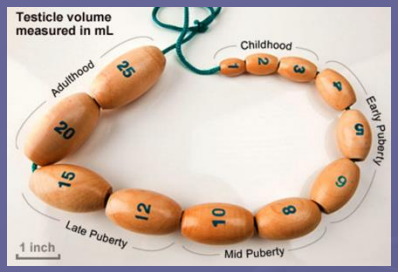
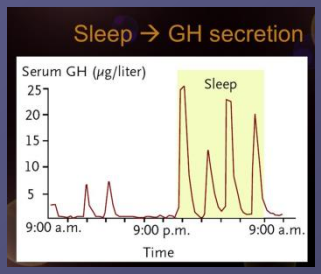
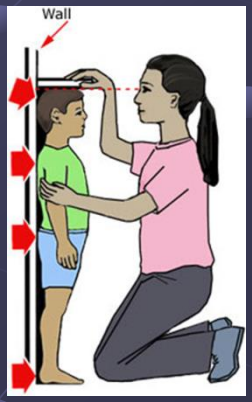


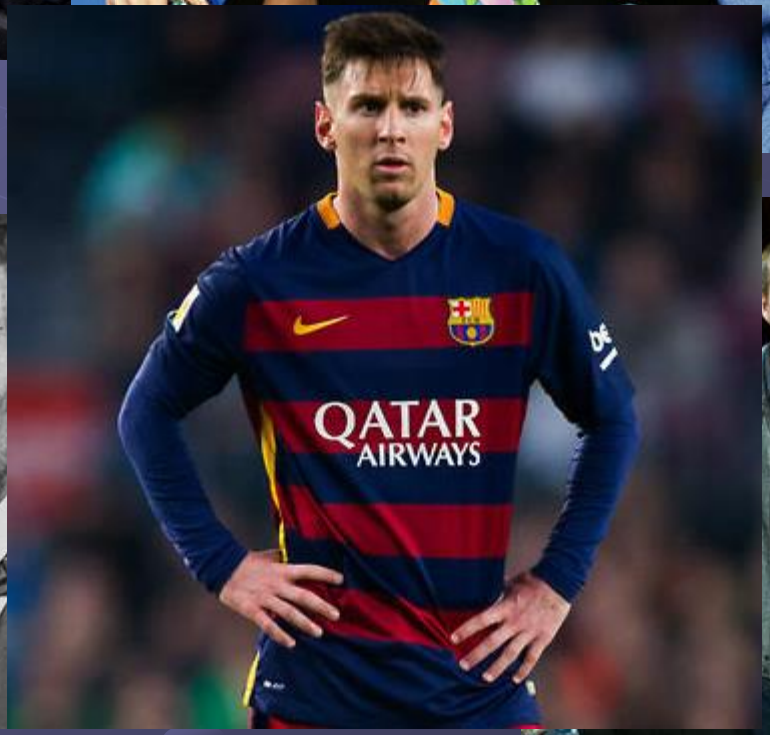


"Common" growth problems in children

Dr Craig Jefferies

Paediatric Endocrinologist
FRACP, MD




QATAR
AIRWAYS

Growth

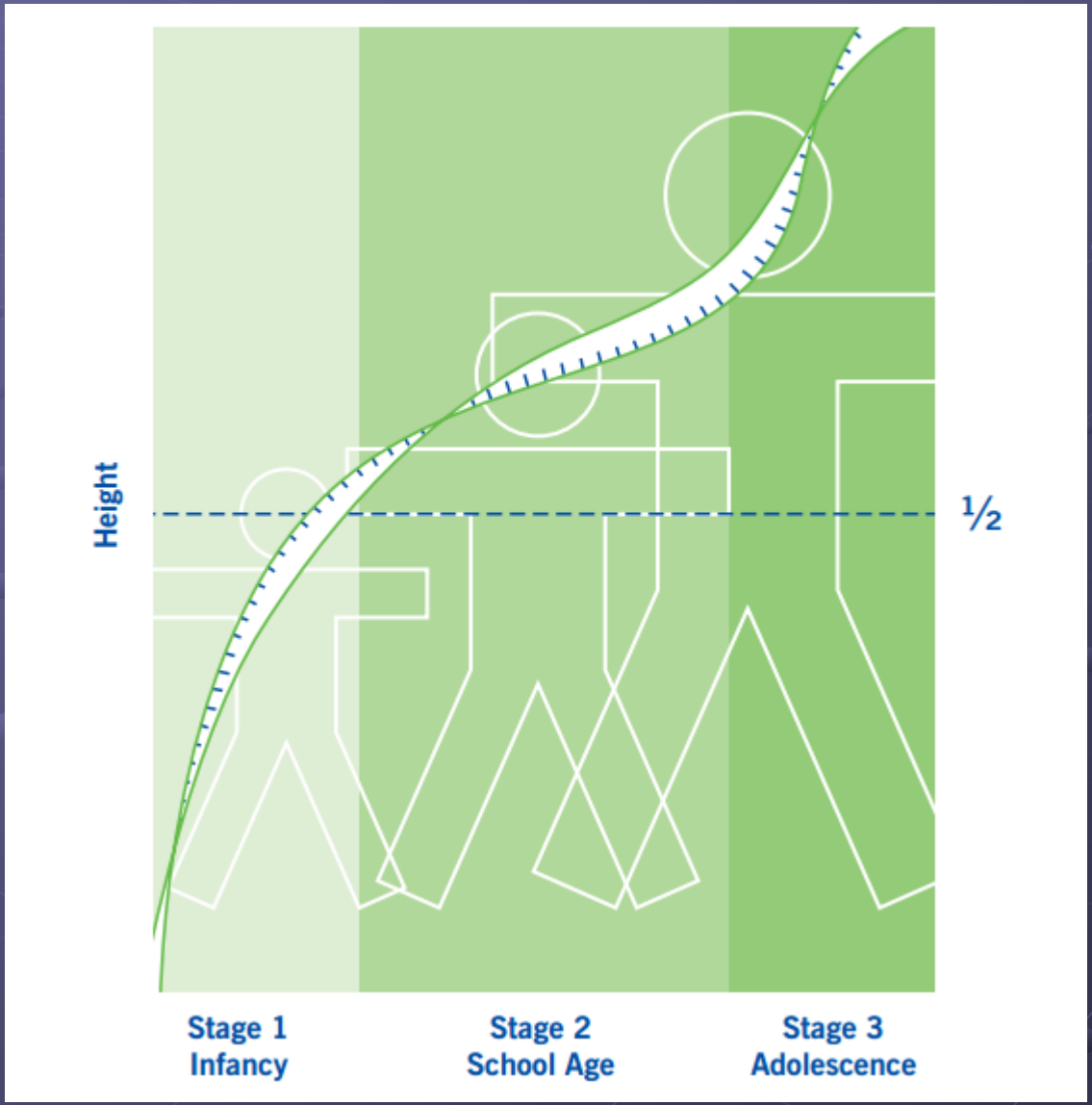
- Growth is the defining characteristic of childhood.
- Normal growth during childhood depends on a combination
  - Good general health
  - Normal nutrition and genetics
  - Adequate nutrition
  - Caring environment
- There are some important underlying conditions that can cause abnormal growth.

Abnormal Growth

- Genetic disorders
- Endocrine disorders
- Cartilage or bone disorders
- General chronic disease.

- Early detection and treatment of underlying conditions can enable many children experiencing abnormal growth to reach their potential.

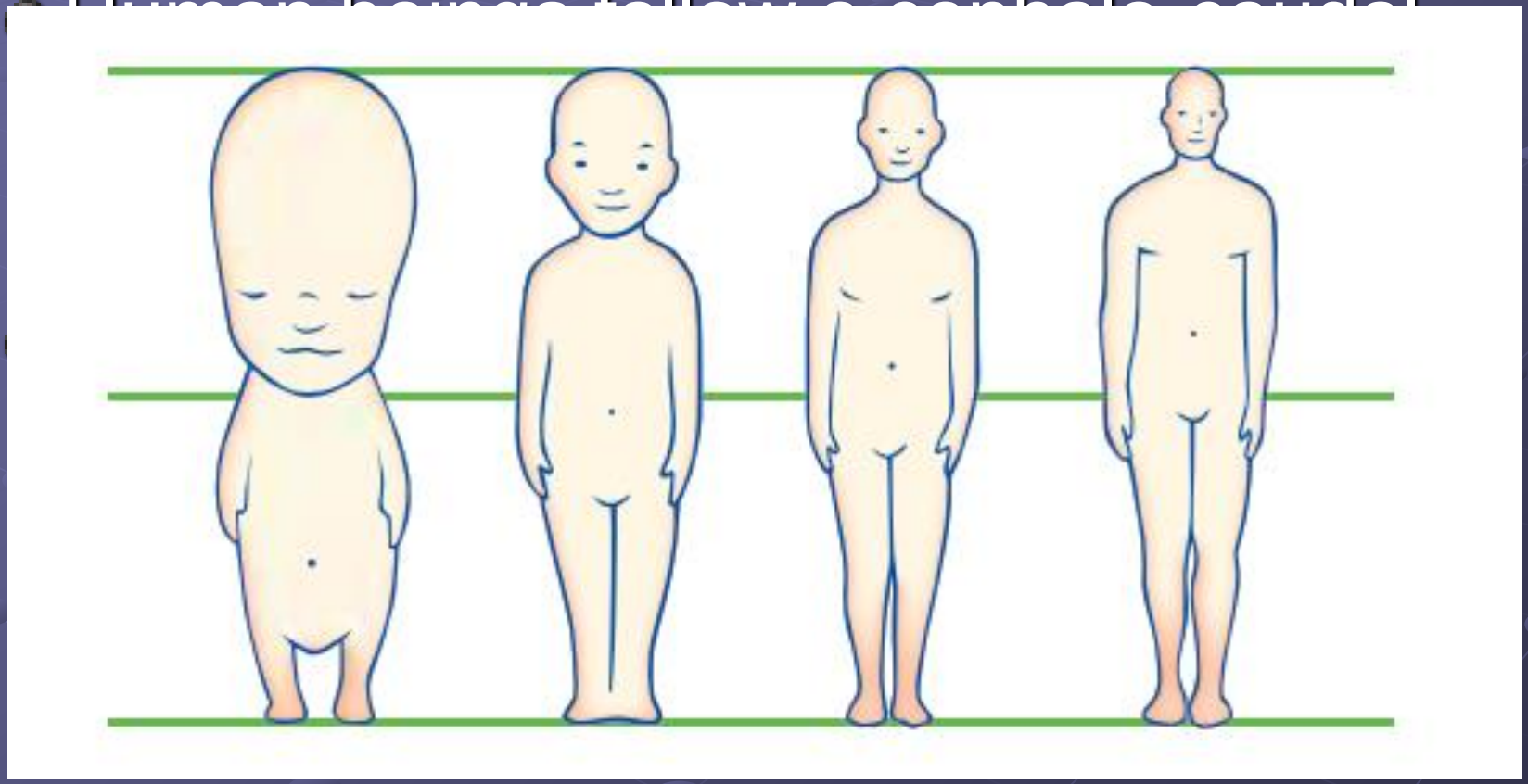
Phases of growth



The ICP (infant/child/puberty) model of growth (Karlberg): 3 periods of growth

- Infant
  - Rapid growth at birth declining rapidly over the first 2 years of life – less GH dependent.
- Childhood
  - Constant annual growth - GH dependent.
- Puberty
  - growth primarily dependent on sex steroids and increased GH release.

