PUBERTY

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DEFINITION OF PUBERTY

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

DEFINITION OF PUBERTY

Physical changes of puberty:

- **Female secondary sex characteristics**
- **Male secondary sex characteristics**

PHYSIOLOGY OF PUBERTY

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:

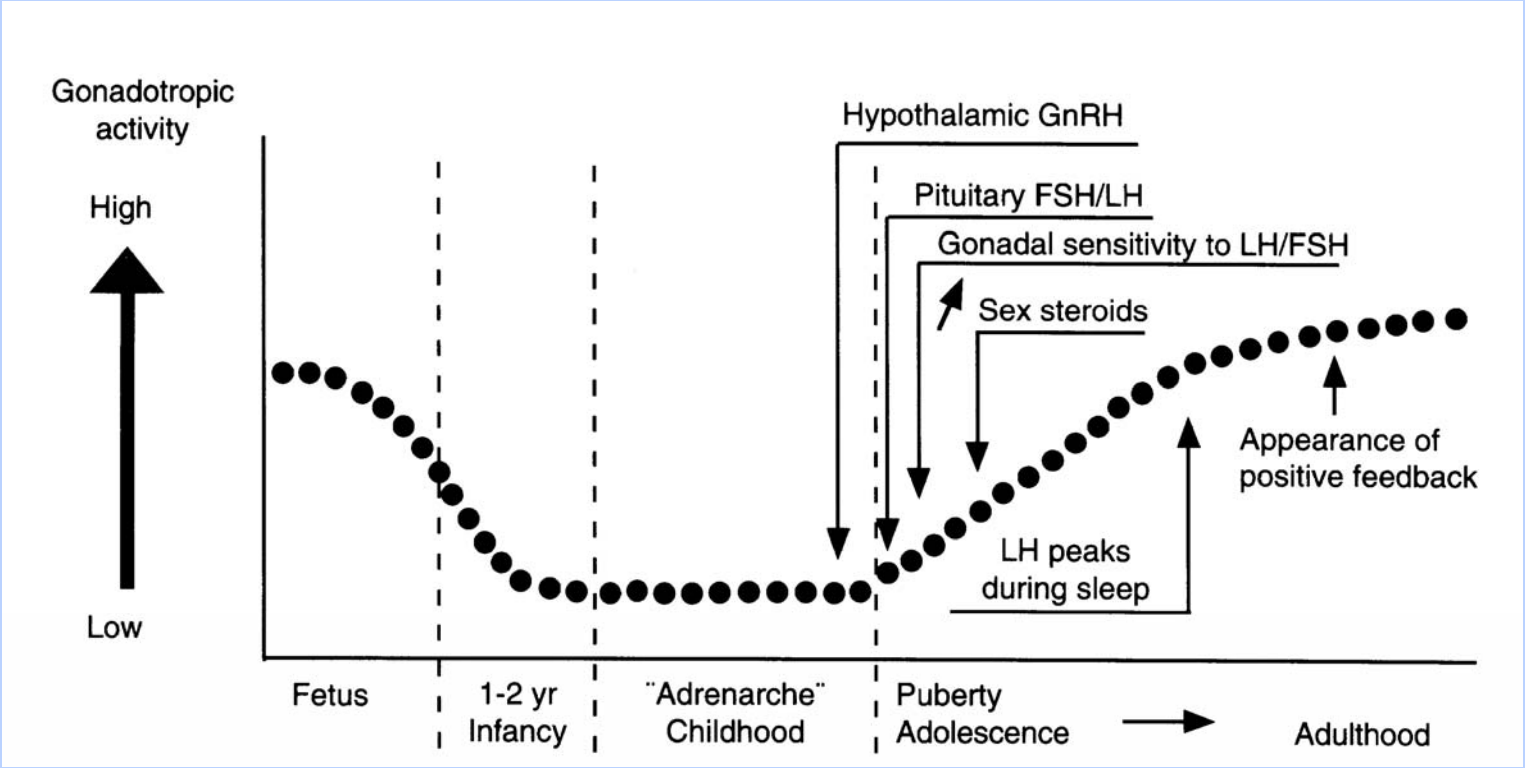
- induces and enhances the progressive ovarian and testicular sex hormone secretion
- responsible for the profound biological, morphological, and psychological changes to which the adolescent is subjected

sex steroid production:

- appearance and maintenance of sexual characteristics
- capacity for reproduction

PHYSIOLOGY OF PUBERTY

Activation of the hypothalamo-pituitary-gonadal axis



80d **juvenile pause**

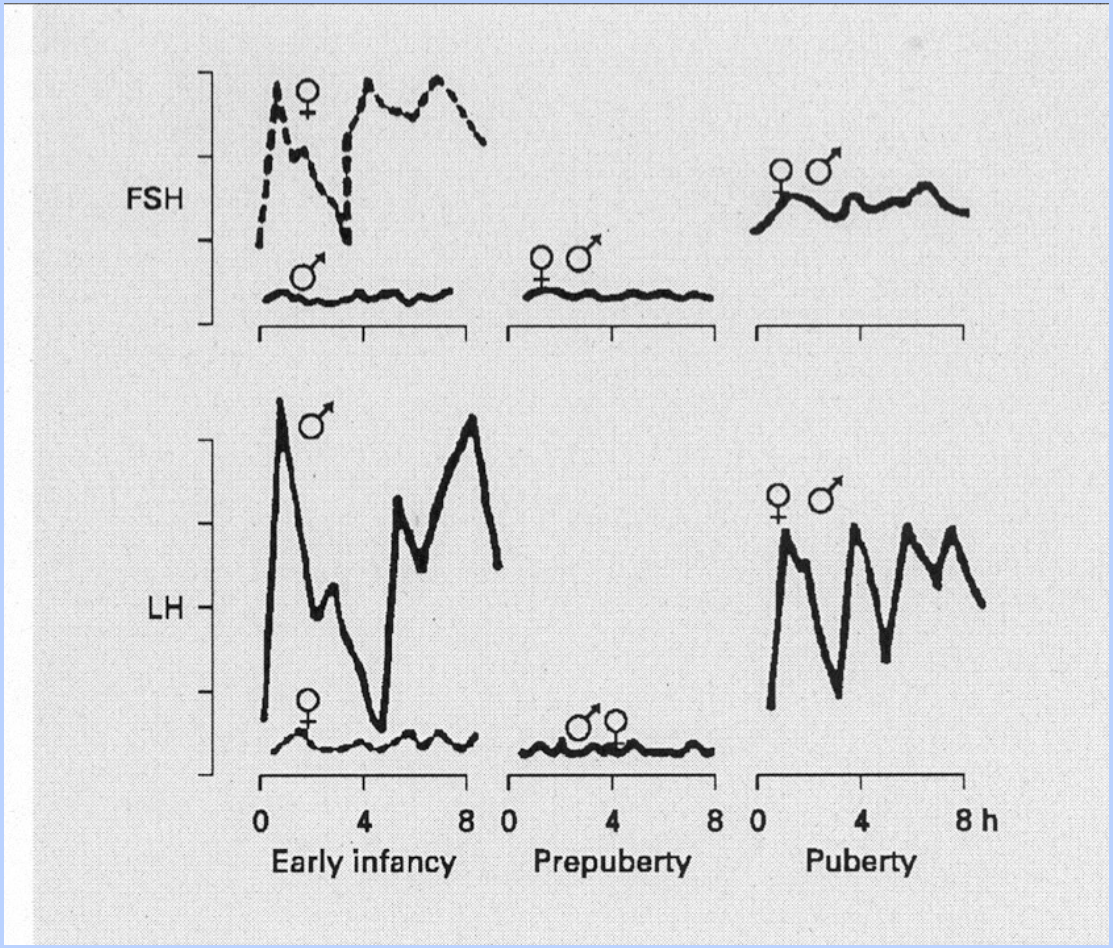
Forest MG et al., 1973.

PUBERTY

After birth the gonades respond to stimuli such as:

- **LH- in boys up to the age of 6 months**
- **FSH- in girls up to the age of 12-24 months**

