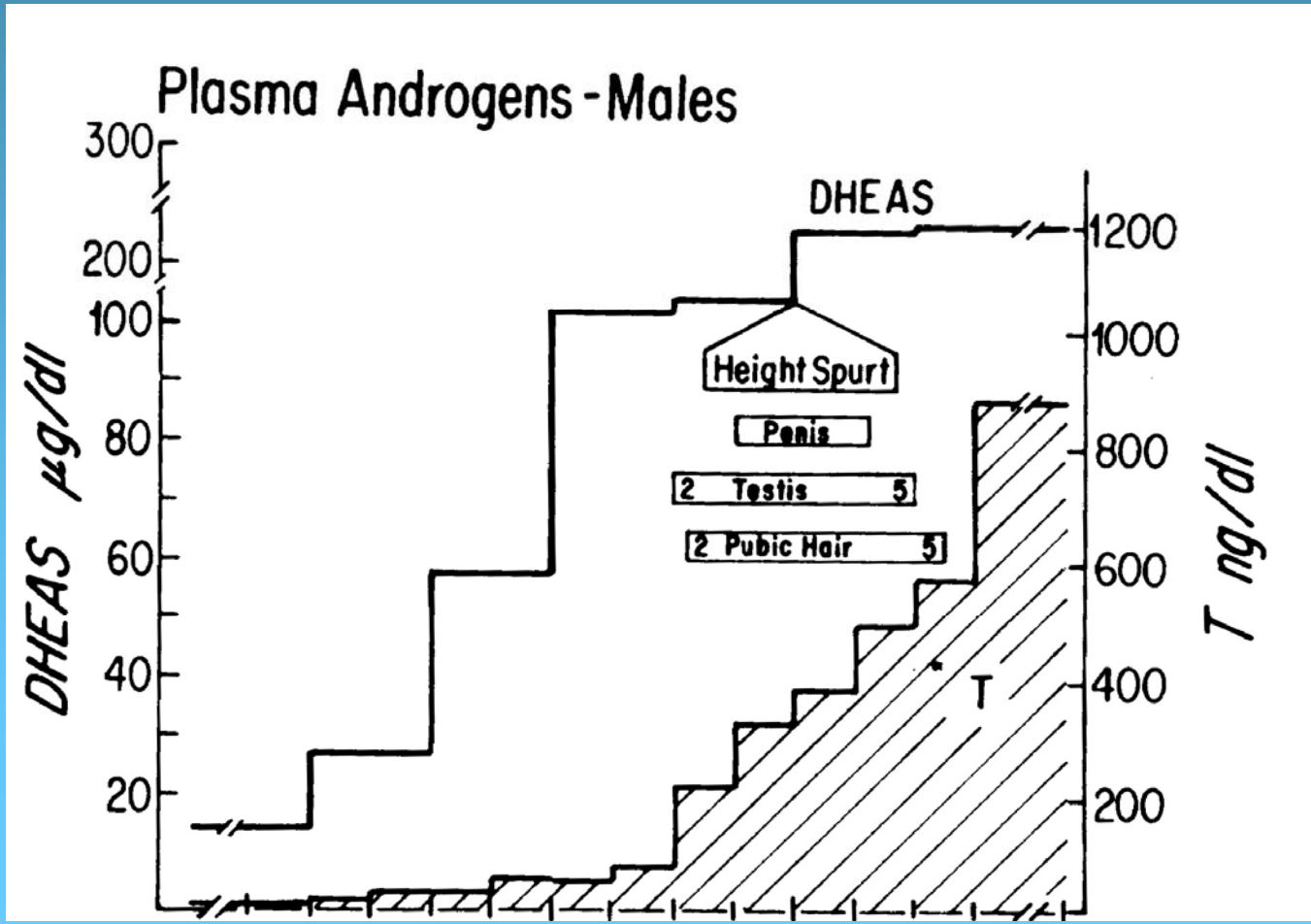


HORMONAL CHANGES:

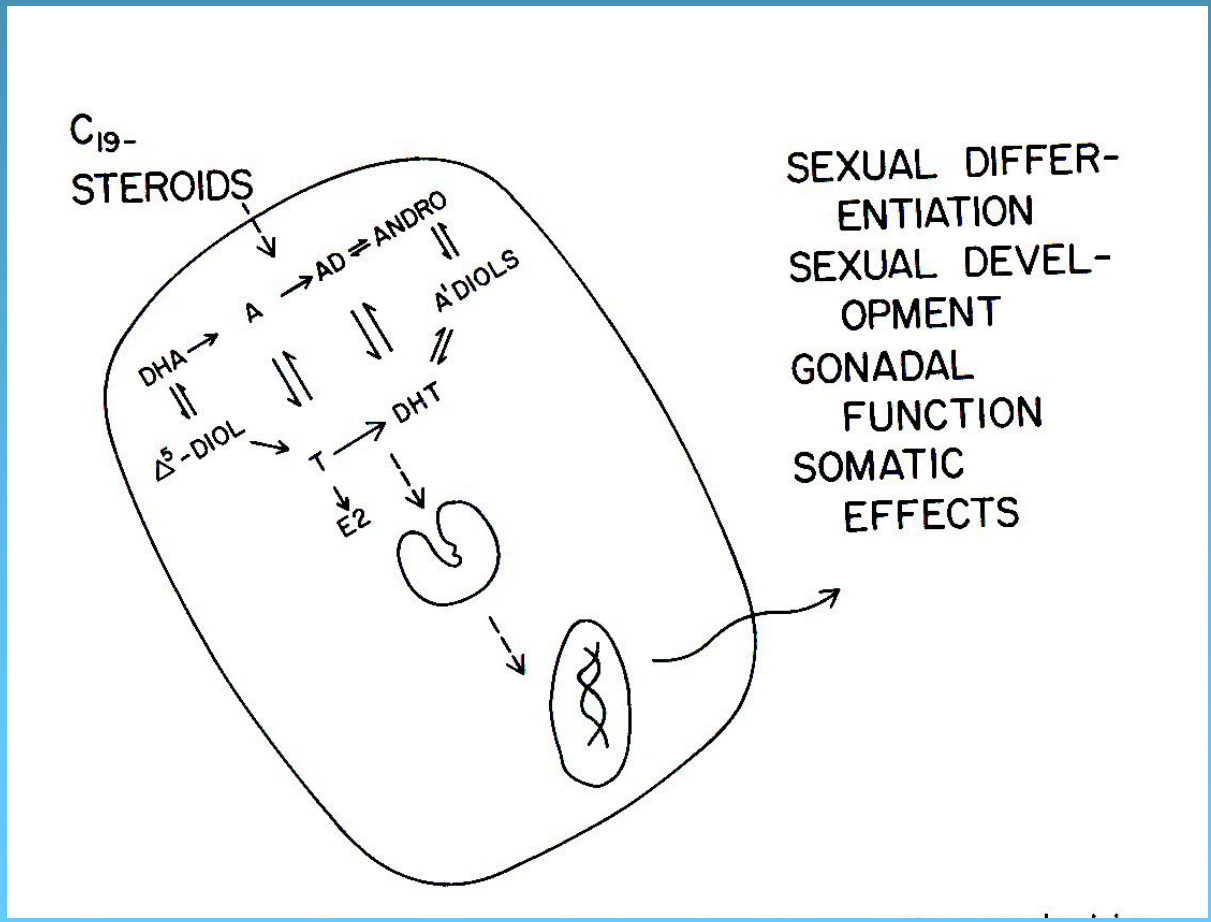
Adrenal Steroids 2

In boys, DHEA and DHEAS increase as early as 8 to 9 years of age, followed by androstenedione 1 to 2 years later. Adrenarche begins before the rise in gonadotropin secretion. The adrenal androgens are responsible for the appearance of axillary hair and, in part, for the appearance of pubic hair in the adolescent; however they do not appear to play a decisive role in determining the initiation of puberty.