- Human beings follow a cephalo-caudal



Growth

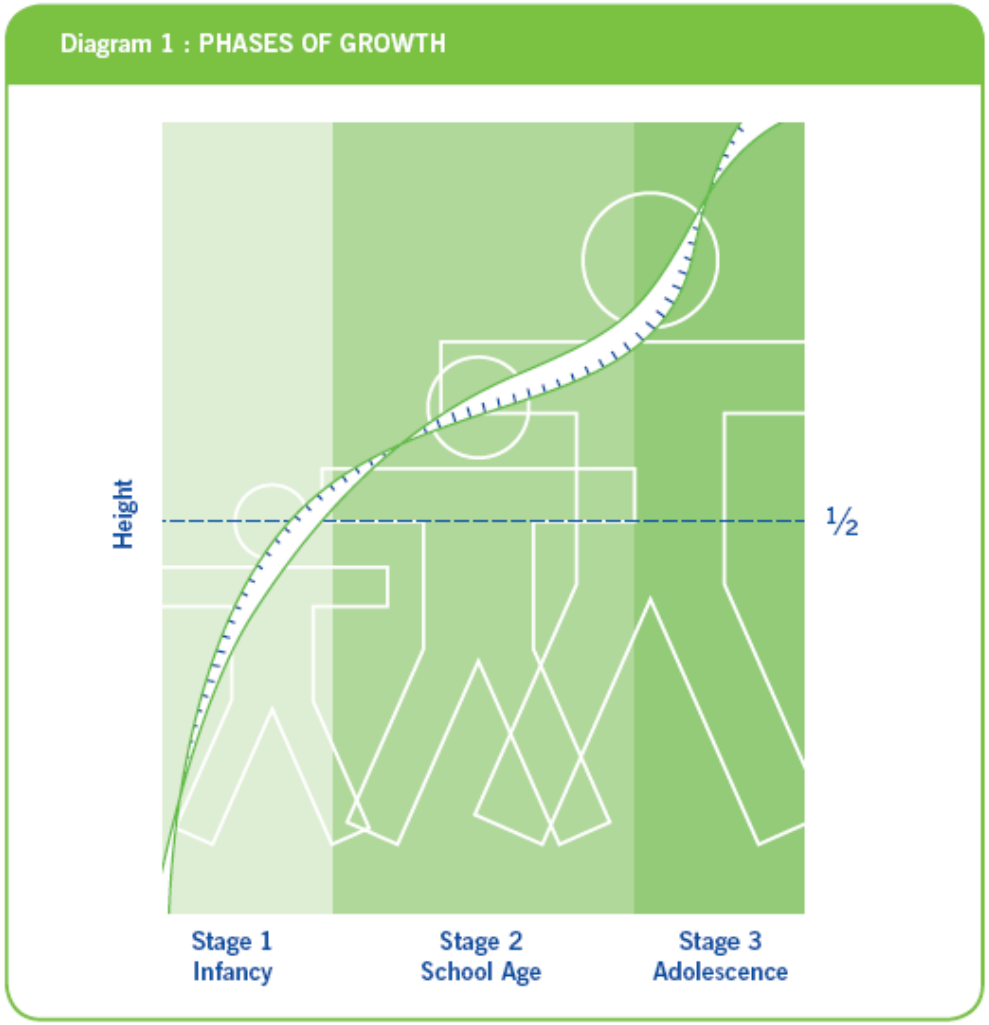


Diagram 1 : PHASES OF GROWTH
Height
1/2
Stage 1
Infancy
Stage 2
School Age
Stage 3
Adolescence

Assessment of Abnormal Growth

Table 1 : DETAILED MEDICAL HISTORY

General Examinations

- measurement of length, height, weight and head circumference
- body proportions, usual physical features, pubertal status
- general health
- height of parents

Screening Investigations

Blood Tests

- full blood count, ESR
- blood chemistry (creatinine, electrolytes, calcium, phosphate)
- coeliac screen
- hormone function (e.g. thyroid hormone levels, IGF1 & IGFBP3)
- chromosome studies

Urine Tests

- microscopic examination
- chemical assessment

Imaging

- X-rays to assess bone structure and maturity

Table 4 : CONDITIONS OF CHRONIC ILLNESS ASSOCIATED WITH POOR GROWTH

- Anaemias & other blood disorders
- Malnutrition
- Asthma, Cystic Fibrosis and other Lung conditions
- Heart Disease
- Coeliac, Inflammatory Bowel Disease & other intestinal disorders
- Kidney Disease
- Liver Disease
- Rheumatoid arthritis
- Metabolic disorders
- Other Long-term Disorders

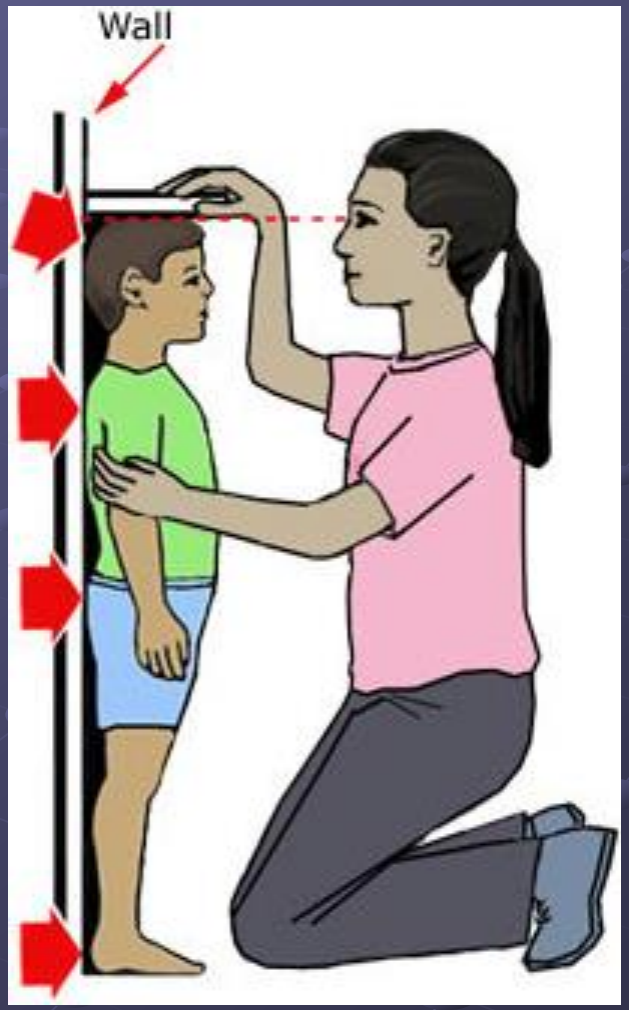
Child Development record

A valuable source of information.

Look at all available height and weight measurements and growth trend.

Remember that Plunket height measurements are not precise and may be misleading.

Check developmental milestones and illnesses.


Wall

Mid parental height

Table 3

To calculate the potential height of a boy, the mother's height is given an additional 13cm and averaged with the father's height. This mid parental or "target height" can be plotted on a growth chart to estimate the centile the boy should grow along.

e.g. FATHER 180cm

MOTHER 157cm +13cm =170cm

AVERAGE 175cm = potential height =50th height centile

(*See Diagram 3*)

To estimate a girl's height, subtract 13cm from the father's height and follow the same steps as above.

MPH = M(cm) + F (cm) +/-13 cm /2.

MPH range +/- 8 cm.

Height Percentile

Mother's Height

Father's Height

Simplified Calculation of Body Surface Area (BSA)

$$BSA\ (m^2) = \sqrt{\frac{Ht\ (cm) \times Wt\ (kg)}{3600}}$$

Reference: Mosteller, R.D. 1987, 'Simplified calculation of body surface area', *N. Engl. J. Med.*, 317:1098.

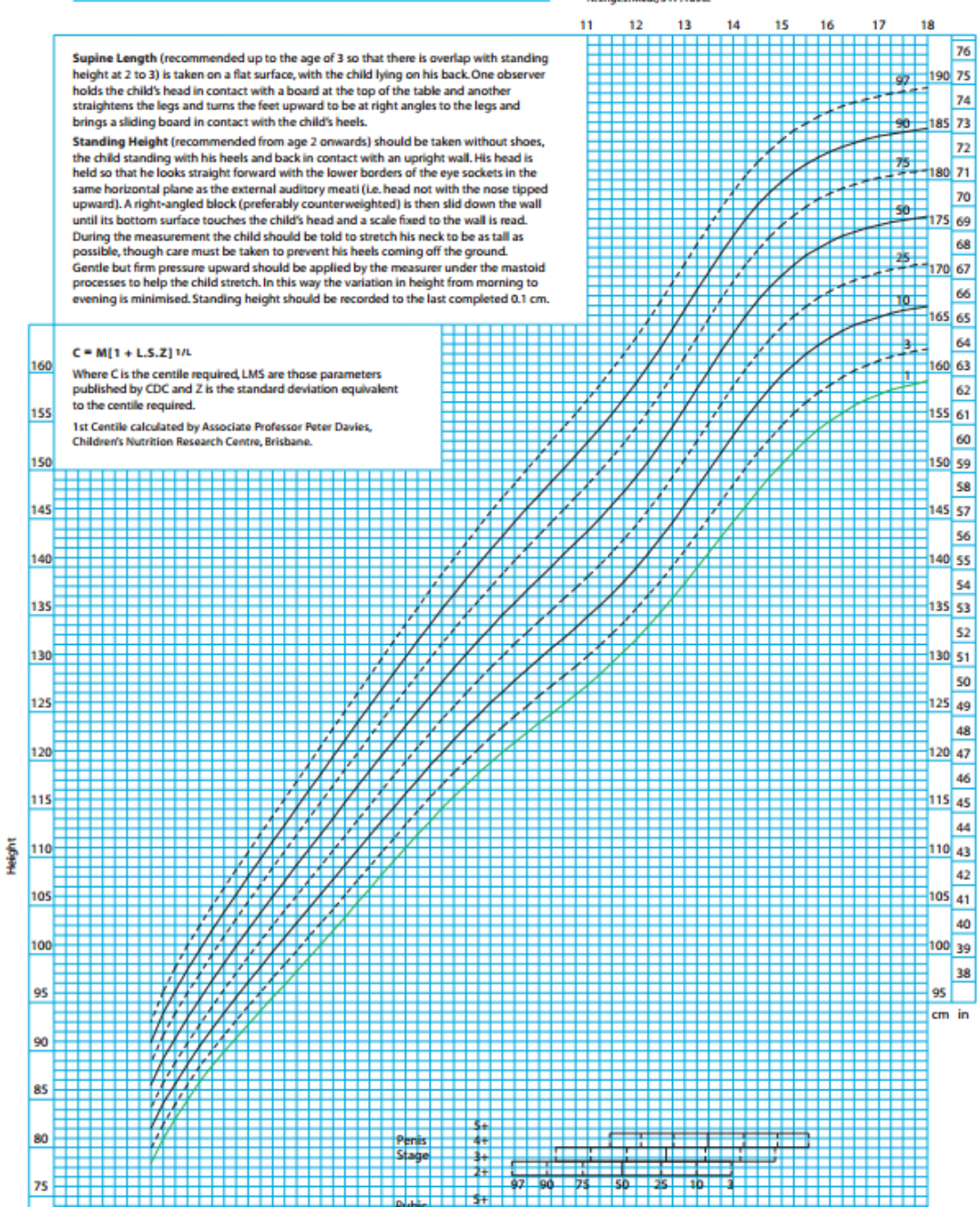
Supine Length (recommended up to the age of 3 so that there is overlap with standing height at 2 to 3) is taken on a flat surface, with the child lying on his back. One observer holds the child's head in contact with a board at the top of the table and another straightens the legs and turns the feet upward to be at right angles to the legs and brings a sliding board in contact with the child's heels.

Standing Height (recommended from age 2 onwards) should be taken without shoes, the child standing with his heels and back in contact with an upright wall. His head is held so that he looks straight forward with the lower borders of the eye sockets in the same horizontal plane as the external auditory meati (i.e. head not with the nose tipped upward). A right-angled block (preferably counterweighted) is then slid down the wall until its bottom surface touches the child's head and a scale fixed to the wall is read. During the measurement the child should be told to stretch his neck to be as tall as possible, though care must be taken to prevent his heels coming off the ground. Gentle but firm pressure upward should be applied by the measurer under the mastoid processes to help the child stretch. In this way the variation in height from morning to evening is minimised. Standing height should be recorded to the last completed 0.1 cm.

$$C = M[1 + L.S.Z]^{1/L}$$

Where C is the centile required, LMS are those parameters published by CDC and Z is the standard deviation equivalent to the centile required.