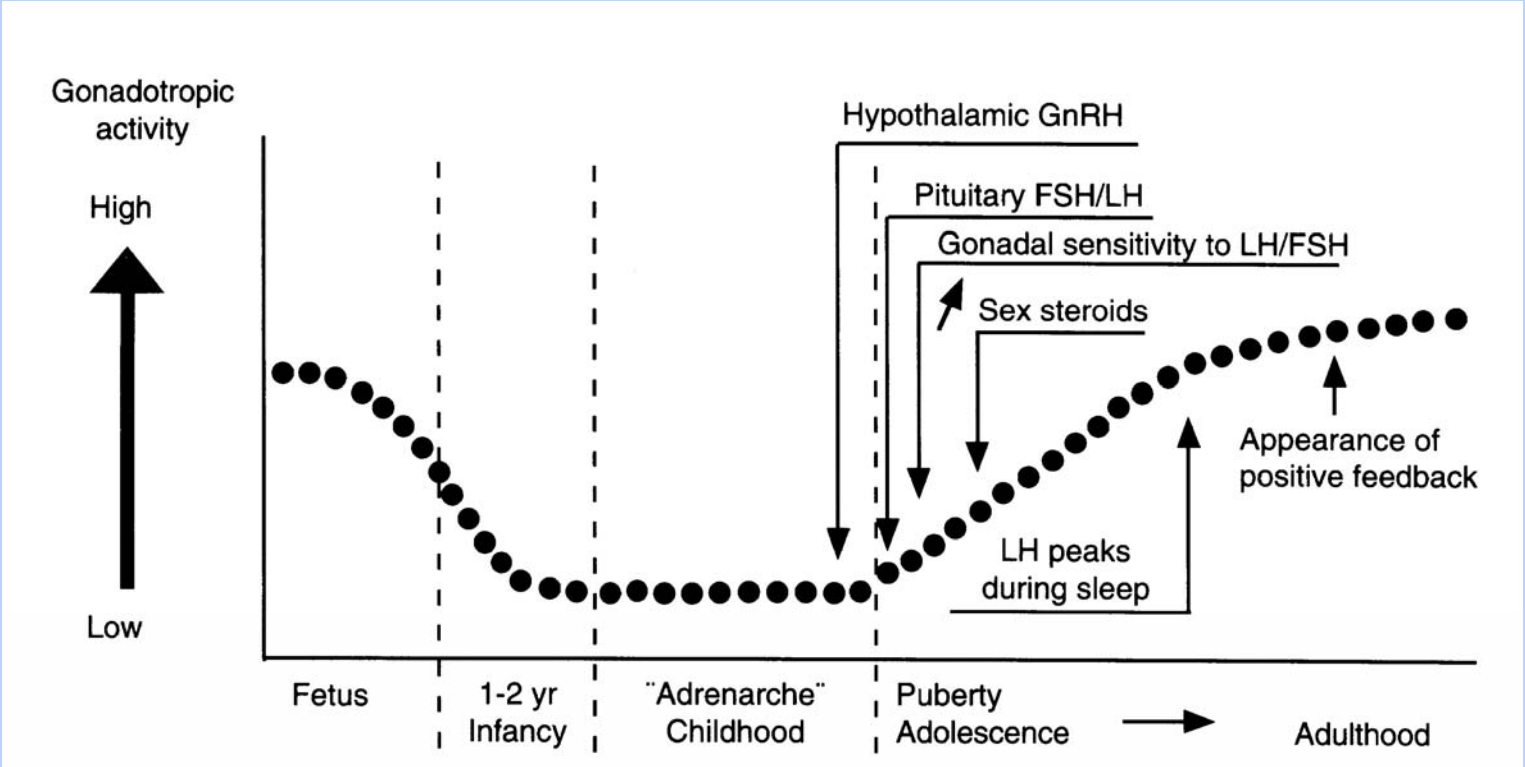
PUBERTY



Grumbach MM, Horm Res 2002

PHYSIOLOGY OF PUBERTY

Activation of the hypothalamo-pituitary-gonadal axis



80d **juvenile pause**

Forest MG et al., 1973

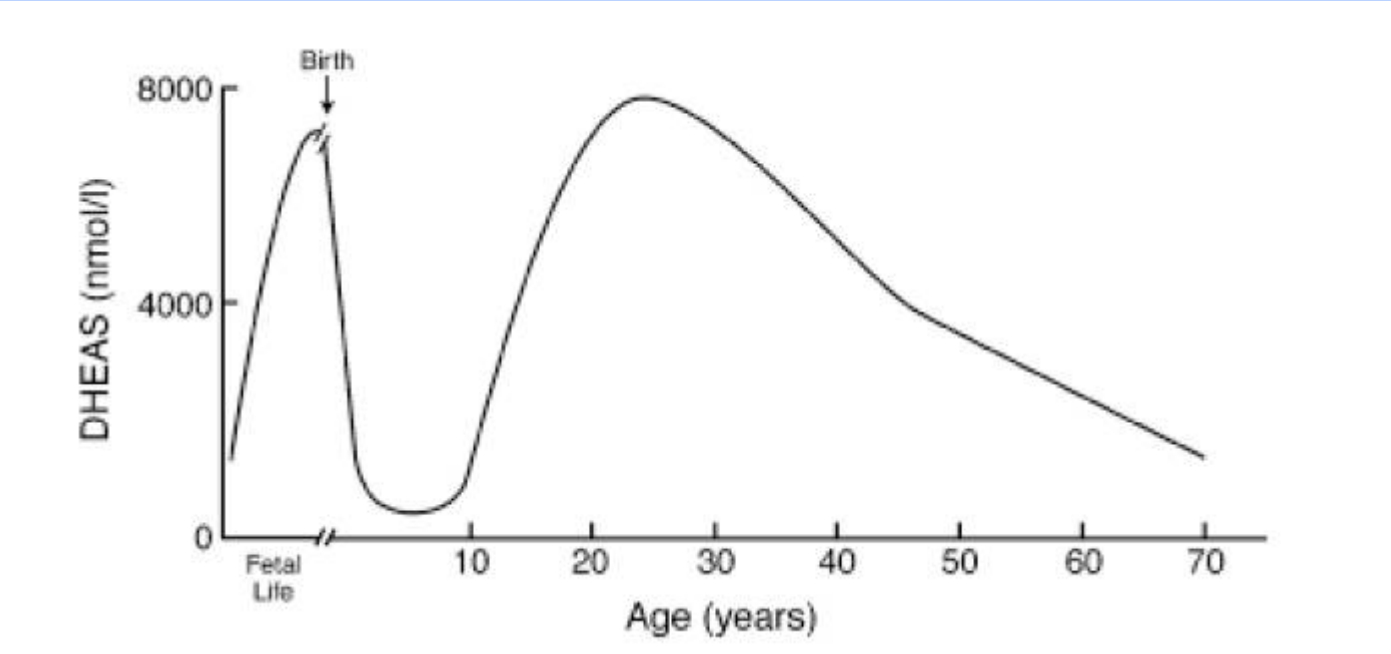
ADRENARCHE

- The onset of DHEAS production from the adrenal zona reticularis leads to the phenomenon of ADRENARCHE
- Adrenarche occurs only in human beings and in some primates
- A specific cell type with the capacity to synthesize DHEAS is needed
- In girls, adrenarche starts around 6 years of age followed within 1 to 2 years by a concomitant increase in androstenedione

ADRENARCHE

- In boys, DHEA and DHEAS increase as early as 8 to 9 years of age, followed by androstenedione 1 to 2 years later
- 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.

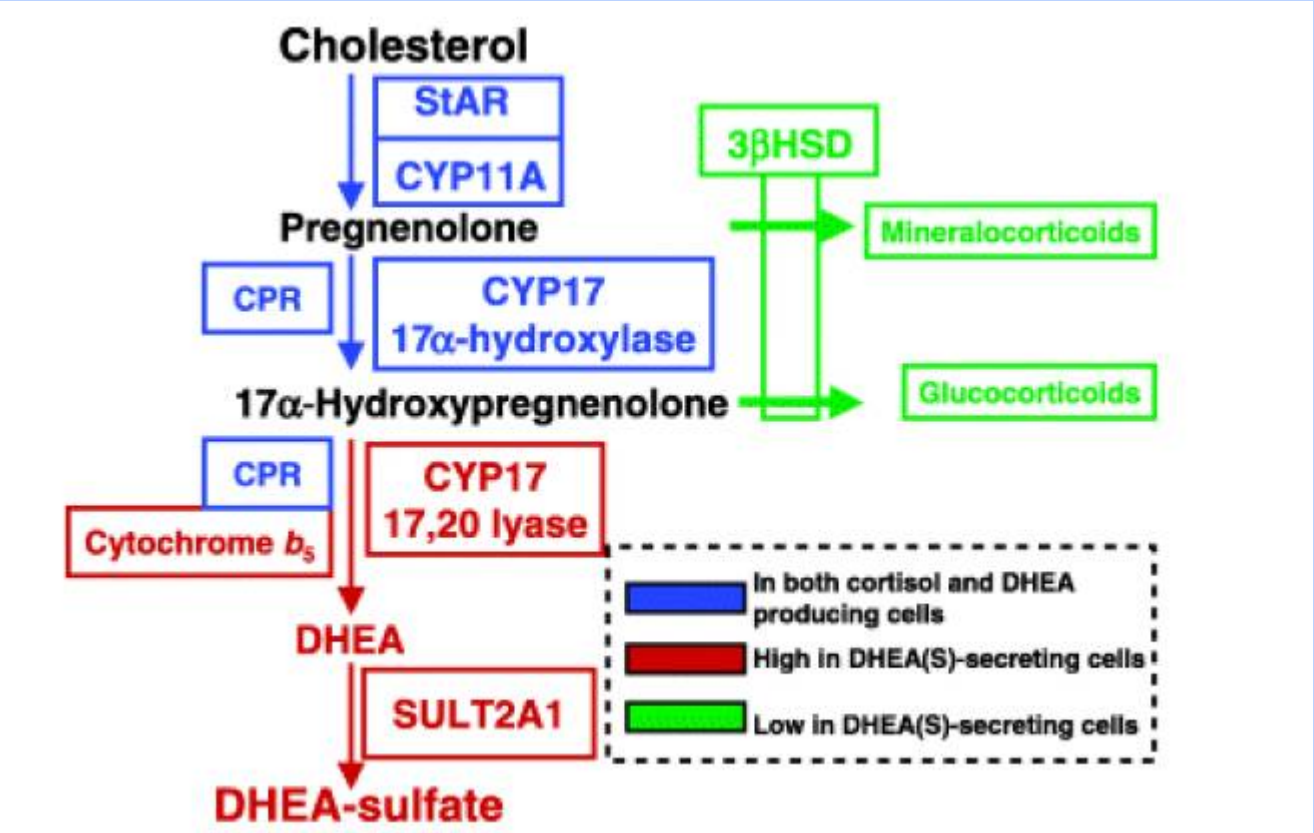
ADRENARCHE



Circulating DHEA and DHEAS rise progressively
Cortisol and ACTH do not change significantly
Adrenarche is not simply a global activation of the pituitary-adrenal axis