HORMONAL CHANGES

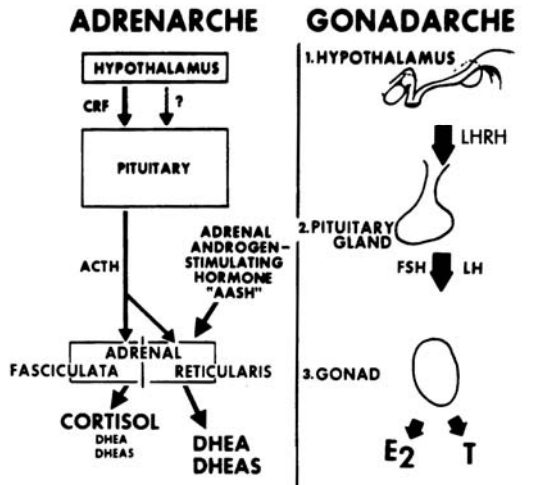


HORMONAL CHANGES



From Nimrod A, Rosenfield RL et al. J Steroid Biochem, 1980.

GONADARCHE-ADRENARCHE



PREMATURE ADRENARCHE	+	−
PRIMARY ADRENAL INSUFFICIENCY	−	+
IDIOPATHIC PRECOCIOUS PUBERTY (ONSET < 6 YRS)	−	+
IDIOPATHIC PRECOCIOUS PUBERTY (ONSET > 6 YRS)	+	+
SYNDROME GONADAL DYSGENESIS	+	−
ISOLATED GONADOTROPIN DEFICIENCY	+	−
CONSTITUTIONAL DELAYED ADOLESCENCE	−	−

From Grumbach MM et al. Williams Textbook of Endocrinology 10th edition. Modified from Sklar CA et al. JCEM 1980.

GH, IGF-I and INSULIN in PUBERTY

There is accumulating evidence that GH plays a role in pubertal development.

In experimental animals, GH seems to stimulate FSH-induced differentiation of granulosa cells directly, increase ovarian levels of IGF-I, and amplify the ovarian response to gonadotropins.

GH, IGF-I and INSULIN in PUBERTY

IGF-I, in turn, enhances the gonadotropin effect on the granulosa cell, and GH seems to act synergistically with a still-developing pattern of gonadotropin secretion to facilitate ovarian maturation postmenarche. It also appears that the local production or accumulation of GH and IGF-I exerts an intraovarian paracrine control on steroidogenesis.

GH, IGF-I and INSULIN in PUBERTY

Puberty of patients with isolated GH deficiency is frequently delayed, Leydig cell function is diminished, and the response to chorionic gonadotropins is decreased. GH administration can restore testicular responsiveness to LH and Leydig cell steroidogenesis.

GH, IGF-I and INSULIN in PUBERTY

Growth hormone-releasing factor (GRF) levels and GH secretion increase considerably during puberty, mainly at night. The amplitude of GH peaks increases early in puberty. IGF-I is an important modulator of growth during childhood and adolescence. Adrenal androgens seem to have no physiological role in normal growth.

GH, IGF-I and INSULIN in PUBERTY

The characteristic pubertal growth spurt results mainly from the synergetic effect of gonadal sex steroids, growth hormone, and IGF-I production, with all showing a significant increase at the time of pubertal growth acceleration.

GH, IGF-I, INSULIN and LEPTIN in PUBERTY

Insulin is also important for normal growth. Plasma insulin levels increase throughout childhood, but the rise is particularly pronounced during puberty with a strong positive correlation with IGF-I.

