MODENA 23 -03- 2011

ENDOCRINOLOGIA:

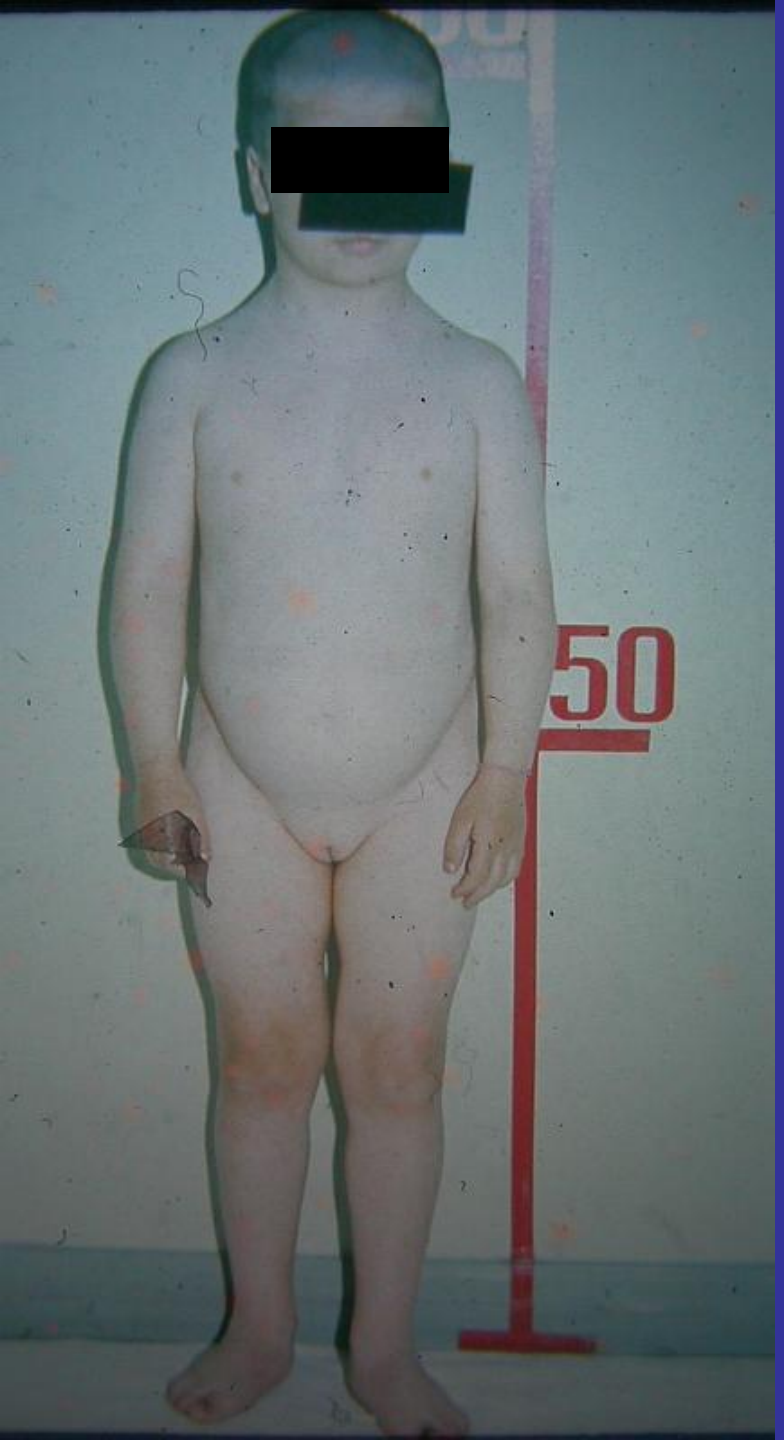
UNA VENTATA DI GIOVINEZZA NELLA MEDICINA

Scoperta della Luna: 20 luglio 1969

Sigla o simbolo	Nome	Valore decimale	Fattore moltiplicativo
G	Grammo	1	
Mg	milligrammo	0,001 (un millesimo di grammo)	10^{-3} grammi
mcg o mg	microgrammo	0,000001 (un milionesimo di grammo)	10^{-6} grammi
Ng	nanogrammo	0,000000001 (un miliardesimo di grammo)	10^{-9} grammi
Pg	picogrammo	0,000000000001 g	10^{-12} grammi
Fg	fentogrammo	0,000000000000001 g	10^{-15} grammi
Ag	attogrammo	0,000000000000000001 g	10^{-18} grammi

PATOLOGIE TIROIDEE

Da “Madonna della pappa” Mazzoni

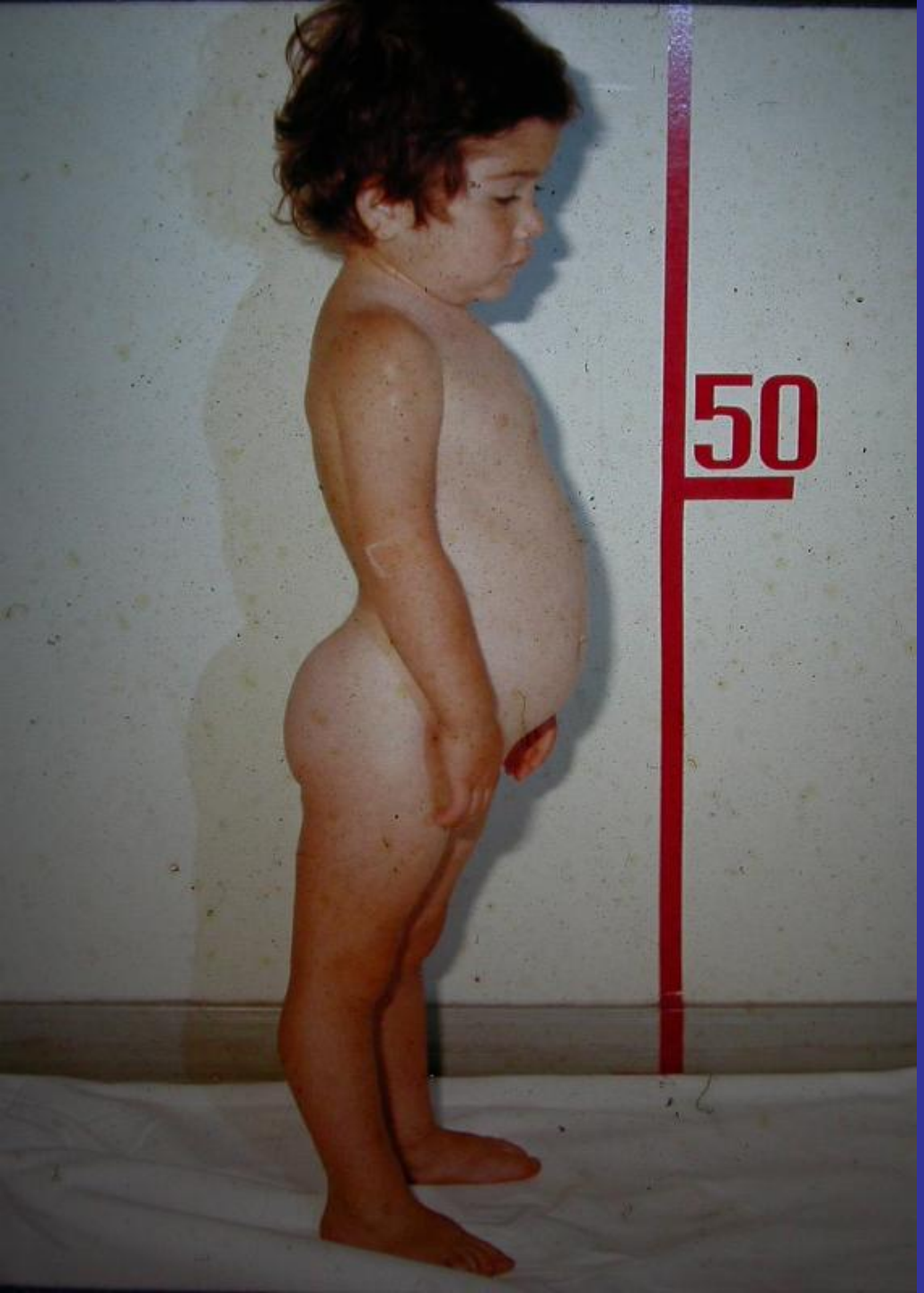


Cretinismo da ipotiroidismo congenito

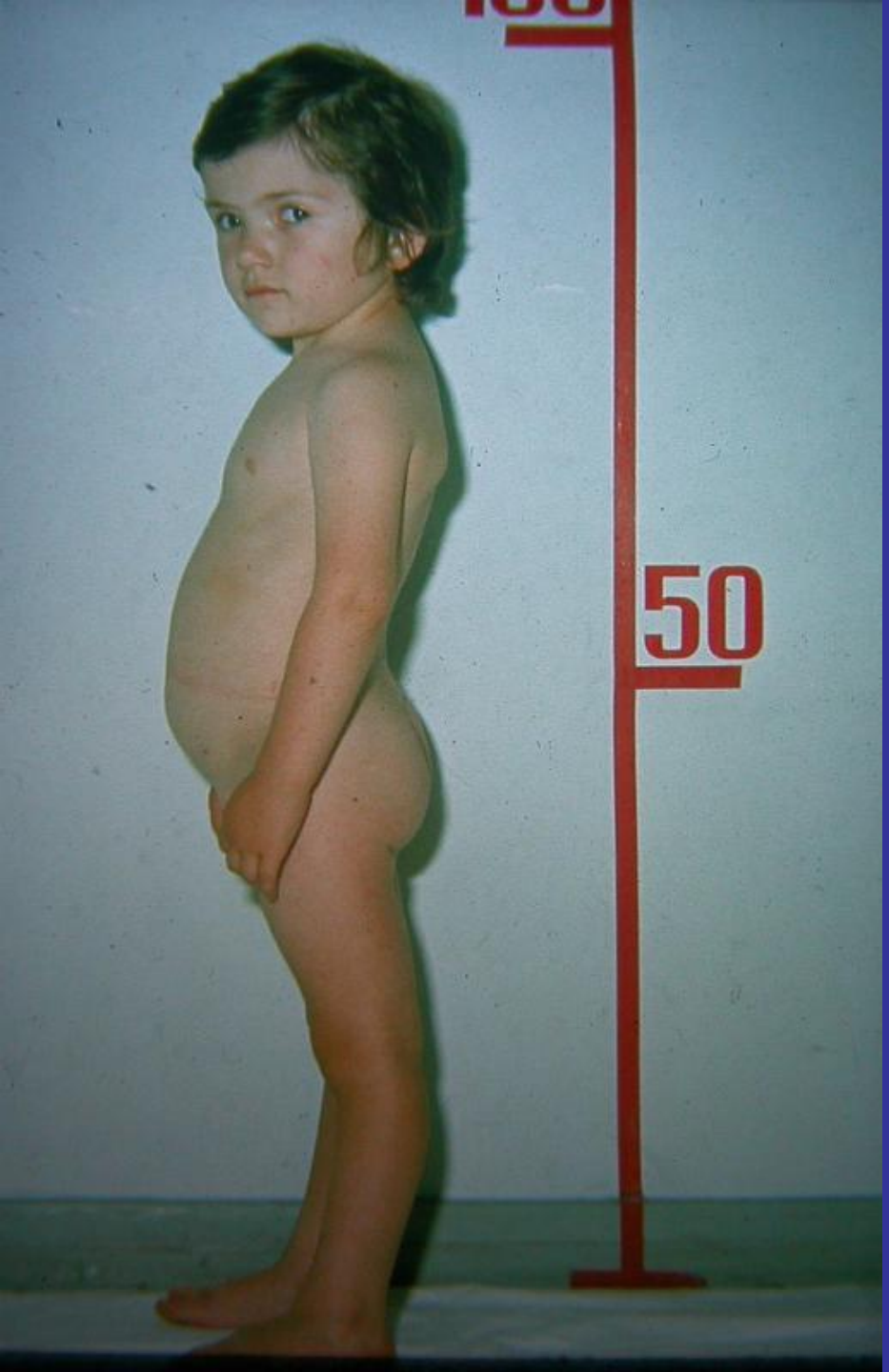
A.A: Anni18, cm 112

- **Legge 5 febbraio 1992, n. 104** disciplina *"nel periodo neonatale, gli accertamenti utili alla diagnosi precoce delle malformazioni e l'obbligatorietà del controllo per l'individuazione ed il tempestivo trattamento dell'ipotiroidismo congenito"*

- **dosaggio di TSH ed fT4 su siero prelevato da cordone ombelicale del neonato**



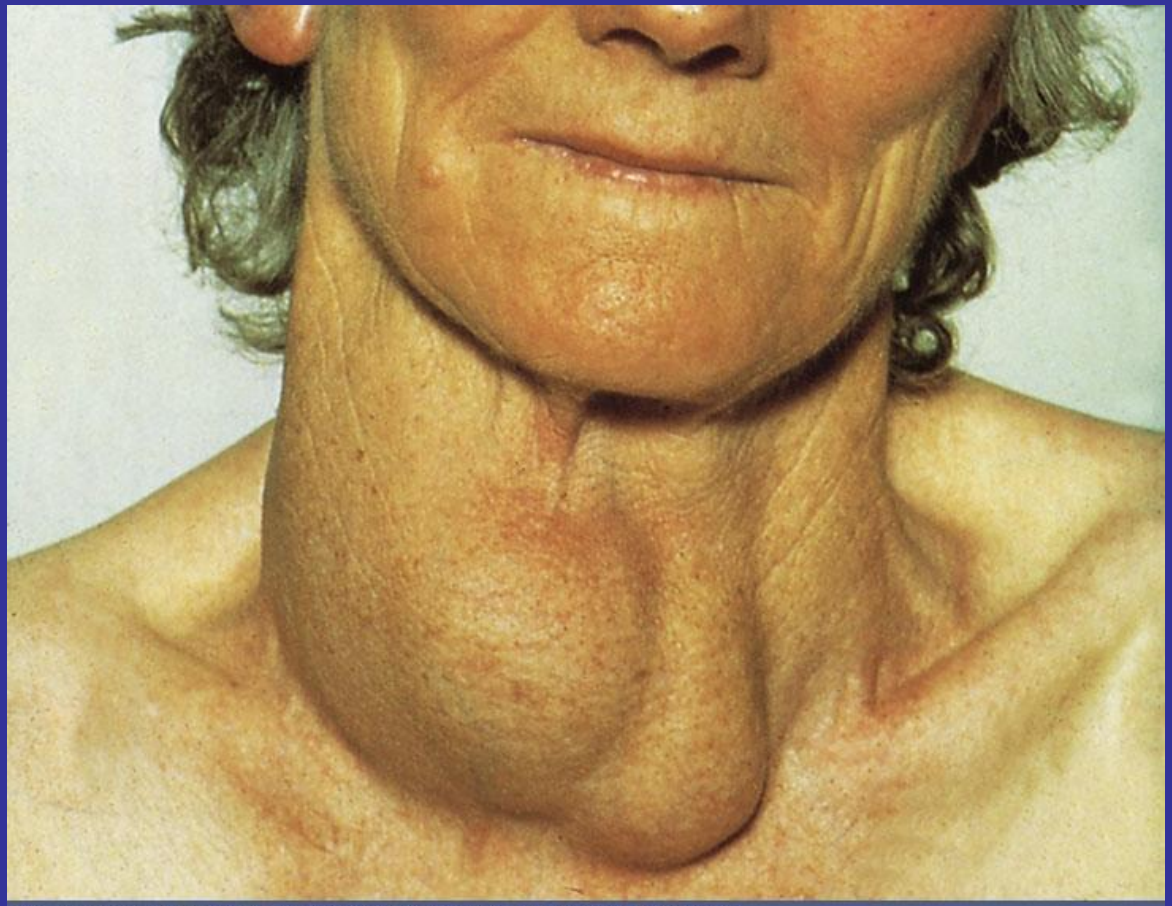
Ipotiroidismo Congenito



Ipotiroidismo Congenito in terapia tiroxinica

Pere Borrel del Caso, 1874

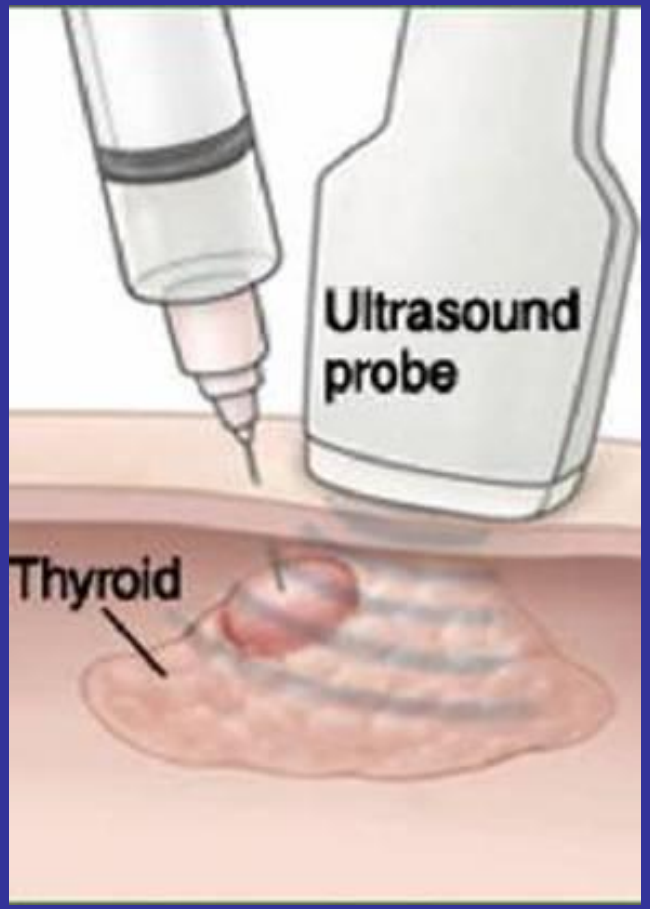
Madonna con bambino addormentato, Mantegna



Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
Elsevier Science Ltd

Agoaspirato tiroideo ecoguidato (FNA)

- Nodulo con diametro ≥ 1 cm
- Nodulo con diametro ≥ 5 mm con caratteristiche ecografiche sospette
- Pazienti a rischio: MEN, familiarità per k tiroideo, irradiazione del collo



Revised American Thyroid Association management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid cancer. Thyroid volume 19, Number 11,2009.

Analisi gene BRAF
Diagnosi precoce del carcinoma papillare della tiroide

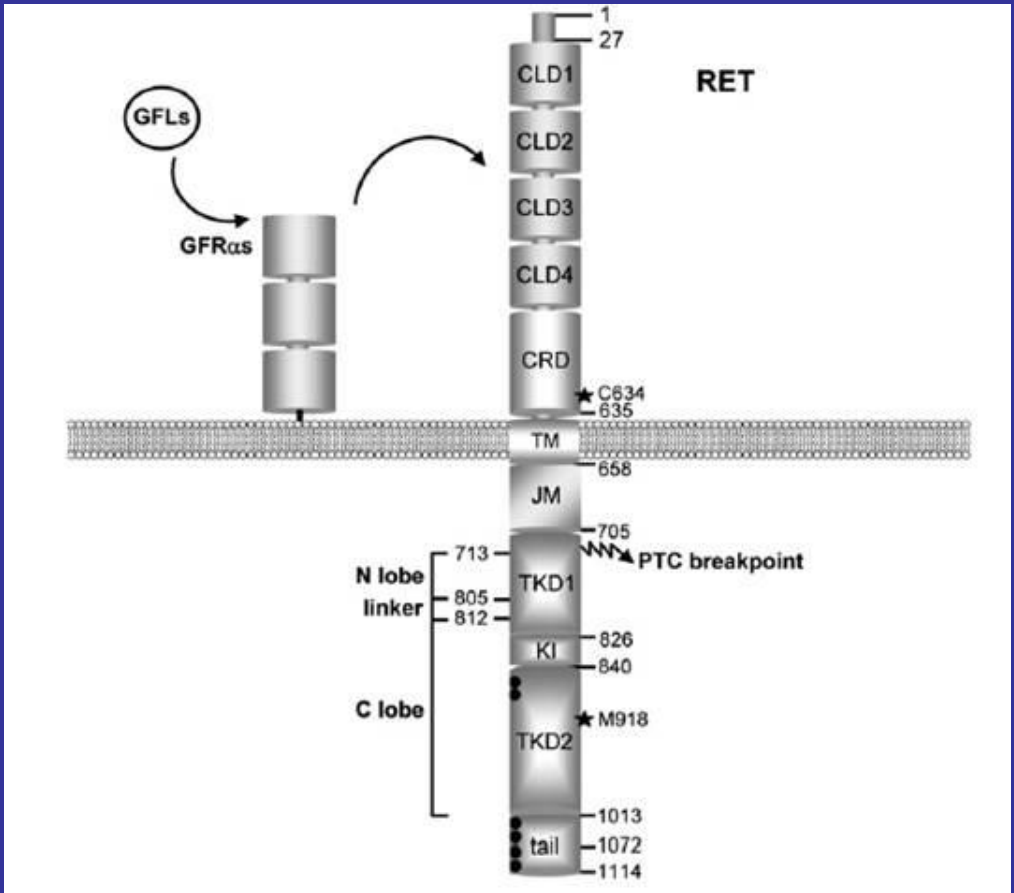
Mutazione con prevalenza variabile dal 30 al 83% nei carcinomi papillari (PTCs)

Mutazione associata a fenotipo aggressivo: invasione extra-tiroidea, metastasi linfonodali, stadio avanzato (III/IV)

Associazione citologia tiroidea + analisi molecolare di BRAF incrementa l'accuratezza diagnostica per PTCs dal 60 % all'80 %

Kam-Tsun Tang et al., BRAF mutation in papillary thyroid carcinoma: pathogenic role and clinical implication. J Chin Med Assoc 2010: 10;113 -128

Analisi gene RET
Diagnosi genetica del carcinoma midollare della tiroide



Schema della proteina RET, con evidenza del punto di rottura responsabile della successiva formazione dei riarrangiamenti RET/PTC

(Endocrinol Metab Clin N Am, 2008;37:363-374)