1st Centile calculated by Associate Professor Peter Davies, Children's Nutrition Research Centre, Brisbane.

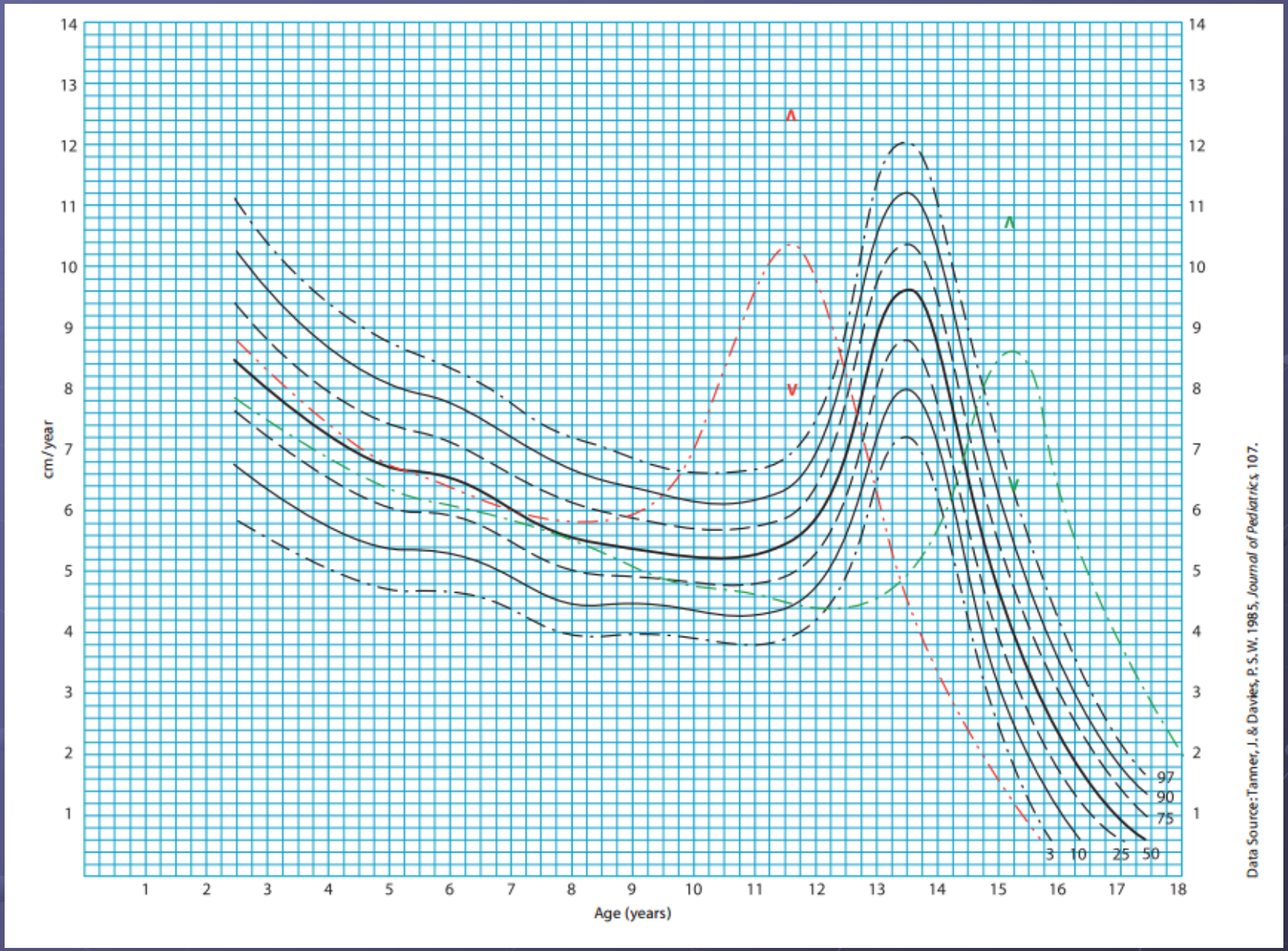


www.rch.org.au/growthcharts/data/files.htm

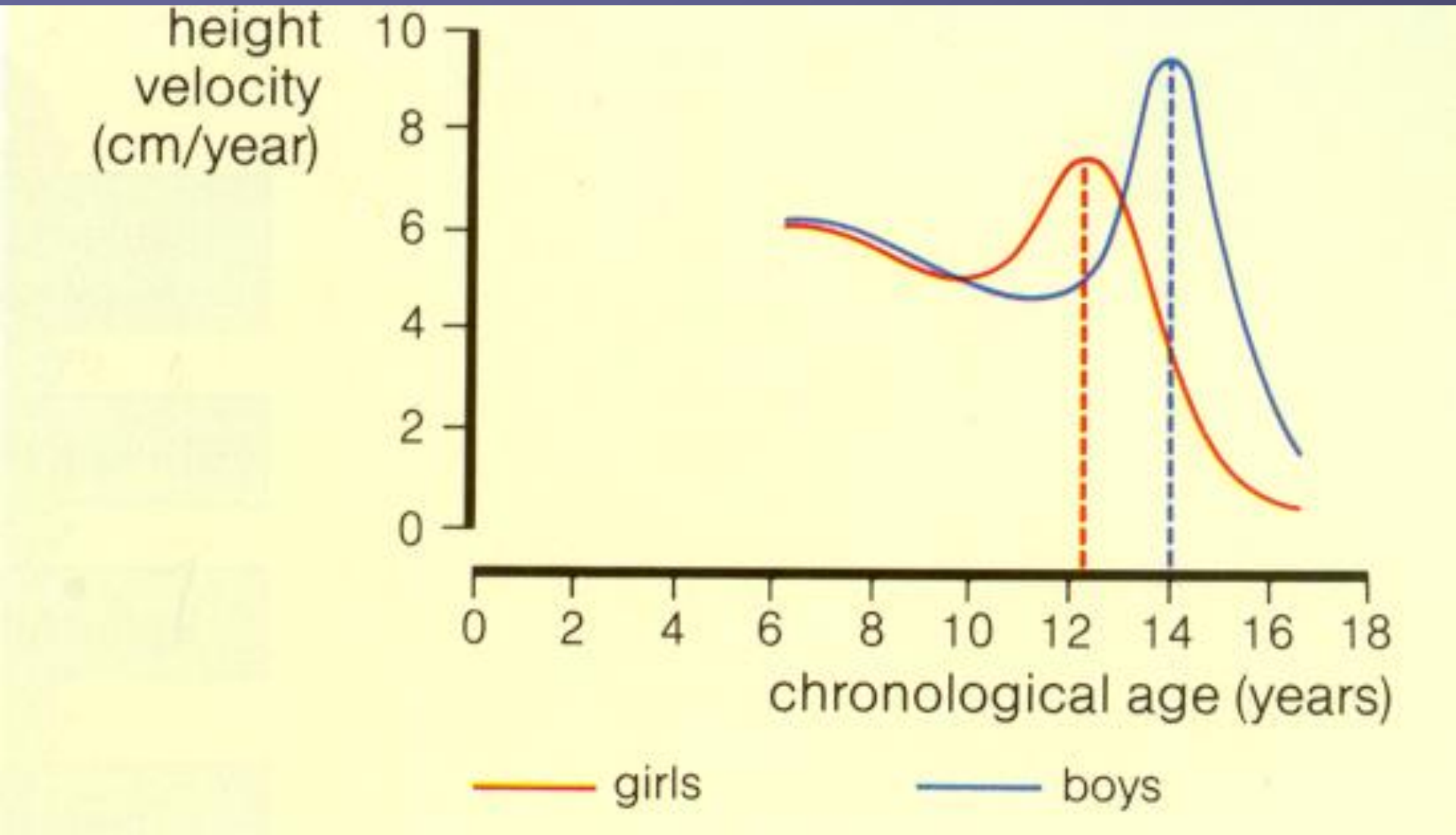
Height velocity (HV)

- HV differentiates normal variant short stature from pathological short stature.
- HV calculated over 6-12 month interval because of errors in measurement.

- Normal height velocity 25-75 PC.
- Note HV curve for children with delayed puberty.



www.apeg.org.au


height
velocity
(cm/year)
10
8
6
4
2
0
0
2
4
6
8
10
12
14
16
18
chronological age (years)
girls
boys

Short Stature

- A common clinical problem.
- A symptom and not a disease.
- May represent a variant of normal growth.
- May indicate pathology.
- One of the commonest manifestations of chronic illness; recognized or unrecognized.

Short Stature History

- Mother and fathers heights.
  - MPH = M(cm) + F (cm) ±13 cm /2.
  - MPH range ±8 cm.
- FHx delayed puberty: menarche >14 yrs in females and continued growth after high school in males.
- Look at other sibs child development records.

Growth Disorders

Normal height velocity:

Familial short stature

Constitutional delay in growth and development

Poor height velocity:

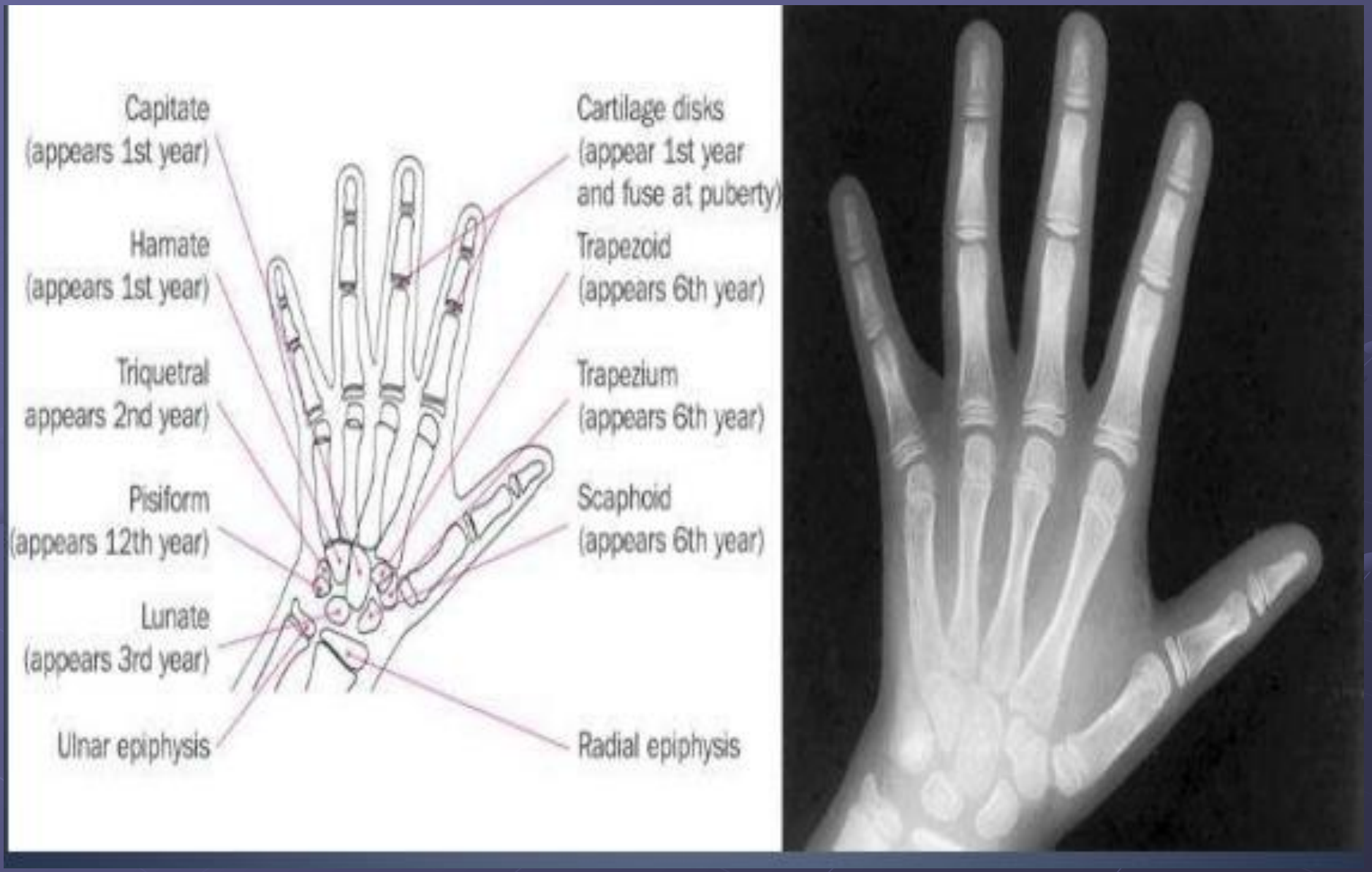
Usually pathological

Proportionate

Disproportionate

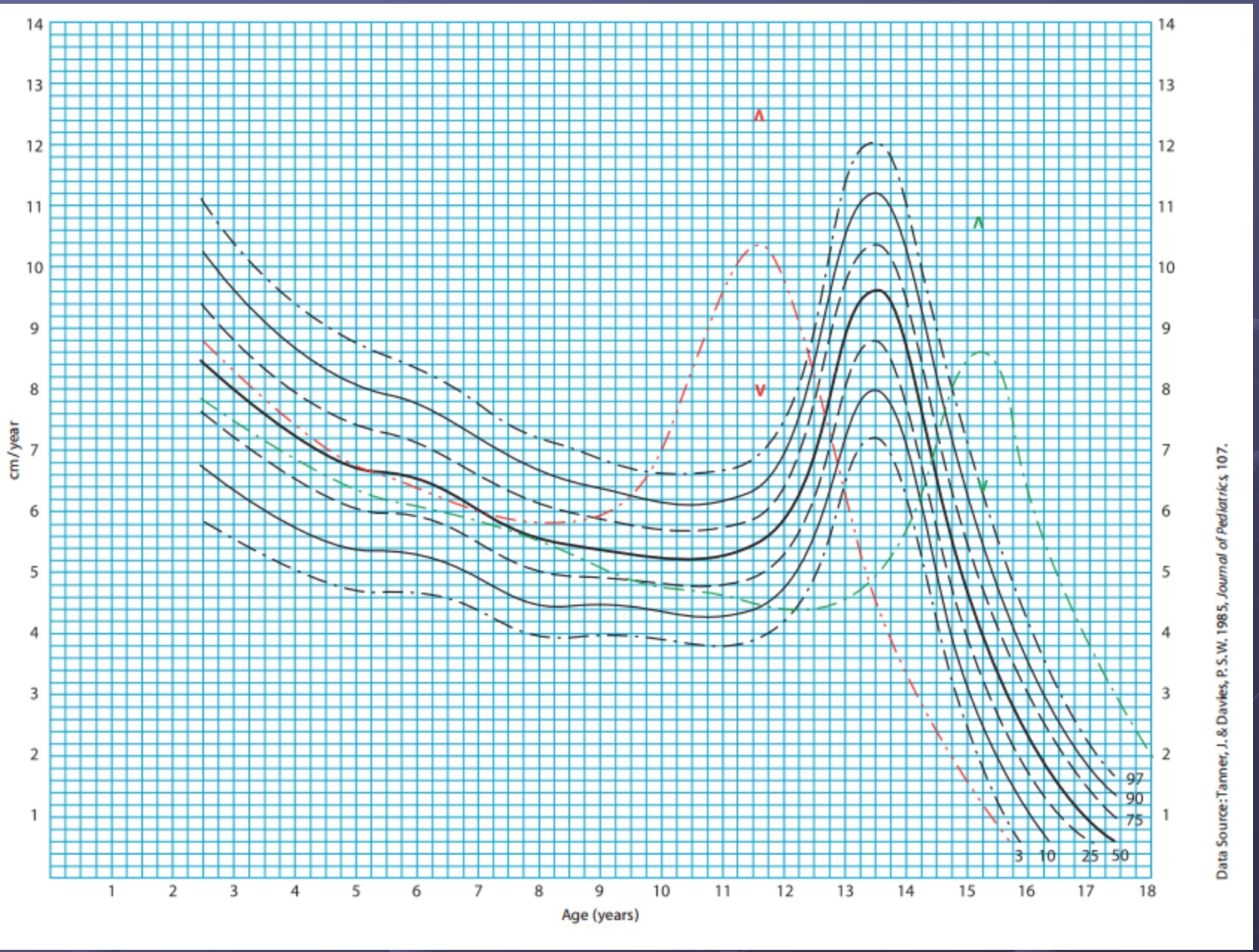
Bone Age

- Gruelich and Pyle standards.
- Imprecise picture matching.
- ~1 yr intervals.
- Tables of Bayley and Pinneau for final Ht prediction.
- Predicted adult height (PAH) useful to distinguish FSS and CDGD for Dx and reassurance.


Capitate
(appears 1st year)
Hamate
(appears 1st year)
Triquetral
appears 2nd year)
Pisiform
(appears 12th year)
Lunate
(appears 3rd year)
Ulnar epiphysis
Cartilage disks
(appear 1st year
and fuse at puberty)
Trapezoid
(appears 6th year)
Trapezium
(appears 6th year)
Scaphoid
(appears 6th year)
Radial epiphysis

Normal Variant Short Stature

- Familial short stature.
- Constitutional delay of growth and development.
- Account for >95% of children who present with short stature.
- HALLMARK IS NORMAL HEIGHT VELOCITY.


cm/year
Age (years)
97
90
75
50
25
10
3
Data Source: Tanner, J. & Davies, P. S. W. 1985, Journal of Pediatrics, 107.

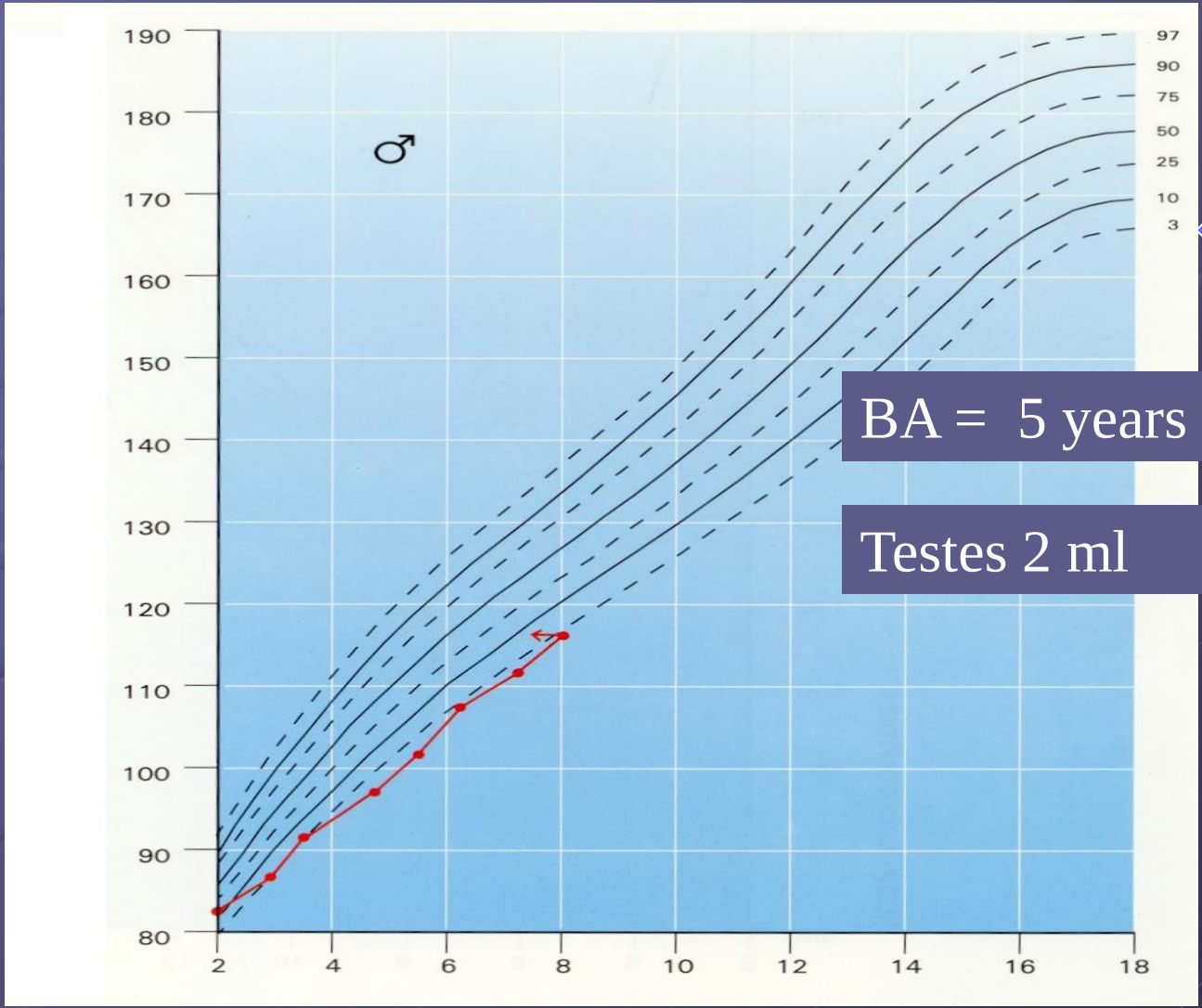
Normal Variant Short Stature

	FSS	CDGD
Birthweight	Normal	Normal
Chronic illness	Absent	Absent
Family history	FSS	CDGD
Infant growth	X centiles	X centiles
Childhood HV	Normal	Normal
Late childhood HV	normal	slow
Bone age	Same	
Delayed		

Normal Variant Short Stature

	FSS	CDGD
Bone Age	<1 yr from CA	>1 yr from CA
Puberty	On time	Delayed
Final Height	Short	Normal