Auchus J et al.Clinical Endocrinolgoy 2004

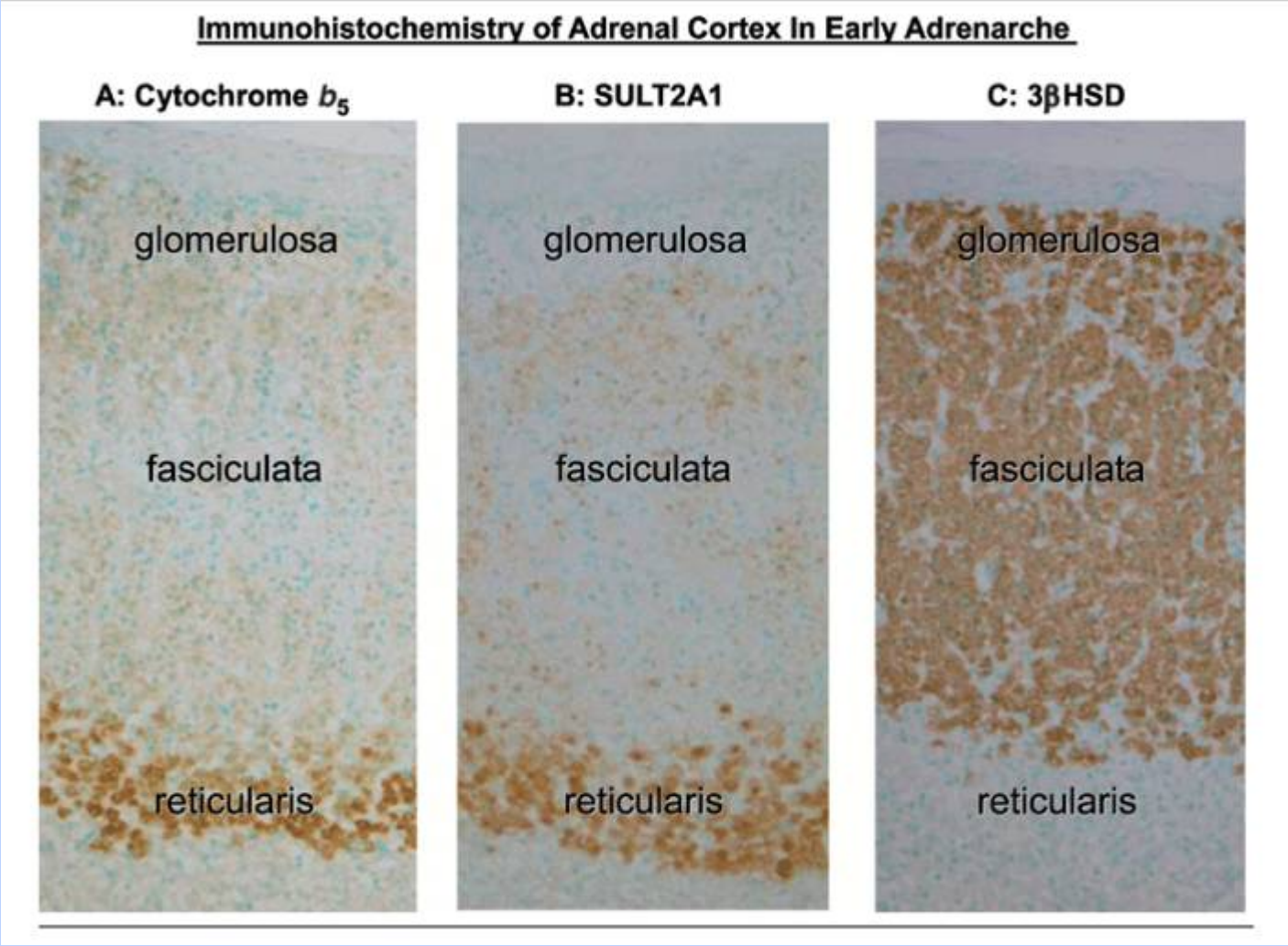
ADRENARCHE



CPR: cytochrome P450 oxidoreductase
SULT2A1: DHEA-sulphotransferase

Auchus J et al.Clinical Endocrinolgoy 2004

ADRENARCHE



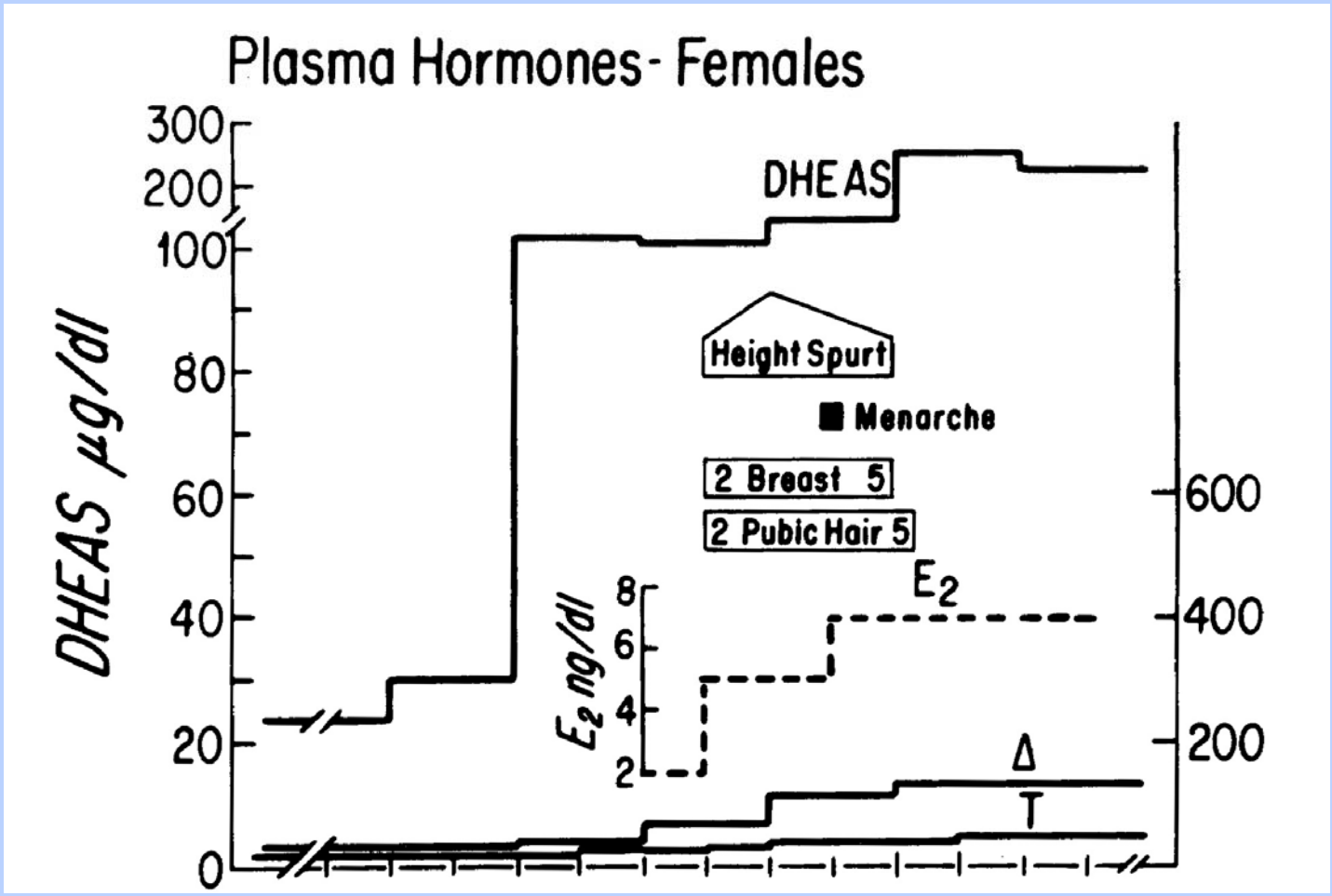
Glomerulosa:
Mineralocorticoides

Fasciculata:
Glucocorticoides

Reticularis:
Sex steroids

Auchus J et al.Clinical Endocrinolgoy 2004

HORMONAL CHANGES



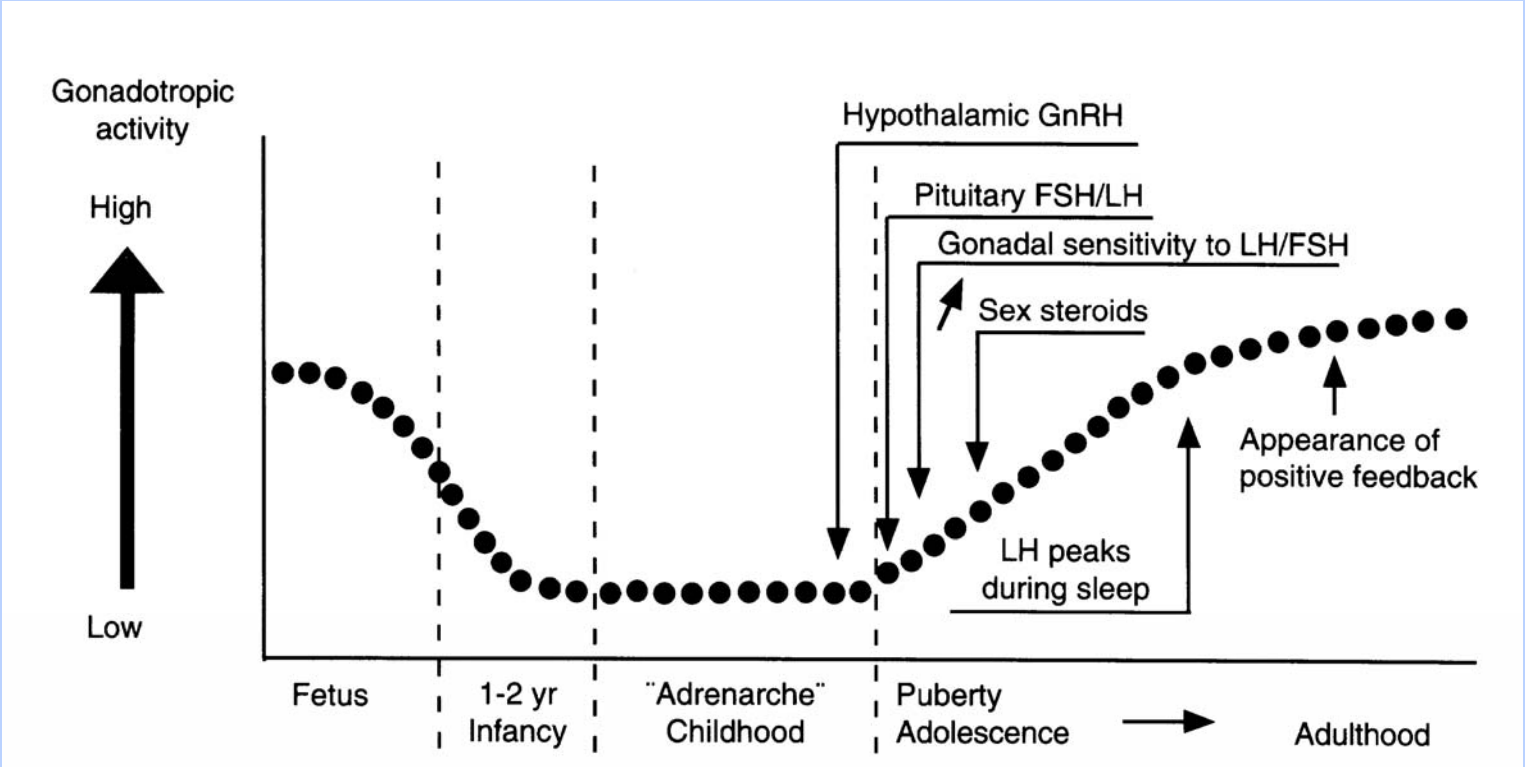
Grumbach MM et al. Williams Textbook of Endocrinology 10th edition

PREMATURE ADRENARCHE

- Girls < 6 years of age
- Often in african american girls
- Often in children with low birthweight
- DD: Cushing's disease, virilizing adrenal tumor, 21-hydroxylase deficiency
- A diagnosis of exclusion
- ♀ high incidence of PCOS later in life
- ♂ high incidence of insulin resistance

PHYSIOLOGY OF PUBERTY

Activation of the hypothalamo-pituitary-gonadal axis



80d **juvenile pause**

Forest MG et al., 1973

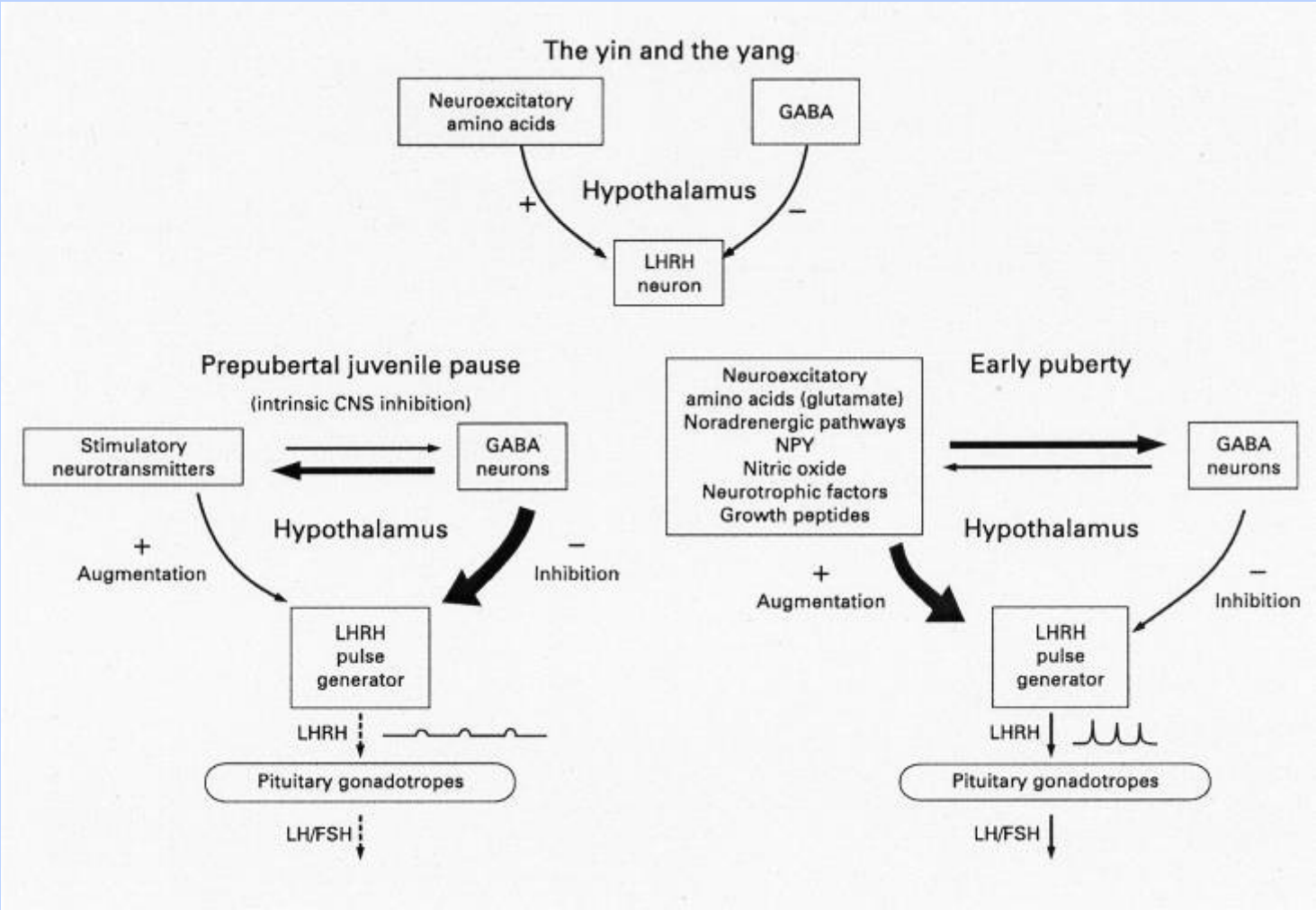
Gonadotropin-Releasing Hormone: 1

- 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.

GONADARCHE

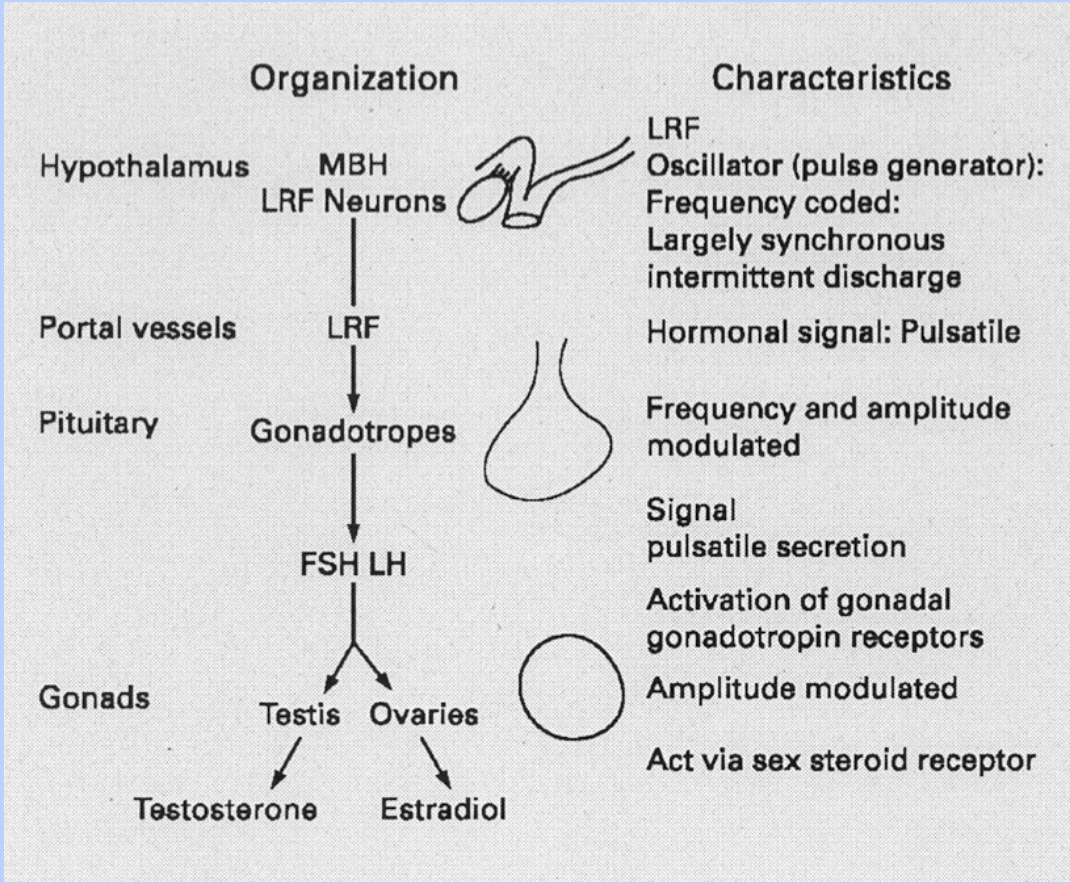
- **Juvenile pause: inhibition of the LHRH pulse generator through the neurotransmitter GABA**
- **Gradual disinhibition and reactivation of the LHRH pulse generator**
- **At puberty decrease of the GABA-ergic transmission**
- **Increase of the excitatory circuit (glutamate,…)**