NANISMI

Evoluzione staturale

Uomo preistorico	164 cm
Mummia egiziana	167 cm
Soldato napoleonico	165 cm
Coscritti italiani	
1880	164 cm
1970	171 cm
2000	175 cm

ACCRESCIMENTO PROGRESSIVO DELLA SPECIE UMANA

In 100 anni le ragazze hanno anticipato il menarca di 4 anni

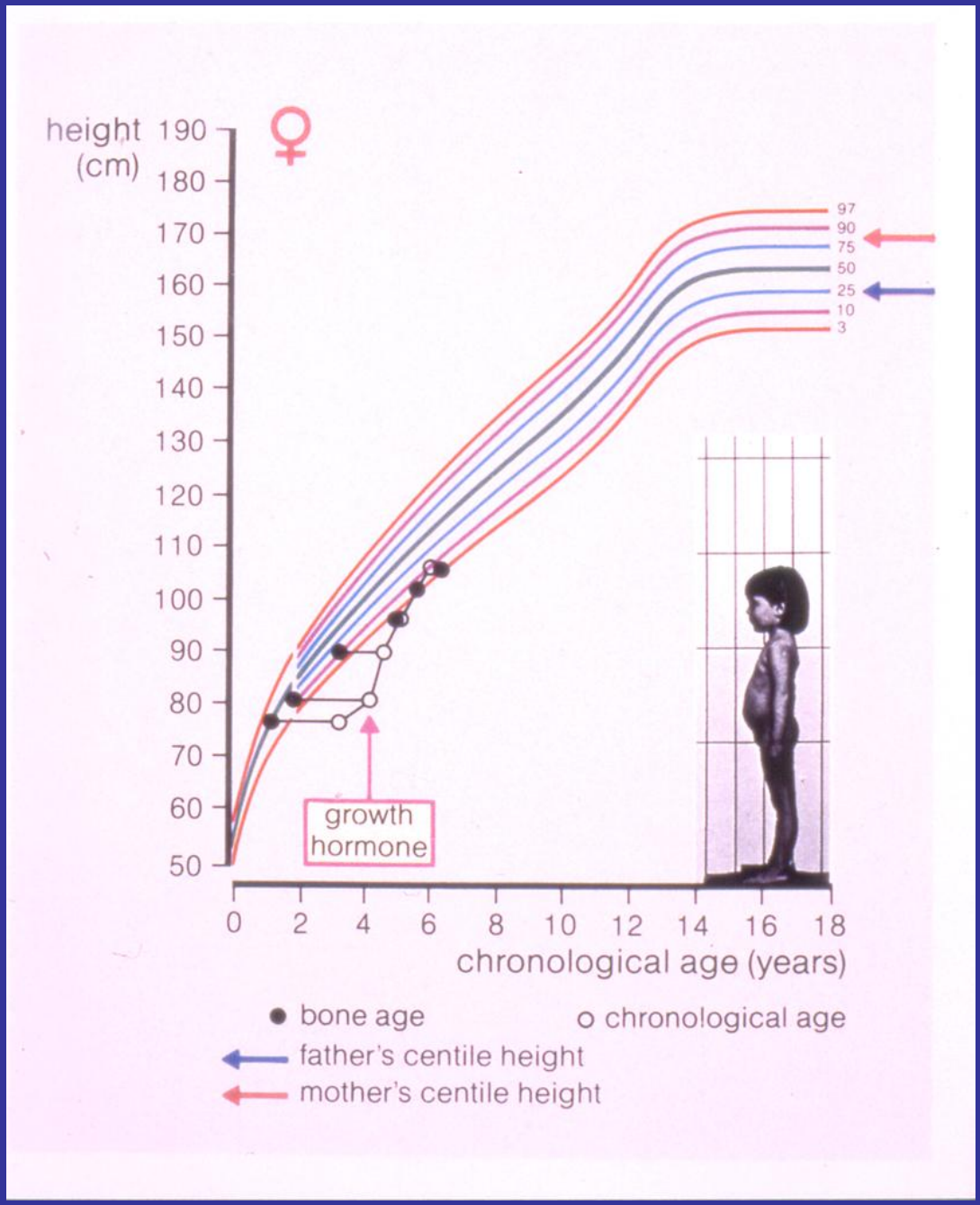
16 anni → 12 anni

Differential diagnoses by short stature

- Constitutional Growth Delay
- Family Short Stature
- Combination of the previous
- Nutritional
  - Hypocaloric
  - Chronic inflamatory bowel disease
  - Malabsorption , Coeliac disease
- Metabolic
  - Kidney failure, Liver diseases
  - Hypoxic, Cardiac
- Endocrine
  - Hypothyroidism
  - Growth Hormone Deficiency
  - Hypopituitarism
  - Excessive cortisol
  - Precosious puberty
- Maternal deprivation
- Low birth weight
  - Small for gestagional age
  - Prematurity
  - Fetal alcohol syndrome
- Bone development disorders
  - Rickets
  - Skeletal dysplasias
- Chromosome defects
  - Turner Syndrome
  - Genetic Syndromes

Deficit di GH

R.A. anni 19, cm 135


height (cm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
97
90
75
50
25
10
3
growth hormone
0
2
4
6
8
10
12
14
16
18
chronological age (years)
bone age
chronological age
father's centile height
mother's centile height

NANISMI IPOFISARI

- **Terapia con GH ricombinante**

Iniezioni s.c. giornaliere

- Iniettori a penna
- Siringhe predosate
- Sistemi di autoiniezione

Dose: 0.033 mg/kg/gg (0.1 U/kg/gg)

- **Analoghi Grhelina**

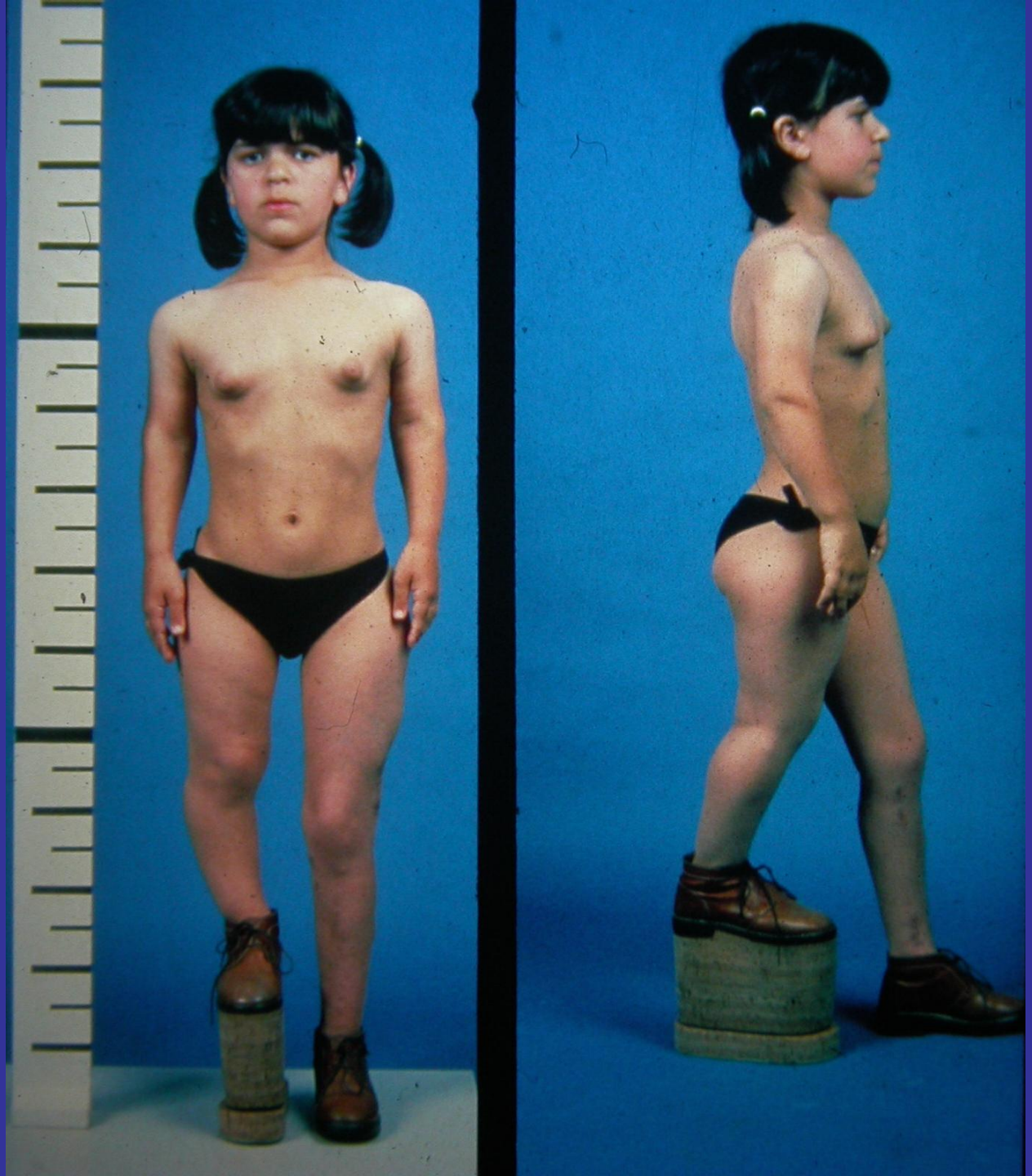
GH secretagoghi, efficacia non provata

Nanismo da Pubertà precoce vera idiopatica

6 anni e 7 mesi, cm 128

NANISMO ACONDROPLASICO

Mantegna, Camera degli Sposi, Palazzo Ducale, Mantova



IPOGONADISMO

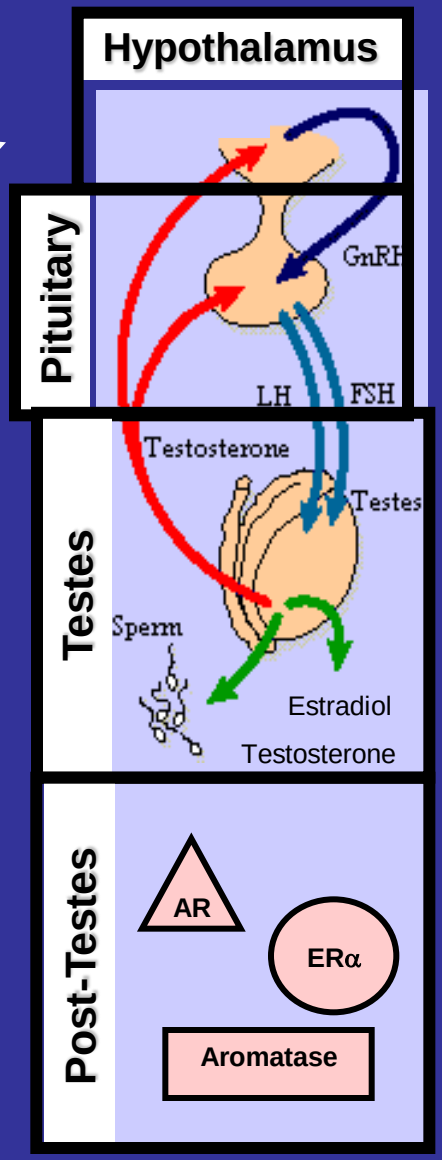
Eros Farnese, Napoli

IPOGONADISMO

- Difetti ipotalamici e/o ipofisari

- Difetti dei testicoli

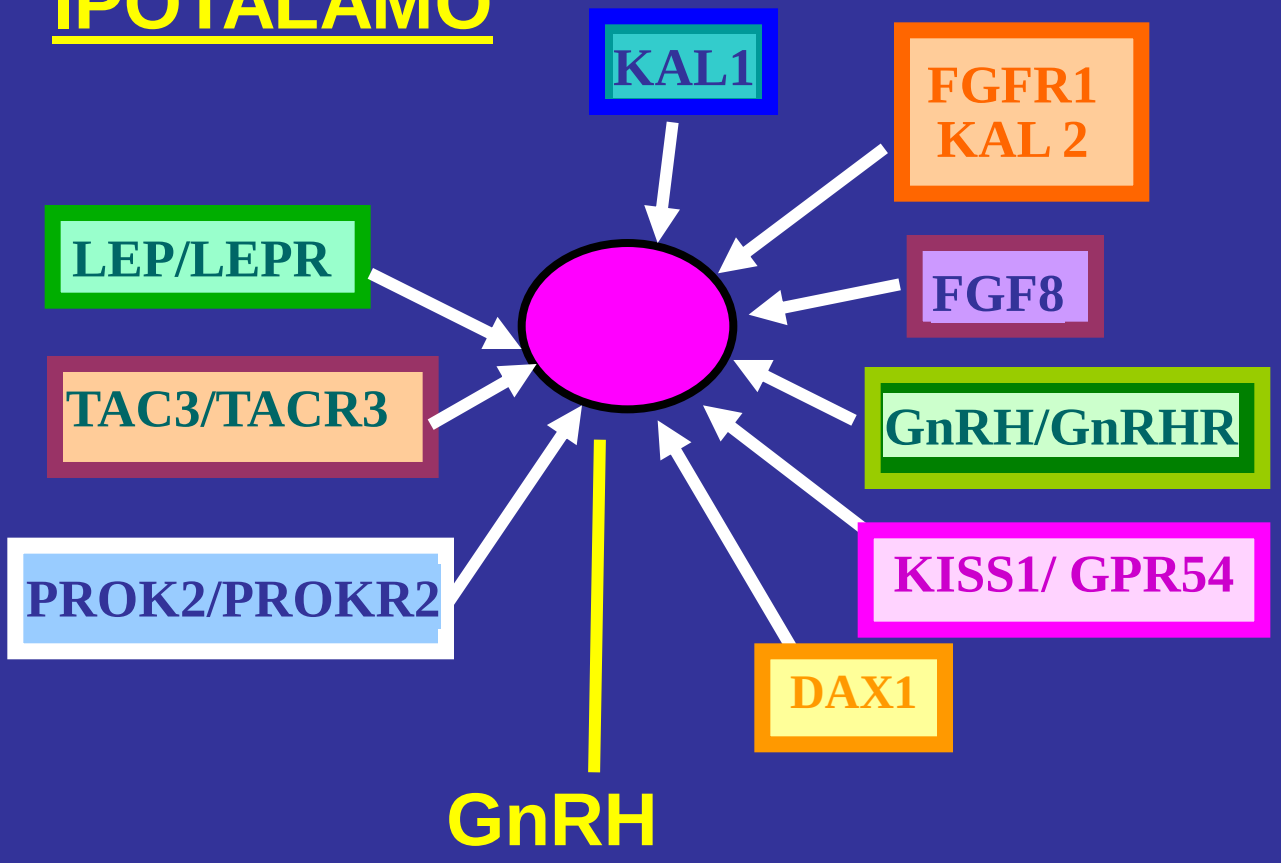
- Difetti nella risposta al testosterone



IPOGONADISMO IPOGONADOTROPO

IPOGONADISMO GENETICO

IPOTALAMO

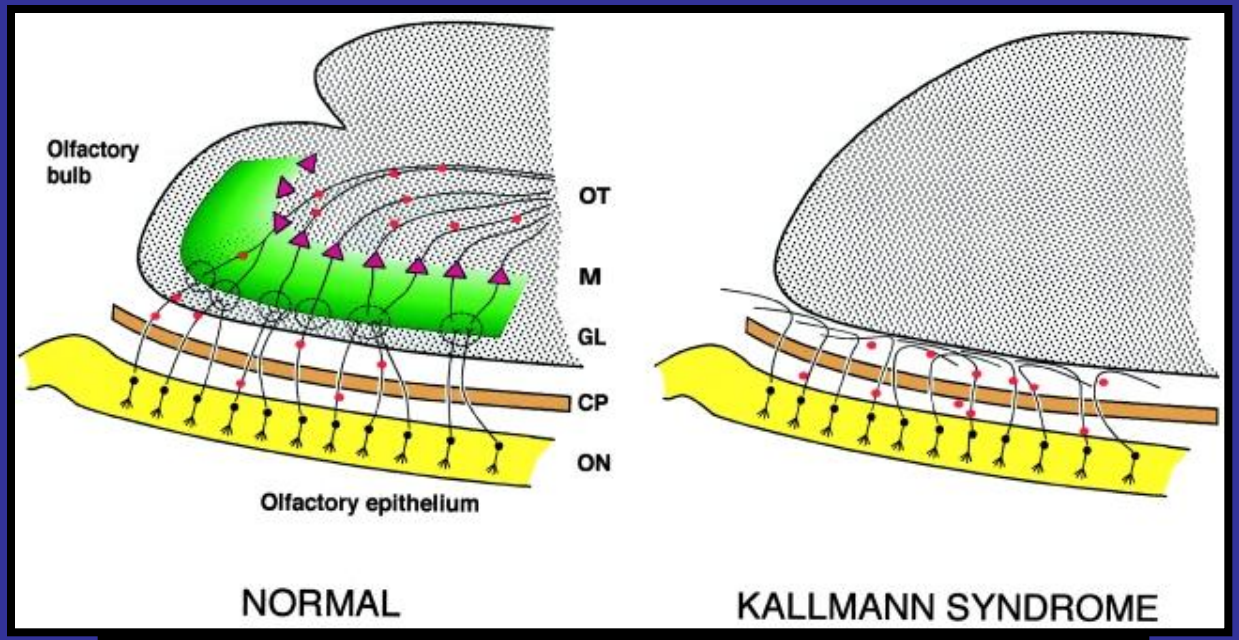


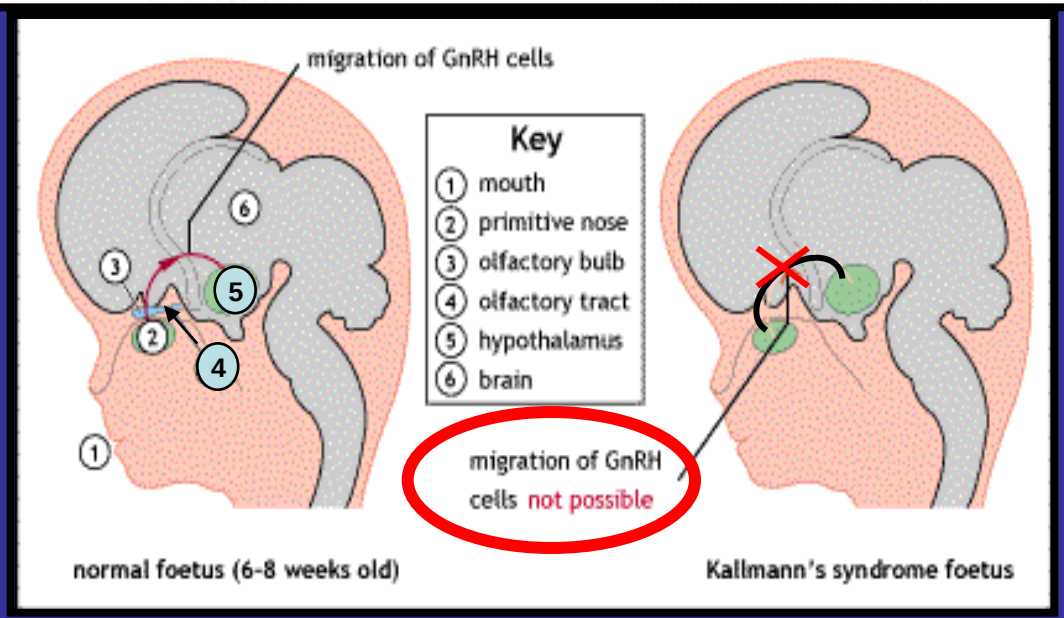
Ipogonadismo e anosmia

Kallmann Syndrome

Model for KALLMAN SYNDROME pathogenesis

Failure of the GnRH secreting neurons to migrate from the olfactory epithelium to their final destination in the mediobasal hypothalamus





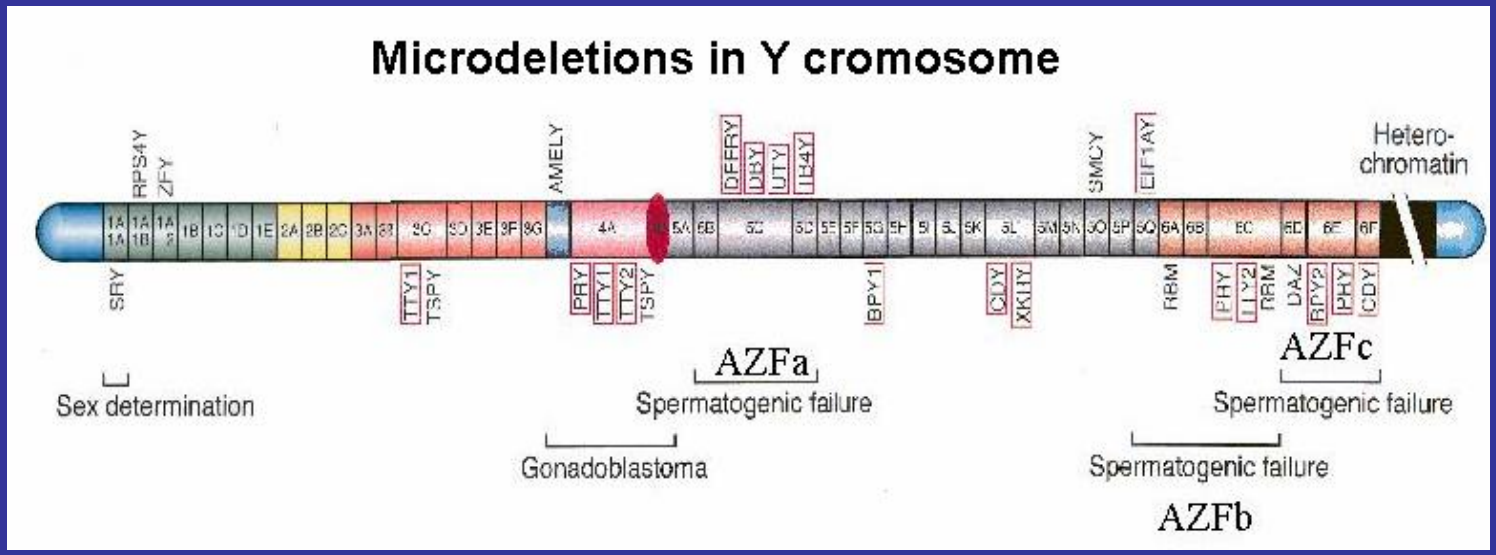
IPOGONADISMO IPERGONADOTROPO

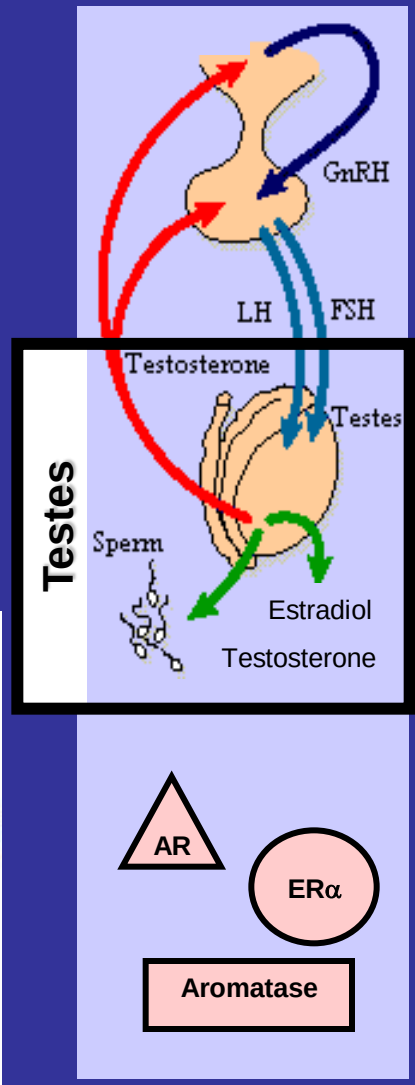
- **Congenito**
  - Sindrome di Klinefelter
  - Criptorchidismo
  - Altre cause (genetiche,…)
- **Acquisito**
  - Varicocele
  - Traumi
  - Radiazioni
  - Chemioterapia e farmaci
  - Patologie croniche