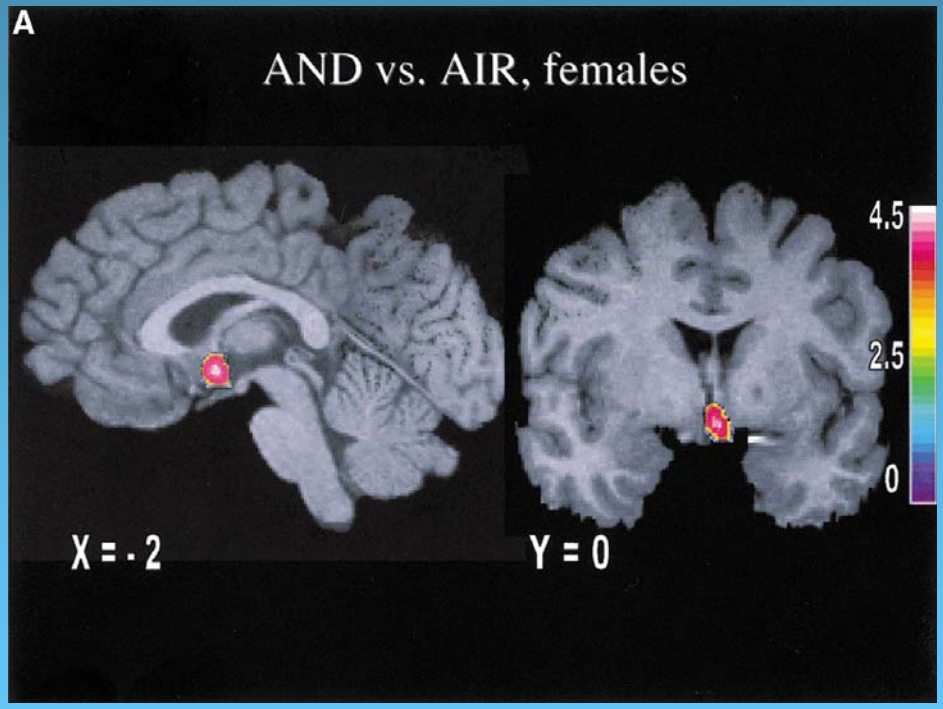
LEPTIN in PUBERTY

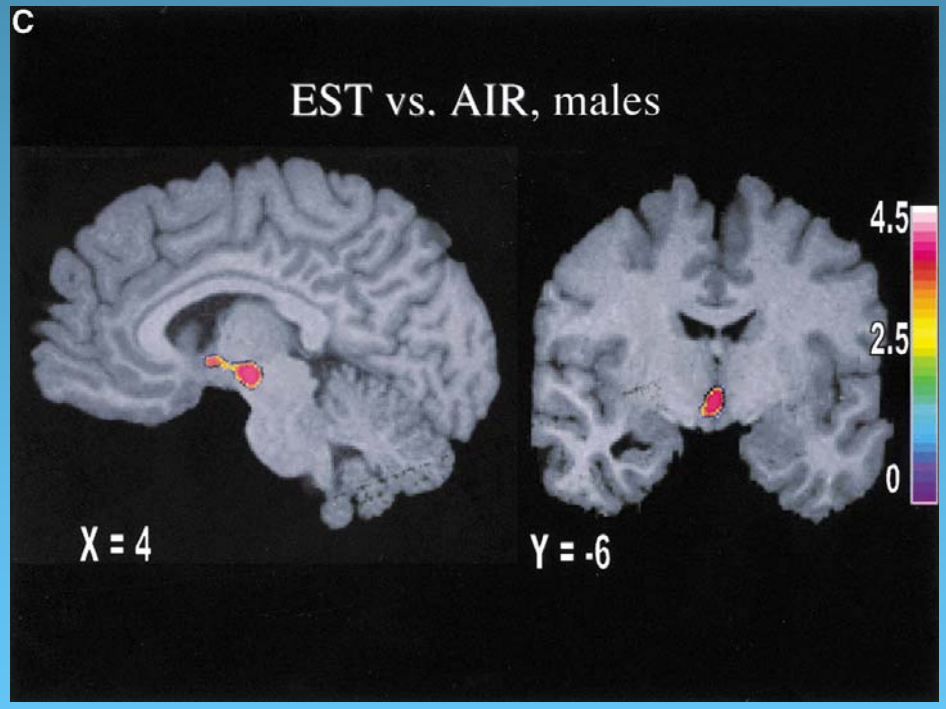
- Peptide hormone
- Regulates food intake and energy expenditure at the hypothalamic level (satiety factor)
- Expressed predominantly in adipocytes
- Regulated by body weight and nutrition
- Involved in the regulation of GnRH secretion
- Permissive factor for puberty (48kg)
- Interacts with insulin, IGF1, GH and glucocorticoids

PUBERTY AND THE BRAIN

- GABA neurons inhibit prepubertal GnRH release
- Puberty advances by pharmacological blockade of GABA A receptors (monkeys)
- GABA inhibits excitatory neuronal systems synaptically connected to GnRH neurons

PUBERTY AND THE BRAIN





Neuron 2002