HYPOTHALAMO-PITUITARY AXIS



Grumbach MM, Horm Res 2002

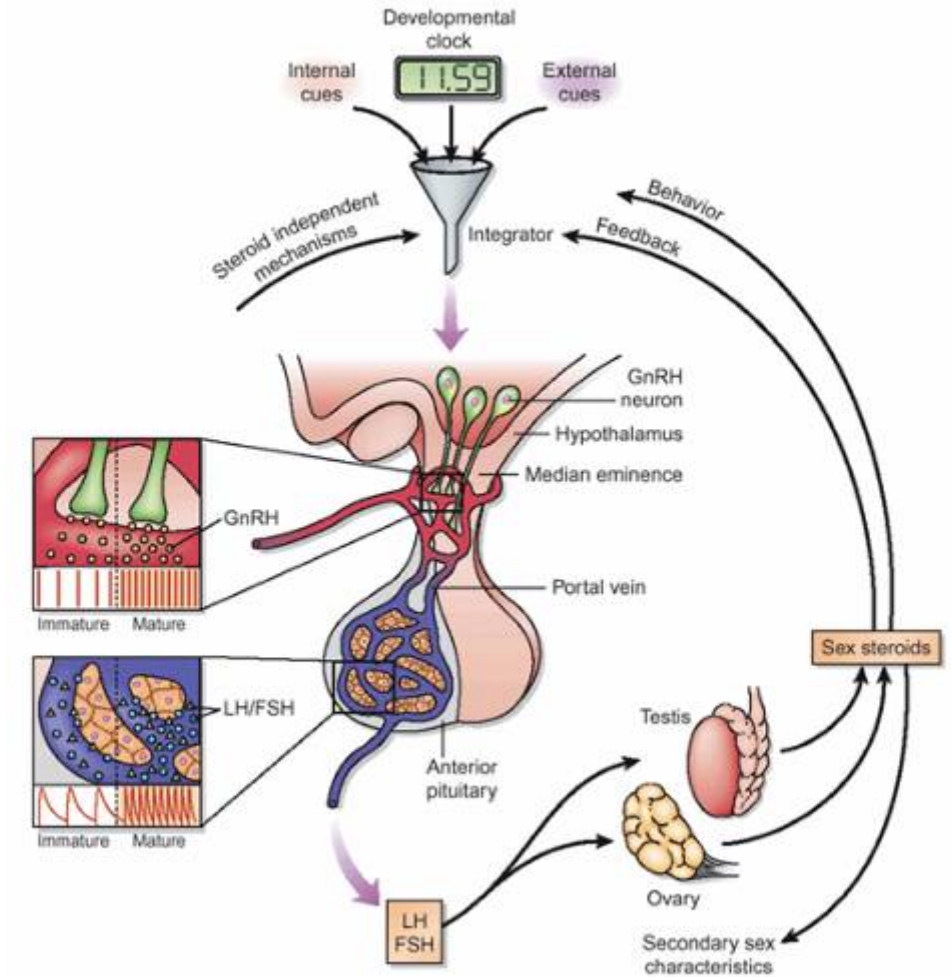
GONADARCHE



- MBH: medial basal hypothalamus
- 1500-2000 LHRH neurons

Grumbach MM, Horm Res 2002

HORMONAL CHANGES OF PUBERTY



Permissive signals (related to energy balance):

Body fat

Leptin

Insulin

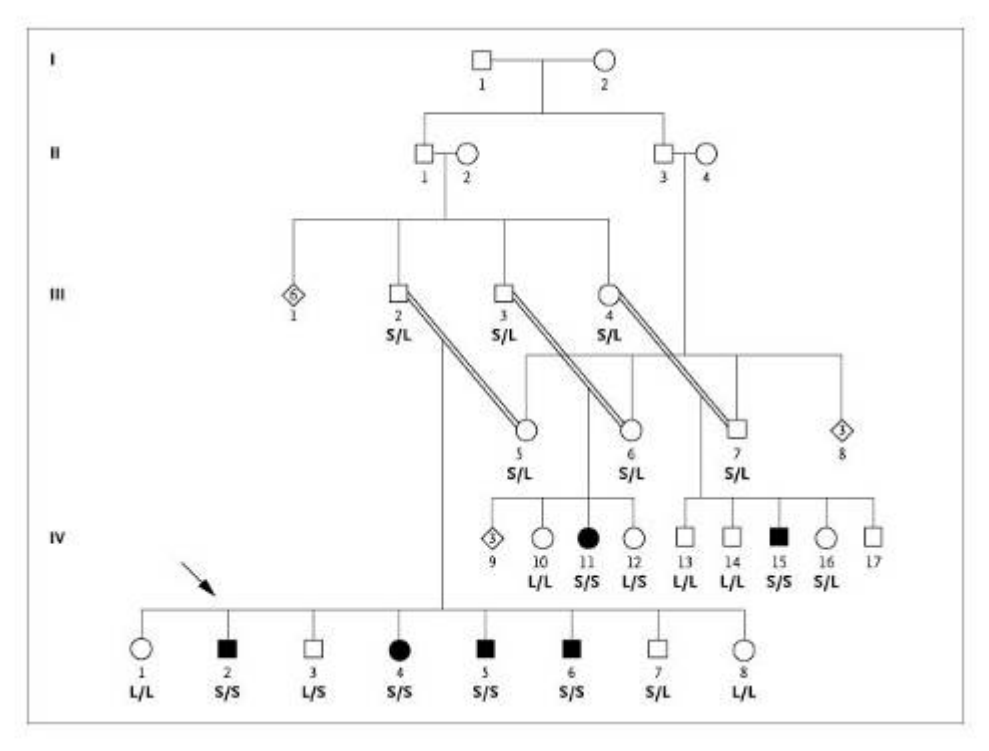
Melatonine

Sisk at al.Nature Neuroscience 2004

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

HYPOGONADOTROPIC HYPOGONADISM



6 family members affected

Genetic analysis:

- **Homozygous mutation GPR54 (G-protein coupled receptor gene) (L148S)**
- **Gene is essential for a « normal » GnRH synthesis and secretion**
- **Ligand metastin (neg.feedback E2/T)**
- **Chromosome 19p13.3**

Seminara B. et al., NEJM, 2003

HORMONAL CHANGES

- **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

- 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).

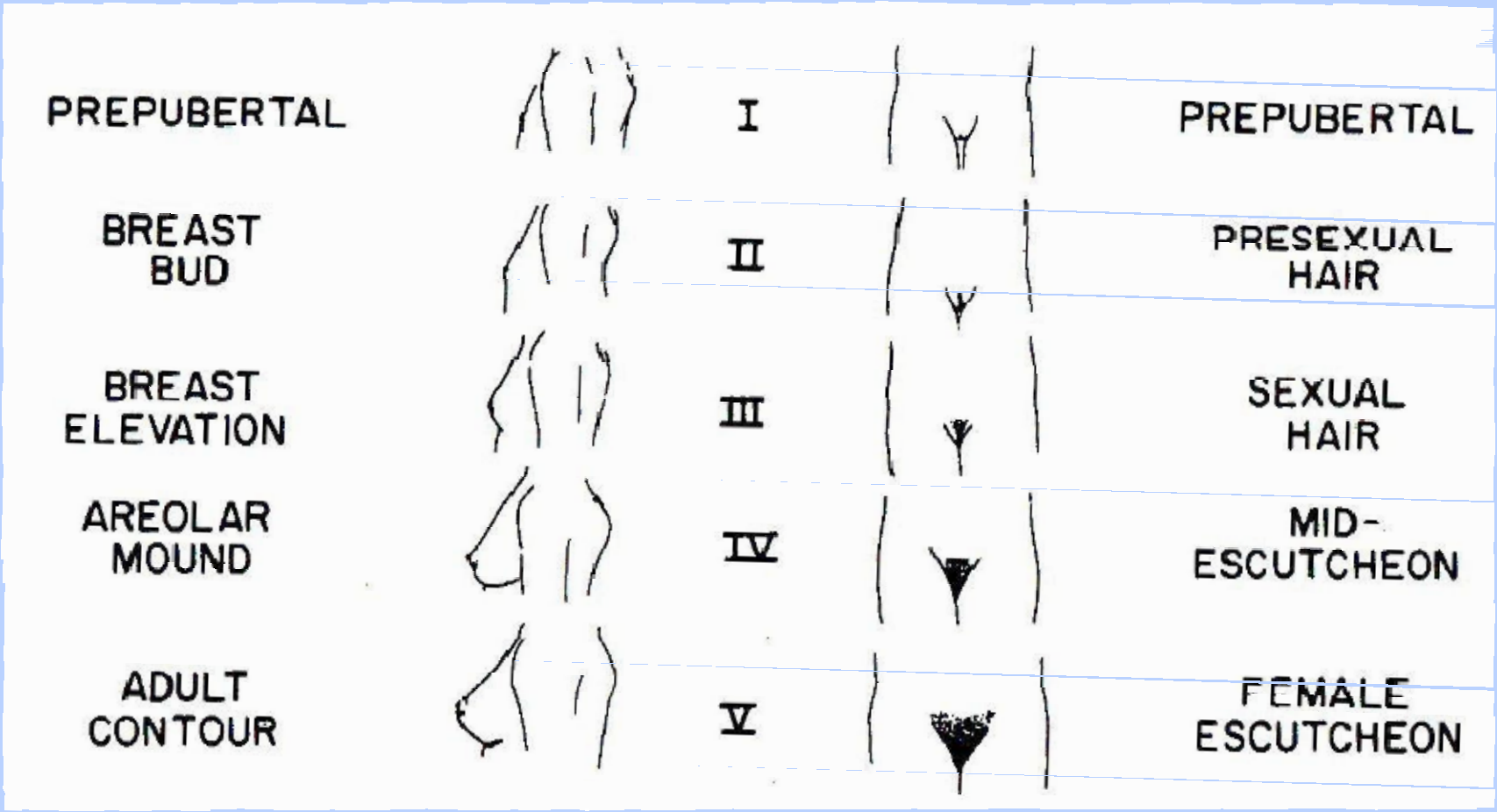
PHYSICAL CHANGES OF PUBERTY

- **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

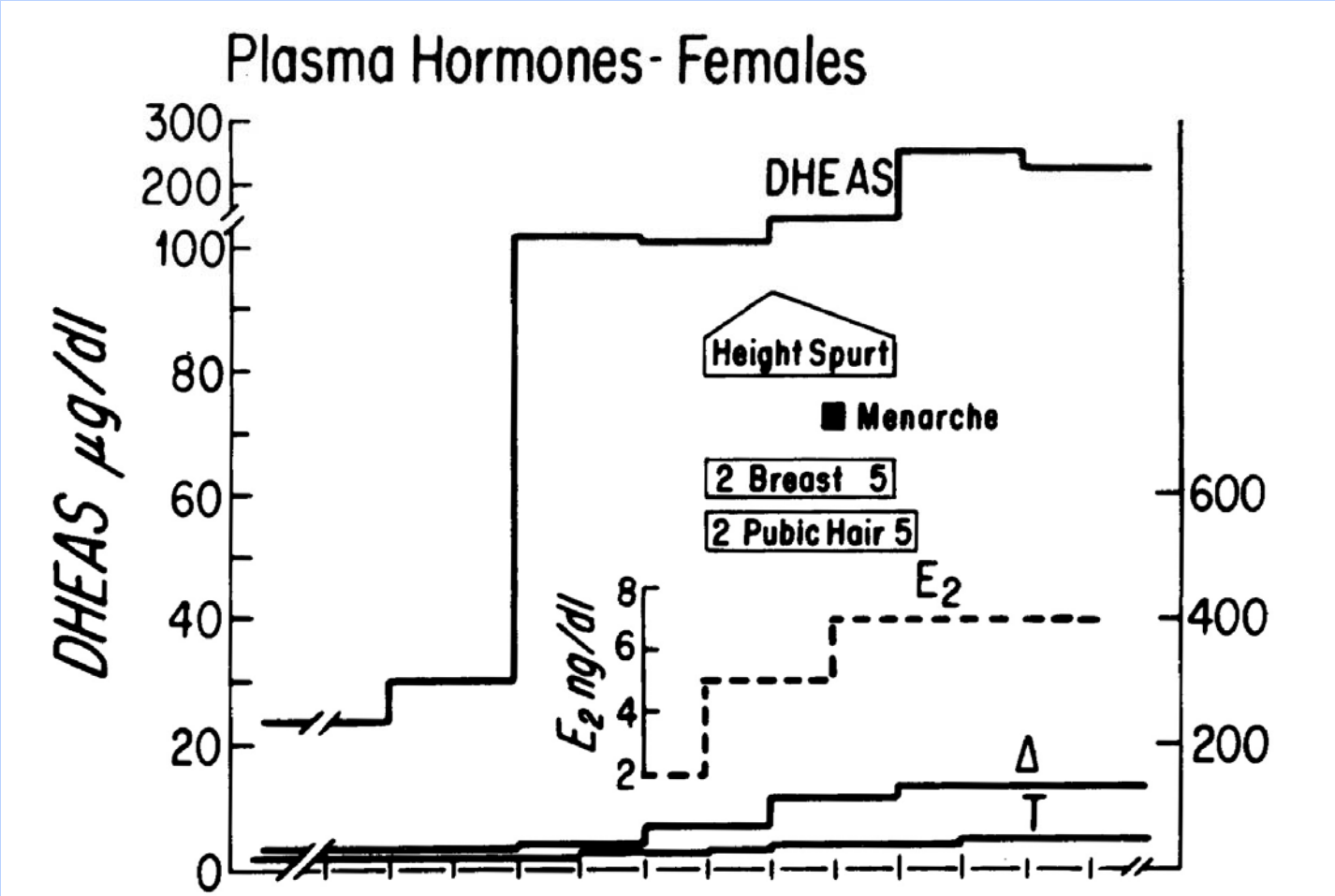
P1	**Prepubertal**
P2	**Early development of subareolar breast bud +/-small amounts of pubic hair and axillairy hair**
P3	**Increase in size of palpable breast tissue and areolae, increased amount of dark pubic hair and of axillary hair**
P4	**Further increase in breast size and areolae that protrude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

PUBERTAL STAGES (TANNER)



Rosenfield R. Pediatric Endocrinology. Sperling 2nd edition.