IPOGONADISMO IPERGONADOTROPO

Con virilizzazione normale

- **Mutazione AZF del cromosoma Y**
- **Circa il 3%- 6% degli uomini azoospermici/ severamente oligozoospermici con infertilità idiopatica hanno microdelezioni Yq .**





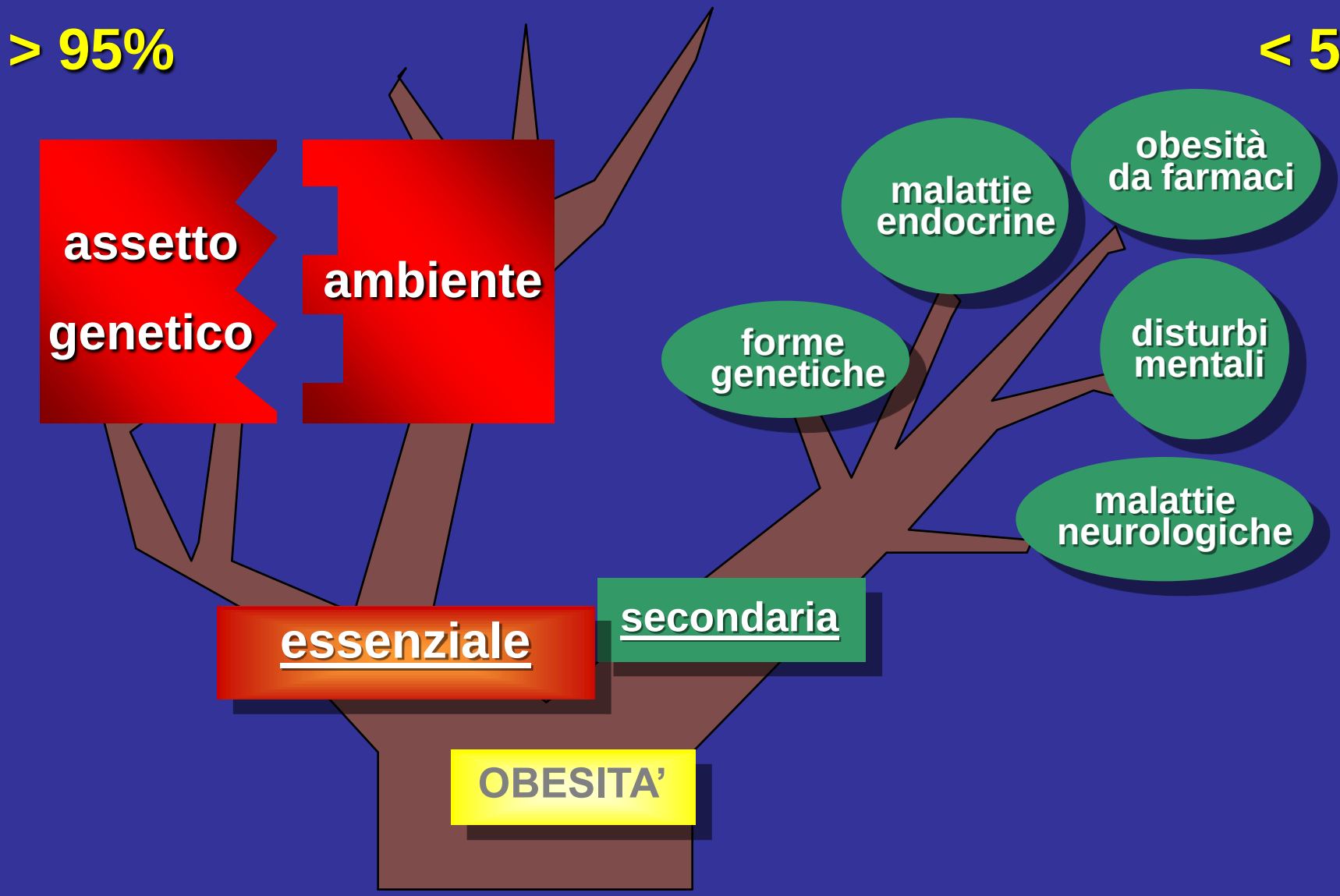
OBESITA’

Botero

Obesità in Italia

Ultimo aggiornamento del giugno 2006. Dati ISS (progetto cuore)

Cause di obesità



L’obesita’ essenziale di per se’ non è una malattia

In passato **condizione protettiva nei confronti di:**

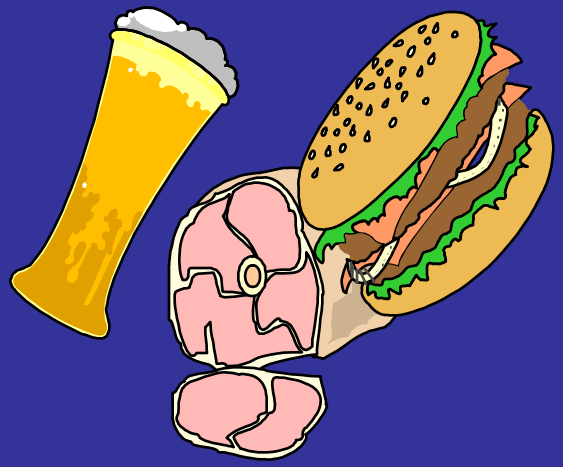
- **Epidemie**
- **Carestie**
- **Malattie carenziali**
- **Malattie intercorrenti**

Oggi **condizione favorente nei confronti di:**

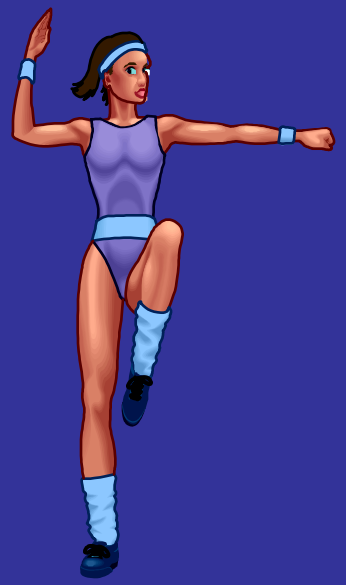
- **Malattie cardiovascolari**
- **Malattie metaboliche**
- **Malattie osteoarticolari**

Fisiologia dell'aumento di peso

Input energetico



Output energetico



Fattori di controllo

Fattori genetici
Dieta

Esercizio
Metabolismo basale
Termogenesi

Terapia dell'obesità

- **Modificazione dello stile di vita**
  -Restrizione calorica
  -Aumento dell'attività fisica

- **Supporto farmacologico**

- **Approccio Chirurgico**

  Riservato a pazienti con BMI $\geq$ 35 (Kg/m2) e due o più fattori di rischio, oppure con BMI superiore a 40 (Kg/m2) che hanno tentato senza successo di perdere peso per 6 mesi

MAGREZZA

Giacometti, Grande femme III

DISTURBI DEL COMPORTAMENTO ALIMENTARE

In Italia

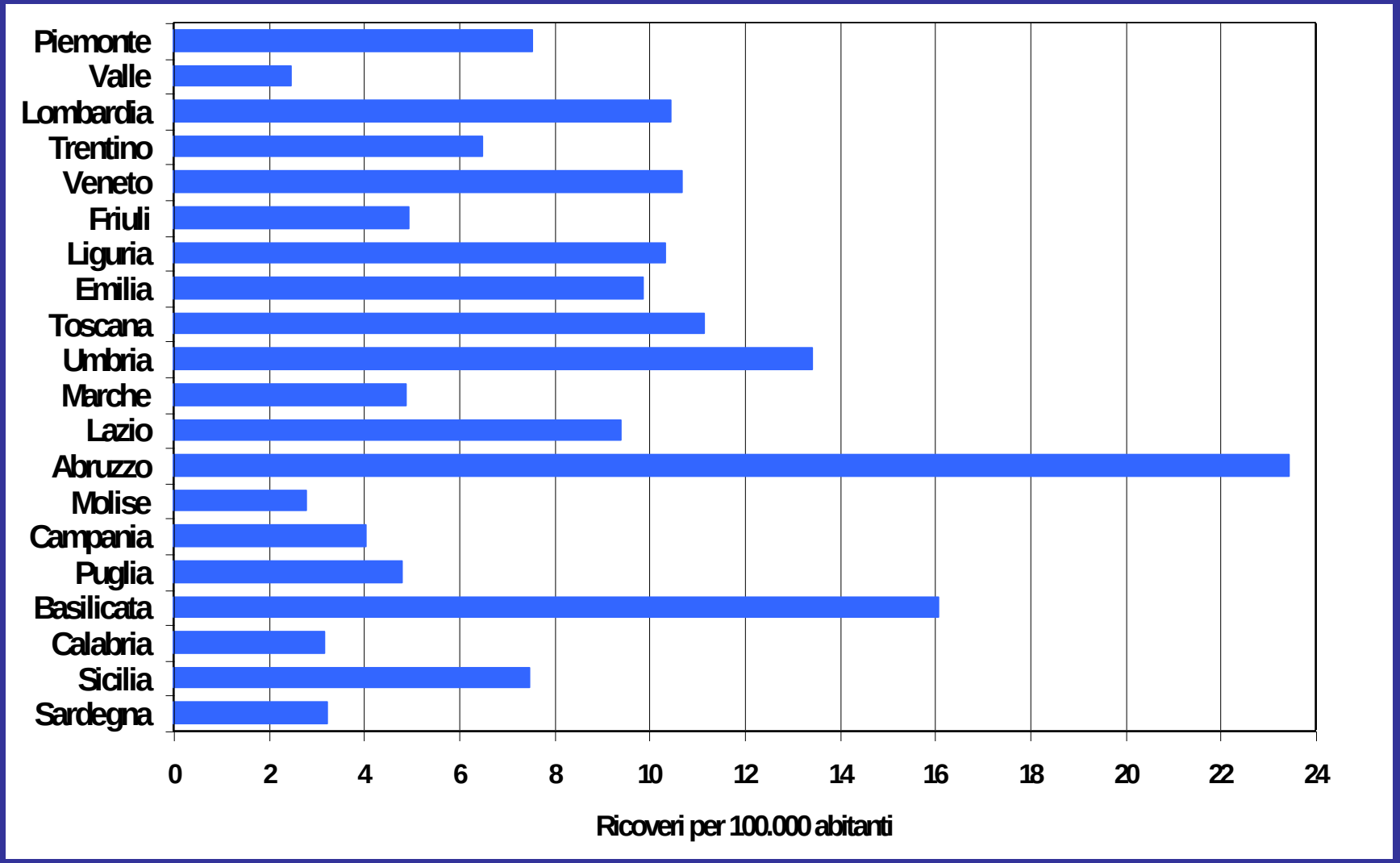
- **Significativo aumento di incidenza e prevalenza a partire dagli anni 70**

- **Prevalenza in Italia:**
  - ✓ **Anoressia nervosa: 0,2-0,8%**
  - ✓ **Bulimia nervosa: 1-5%**

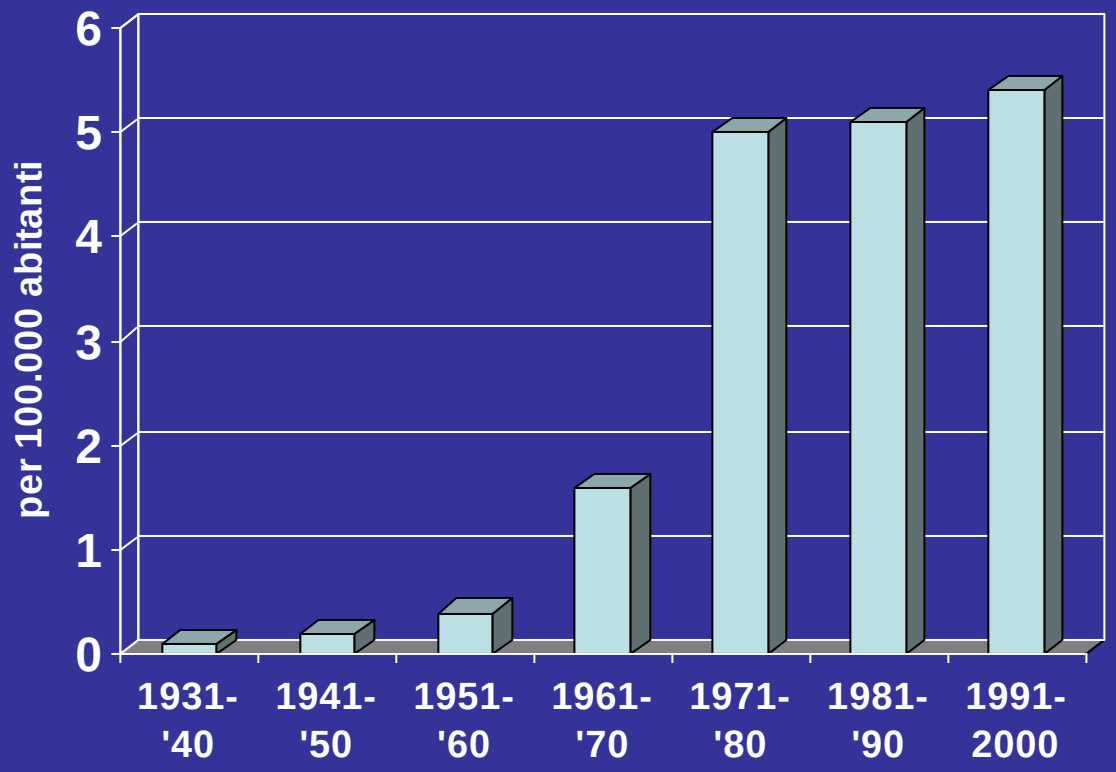
- **Età media all'esordio: tra 15 e 18, con due picchi (a 15 e 18 anni)**

(Fonte: Istituto Superiore Sanità, 2008)

Ricoveri nell'anno 2003 per Anoressia Nervosa
Ricoveri ordinari e Day Hospital. Tasso per 100.000 abitanti



Incidenza annuale di anoressia nervosa nei Centri psichiatrici nel Nord Europa



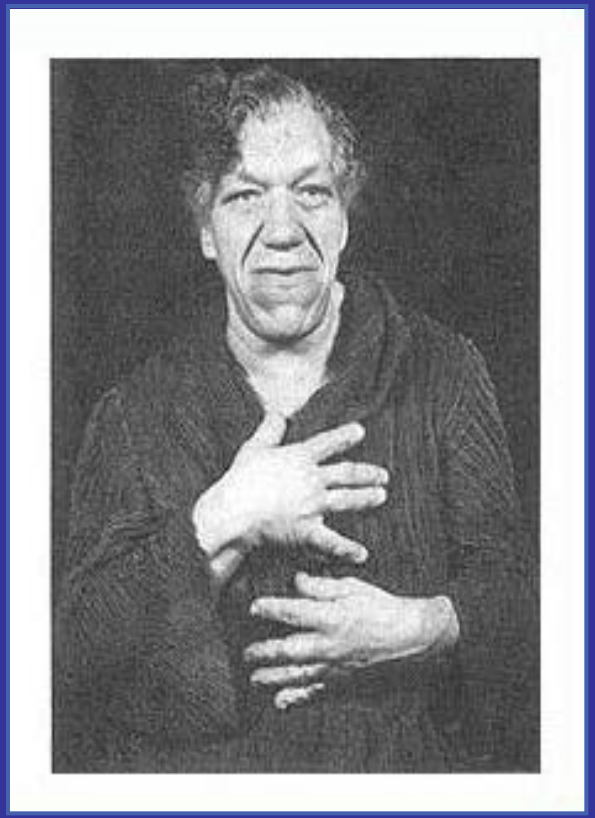
(Hans Wijbrand Hoek. Current Opinion in Psychiatry. Jul 2006)