Growth Case 1

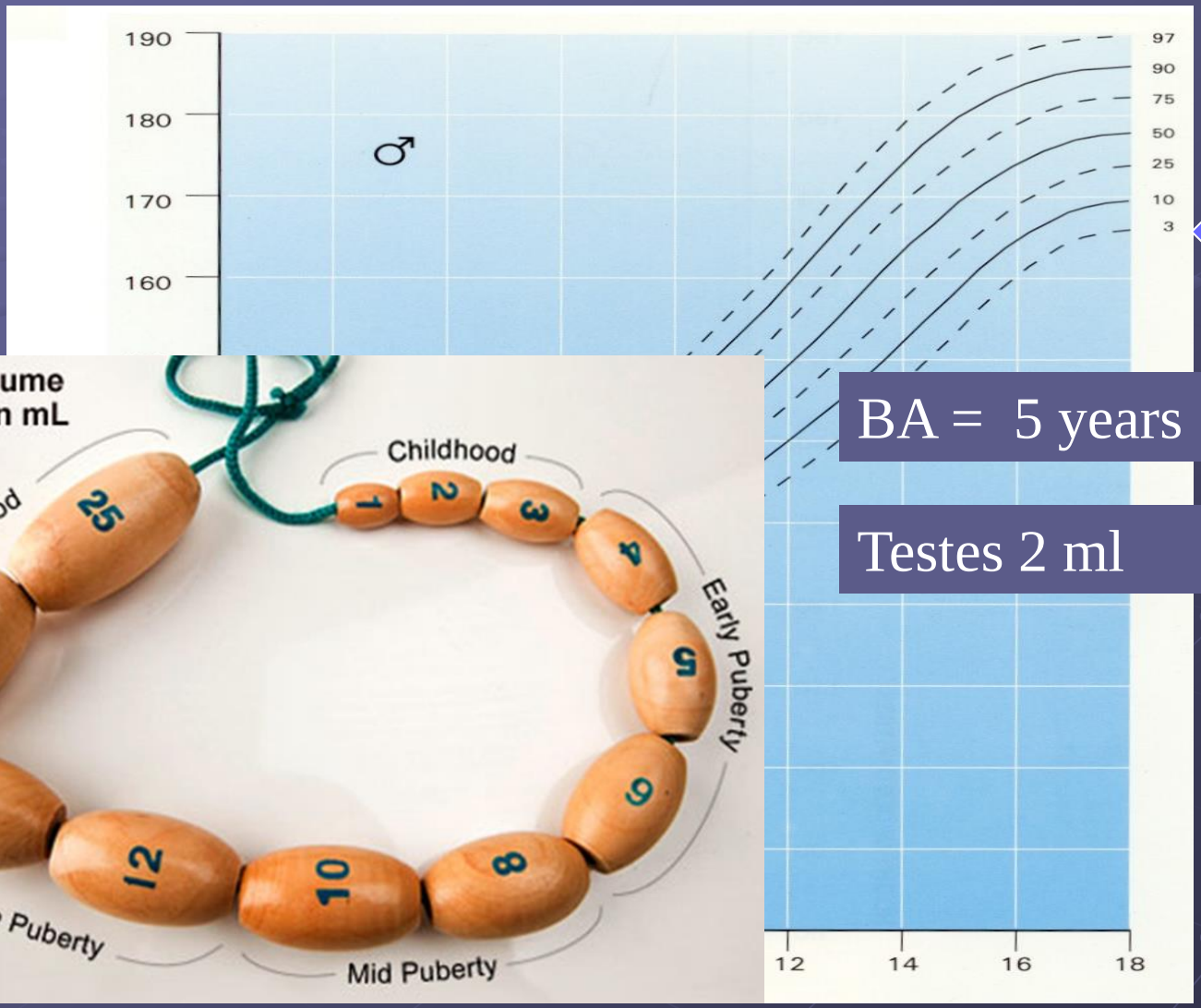


MPH

BA = 5 years

Testes 2 ml

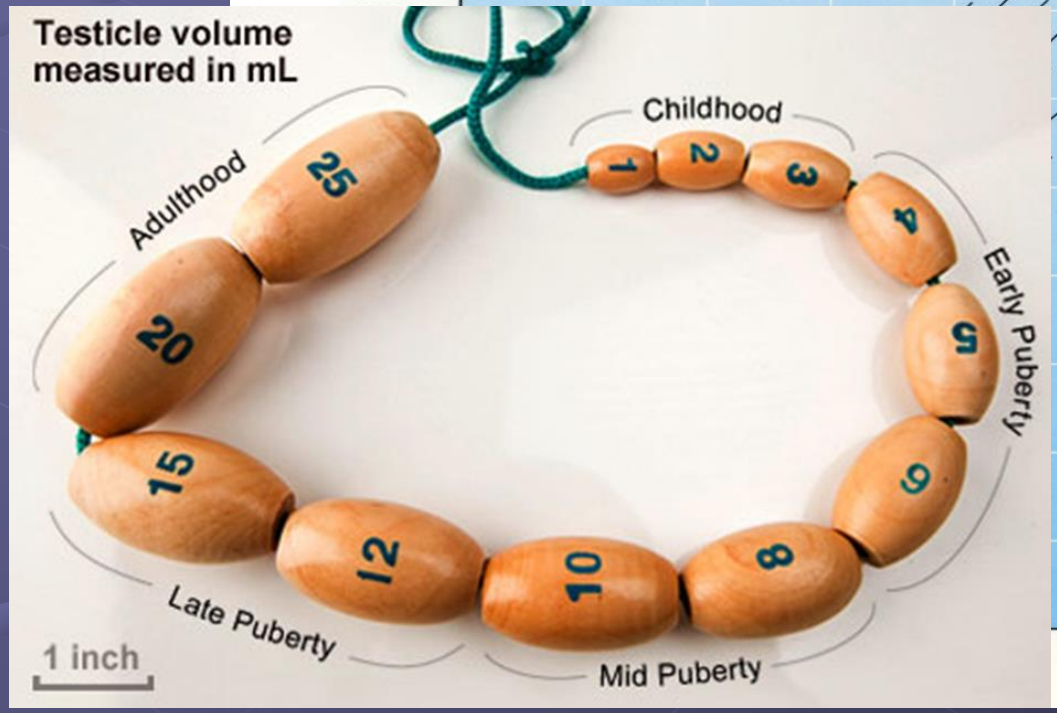
Growth Case 1

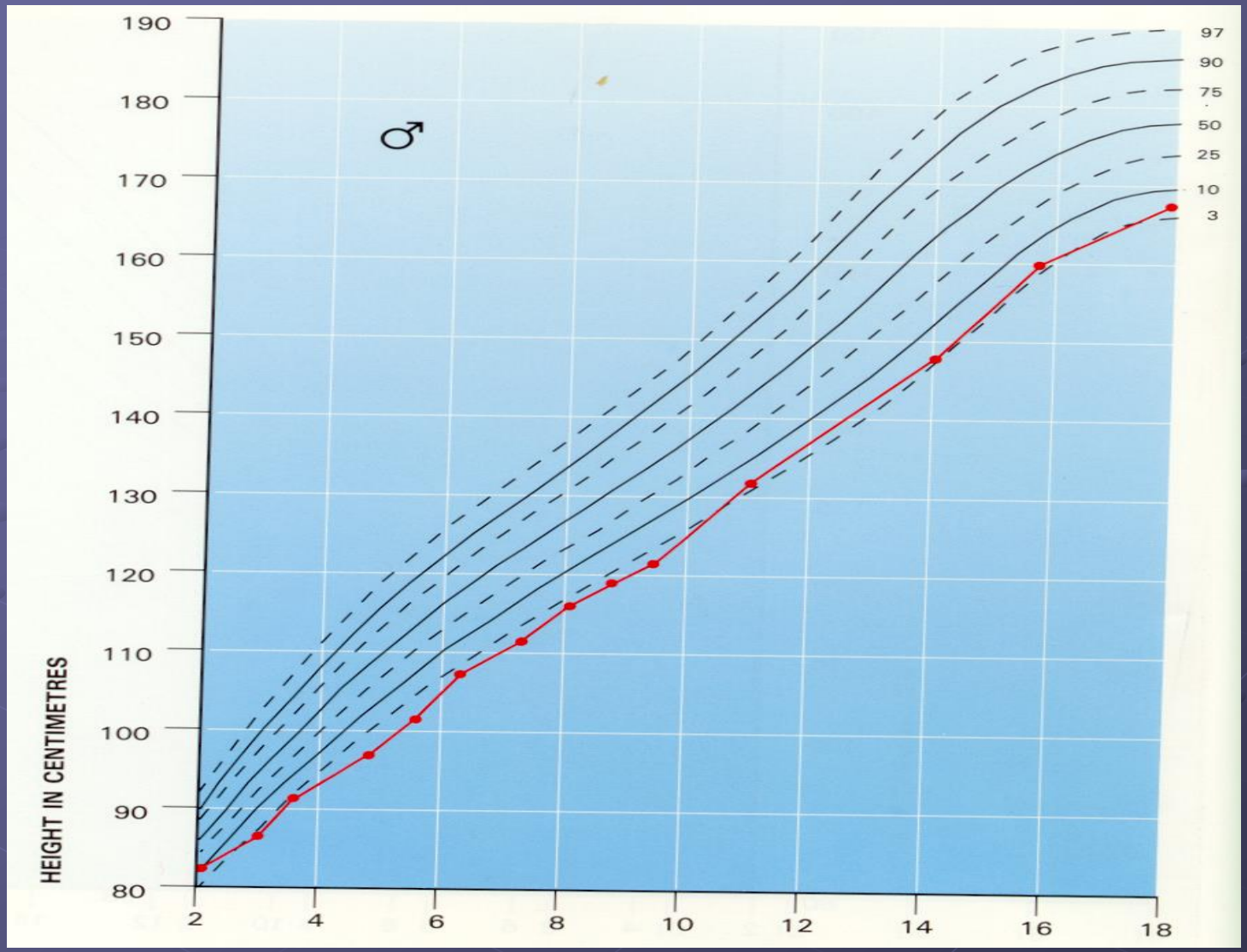


MPH

BA = 5 years

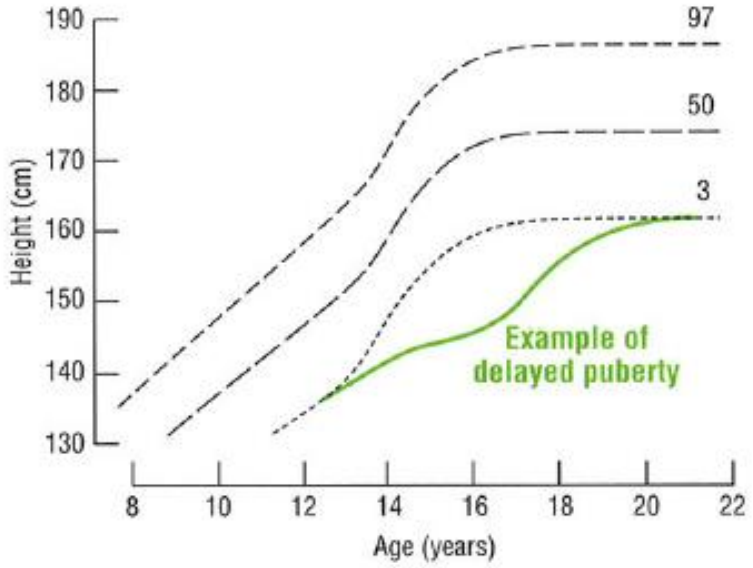
Testes 2 ml