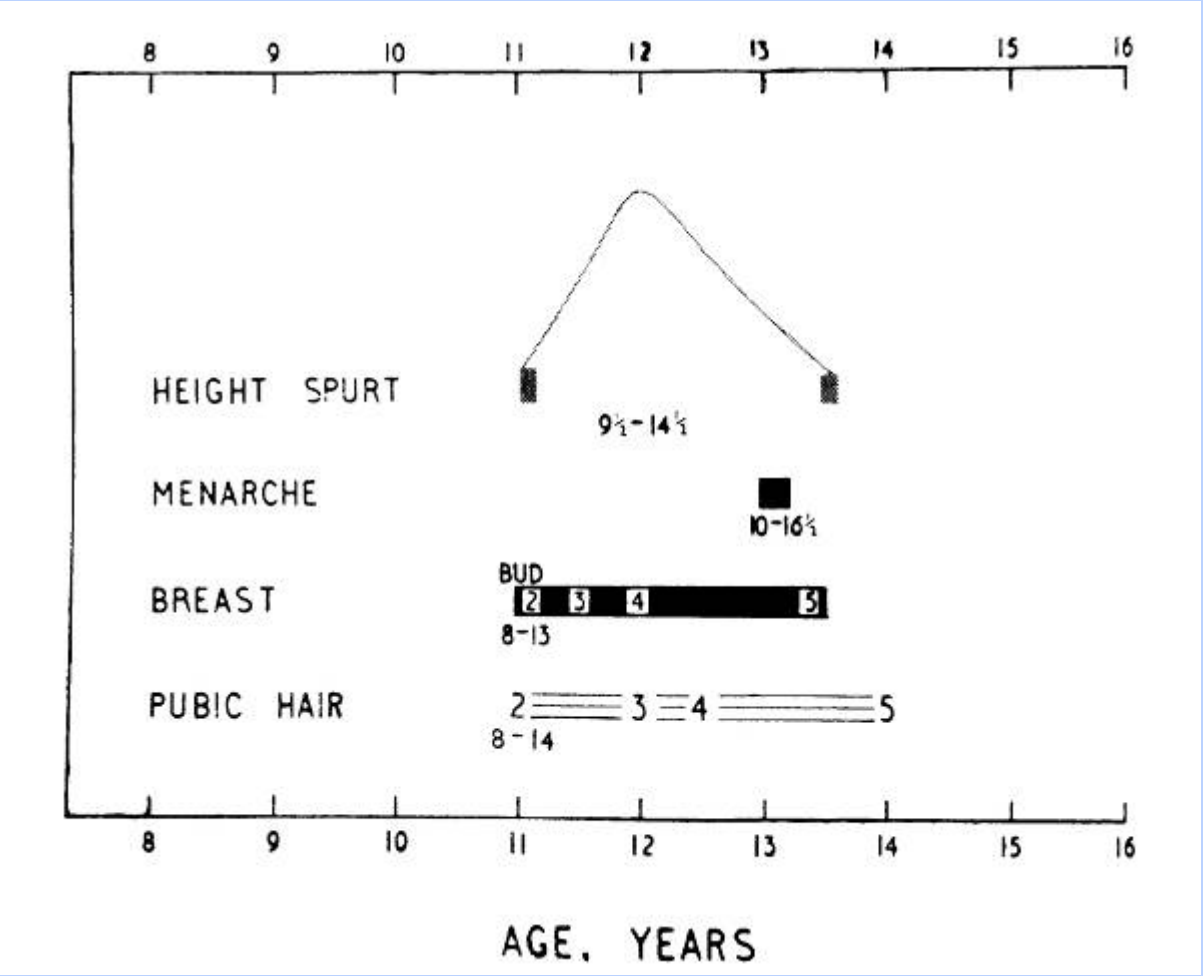
HORMONAL CHANGES



Grumbach MM et al.

SECONDARY SEX CHARACTERISTICS

Female

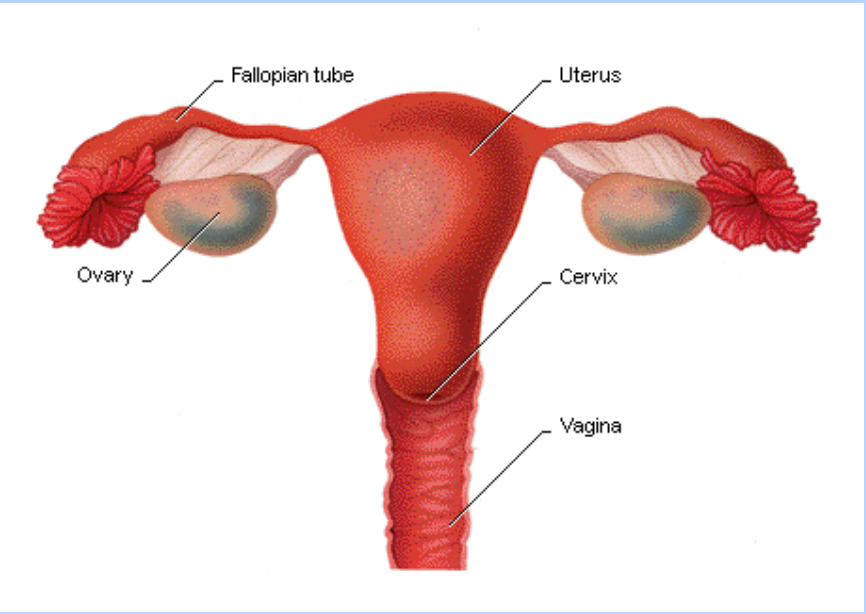


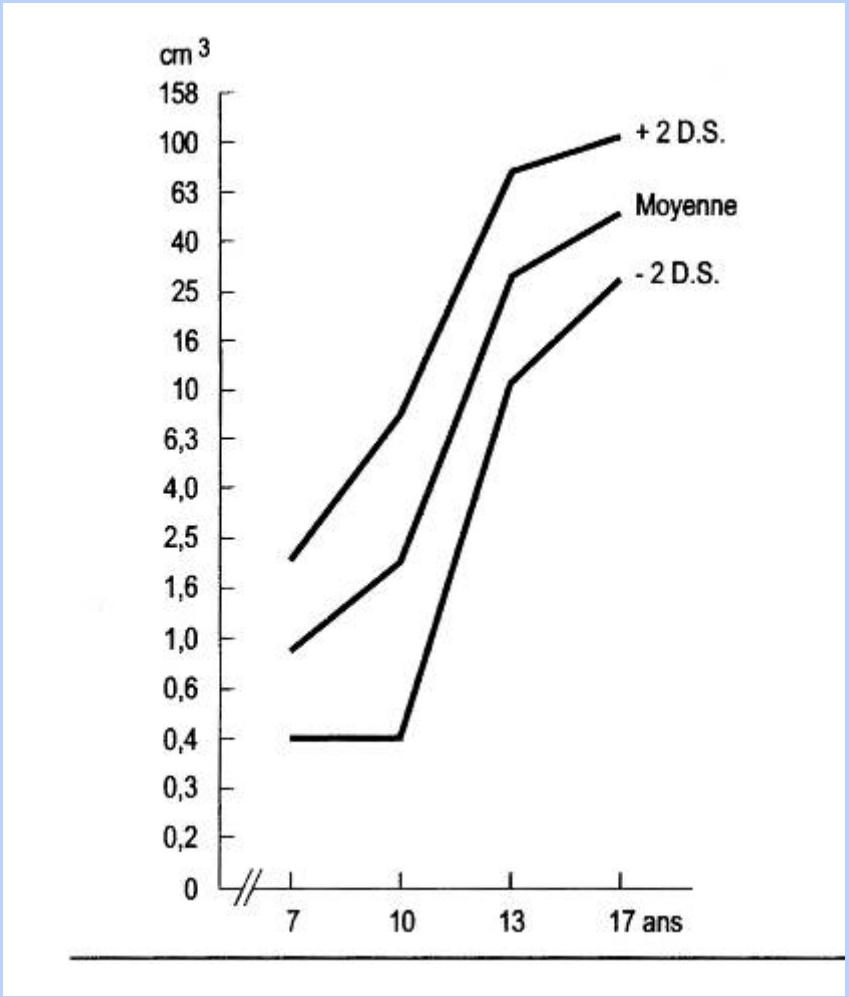
Marshall WA, Tanner JM, ArchDis Child 1969

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.

GROWTH OF THE UTERUS



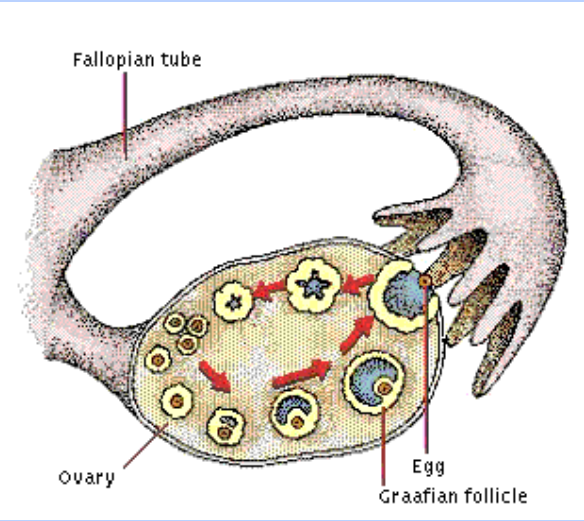


Ivarsson SA et al., Arch Dis Child 1983

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.**

FEMALE SECONDARY SEXUAL CHARACTERISTICS

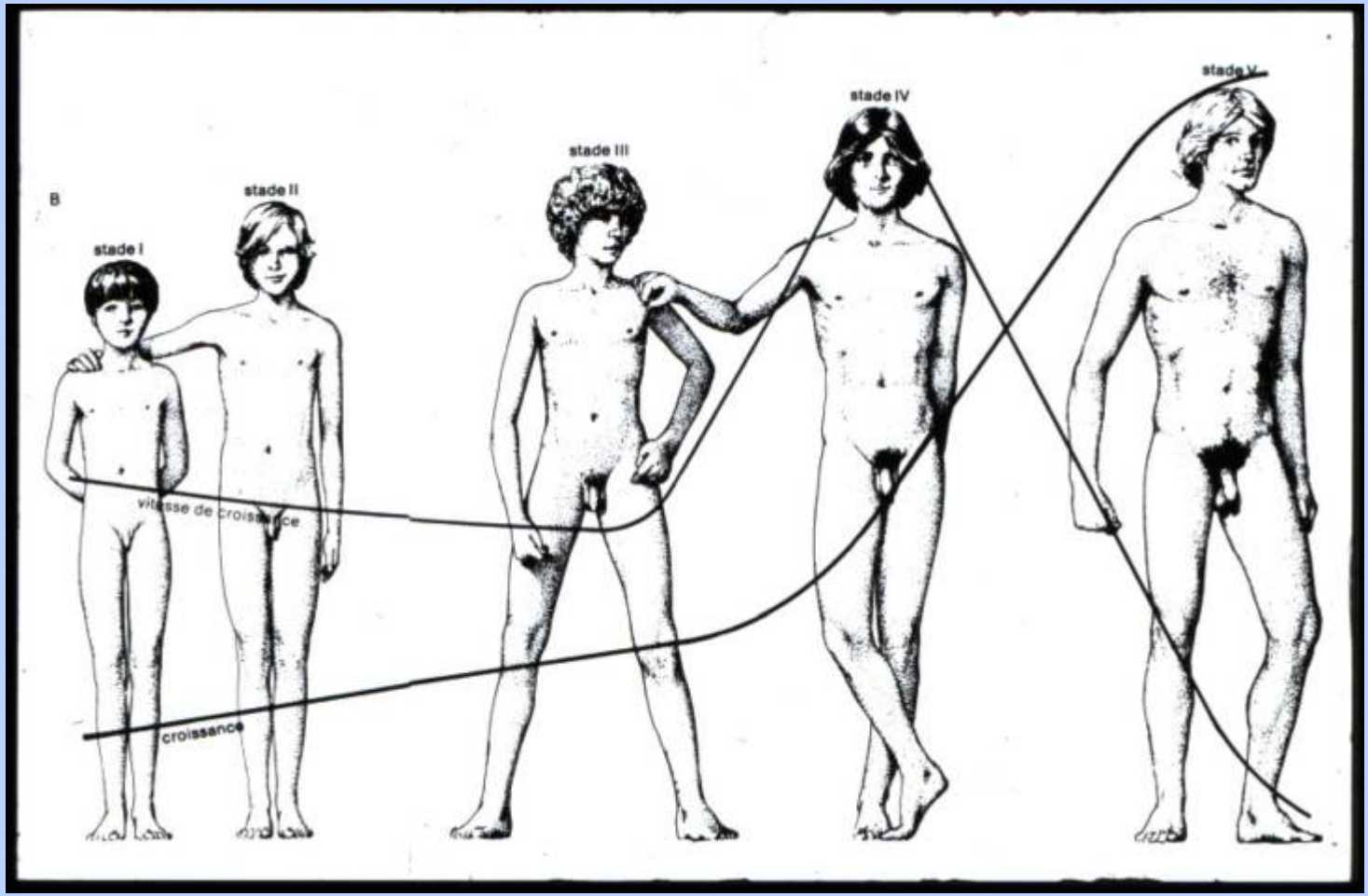
Precocious development:

- **breast development- *premature* thelarche**
- **pubic and/or axillary hair- *premature* pubarche and/or adrenarche**
- **Menses- *premature* menarche**

PUBERTAL STAGES (TANNER) MALE

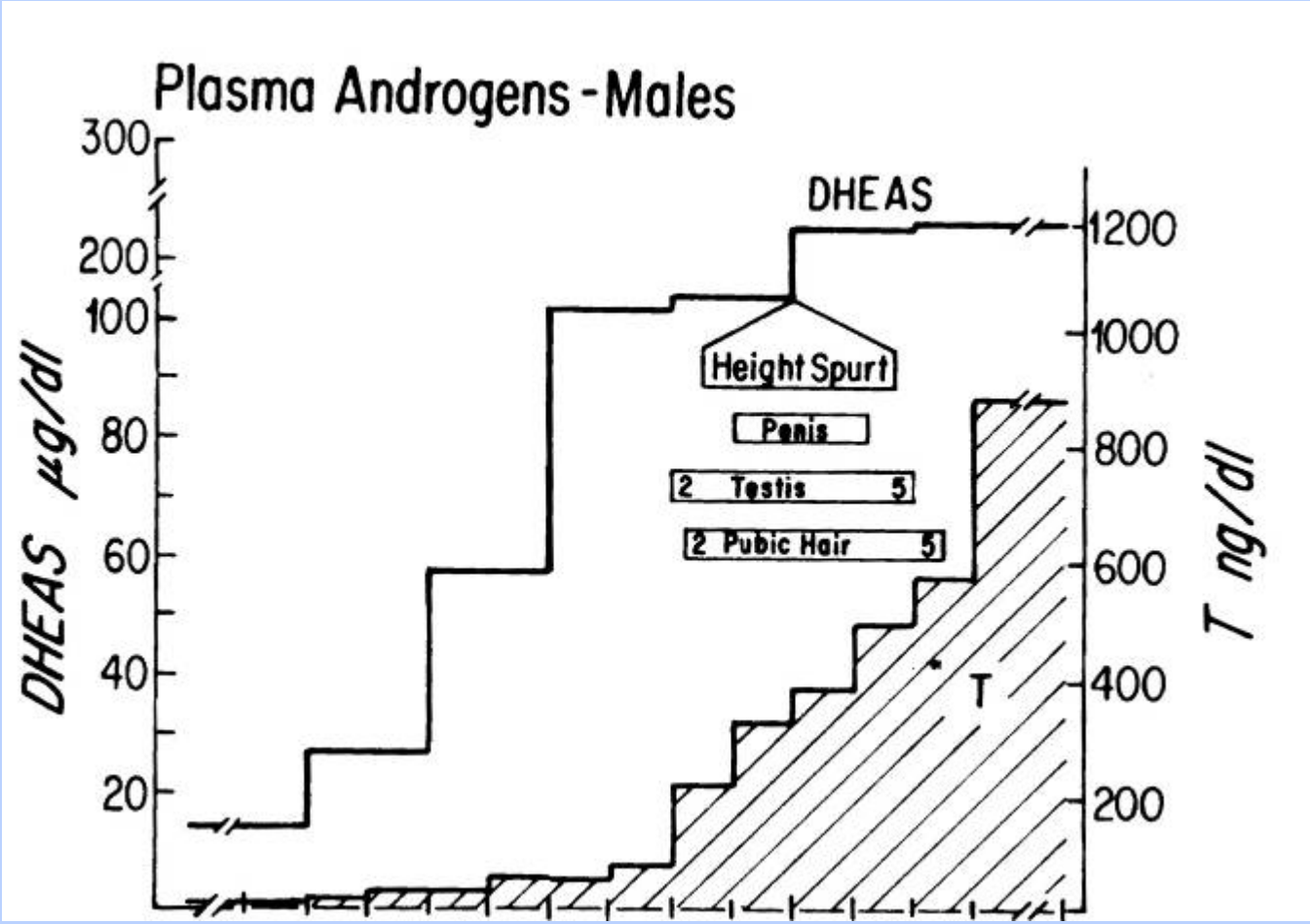
P1	**Prepubertal, testicular length less than 2.5cm**
P2	**Early increase in testicular size, scrotum slightly pigmented, few long and dark pubic hair**
P3	**Testicular length 3.3-4 cm, lenghtening of the penis, increase in pubic hair**
P4	**Testicular length 4.1-4.5cm, increase in length and thickening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

PUBERTY: MALE



From Sizonenko PC.

HORMONAL CHANGES



Grumbach MM et al.

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

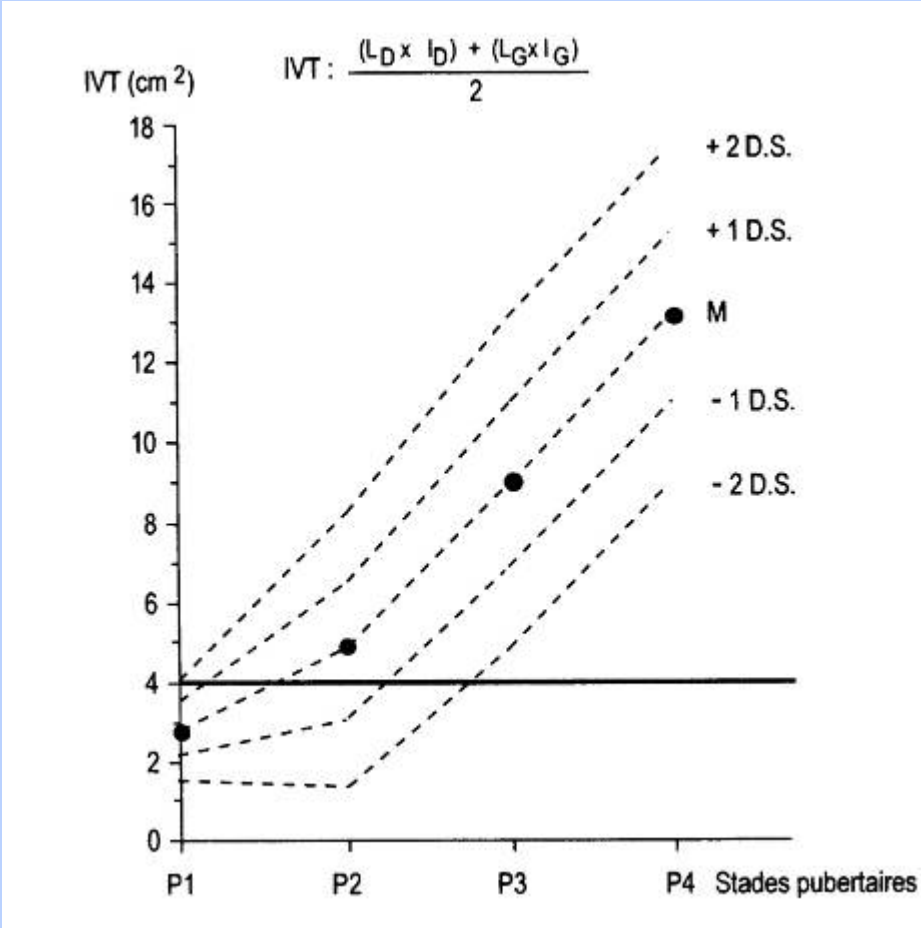
Secondary sexual development in boys:

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:

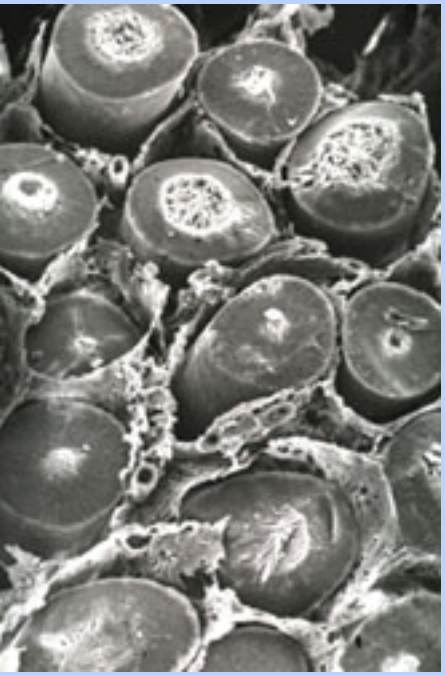
TESTICULAR GROWTH



Index of testicular volume

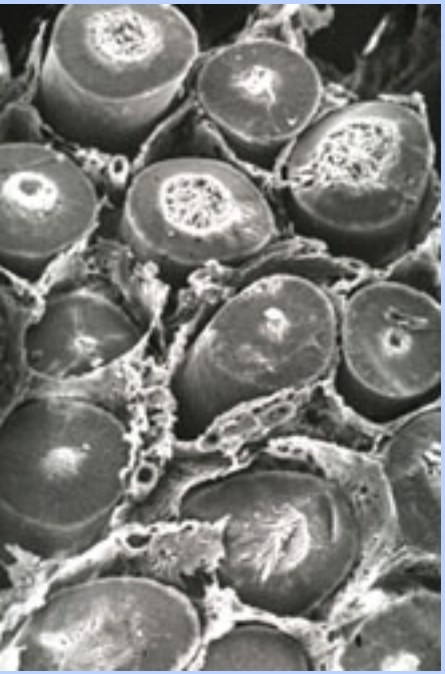
Burr IM, Sizonenko PC, Pediatr Res 1970

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

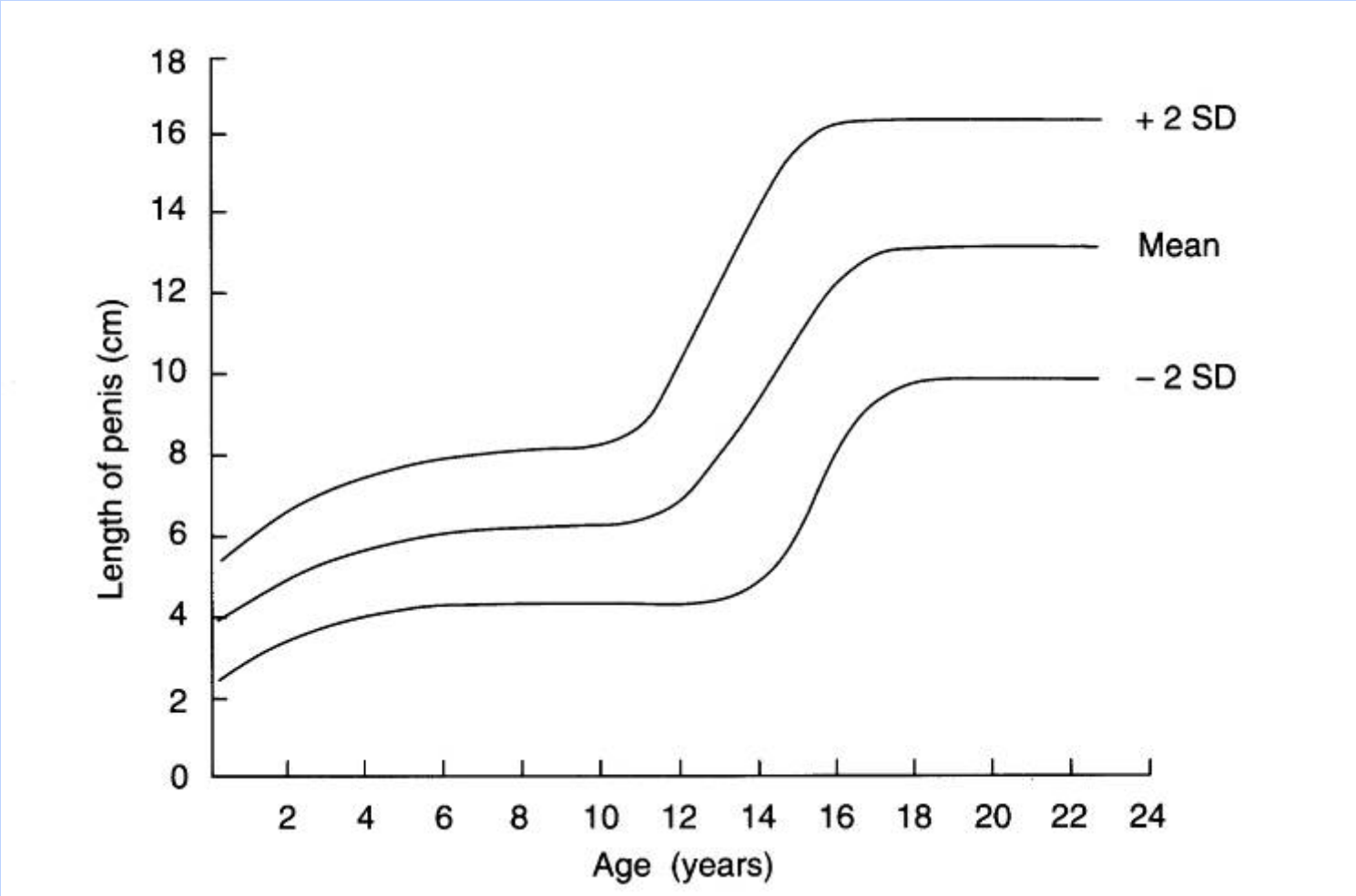


- **Long-standing pulsatile LH secretion induces the differentiation of interstitial cells into testosterone-secreting Leydig cells, which, in turn, exert a negative feedback control on LH secretion.**
- **As puberty progresses, spermato-genesis is initiated and then sustained by FSH and by testosterone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