ACROMEGALIA E GIGANTISMO

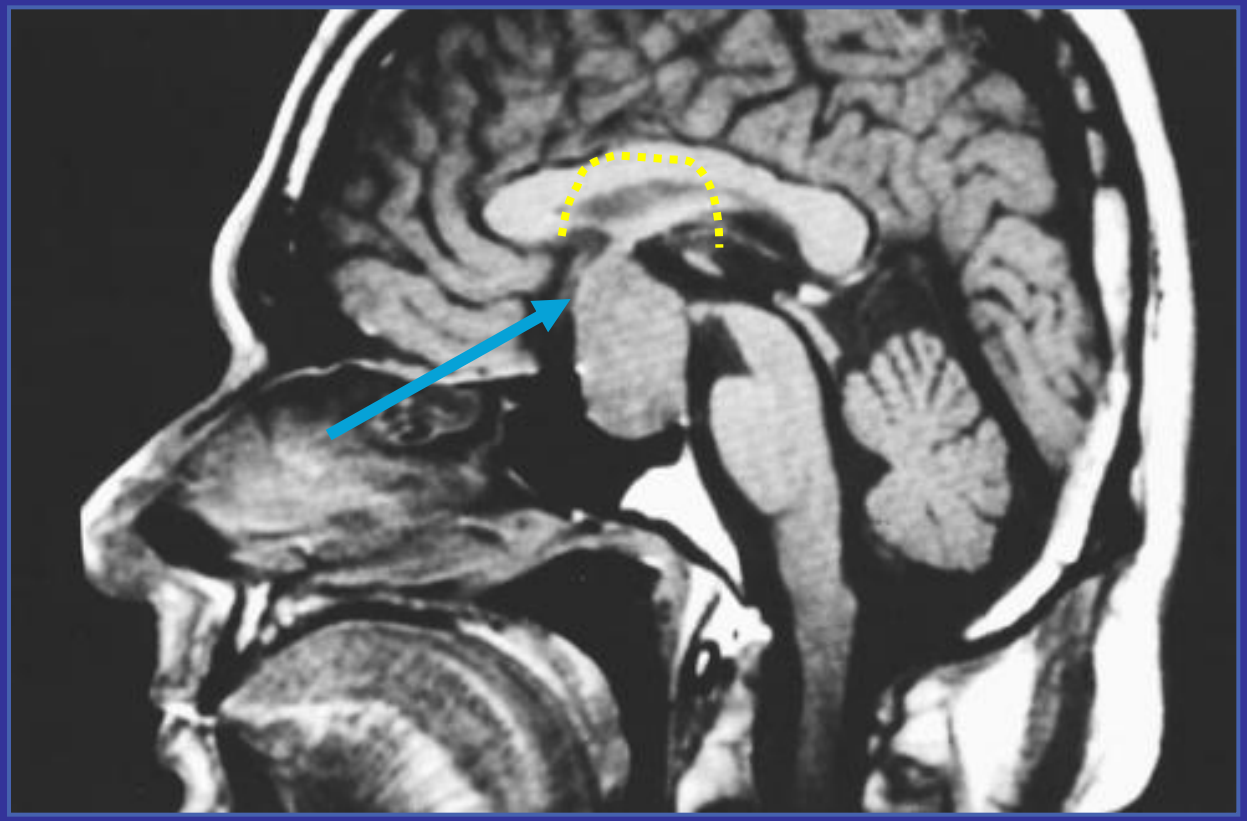
Robert Waldow

Paziente acromegalica di Pierre Marie

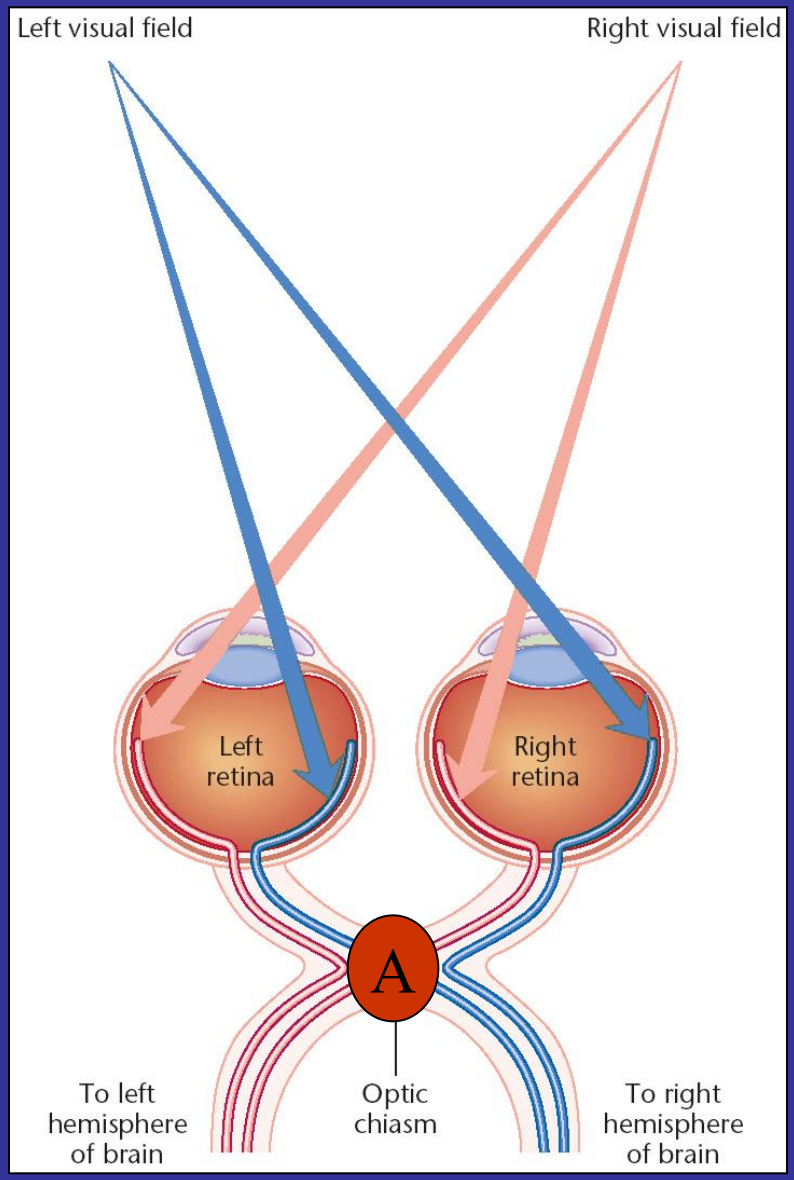
FENOTIPO



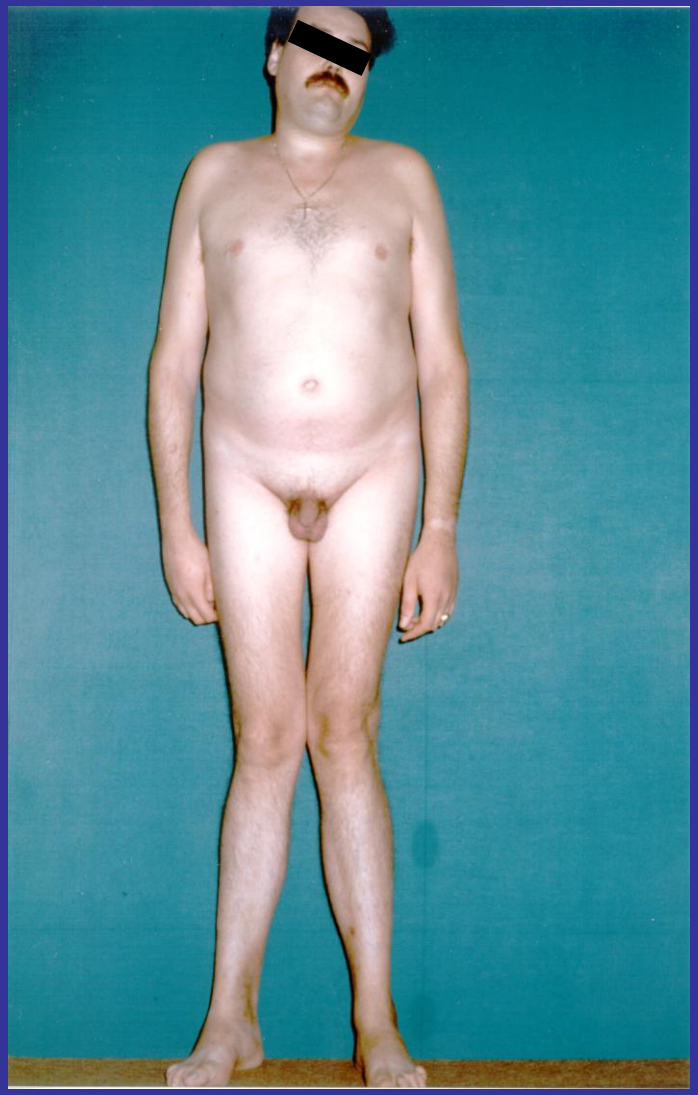
Macroadenoma GH-secernente: RMN ipofisi



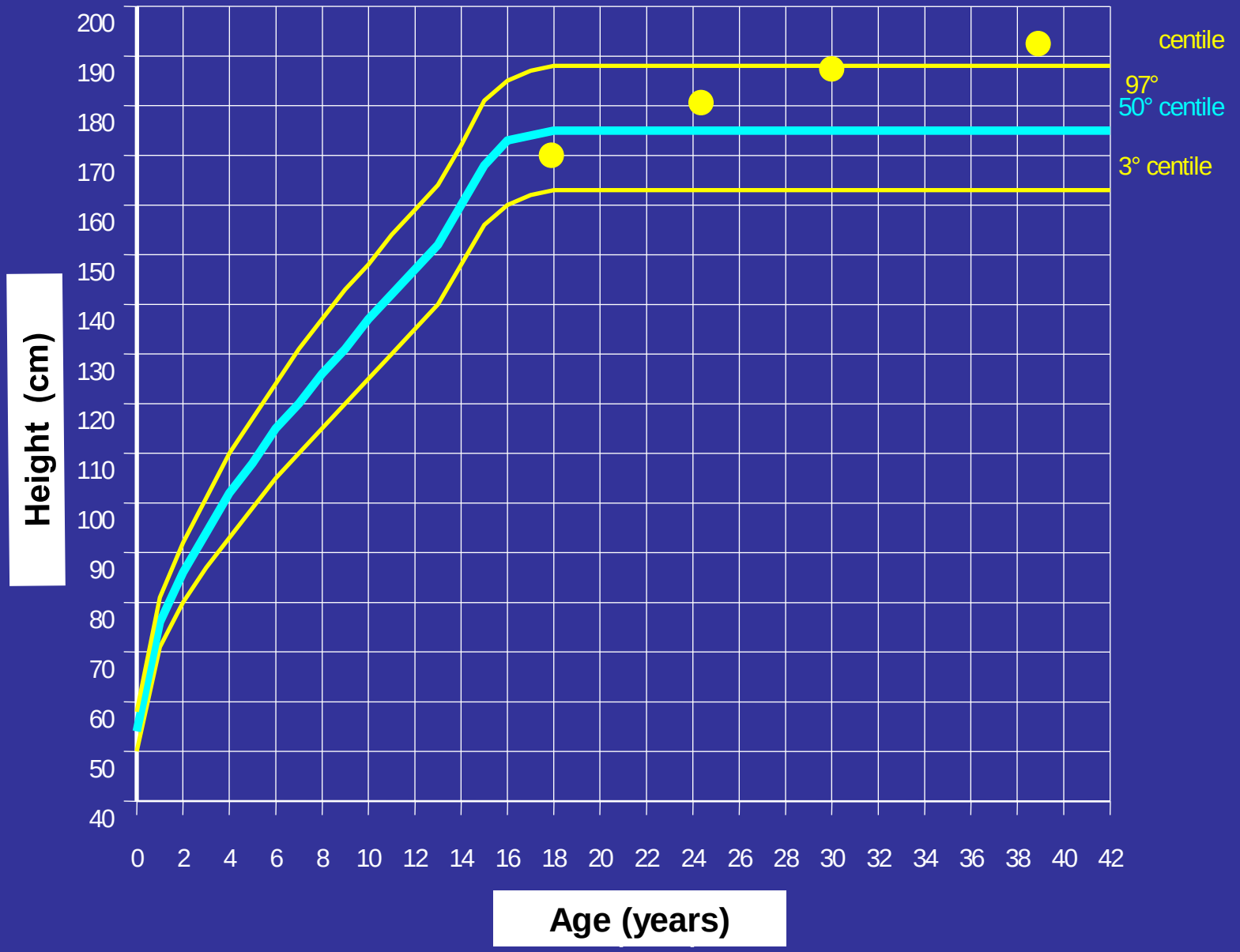
Emianopsia bitemporale

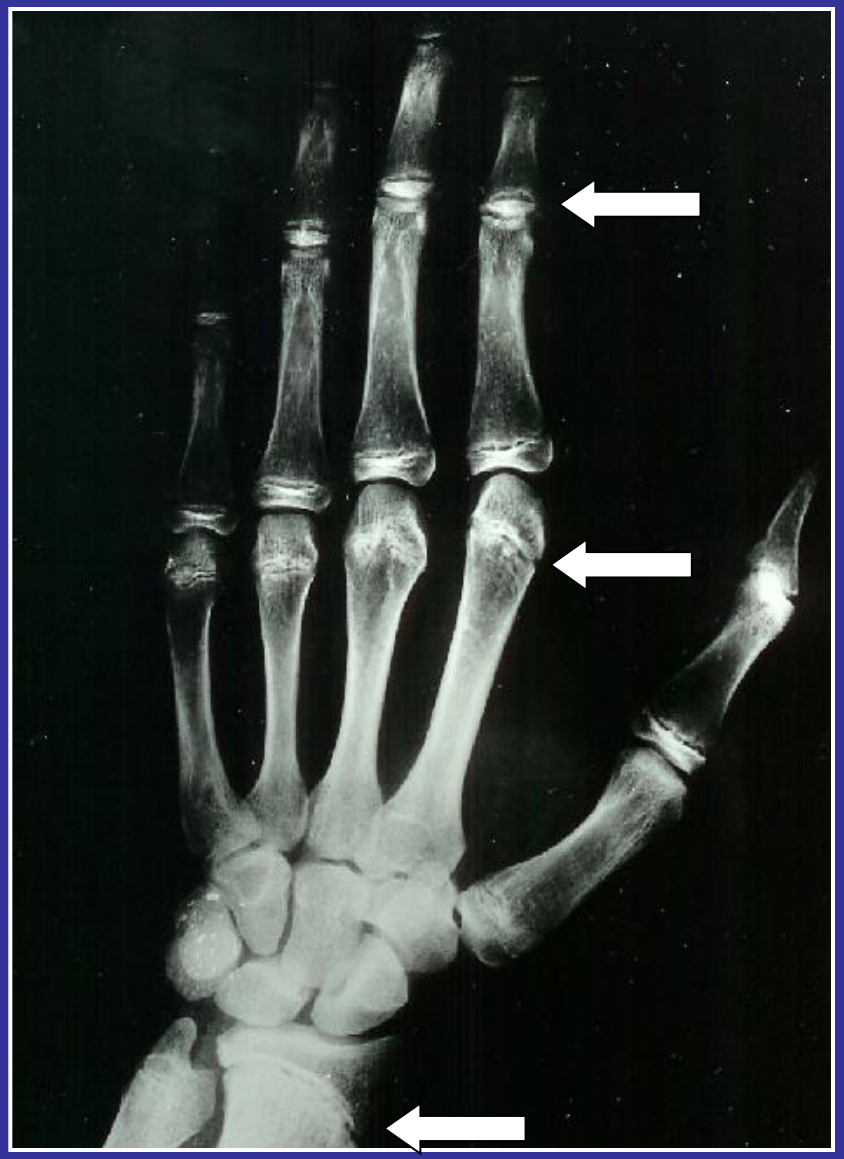


GIGANTISMO…..



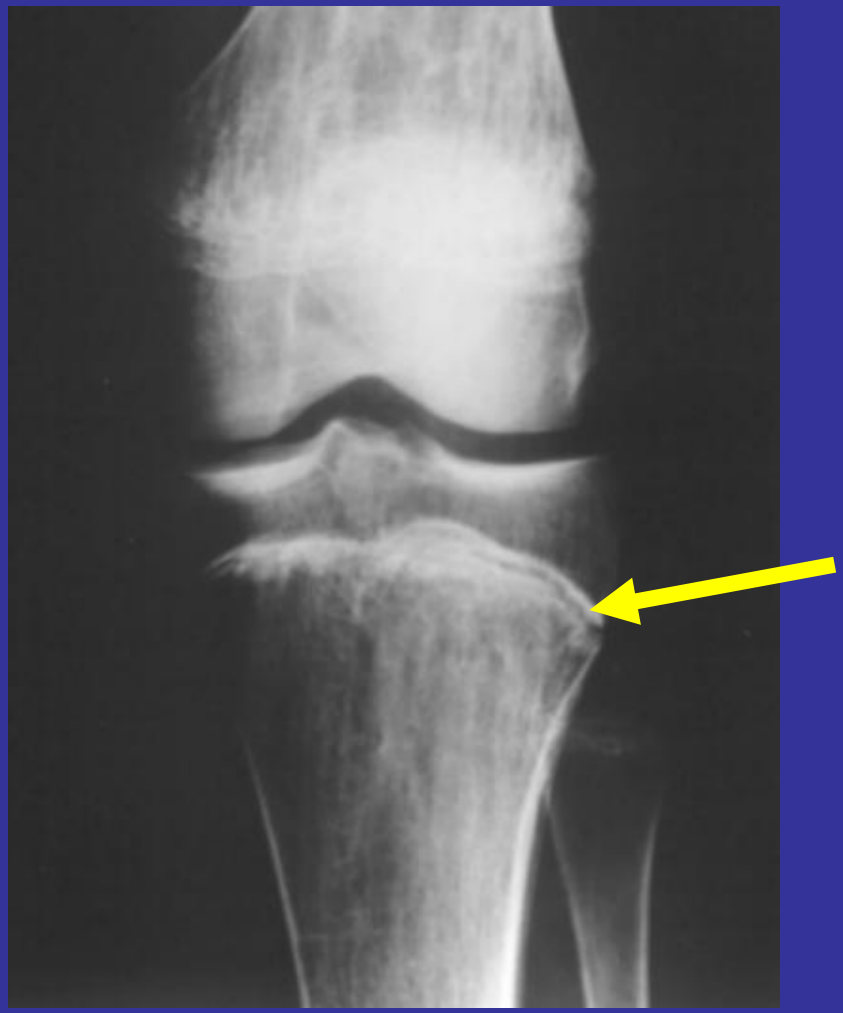
Persistent linear growth and undetectable estrogen's serum levels





Chronological age: 31 yr
Bone age: 14,8 yr

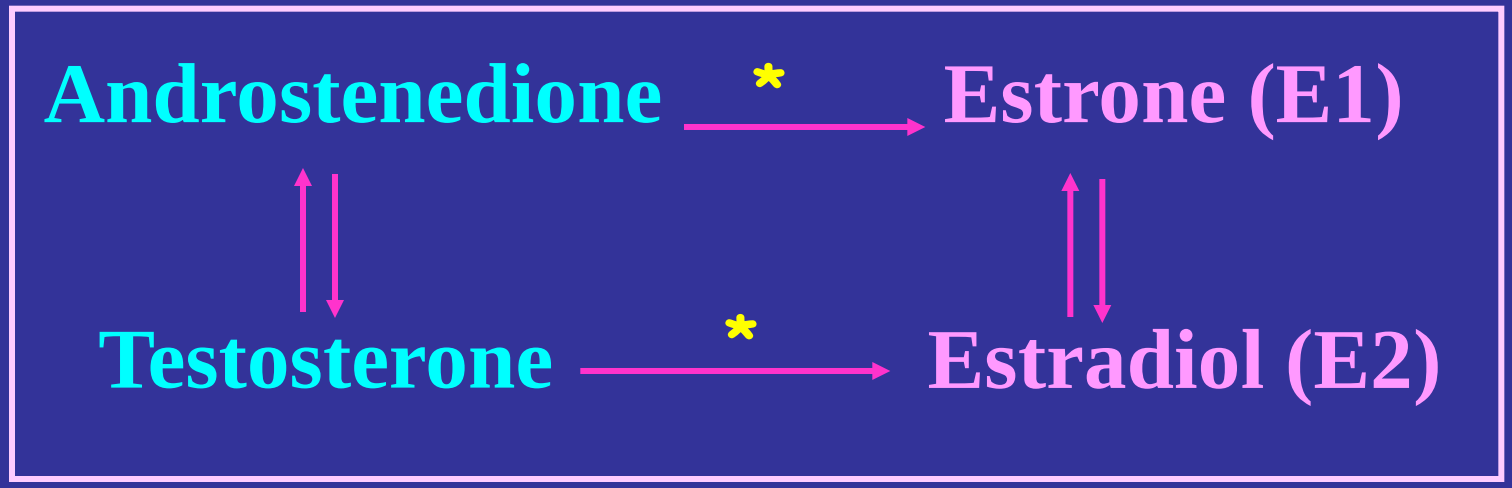
Carani, NEJM 1997



Chronological age: 31 yr
Bone age: 14,8 yr

Carani, NEJM 1997

Aromatase (P450 Arom): key-enzyme in estrogen's synthesis

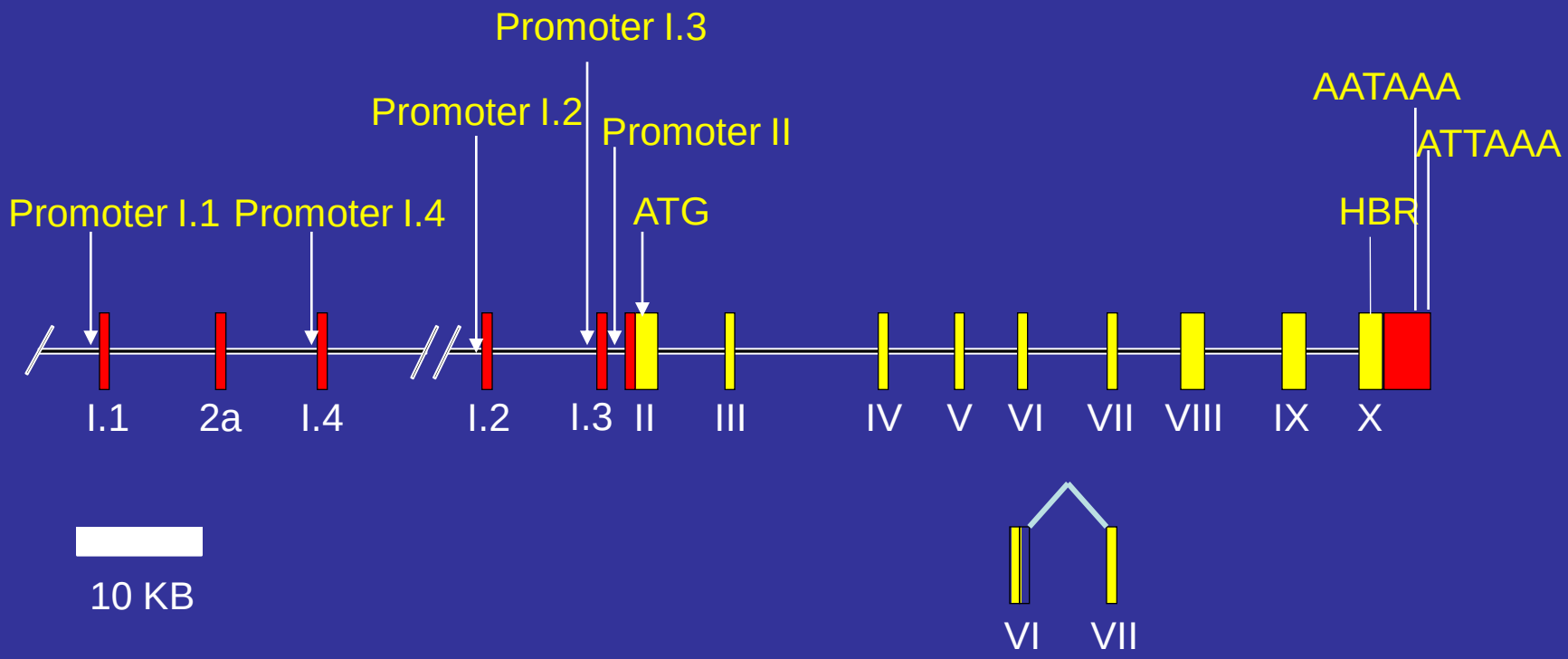


Enzimatic Complex: cytochrome P450

+

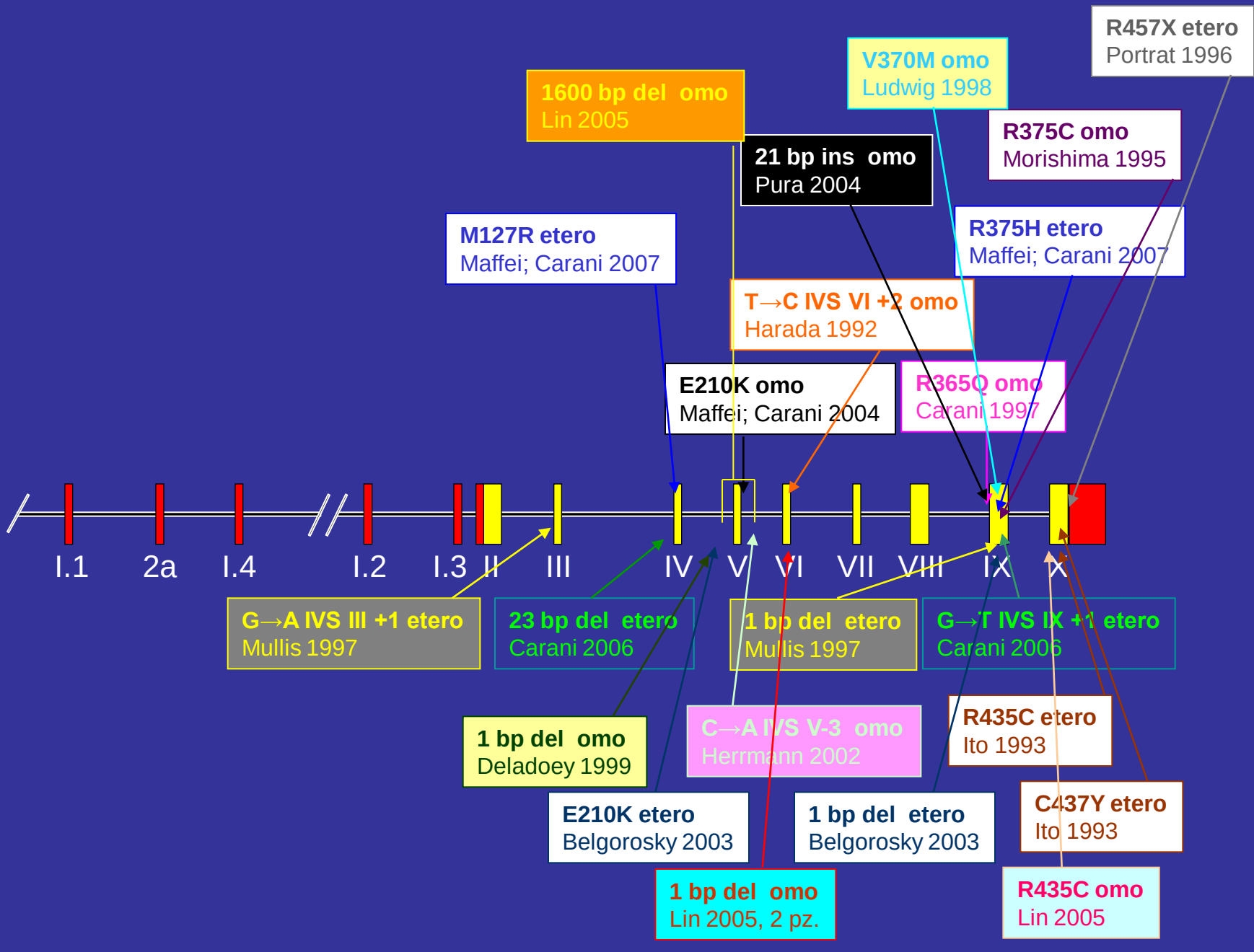
flavoprotein NADPH-P450 reductase

THE HUMAN AROMATASE GENE (*CYP19*)