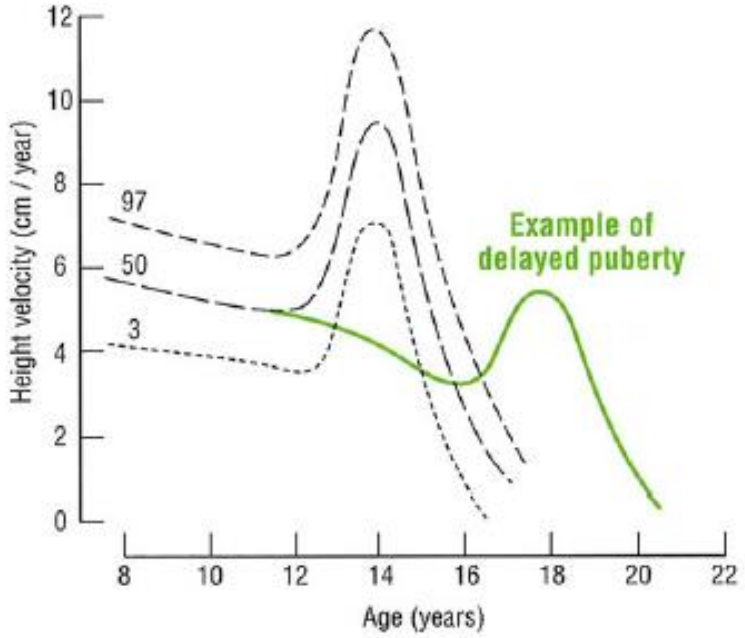
Familial short stature

a) Growth

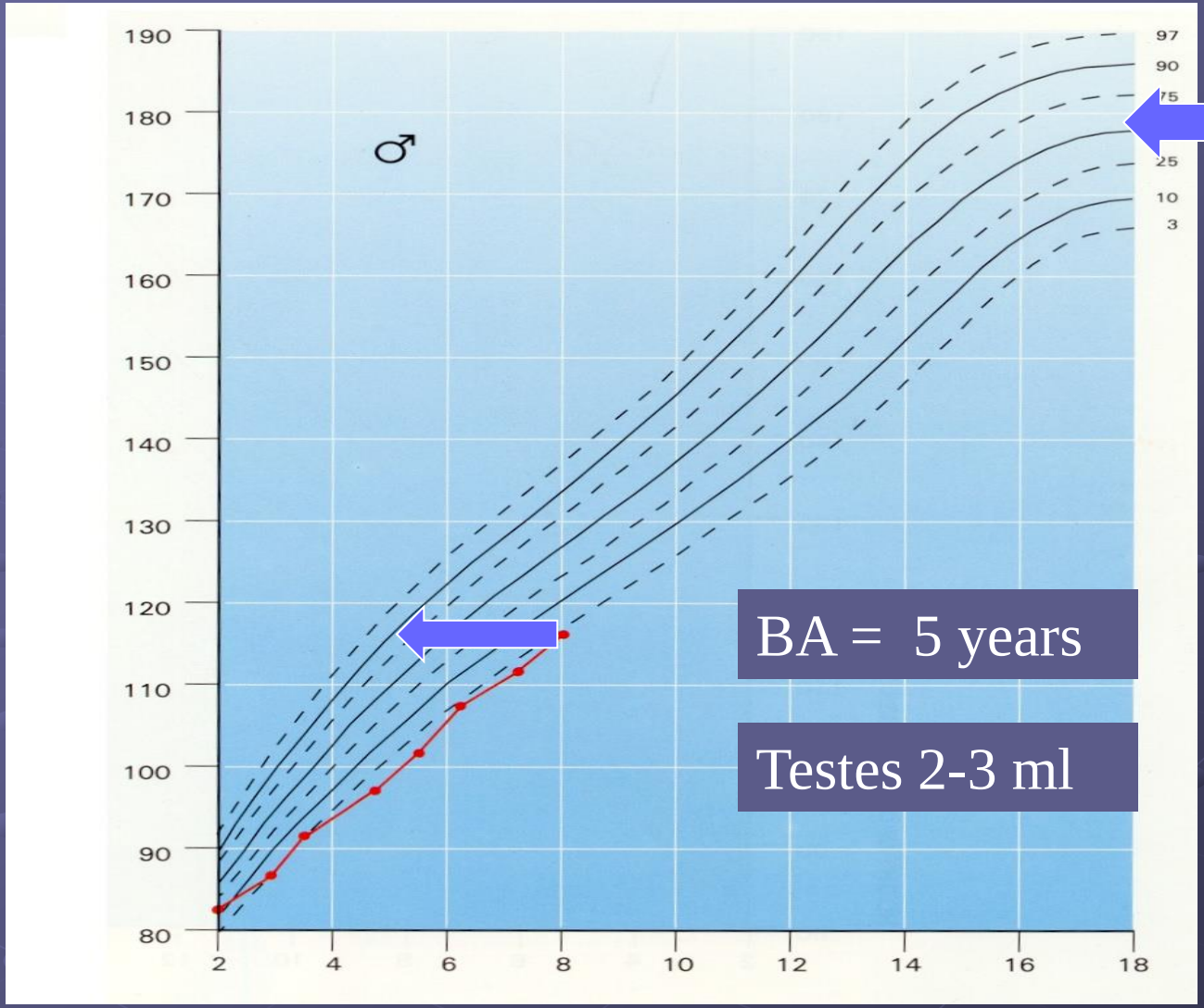


Mid Parental He

b) Velocity

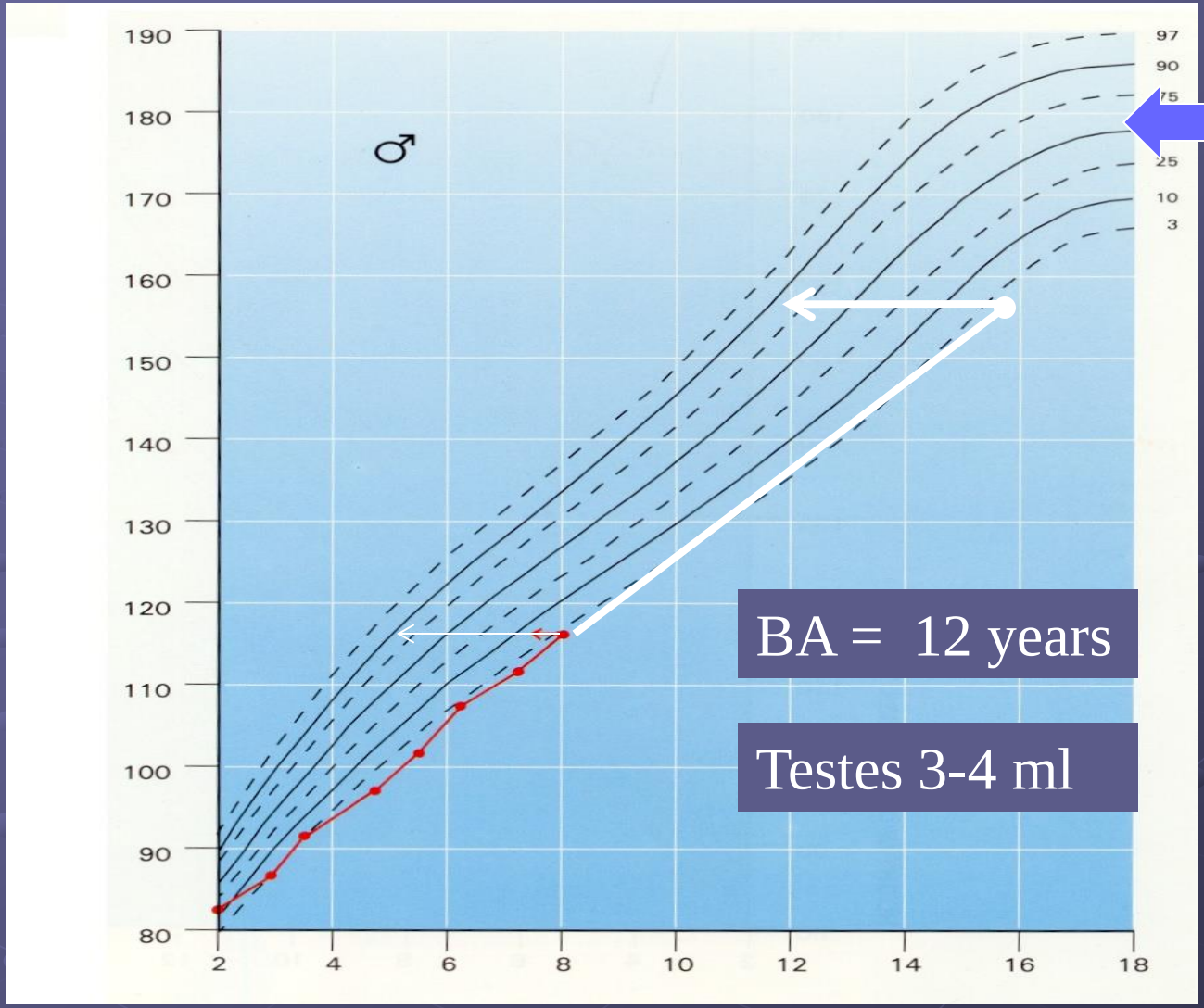


Case 2



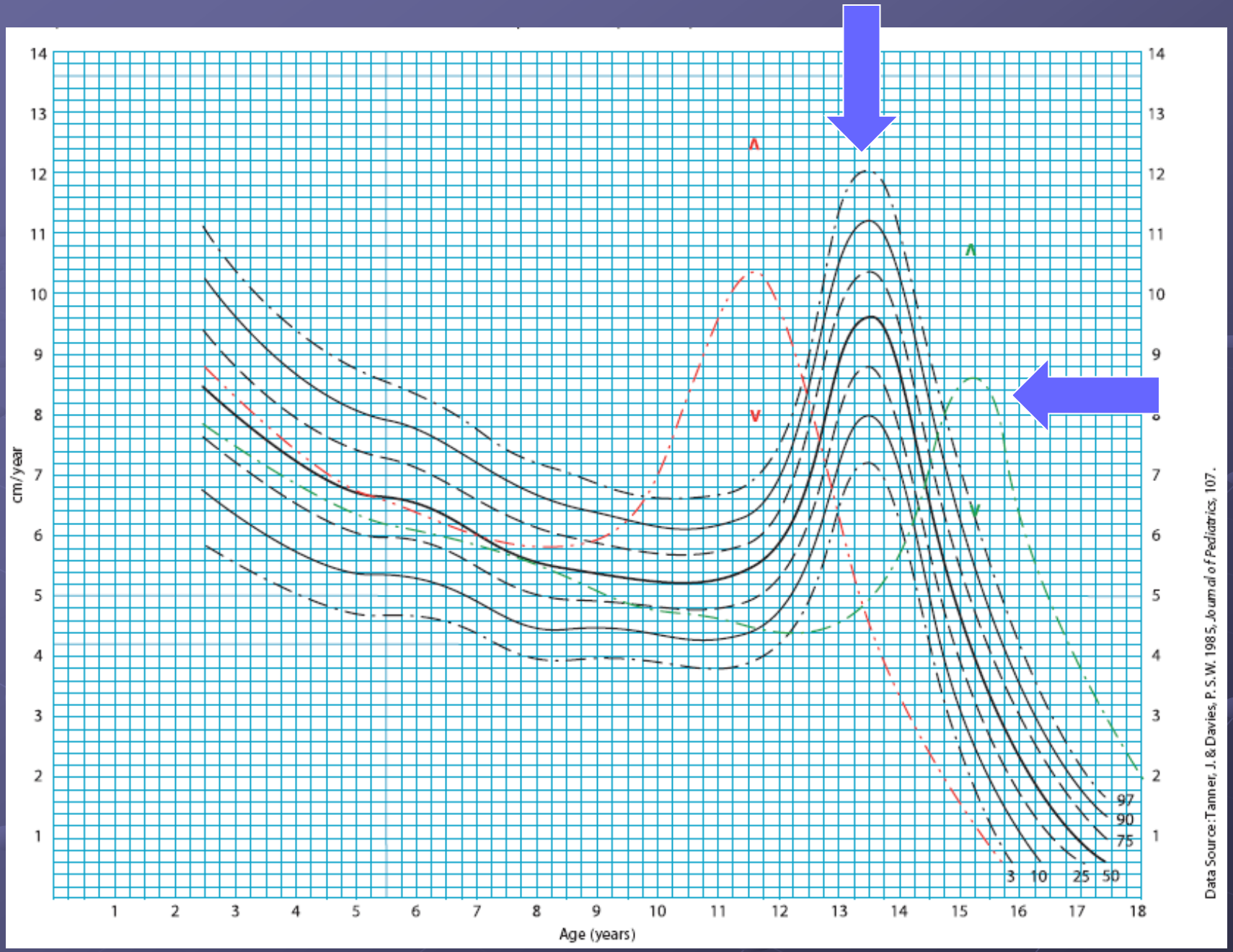
Dad is 178 cm, didn't stop growing till university