TESTES DEVELOPMENT: 3

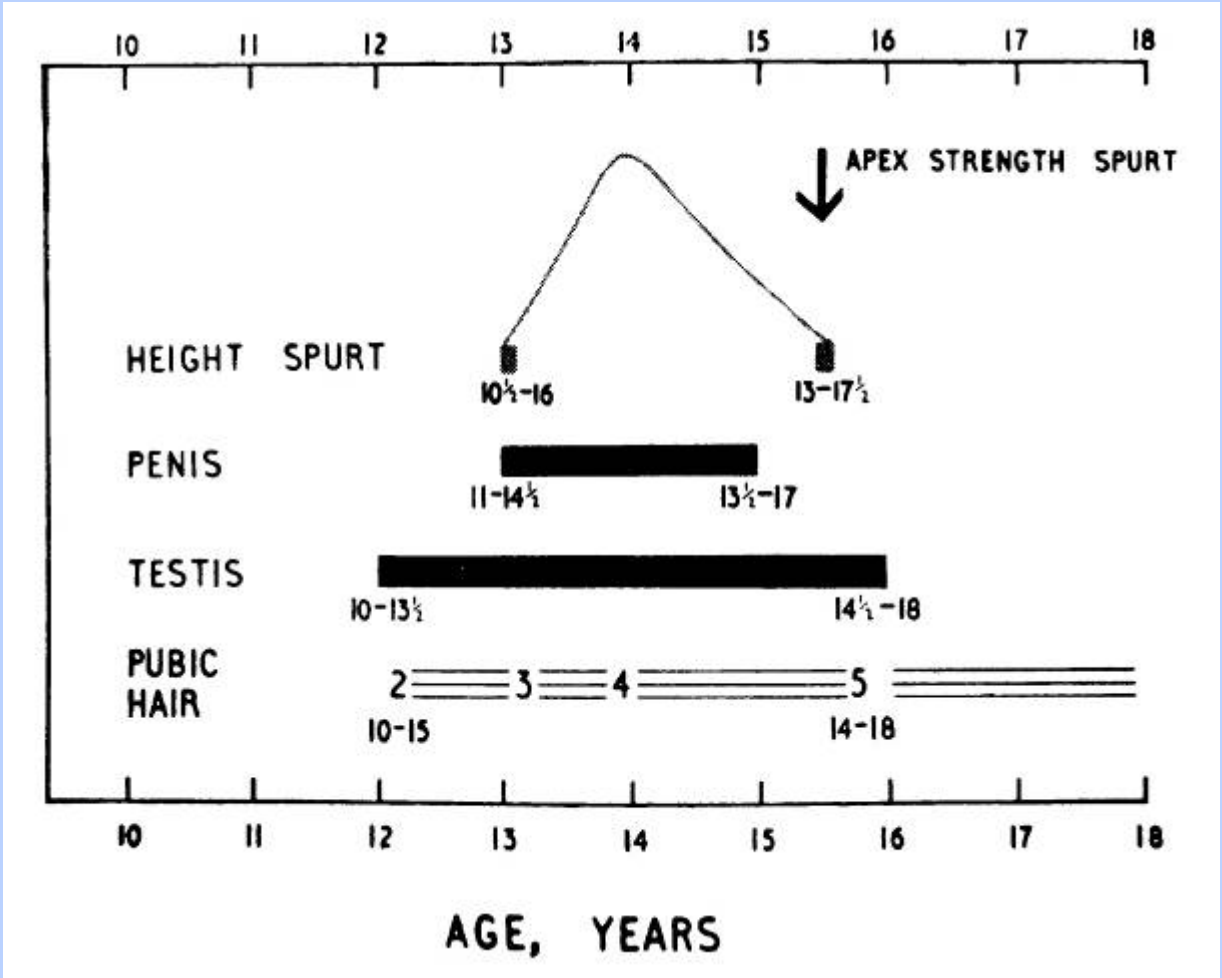
- A significant increase of plasma testosterone is found only between Tanner pubertal stages P3 and P4
- Dihydrotestosterone shows a pattern similar to that of testosterone, and the proportion of dihydrotestosterone to testosterone decreases gradually until adulthood, when dihydrotestosterone levels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

PENILE GROWTH



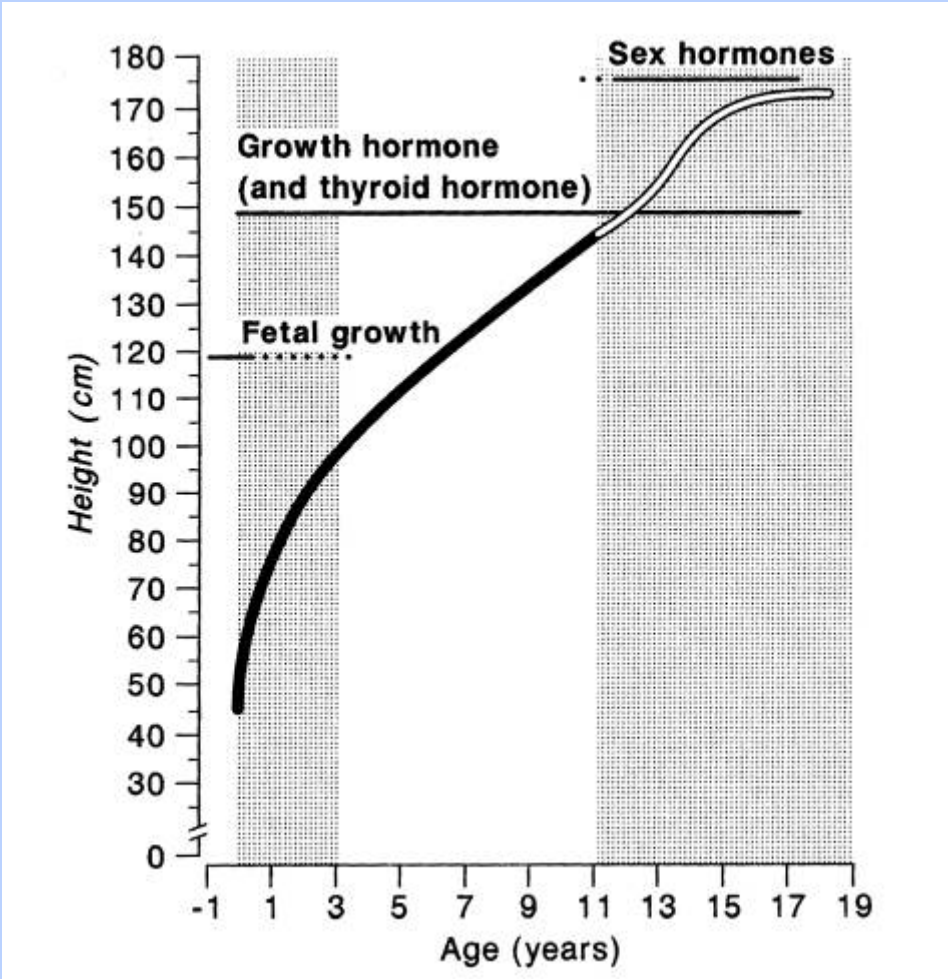
Schonfeld WA. Am J Dis Child 1943

SECONDARY SEX CHARACTERISTICS



Marshall WA, Tanner JM, ArchDis Child 1970

PUBERTAL GROWTH SPURT



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

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, and INSULIN 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.

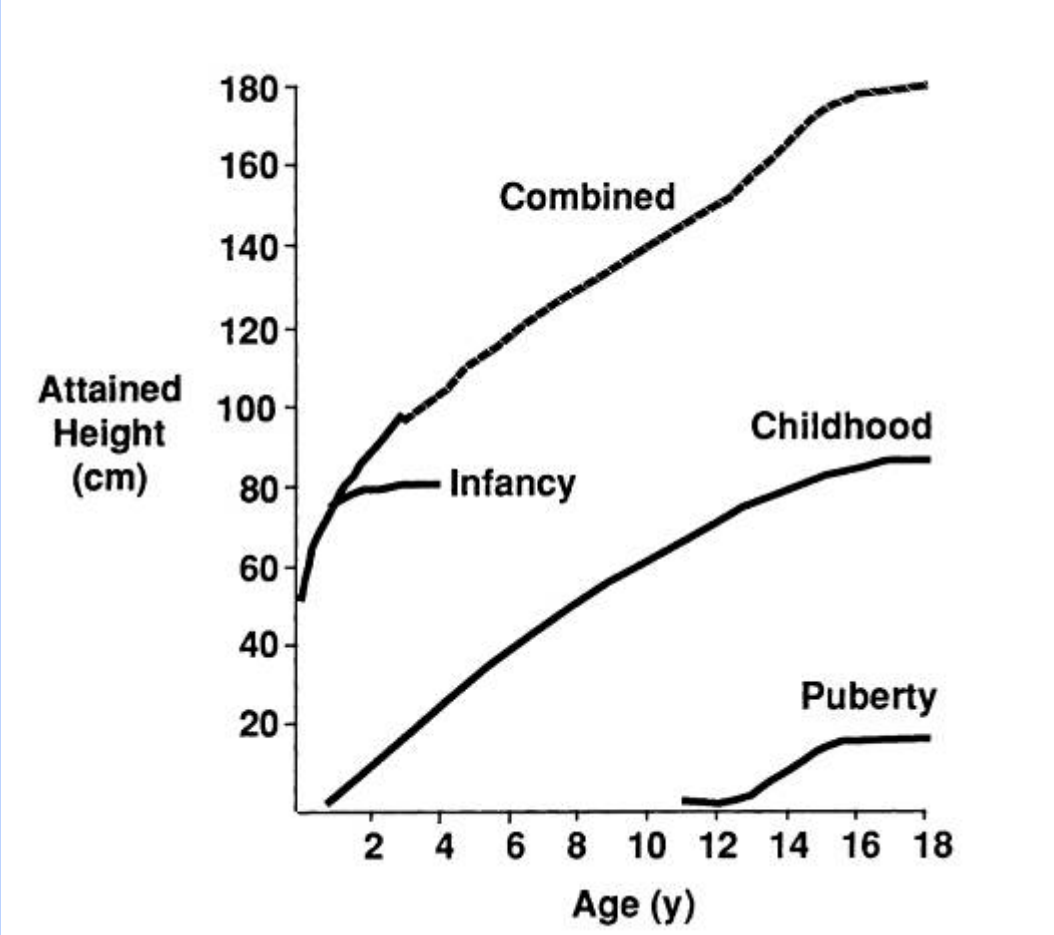
GH, IGF-I and INSULIN in PUBERTY

- **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

- **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**

PUBERTAL GROWTH SPURT



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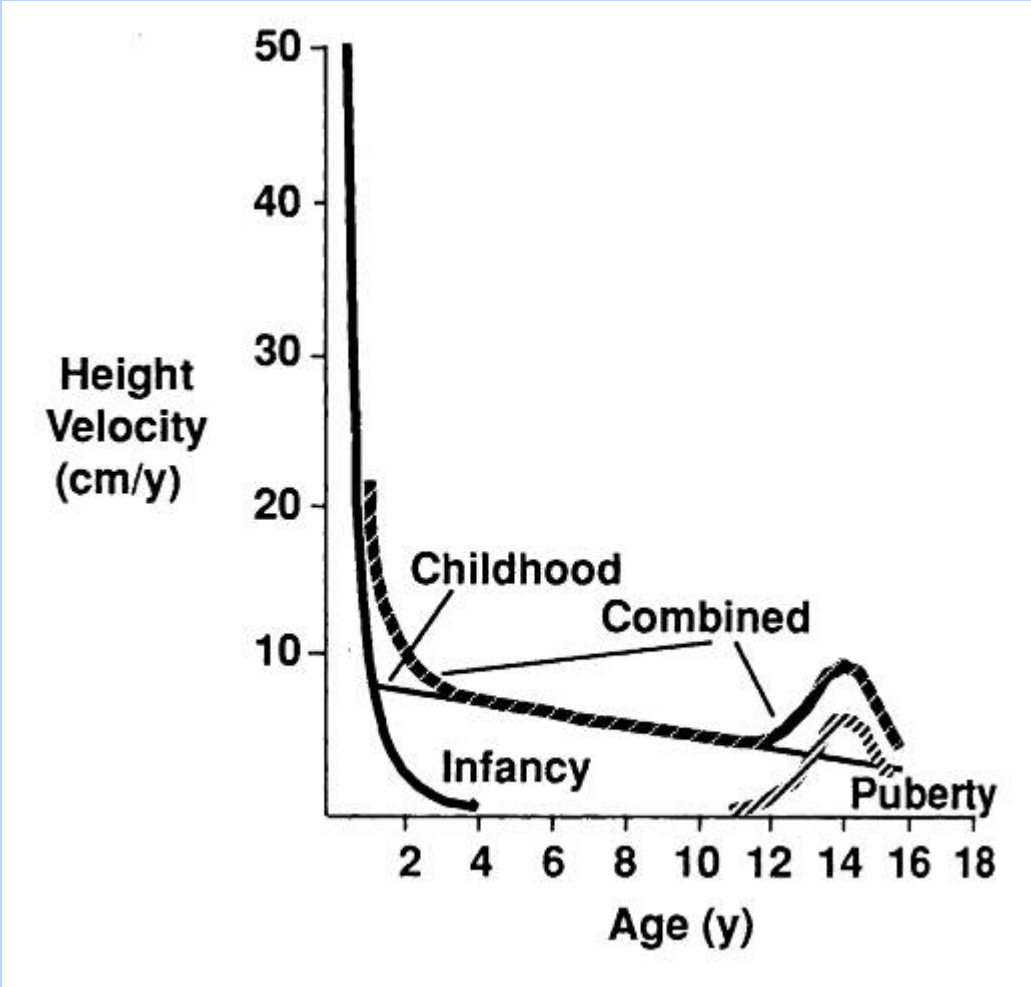
HEIGHT VELOCITY



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.