Located on the long arm of chromosome 15 (q21.1)

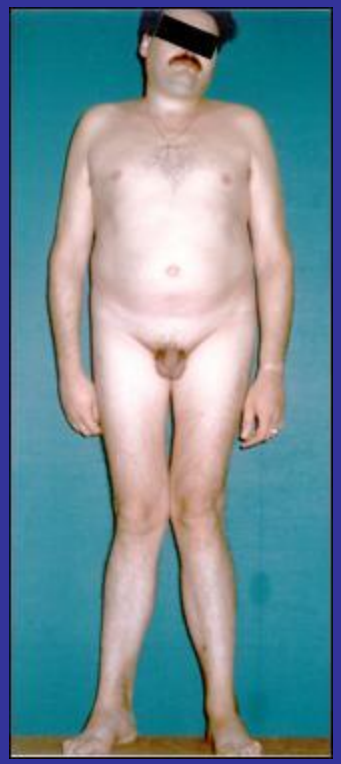
AROMATASE MUTATIONS IN HUMAN MALES and FEMALES



AROMATASE DEFICIENCY

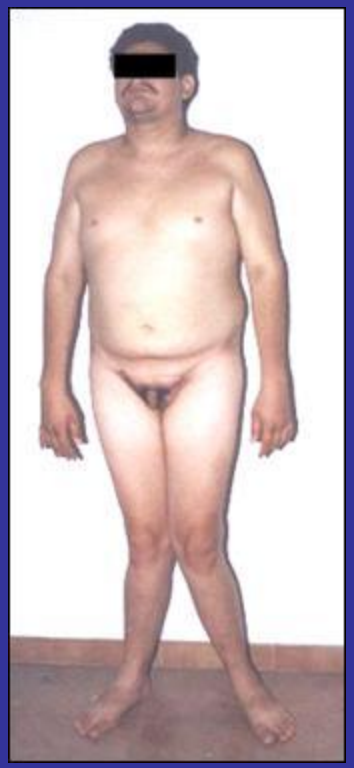
Patients studied in Modena and Buenos Aires

ITALY
Homozygous
R365Q in exon IX



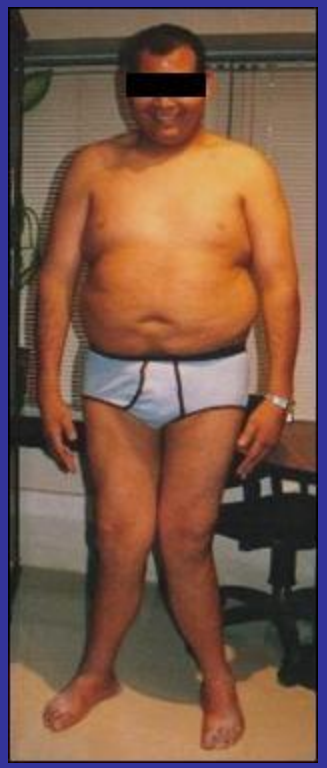
Carani
NEJM 1997

ARGENTINA
Homozygous
E210K in exon V



Carani, Maffei
JCEM 2004

ARGENTINA
Compound heterozygous
M127R in exon IV
R375H in exon IX

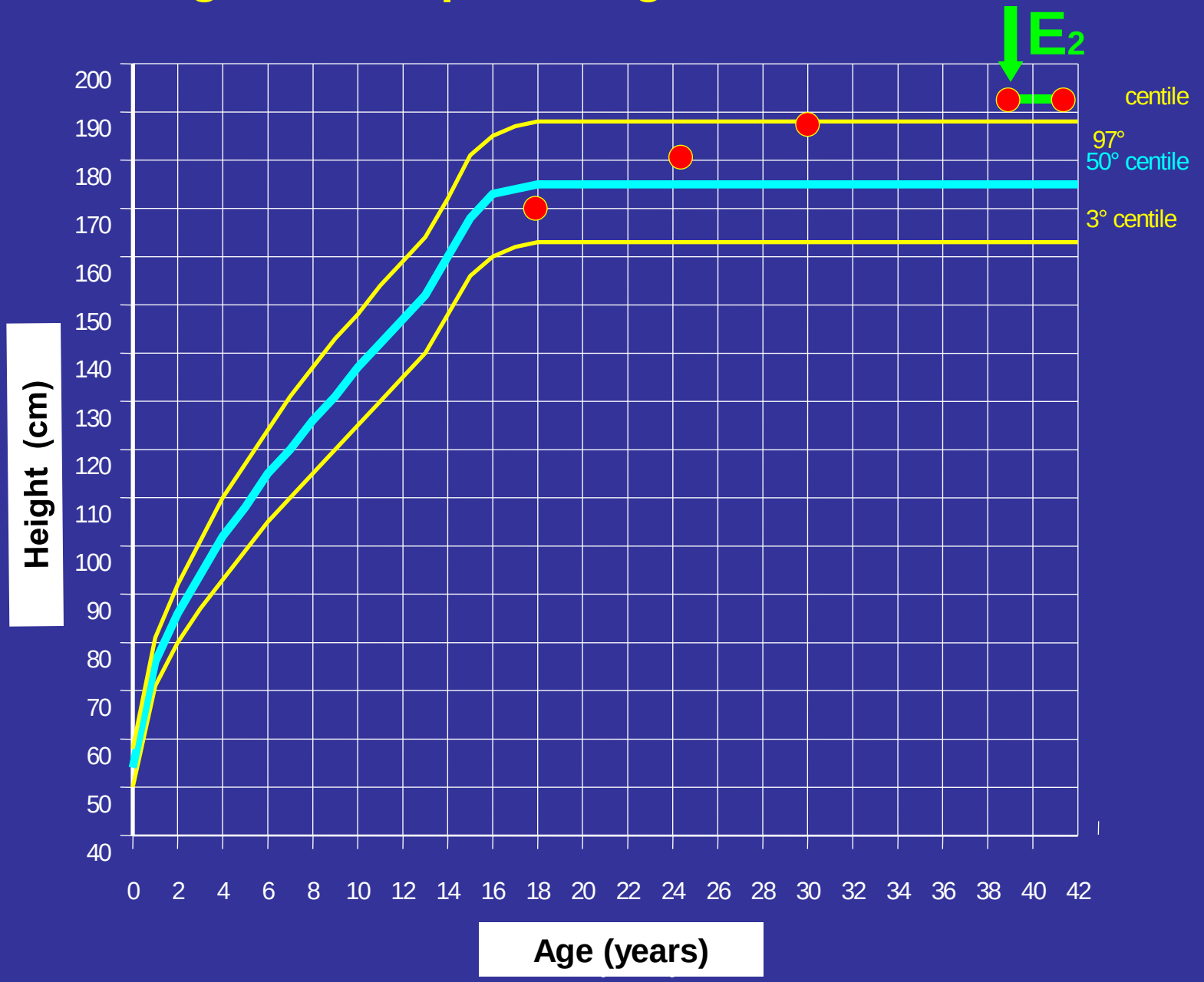


Carani, Maffei
Clin Endocrinol 2007

ITALY
Compound heterozygous:
23 bp deletion in Exon IV
G to T IVS IX +1

Carani, Aimaretti
J Endocrinol Invest 2007

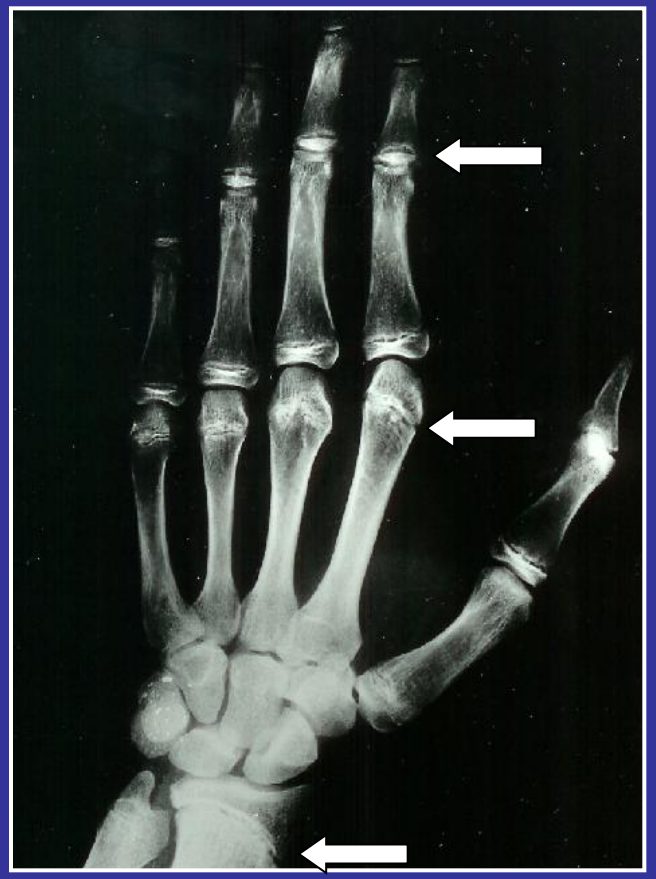
AROMATASE DEFICIENCY (I.R.)
Linear growth stops during estradiol treatment



Unfused epiphyses and delayed skeletal maturation

Adult man with Aromatase Deficiency

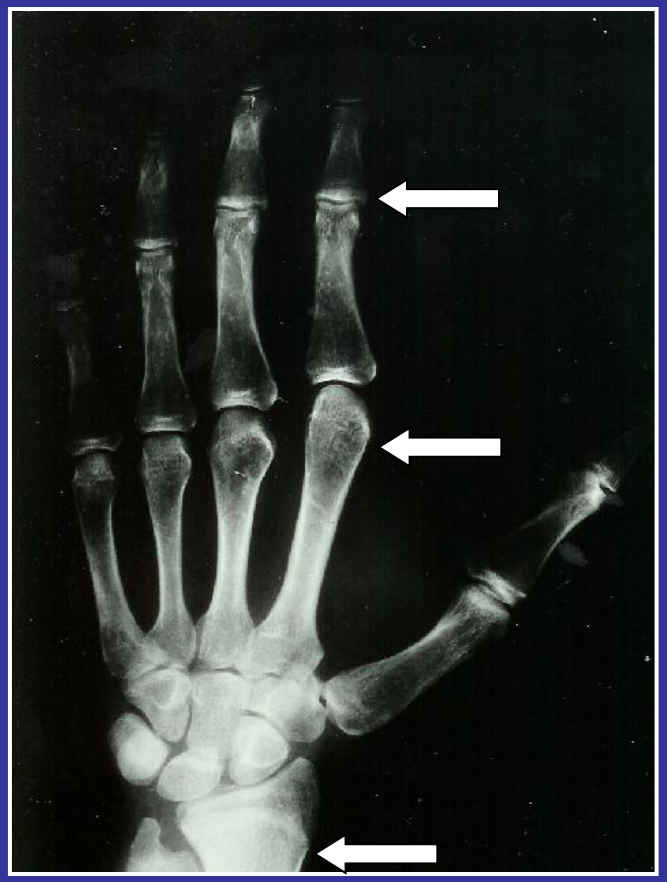
Before and during E2 treatment



Before treatment

Chronological age: 31 yr

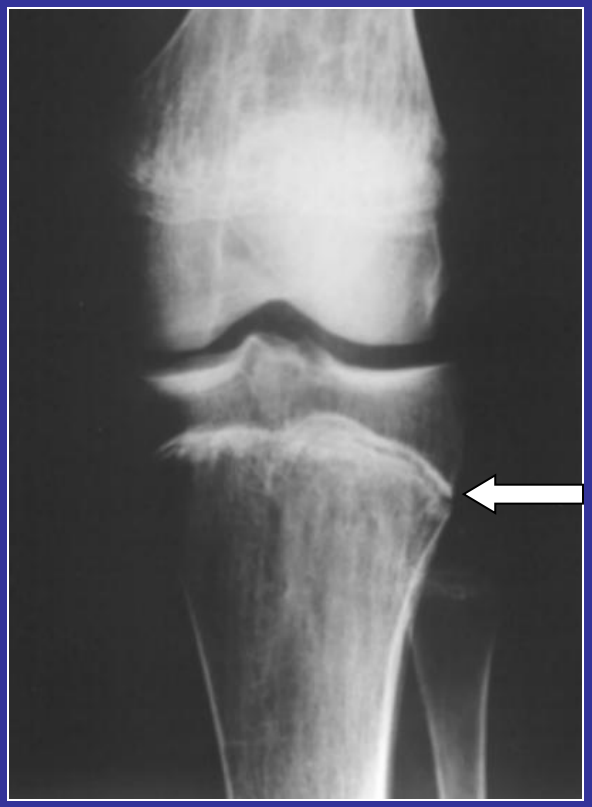
Bone age: 14,8 yr



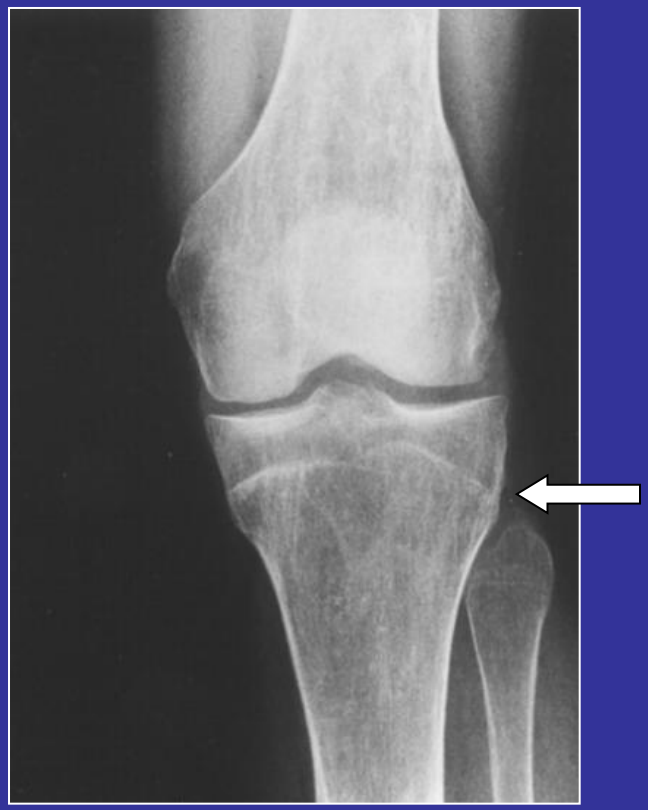
After estradiol 50 µg twice weekly (6 months)

Carani, NEJM 1997

Adult man with Aromatase Deficiency
Before and during E2 treatment



Before treatment

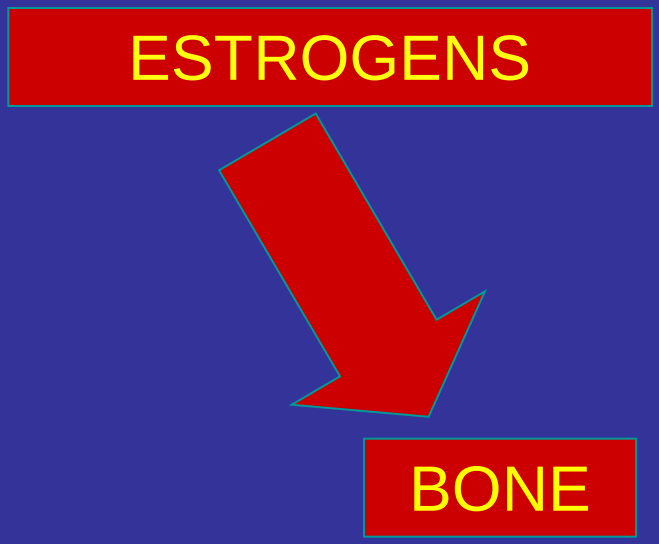


After 10 months estradiol treatment

Chronological age: 31 yr
Bone age: 14,8 yr

Carani, NEJM 1997

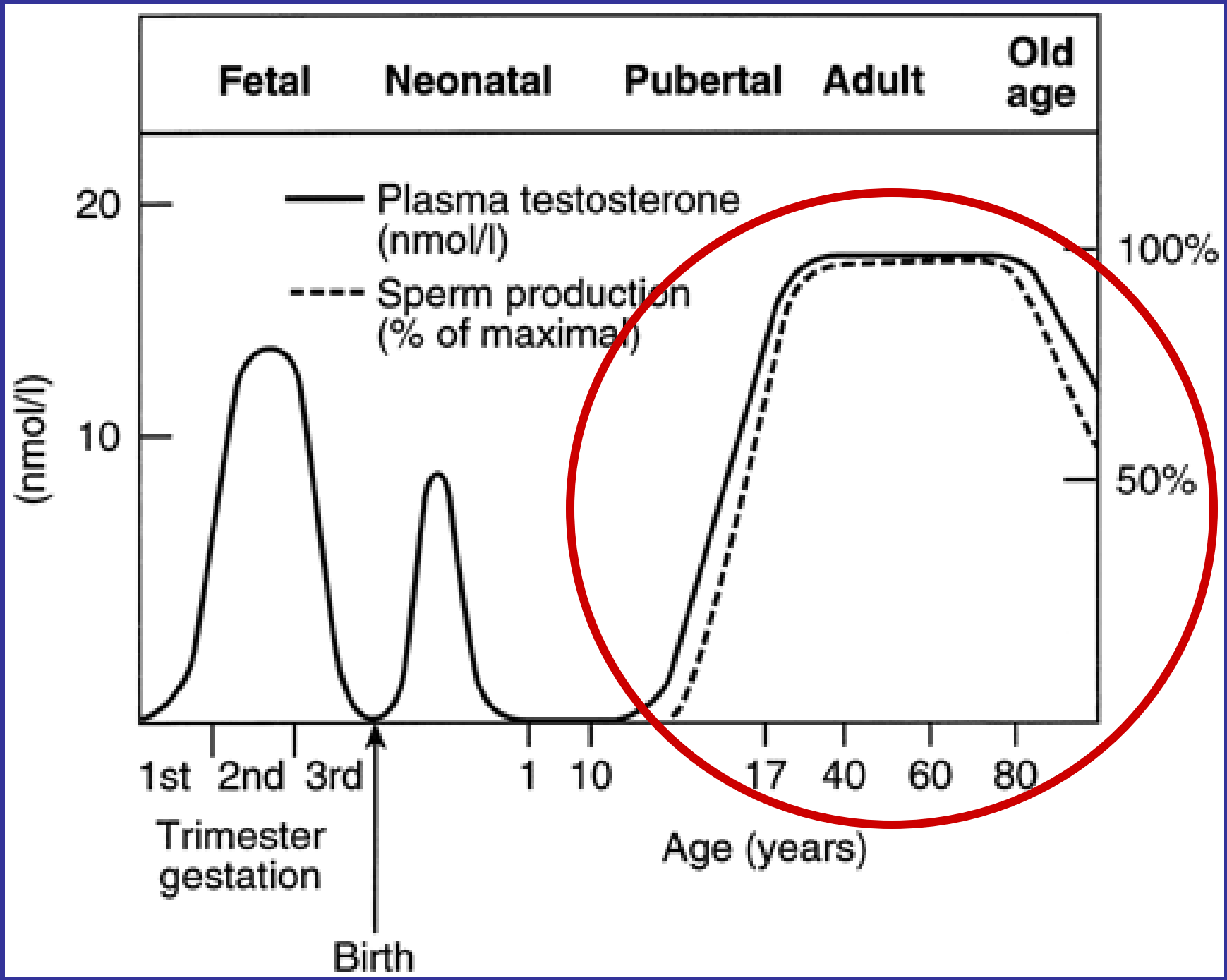
ESTROGEN ROLE IN THE HUMAN MALE



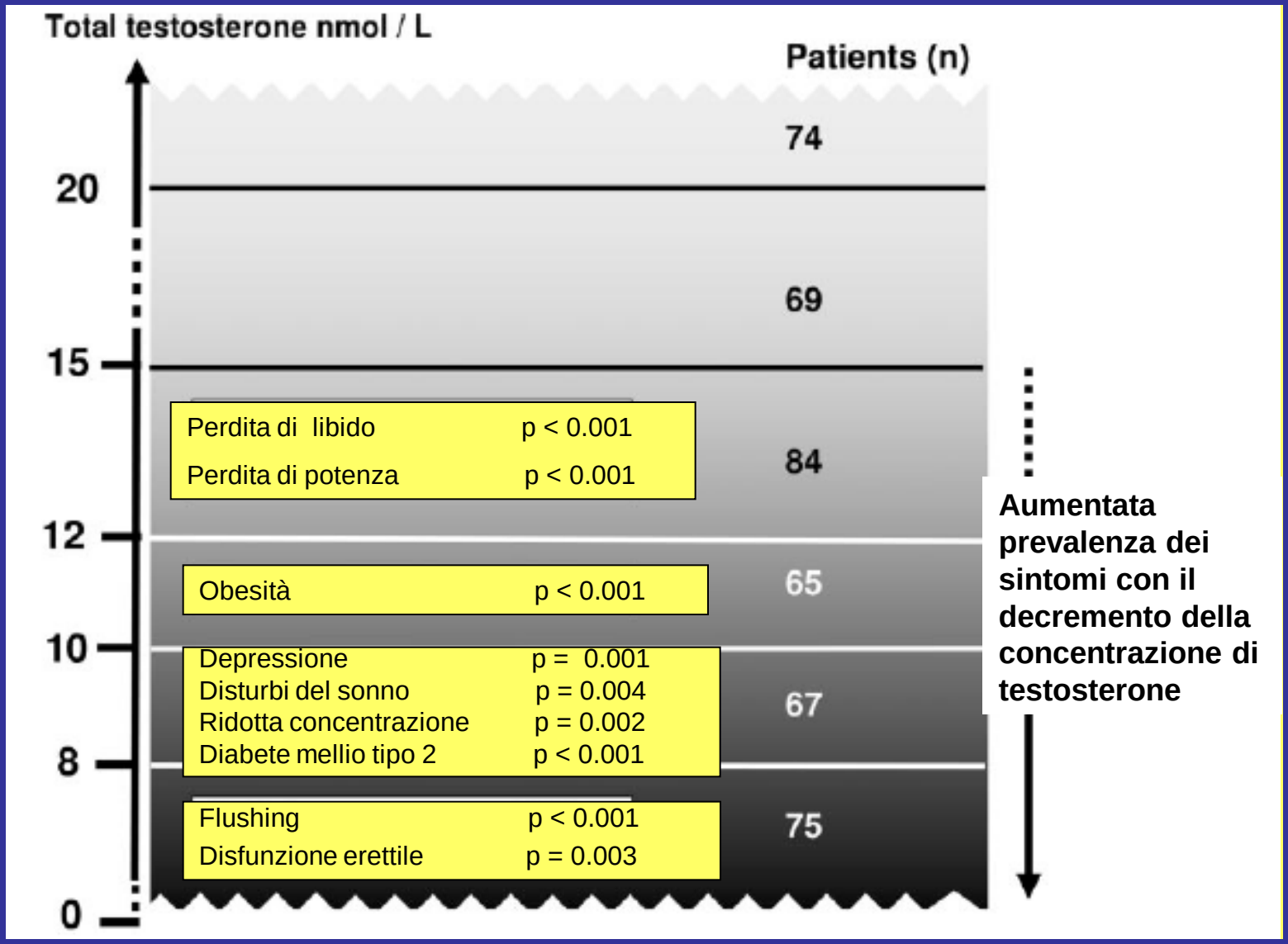
- Epiphyseal closure and growth arrest
- Induction of pubertal growth spurt
- Achievement and maintenance of normal skeletal proportions
- Achievement and maintenance of peak bone mass
- Inhibition of bone resorption