Diagnosis: Constitutional delay in growth and puberty



Still Prepubertal

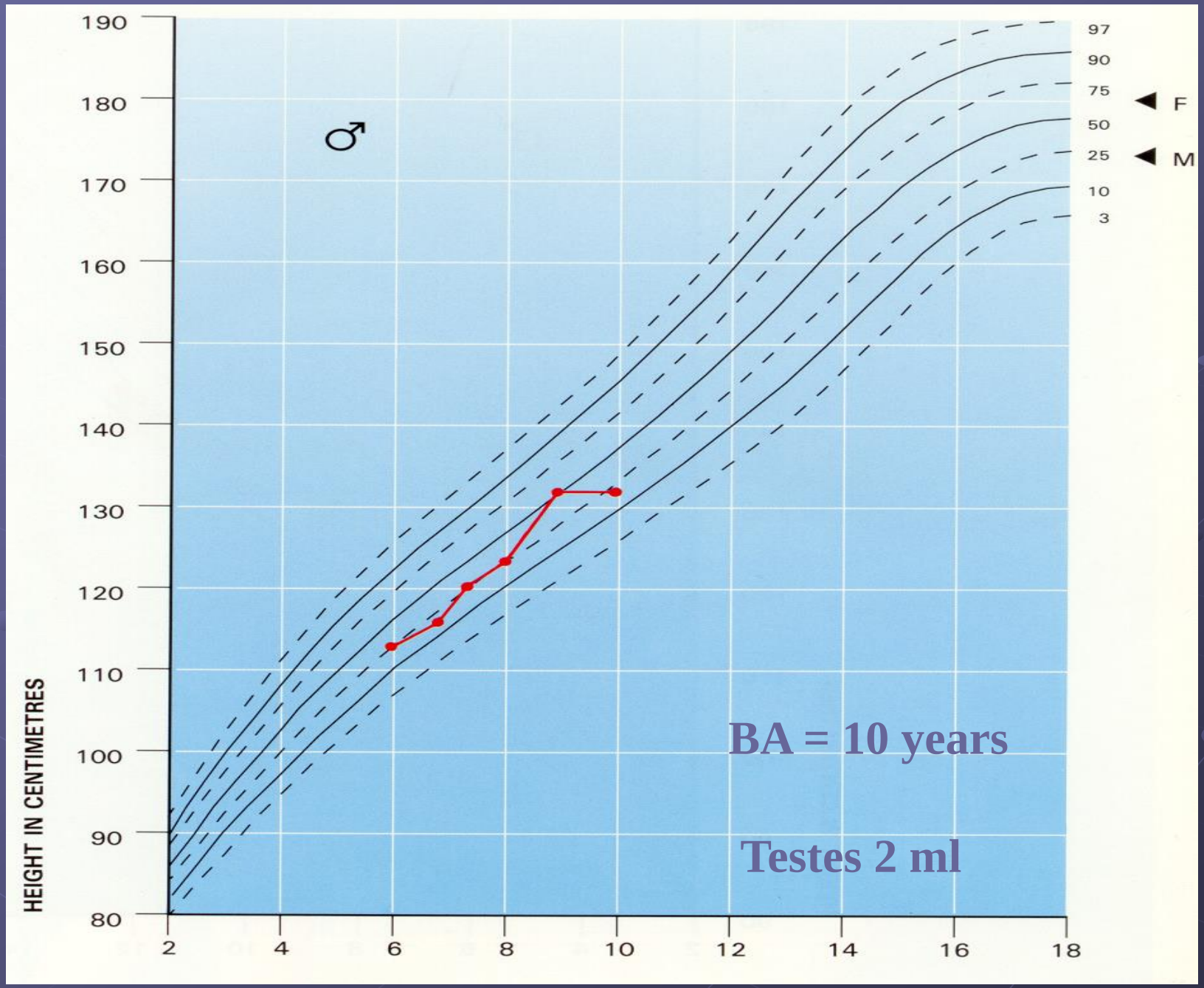
“not bothered”: but then again if there is anything to do.


cm/year
Age (years)
97
90
75
3
10
25
50
Data Source: Tanner, J. & Davies, P. S. W. 1985, Journal of Pediatrics, 107.

Growth Case 3

Ten year old boy

Stopped Growing since the last visit one year ago

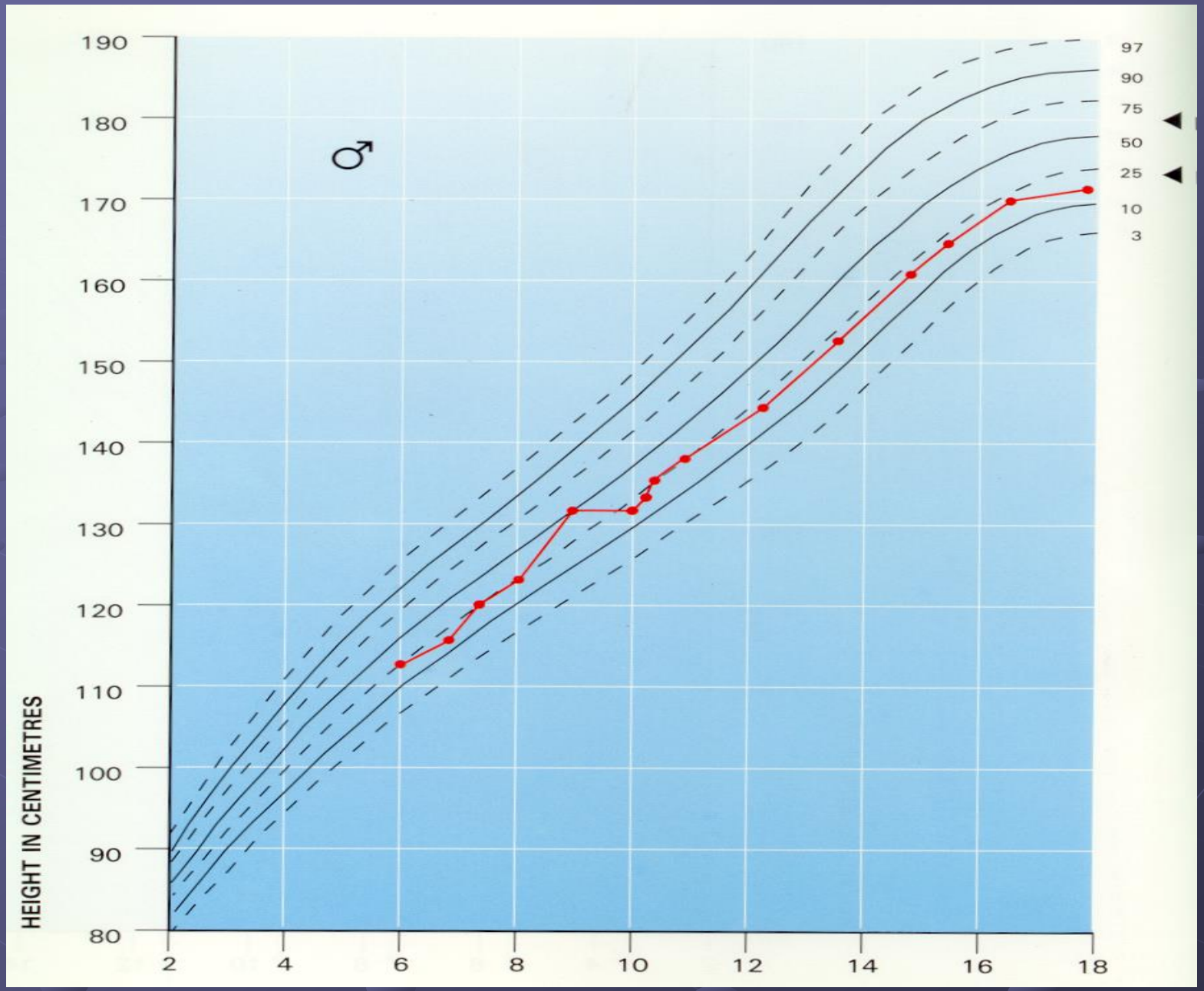

HEIGHT IN CENTIMETRES
190
180
170
160
150
140
130
120
110
100
90
80
2
4
6
8
10
12
14
16
18
♂
97
90
75
50
25
10
3
F
M
BA = 10 years
Testes 2 ml

Case 3
Not Grown

? Investigate

N Exam

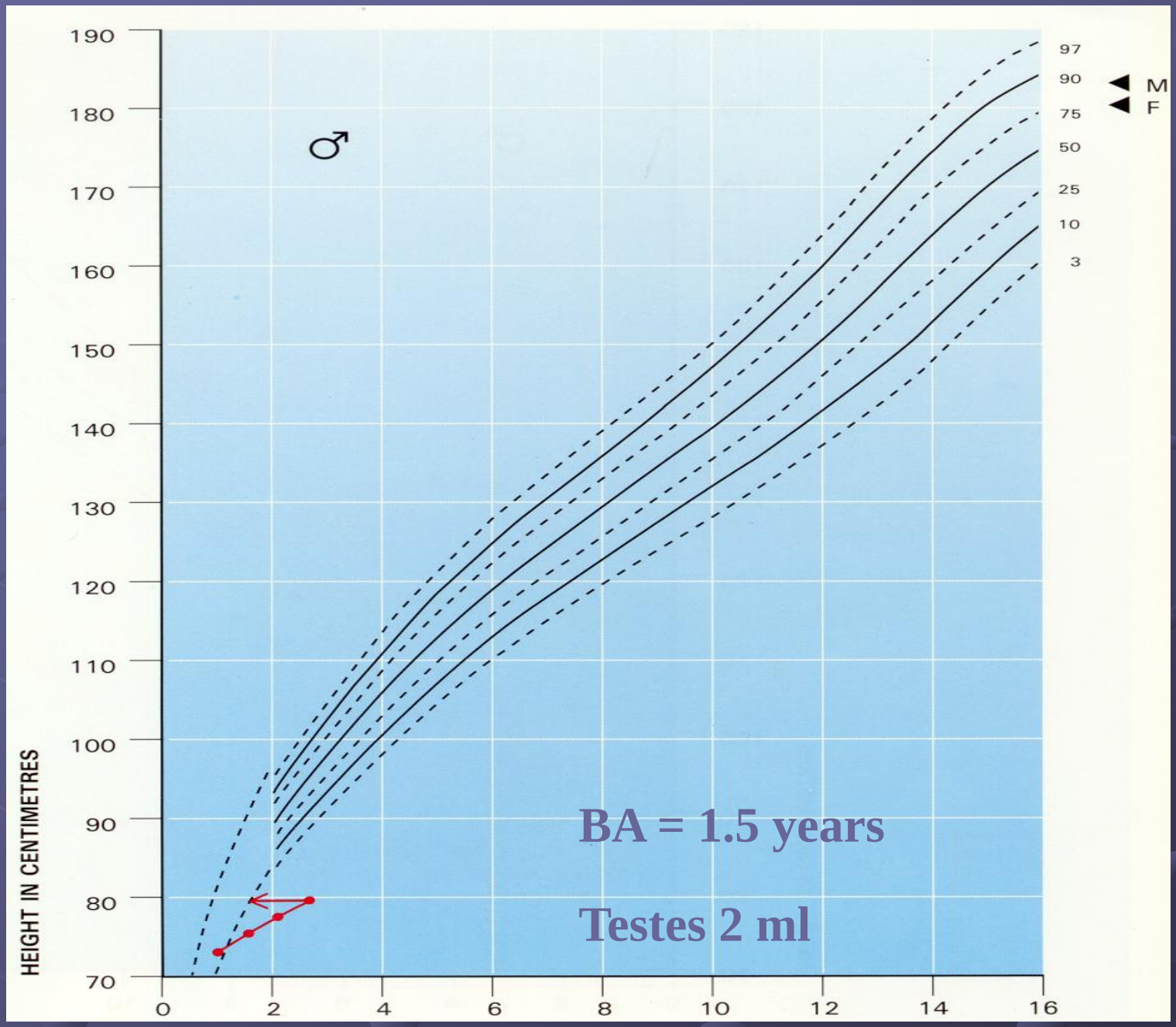
Measurement error


♂
HEIGHT IN CENTIMETRES
190
180
170
160
150
140
130
120
110
100
90
80
2
4
6
8
10
12
14
16
18
97
90
75
50
25
10
3

Growth Case 4

Three Year Old Boy

Not Growing too well


HEIGHT IN CENTIMETRES
190
180
170
160
150
140
130
120
110
100
90
80
70
0
2
4
6
8
10
12
14
16
♂
97
90
75
50
25
10
3
M
F
BA = 1.5 years
Testes 2 ml

Relevant History and Examination

Birth weight

Family History

Developmental history

Central Adiposity

Body Proportions (arm span etc)

Tests required

- FBC
- ESR
- RFT
- CRP
- TSH, T4
- SKELETAL SURVEY
- HCO3
- IGF-1

GH stimulation

Arginine and Clonidine

Growth Hormone peak >5 is normal (mcg/l)