Greulich WW, Pyle SI, 1959

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

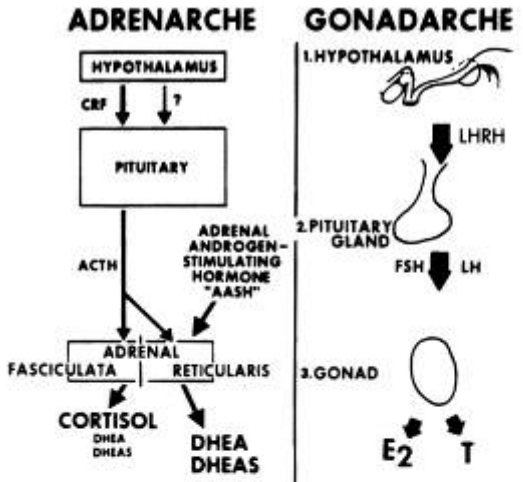
SUMMARY

	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)

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).

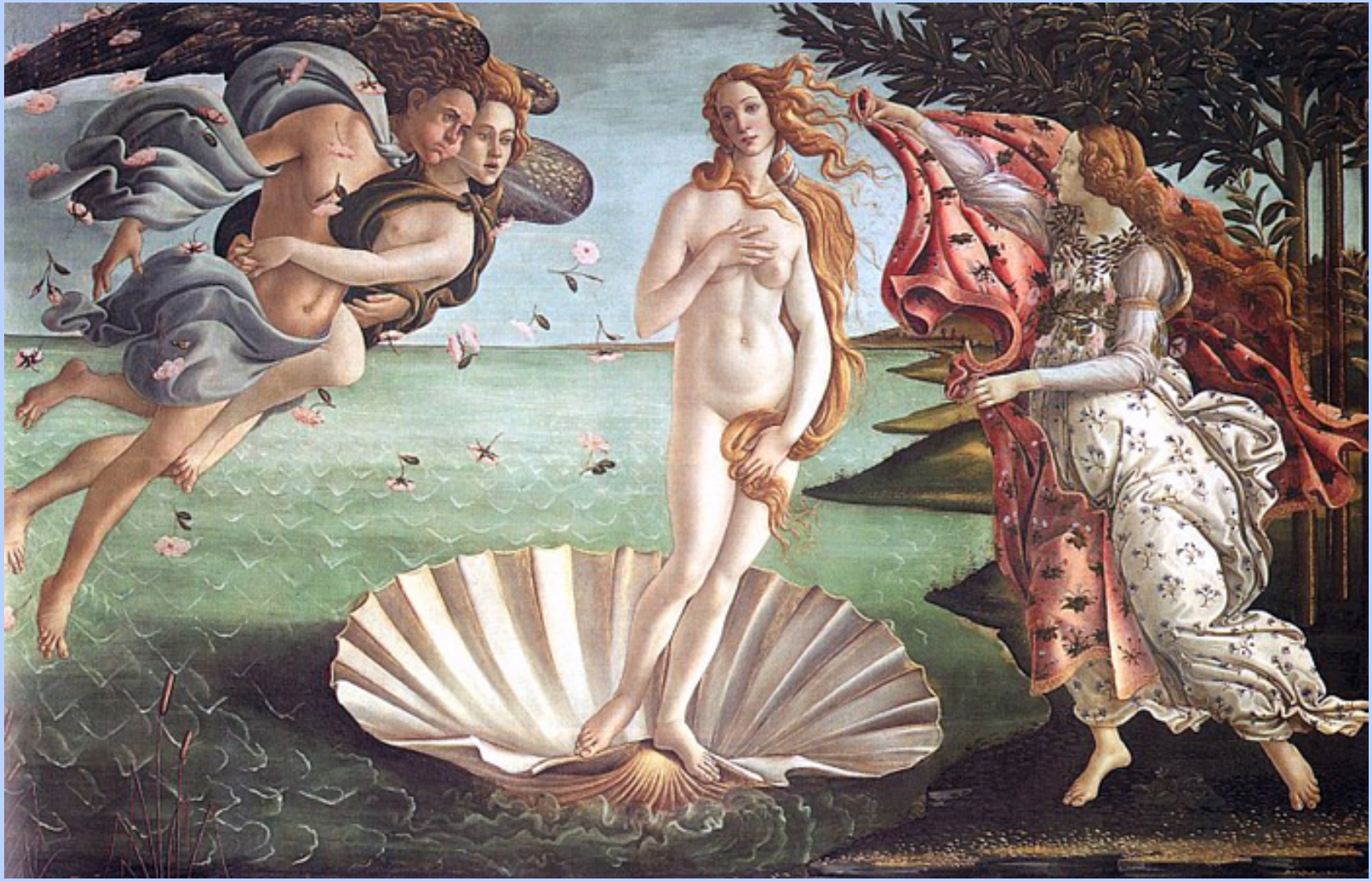
GONADARCHE-ADRENARCHE



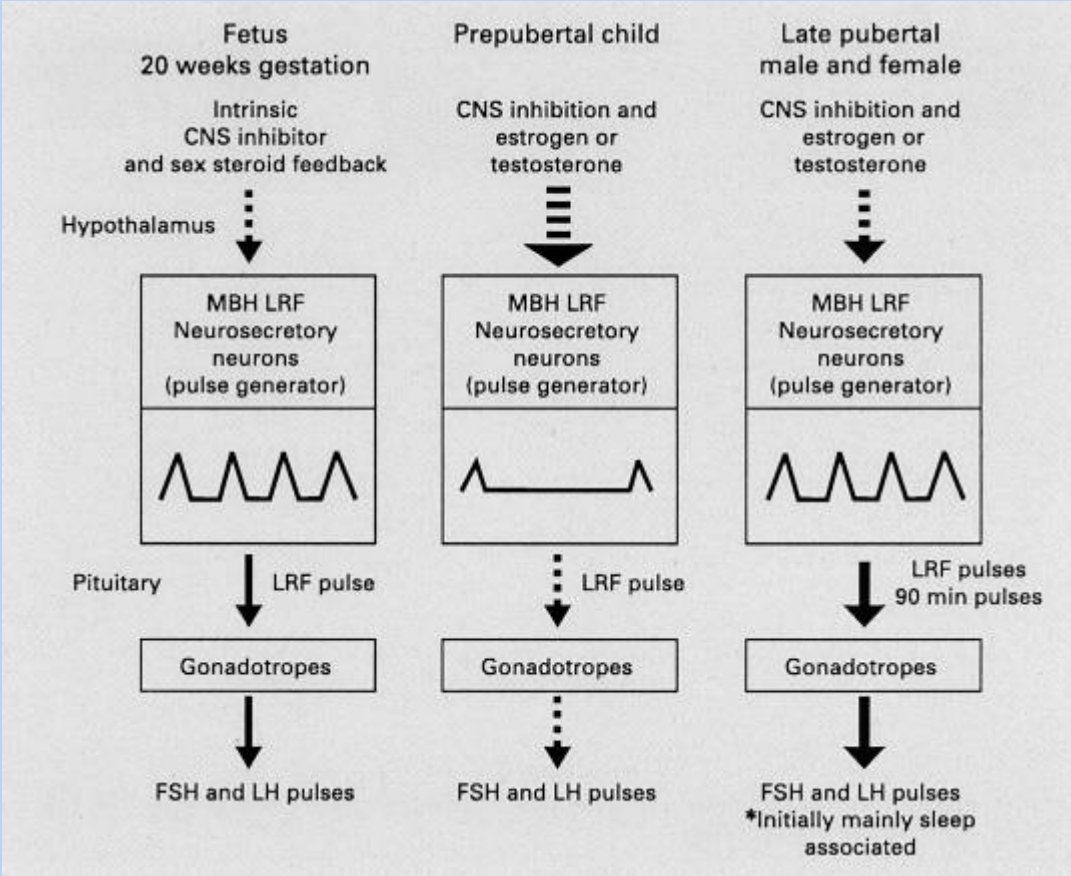
PREMATURE ADRENARCHE	+	−
PRIMARY ADRENAL INSUFFICIENCY	−	+
IDIOPATHIC PRECOCIOUS PUBERTY (ONSET < 6 YRS)	−	+
IDIOPATHIC PRECOCIOUS PUBERTY (ONSET > 6 YRS)	+	+
SYNDROME GONADAL DYSGENESIS	+	−
ISOLATED GONADOTROPIN DEFICIENCY	+	−
CONSTITUTIONAL DELAYED ADOLESCENCE	−	−

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

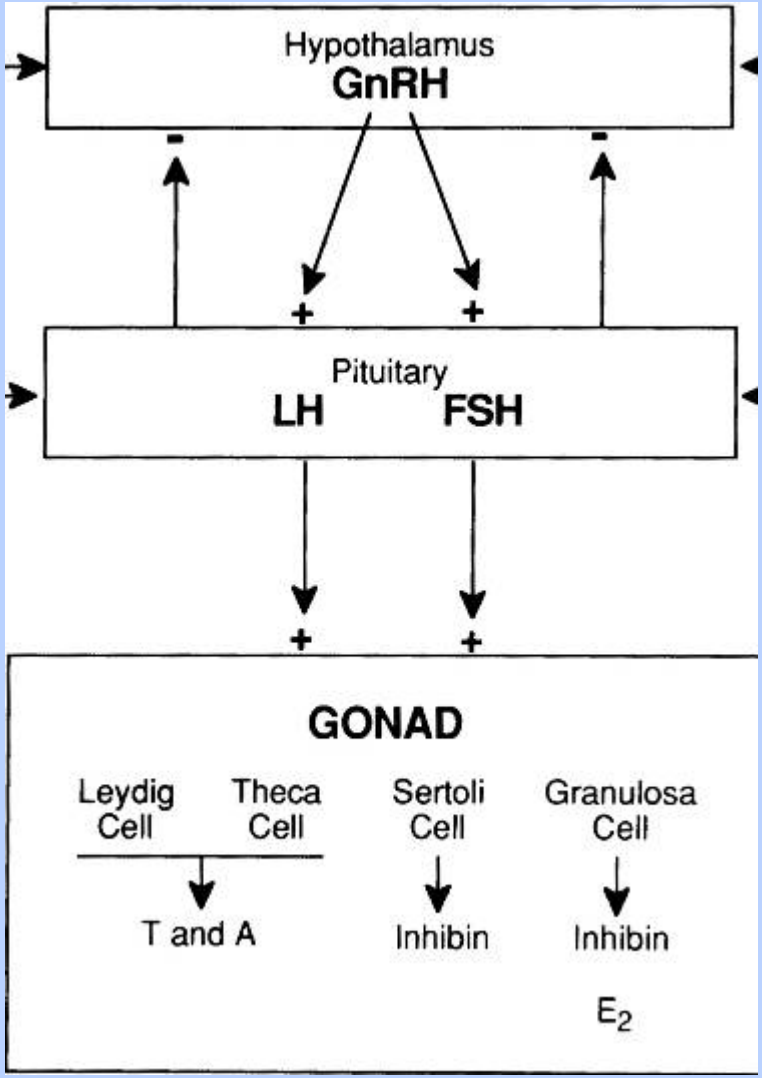
PUBERTY



PUBERTY


Fetus
20 weeks gestation
Intrinsic
CNS inhibitor
and sex steroid feedback
Hypothalamus
MBH LRF
Neurosecretory
neurons
(pulse generator)
Pituitary
LRF pulse
Gonadotropes
FSH and LH pulses
Prepubertal child
CNS inhibition and
estrogen or
testosterone
MBH LRF
Neurosecretory
neurons
(pulse generator)
LRF pulse
Gonadotropes
FSH and LH pulses
Late pubertal
male and female
CNS inhibition and
estrogen or
testosterone
MBH LRF
Neurosecretory
neurons
(pulse generator)
LRF pulses
90 min pulses
Gonadotropes
FSH and LH pulses
*Initially mainly sleep
associated

HYPOTHALAMO-PITUITARY-GONADAL AXIS



MacGilliwray MH, Endocrinology and Metabolism, 1995.

STEROIDOGENESIS