DISTURBI DELLA SESSUALITA' MASCHILE

Giulio Romano, Giove e Olimpia


Fetal
Neonatal
Pubertal
Adult
Old age
20
10
(nmol/l)
Plasma testosterone (nmol/l)
Sperm production (% of maximal)
100%
50%
1st
2nd
3rd
1
10
17
40
60
80
Trimester gestation
Birth
Age (years)

Associazione di sintomi specifici e rischio metabolico con i livelli sierici di Testoterone in uomini anziani



M. Zitzmann et. al. J Clin Endocrinol Mateb 91: 4335 – 4343, 2006

Prevalenza del Deficit Erettivo in ITALIA

2010 uomini:

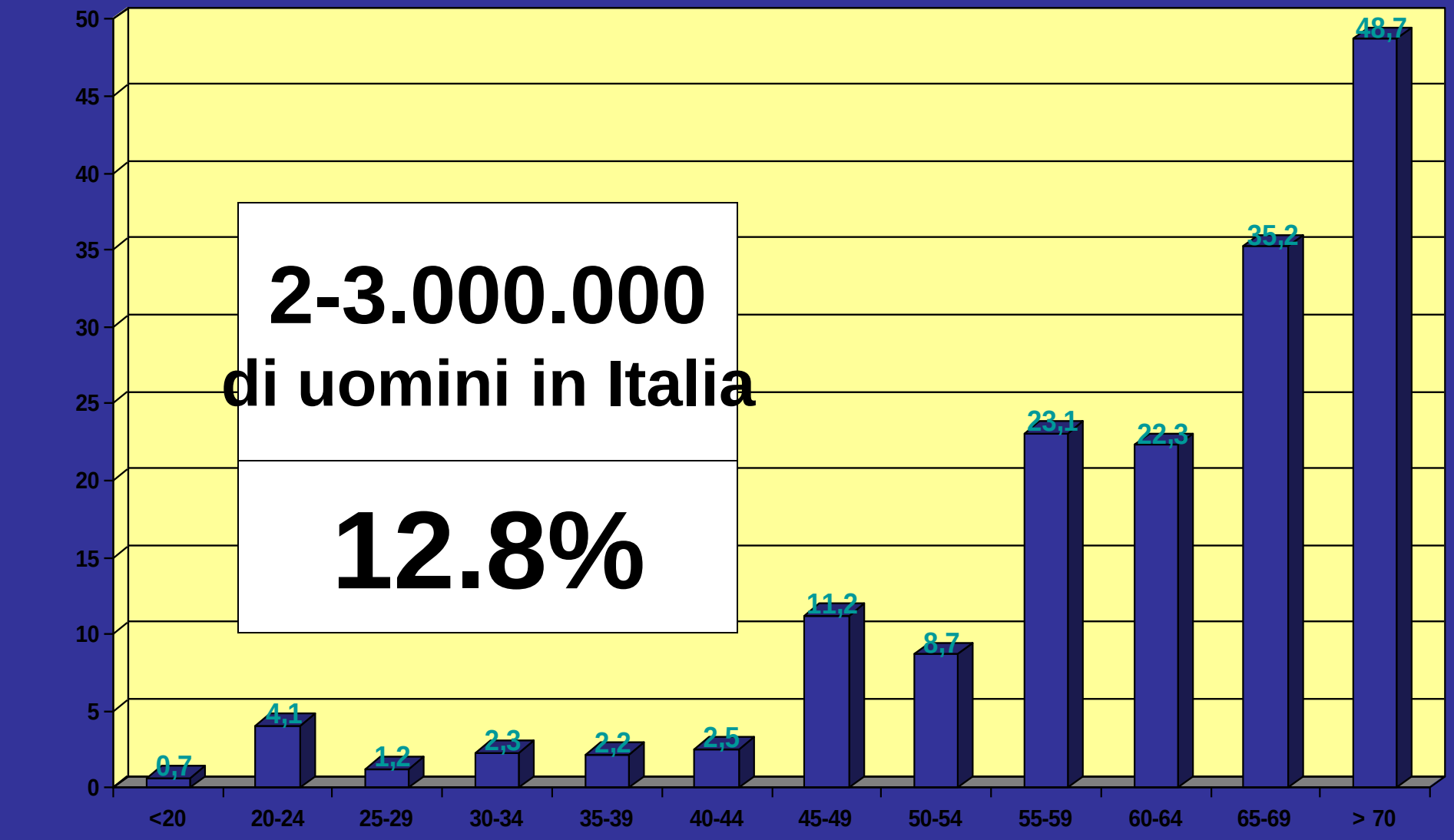
257 (12.8%) deficit erettivo

178 (70%) parziale

78 (30%) completo

Parazzini et al. European J Urology, 200

Prevalenza D.E. in Italia



2-3.000.000
di uomini in Italia

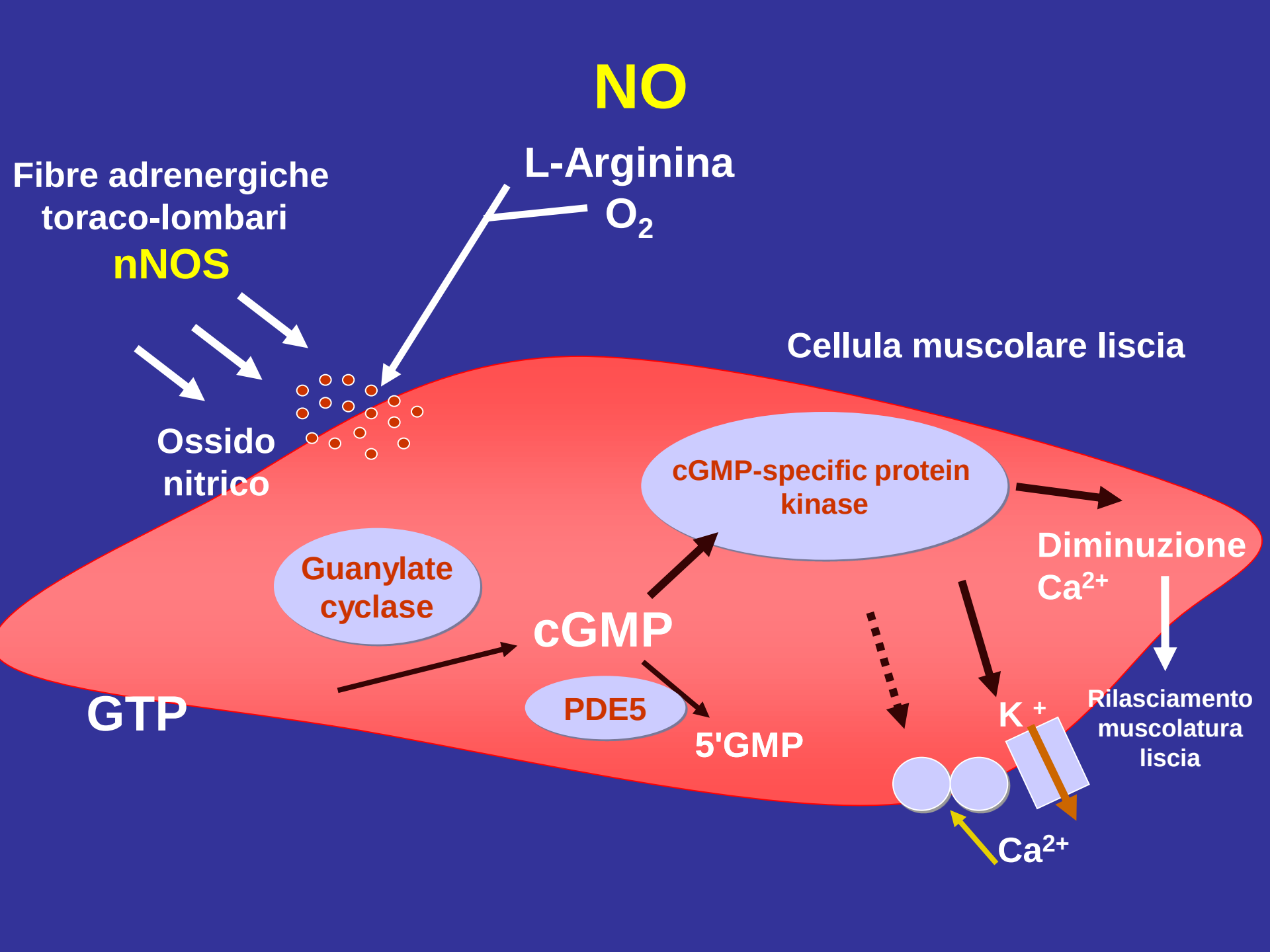
12.8%

Parazzini et al. European J Urology, 2000

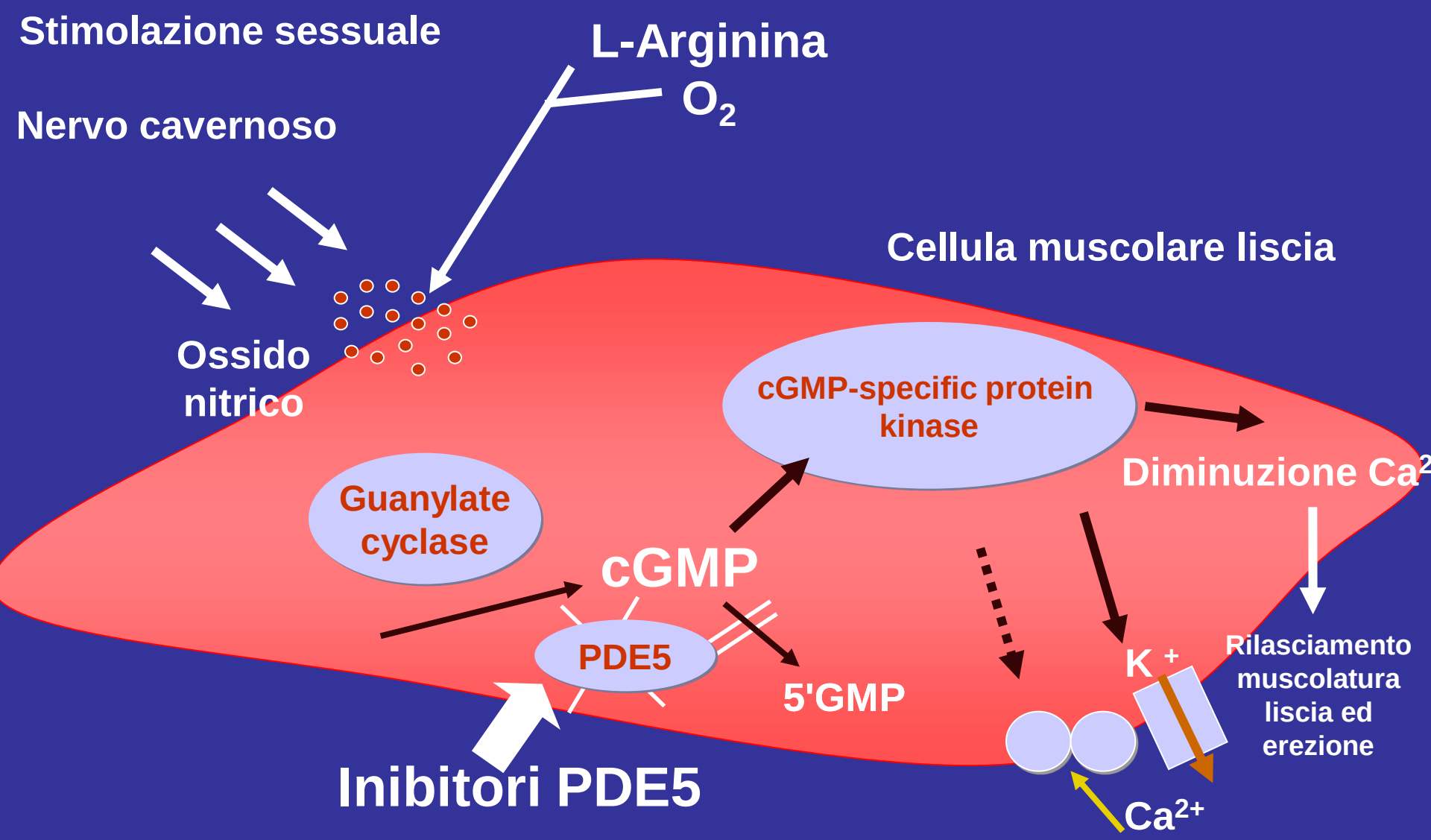
Mimnermo (630 a.C. - ?)

“….mi colga
a sessanta anni
il destino di morte.”

“ Che vita mai, che gioia senza Afrodite d'oro?
Ch'io sia morto quando più non mi stiano a cuore
l'amore segreto, i dolci doni e il letto:
questi sono i fiori della giovinezza, desiderabili
per gli uomini e le donne….”


NO
L-Arginina
O_2
Fibre adrenergiche
toraco-lombari
nNOS
Cellula muscolare liscia
Ossido
nitrico
cGMP-specific protein
kinase
Diminuzione
Ca^{2+}
Guanylate
cyclase
cGMP
GTP
PDE5
5'GMP
K^+
Rilasciamento
muscolatura
liscia
Ca^{2+}

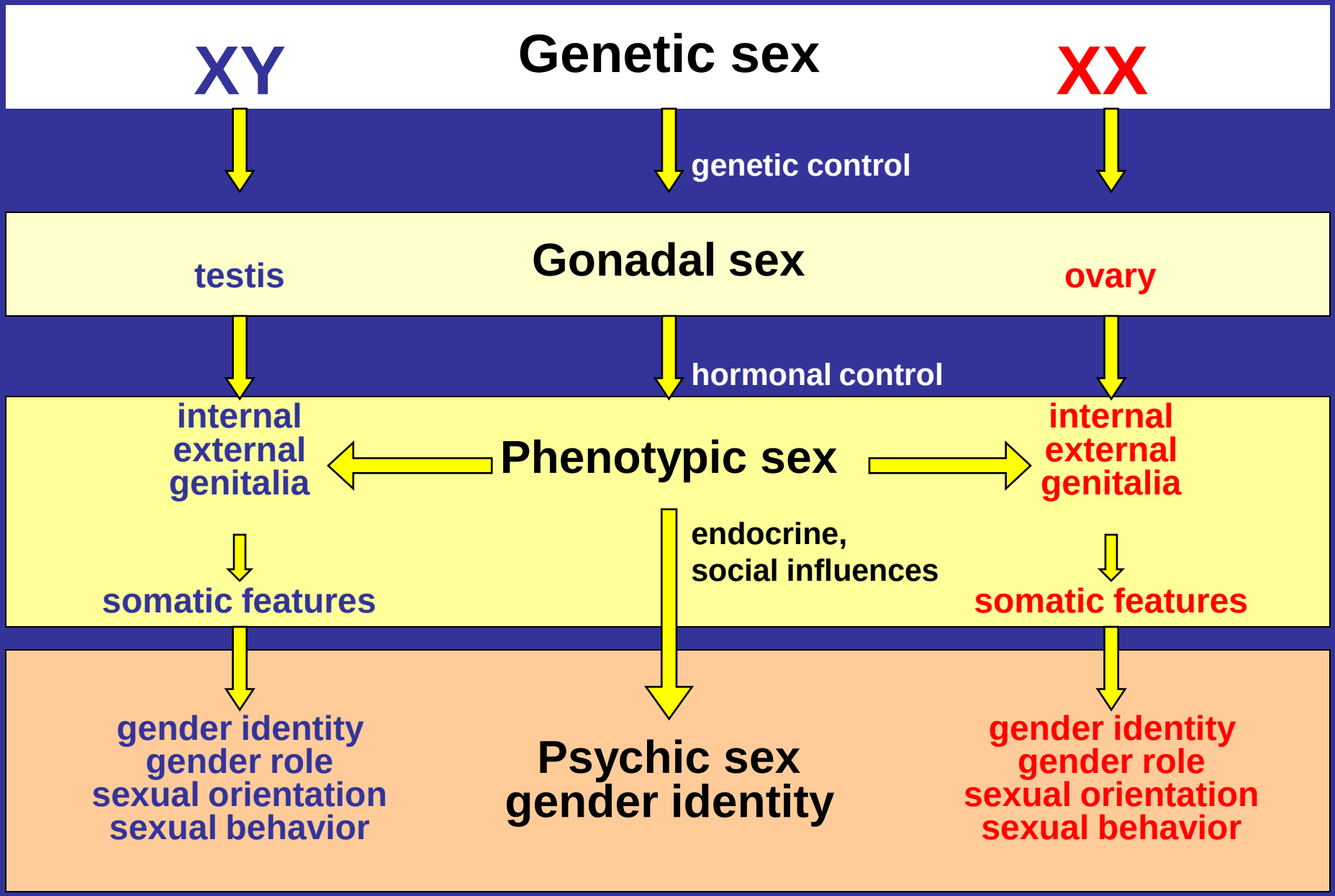
Meccanismo d'azione periferico



DISTURBI DELLA DIFFERENZIAZIONE SESSUALE

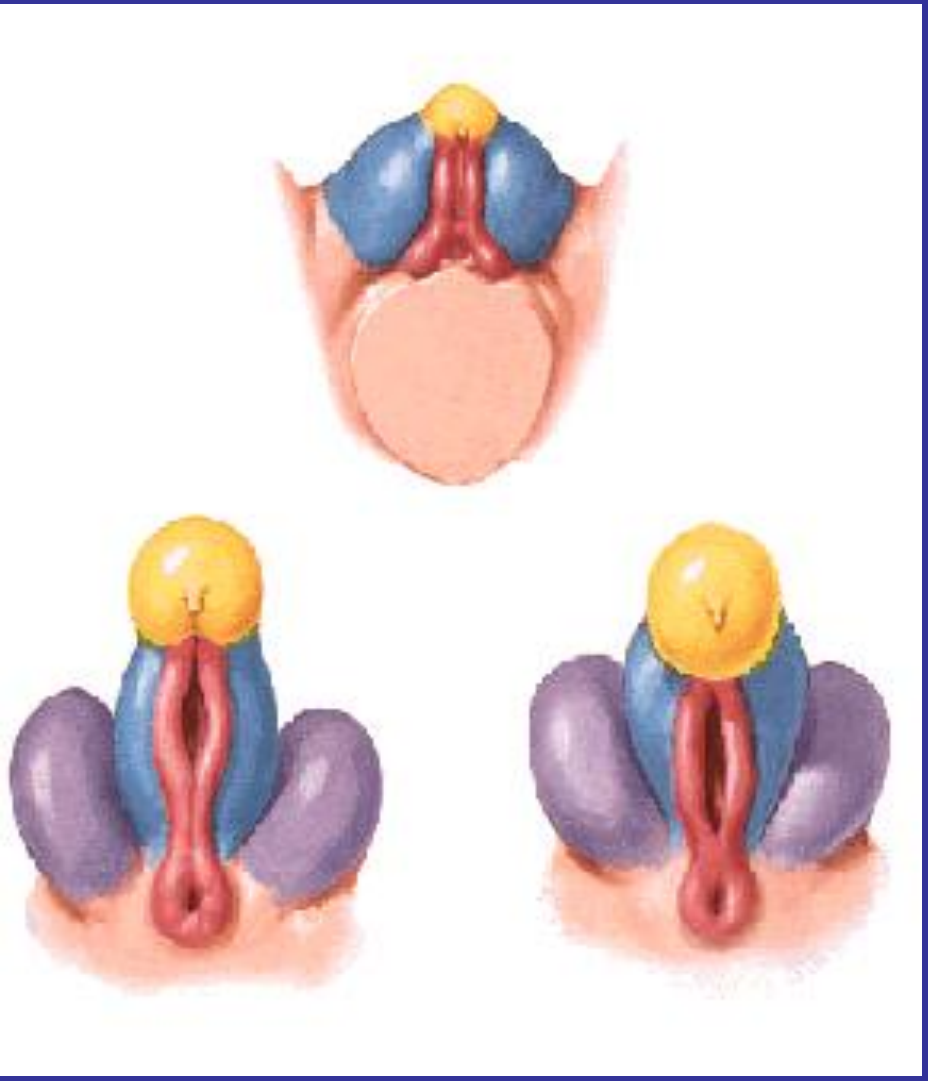
L’ermafrodito, Duomo di Modena

Normal sexual differentiation

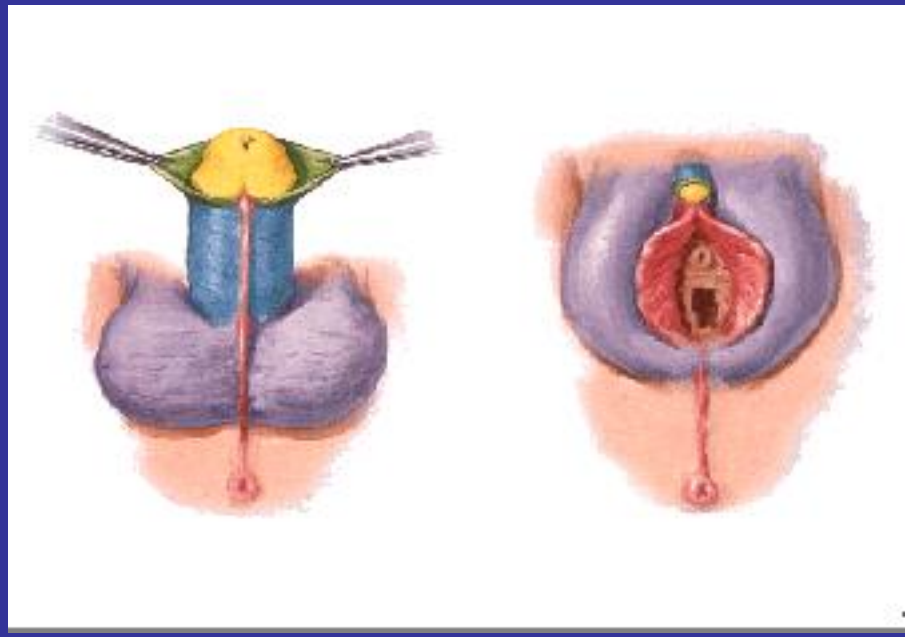


Sesso fenotipico

Abbozzi genitali esterni fetali



Maschio Femmina



DISORDERS of SEX DEVELOPMENT

XXY
(Sdr Klinefelter)

Chromosomic sex

X
(Sdr Turner)

Gonadal sex

Testis

- **Disorders of gonadal development**
  - **gonadal dysgenesis (SF1, SRY etc)**
- **Disorders of androgen synthesis**
- **Disorders of androgen action**

Ovary

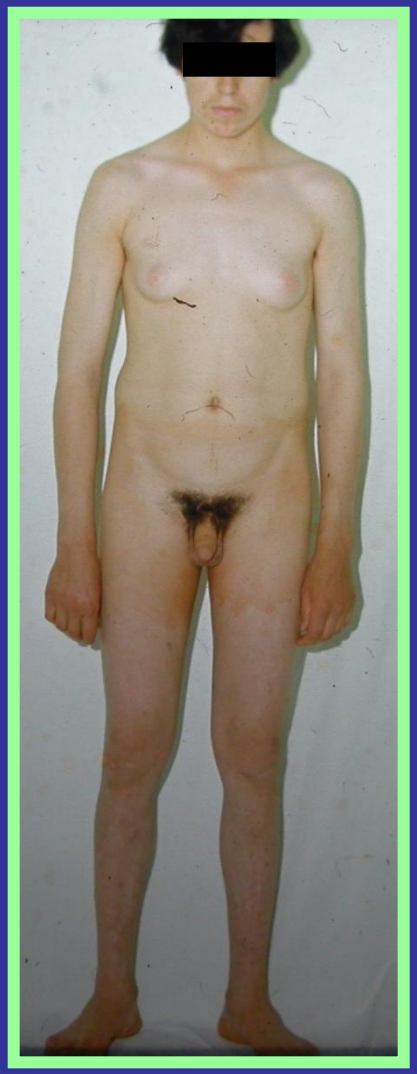
- **Disorders of gonadal development**
  - **ovotesticular DSD**
- **Androgen excess**

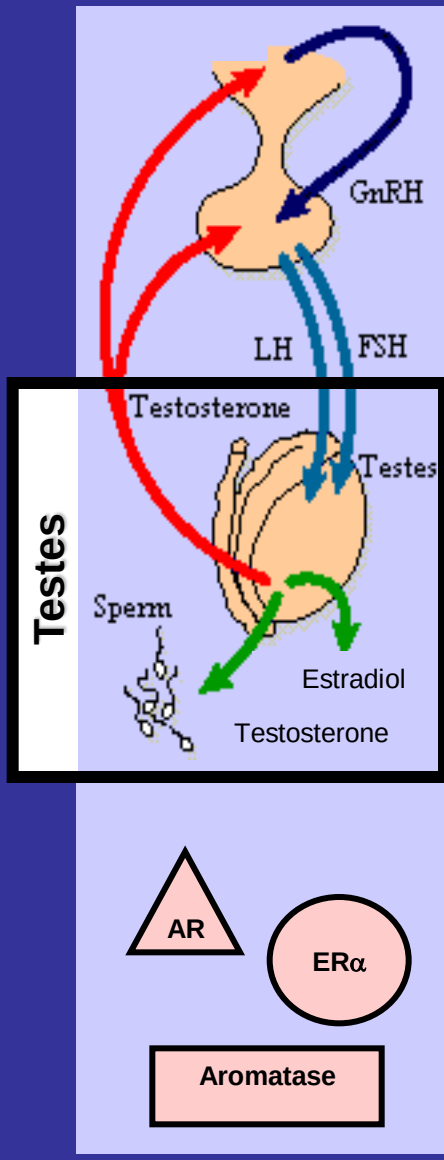
IPOGONADISMO IPERGONADOTROPO

Sindrome Klinefelter

- **La anomalia congenita più frequentemente causa di ipogonadismo ipergonadotropo in maschi.**

- Frequenza: 1/500 maschi nati vivi
- Chromosoma X sovrannumerario
- Il genotipo più frequente è 47, XXY.





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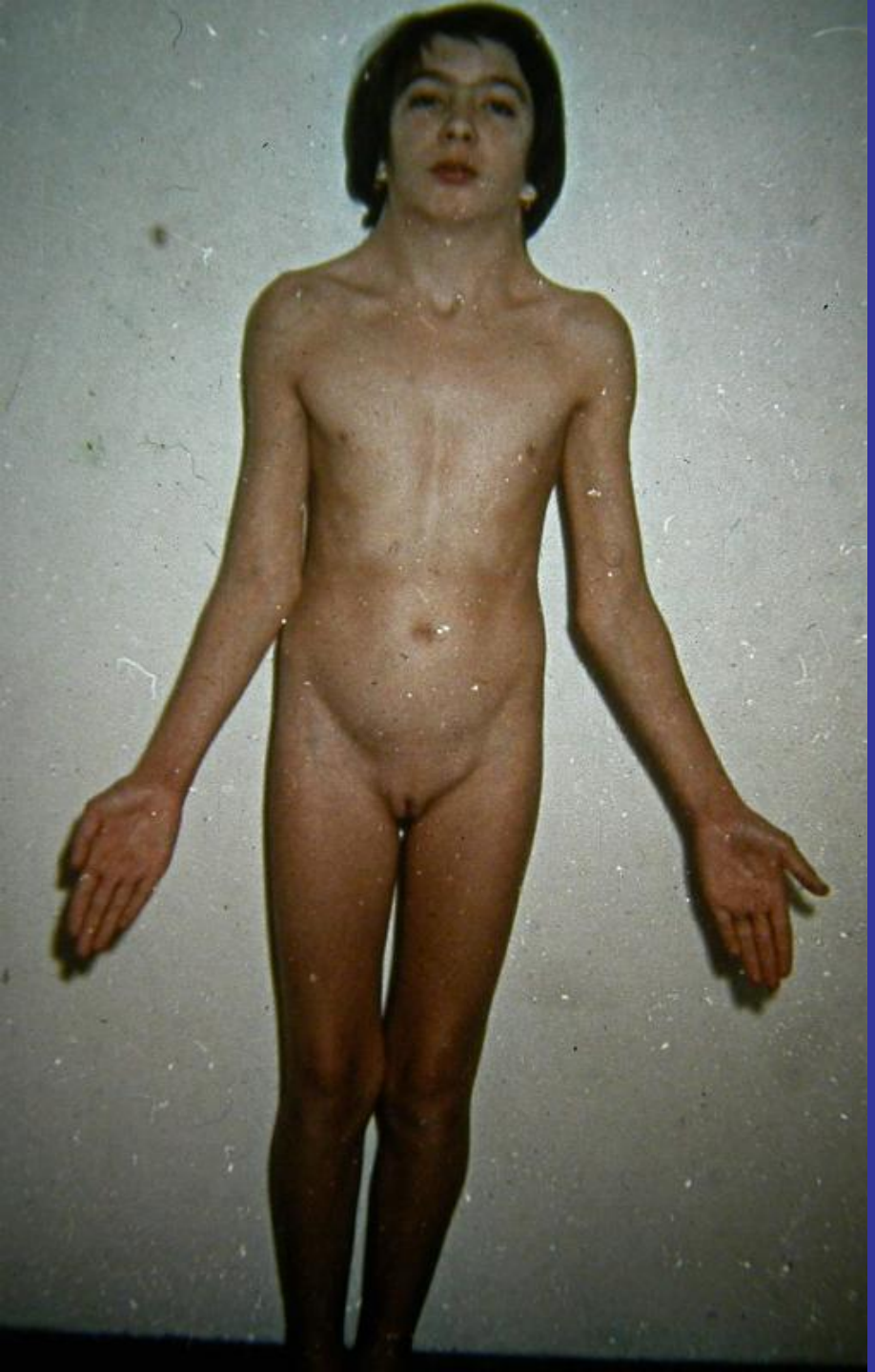

Sindrome di Turner

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Amenorrea primaria

D. V. 23 anni

Altezza 169 cm

Genitali esterni femminili, canale vaginale normale

Minimo sviluppo delle ghiandole mammarie (B2)

Peli pubici da adulta (P5) Ircarca ++++

Non irsutismo

cariotipo 46, XY

Verifica molecolare del crom Y: confermata la presenza di loci appartenenti sia al braccio corto (ZFY, SRY) che al braccio lungo (sY84, sY86, sY127, sY134, sY254, sY255) del cromosoma Y

Gene SF1: mutato

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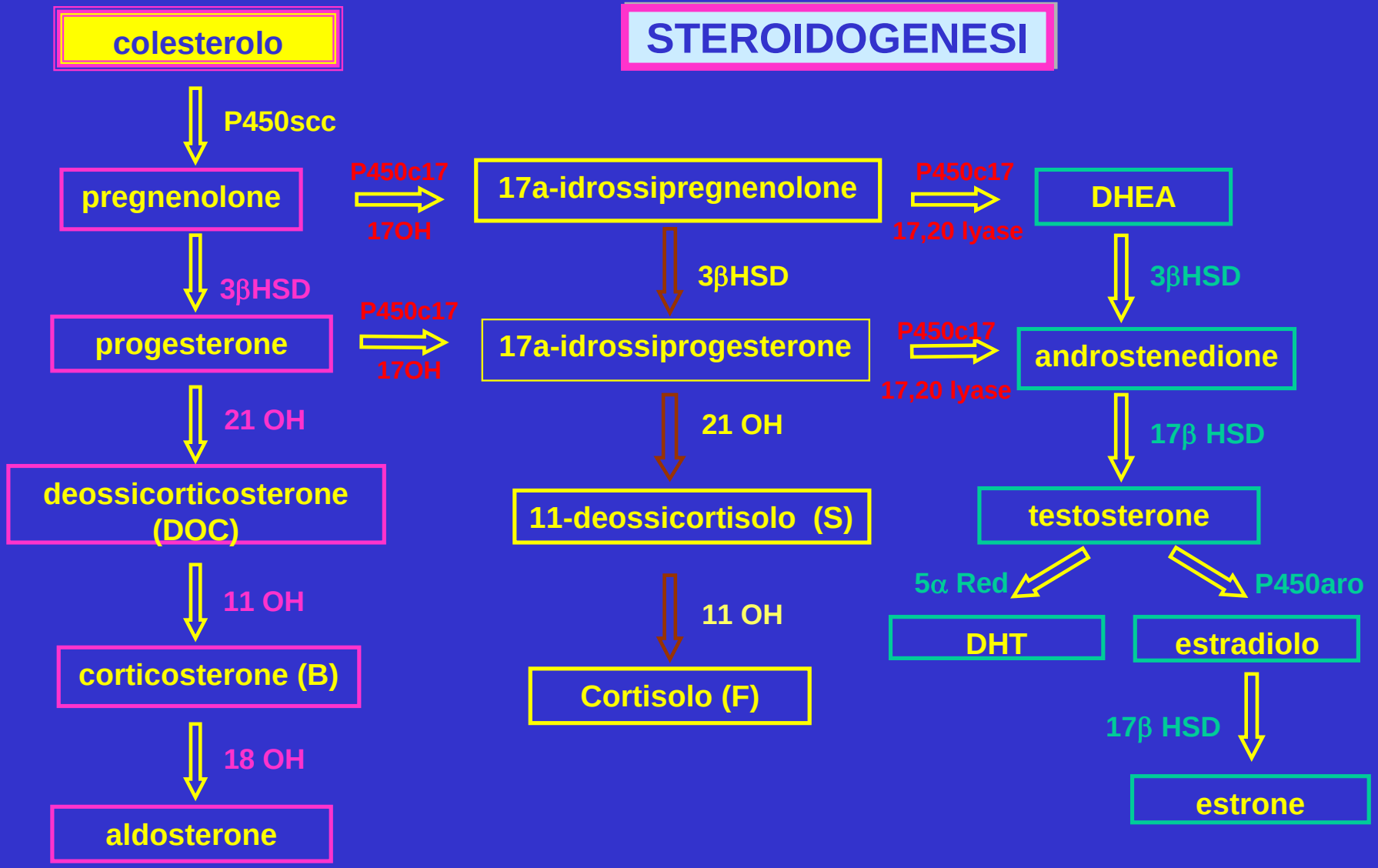
Amenorrea primaria

ACTH ore 8: 721 pg/ml(5-60)
Progesterone: 11,14 ng/ml (0,2-1,4)

- **Cortisolo ore 8: 3,7 mcg/dl (6,2-19,4)**
- **T.Totale: 0.5 ng/ml (3-7.5)**
- **DHEAS: 24,07 mcg/dl(100-300)**
- **Androstenedione: 0,04 ng/ml(0,1-3)**
- **17beta E2: 5,01 pg/ml (13,5- 59,5)**
- **17OH-Progesterone: 0,79 ng/ml(0,5-2,4)**

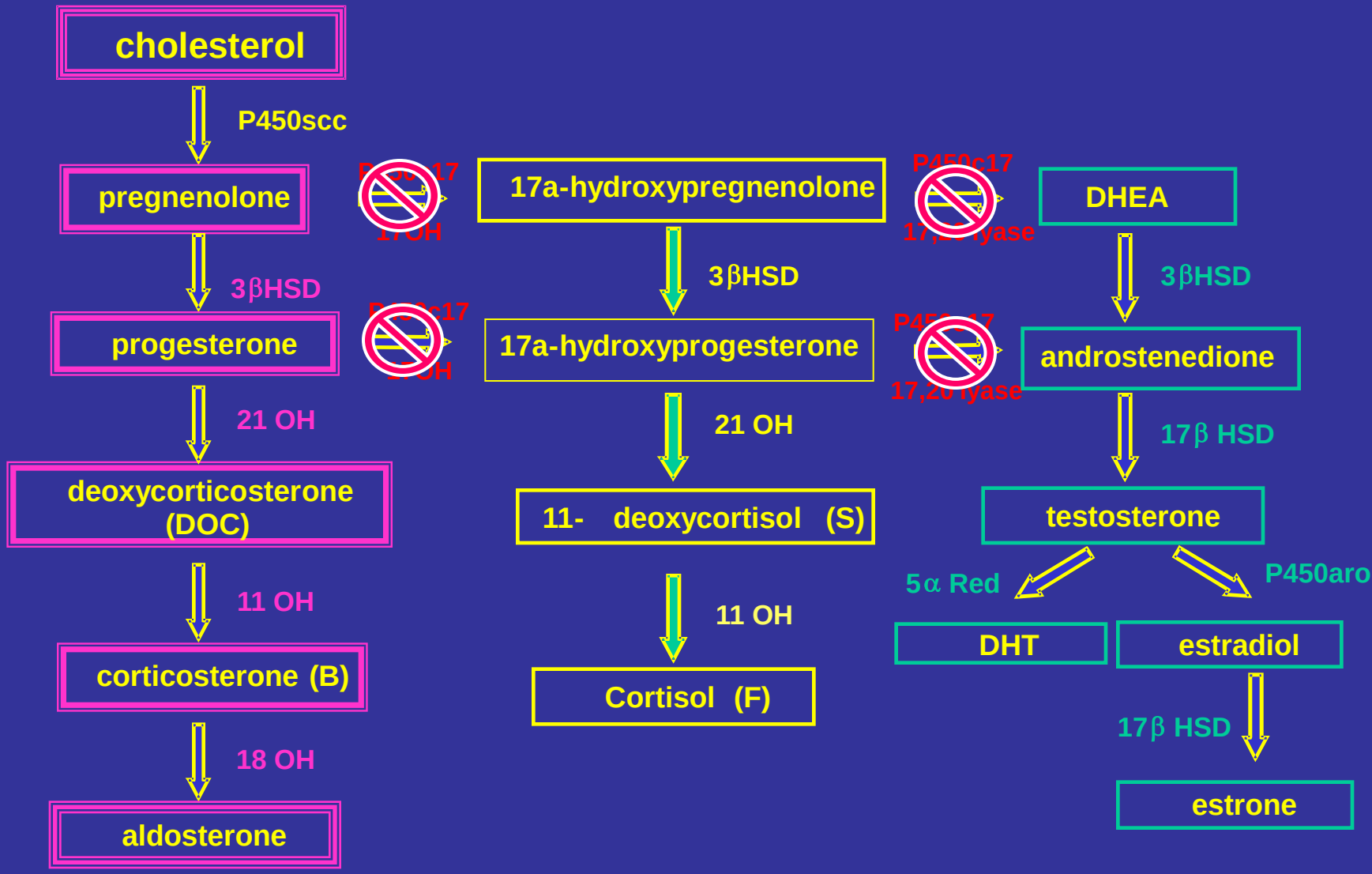
V.Z: 16 anni **cariotipo XY**

STEROIDOGENESI



STEROIDOGENESIS

17α-Hydroxylase/17,20-lyase deficiency



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Amenorrea primaria

- spontaneous pubertal growth spurt takes place
- spurt is quantitatively equal to that of normal girls
- spurt occurs at an appropriate chronological age for girls, but earlier for boys
- bone maturation corresponds better to chronological age for boys than for girls

cariotipo 46, XY

ANDROGEN RESISTANCE COMPLETE

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G.C., 15 years old

AT BIRTH: Hypospadias

AT PUBERTY:
Gynecomastia

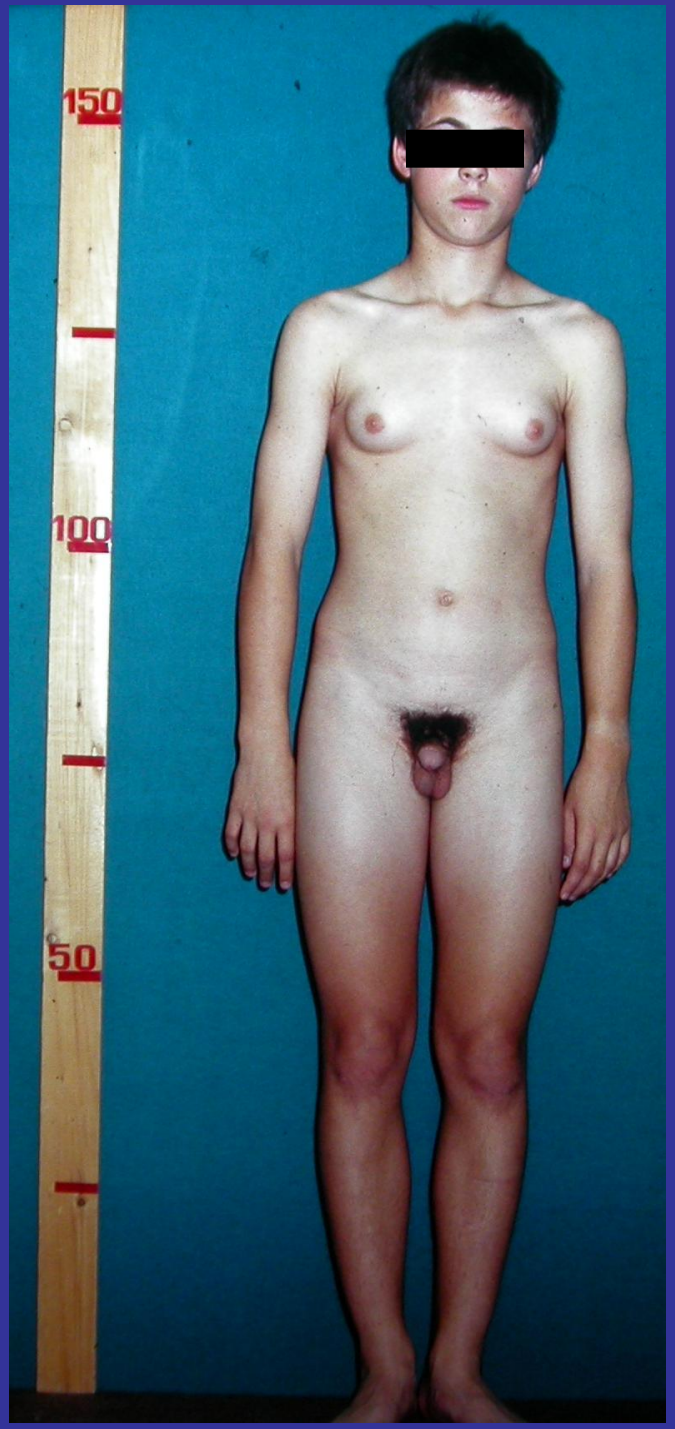
Arise of E2 plasma levels and slight arise of T

Gonadal biopsy: ovarian tissue

XX kariotype

NMR: uterus and prostate

Male gender identity
Male gender role
Male gender



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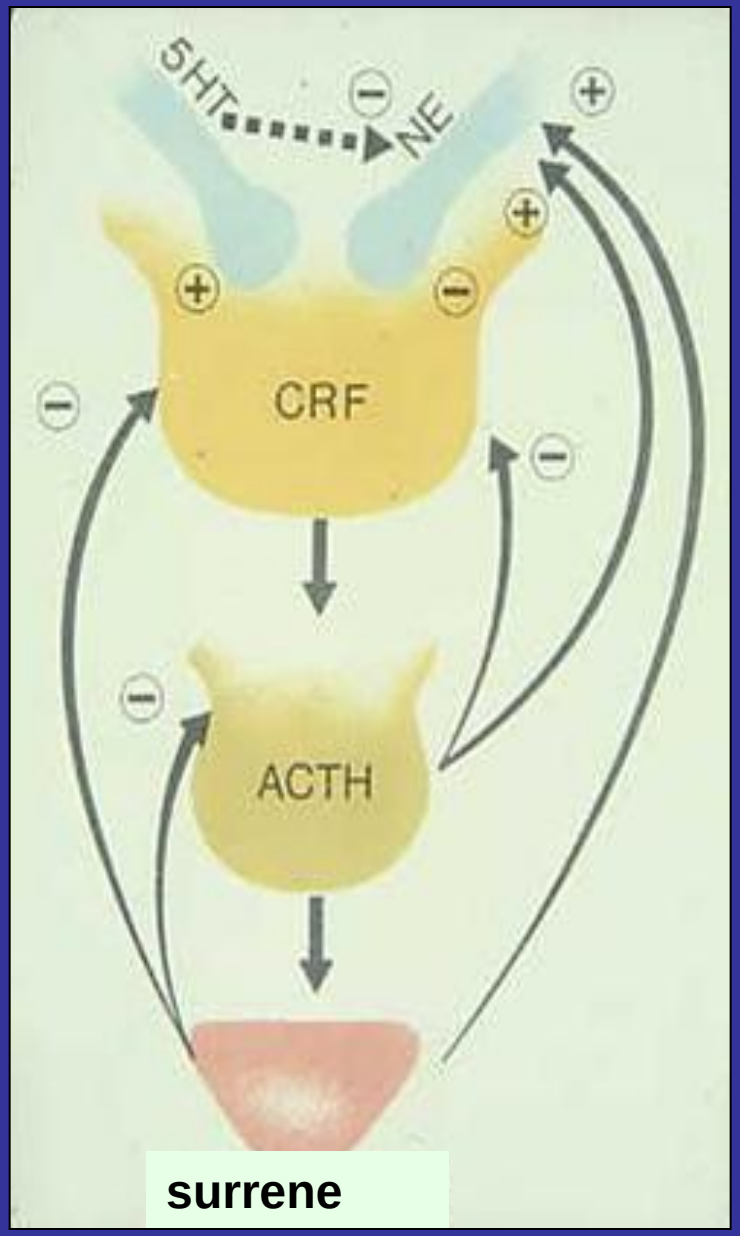
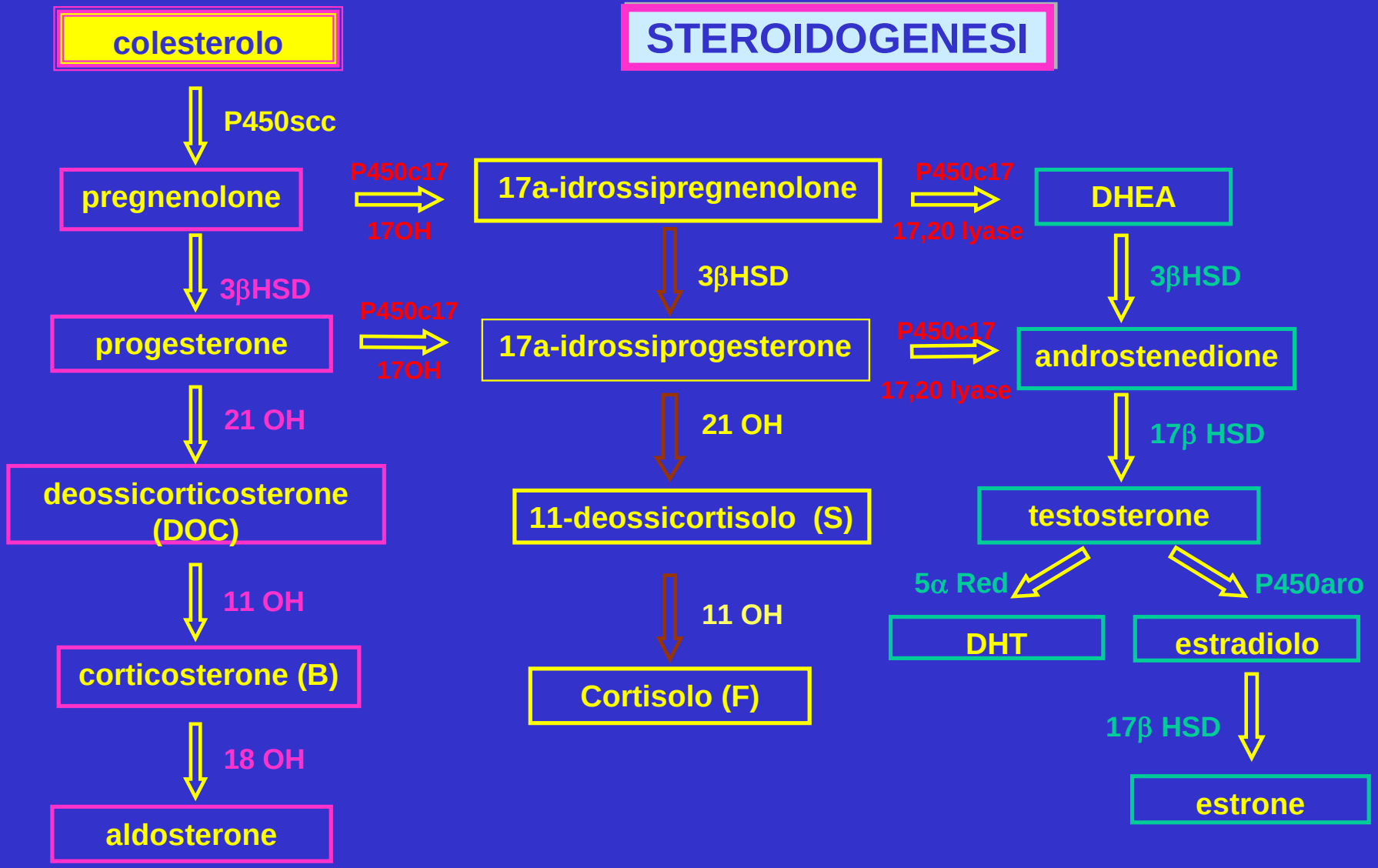
Asse ipotalamo-ipofisi-surrene

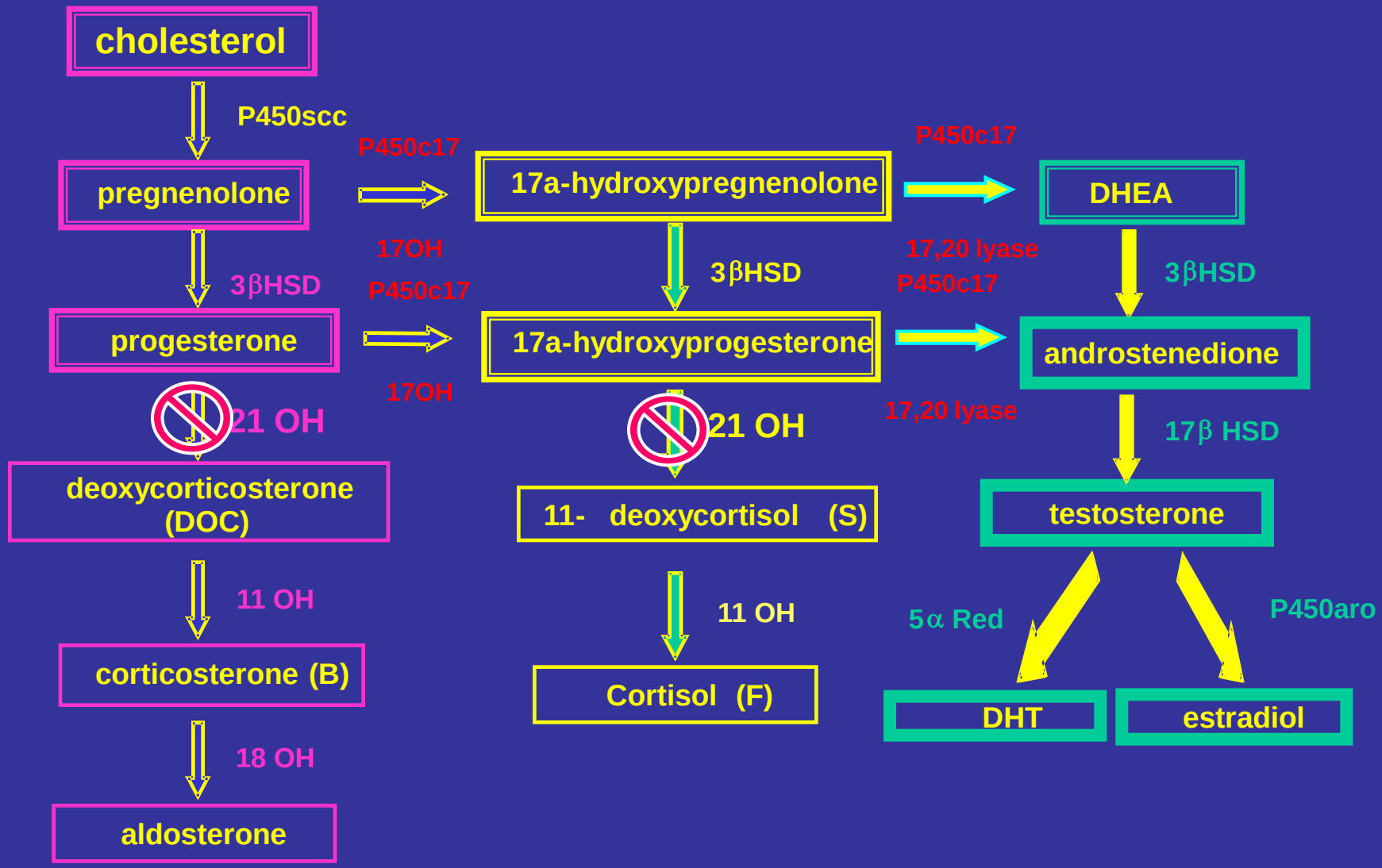


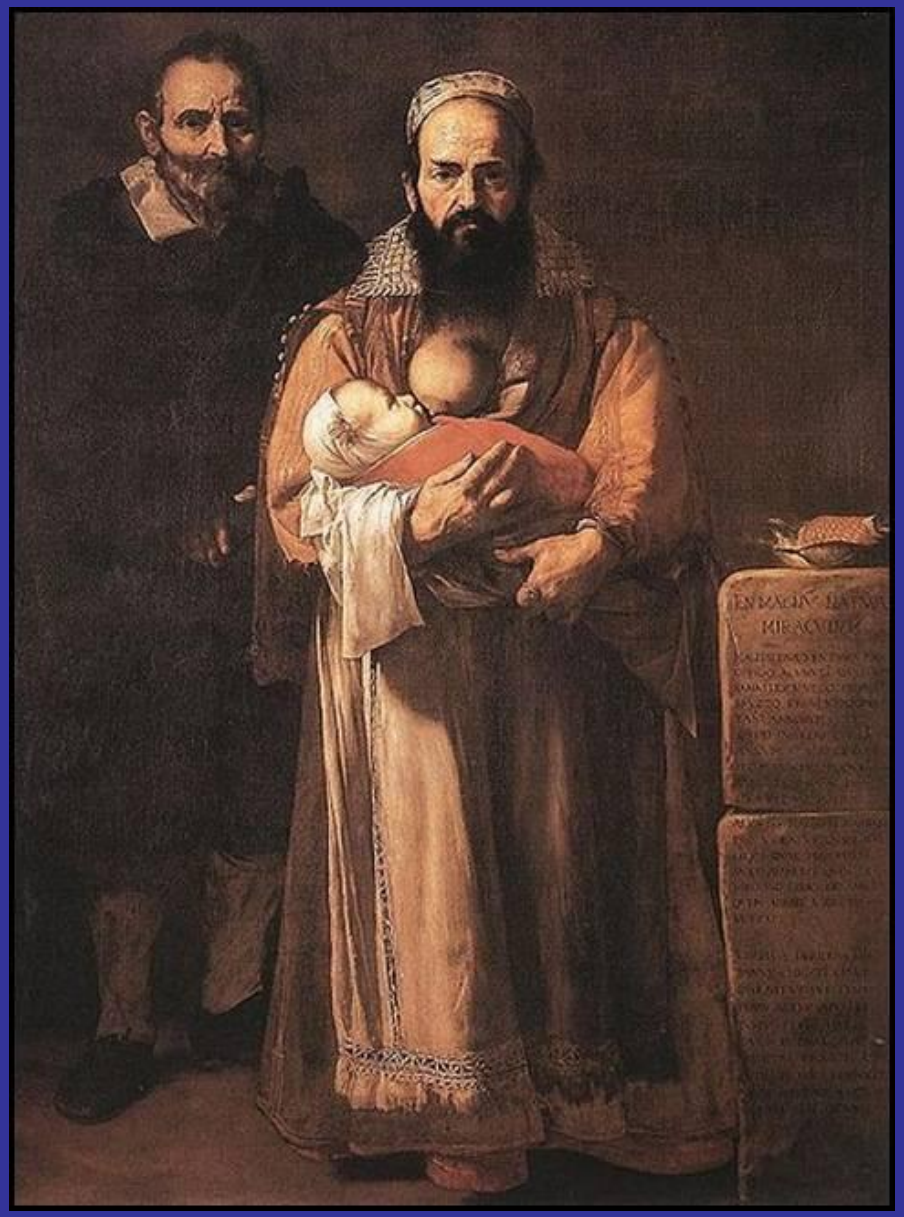
STEROIDOGENESI



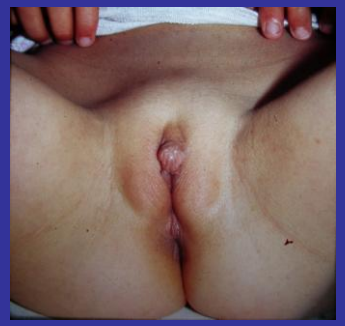
CONGENITAL ADRENAL HYPERPLASIA

21-HYDROXYLASE DEFICIENCY





Ribera, La donna barbuta, 1631



Urogenital sinus

Labial fusion

Scrotalization of labia maiora

Clitoromegaly

Penile enlargment

Precocious adrenarche

Bone age advancement

Rapid growth

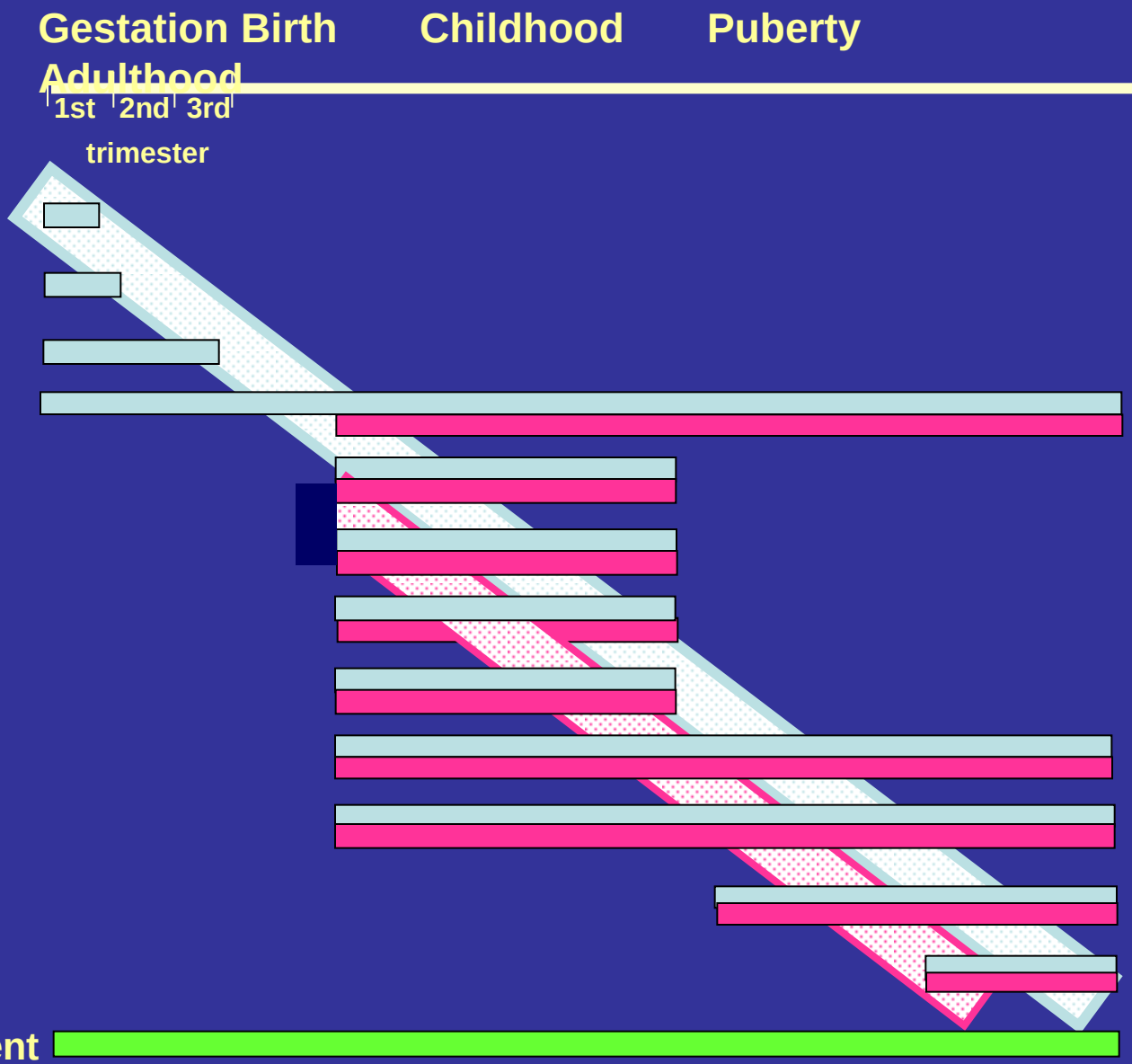
Acne

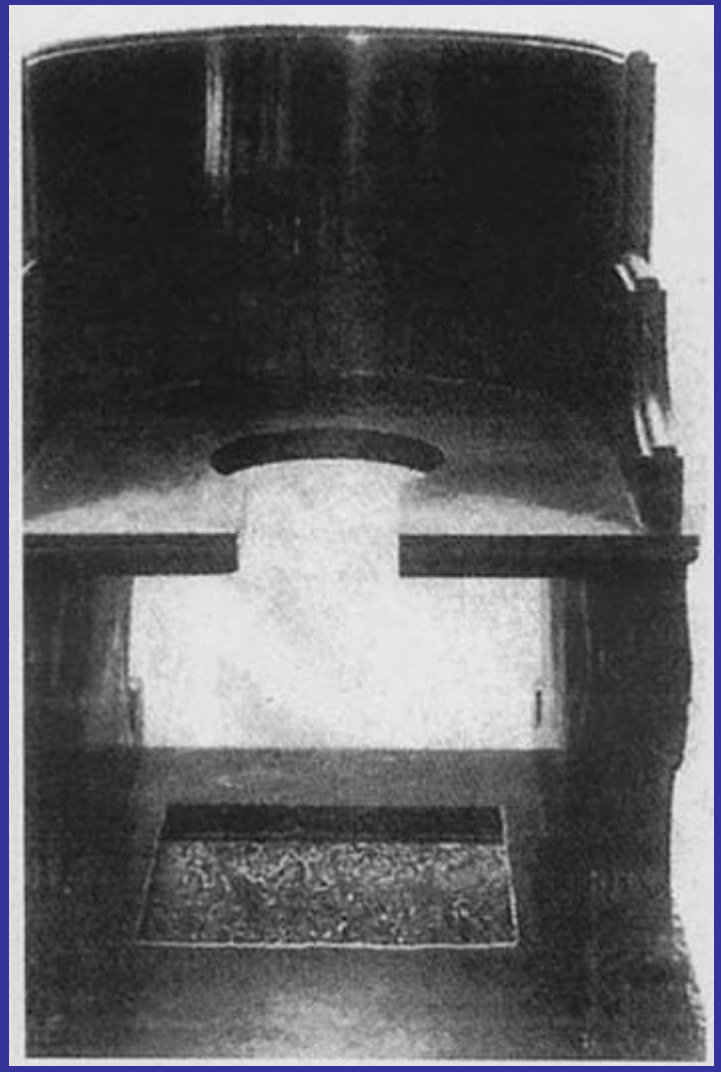
Hirsutism

Menstrual abnormalities

Infertility

Normal growth and development






HABET

Sesso psico-sociale

Femminielli napoletani, 1700

Romano, Palazzo Te, Mantova