? Other GH stimulants

Exercise

Glucagon

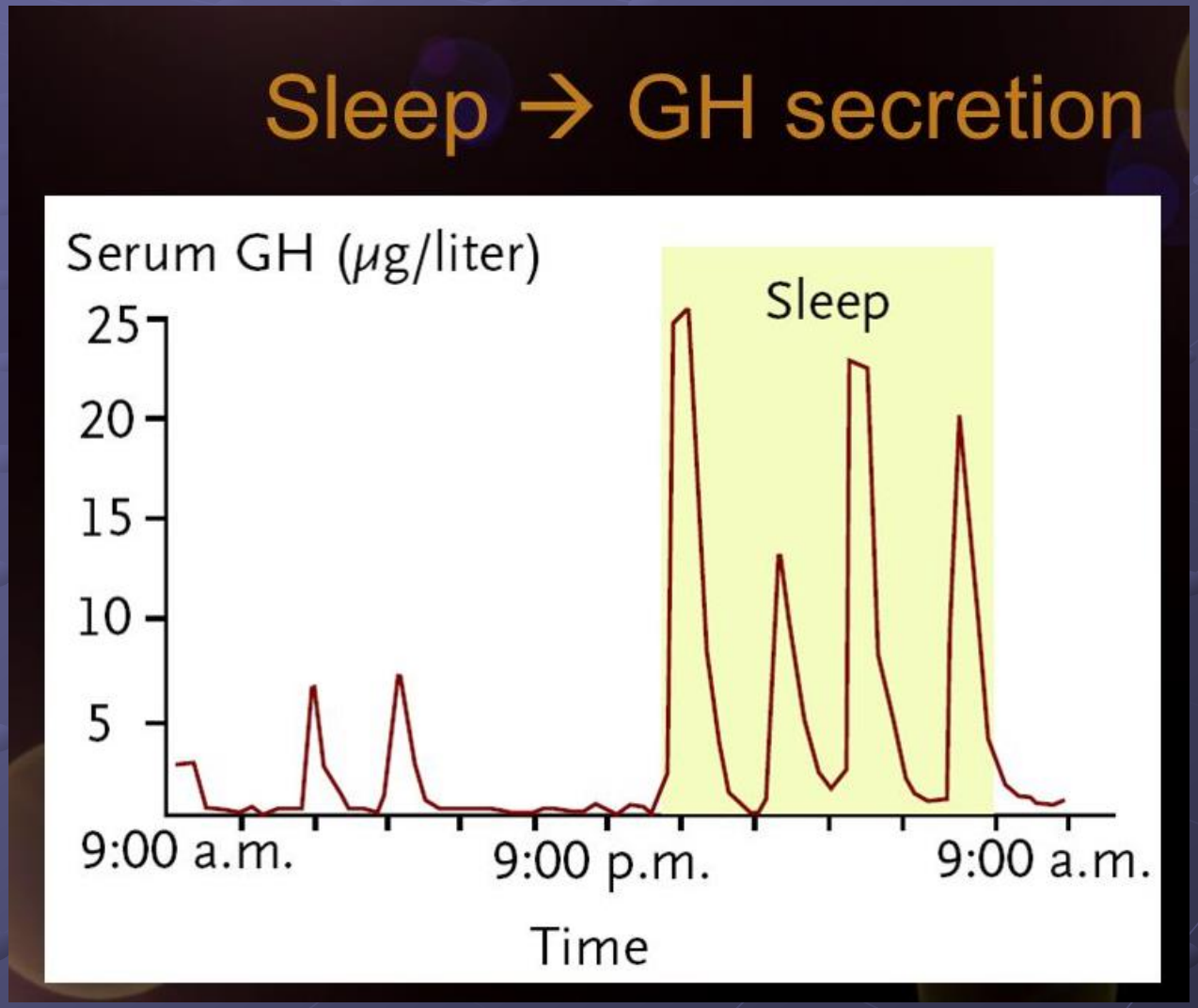
Insulin induced hypoglycaemia

Levodopa

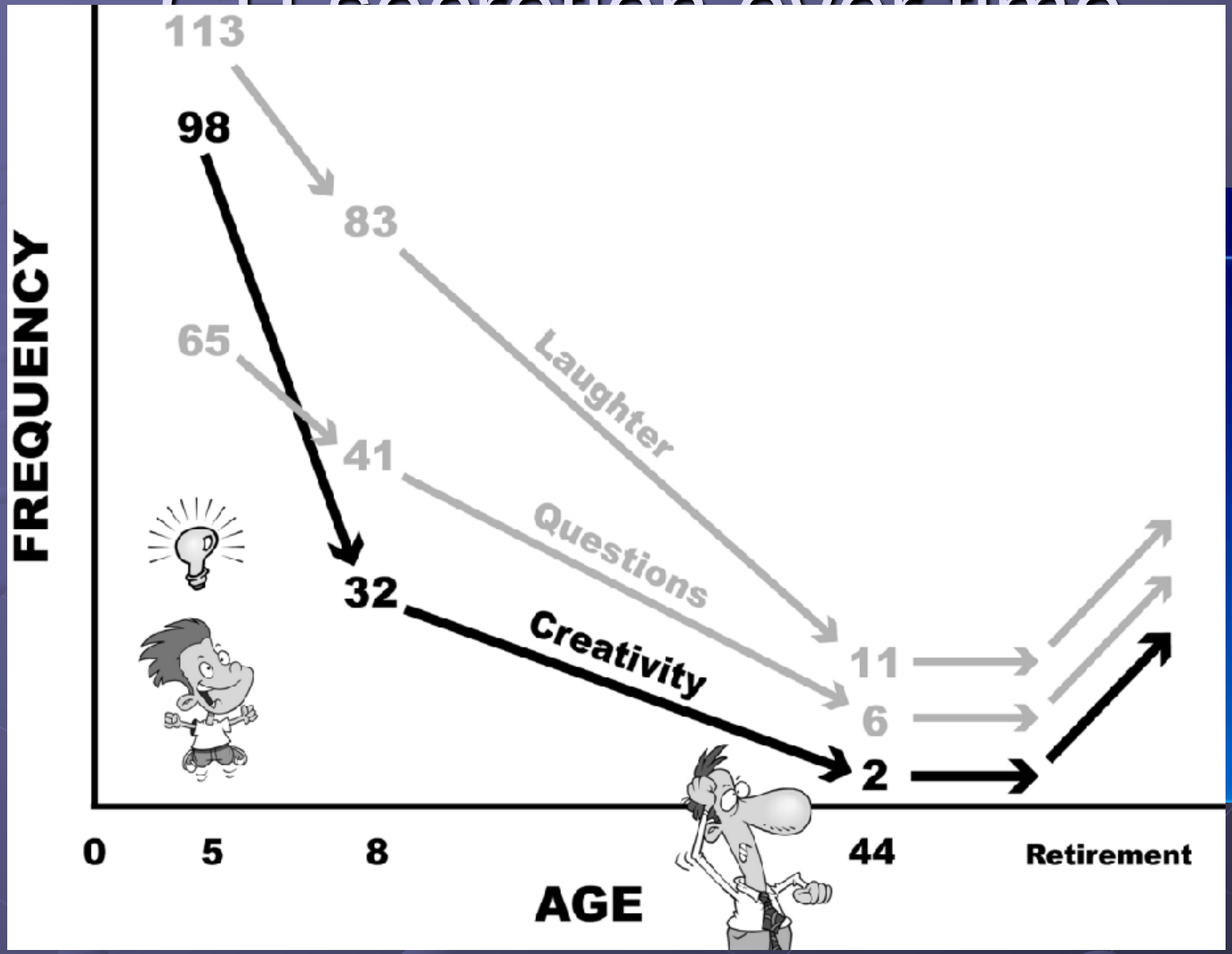
Growth Hormone secretion

- Pulsatile with low baseline.
- Primarily at night (stages III - IV sleep).
- Increased by
  - sleep, exercise stress hypoglycaemia, amino acids, malnutrition, sex steroids.
- Decreased by
  - obesity, psychosocial deprivation.

Growth Hormone secretion



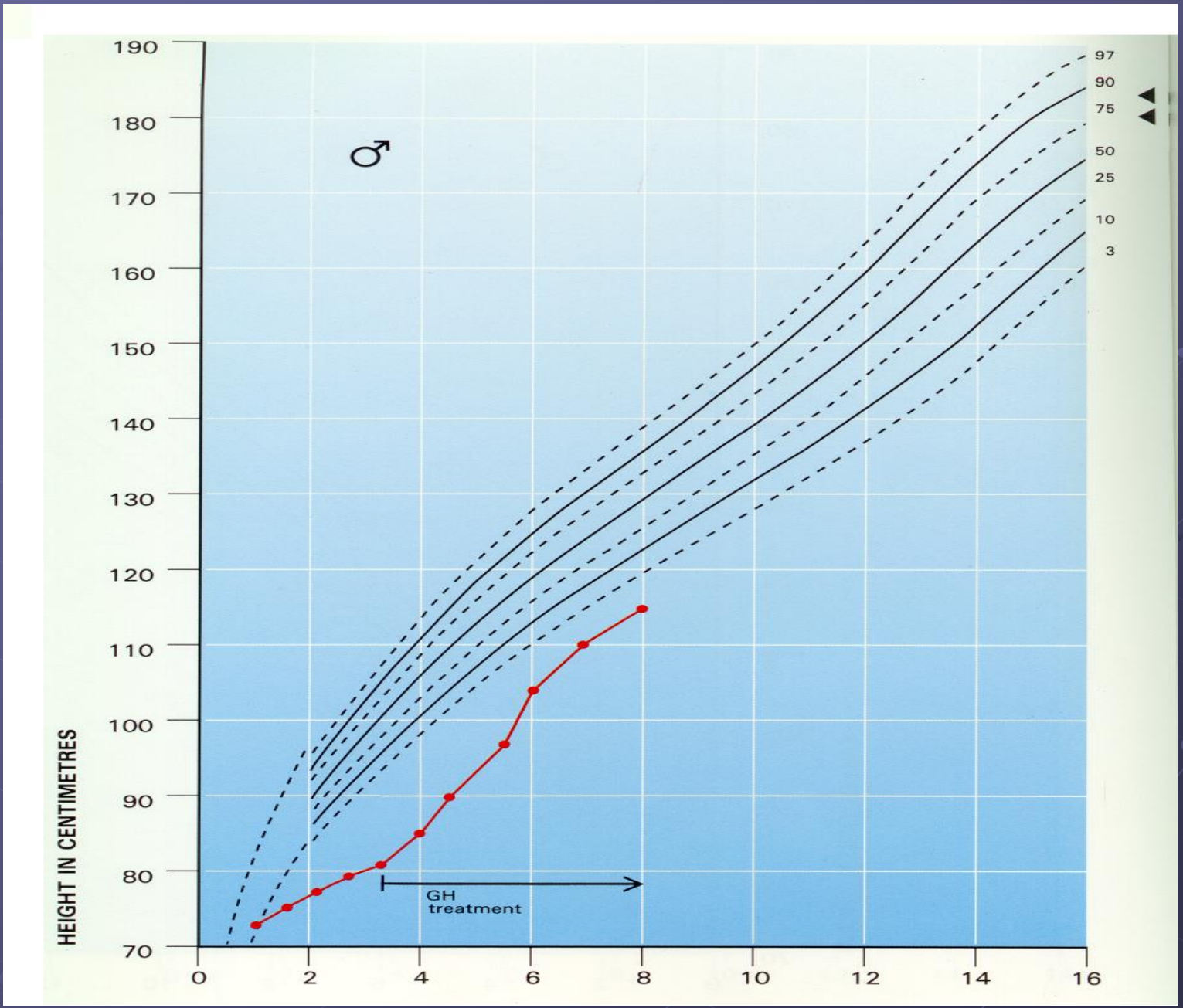
GH secretion over time



GH stimulation (Arginine and Clonidine)

	Growth Hormone mcg/l	
	Arginine	Clonidine
T0	1.0	1.4
T 30	1.2	1.5
T 60	1.5	0.6
T 90	1.8	1.1

Peak GH to stimulus is less than 3
Growth Hormone deficient
MRI Normal
(Exclude other pituitary hormone deficiency


♂
HEIGHT IN CENTIMETRES
190
180
170
160
150
140
130
120
110
100
90
80
70
0
2
4
6
8
10
12
14
16
97
90
75
50
25
10
3
GH
treatment

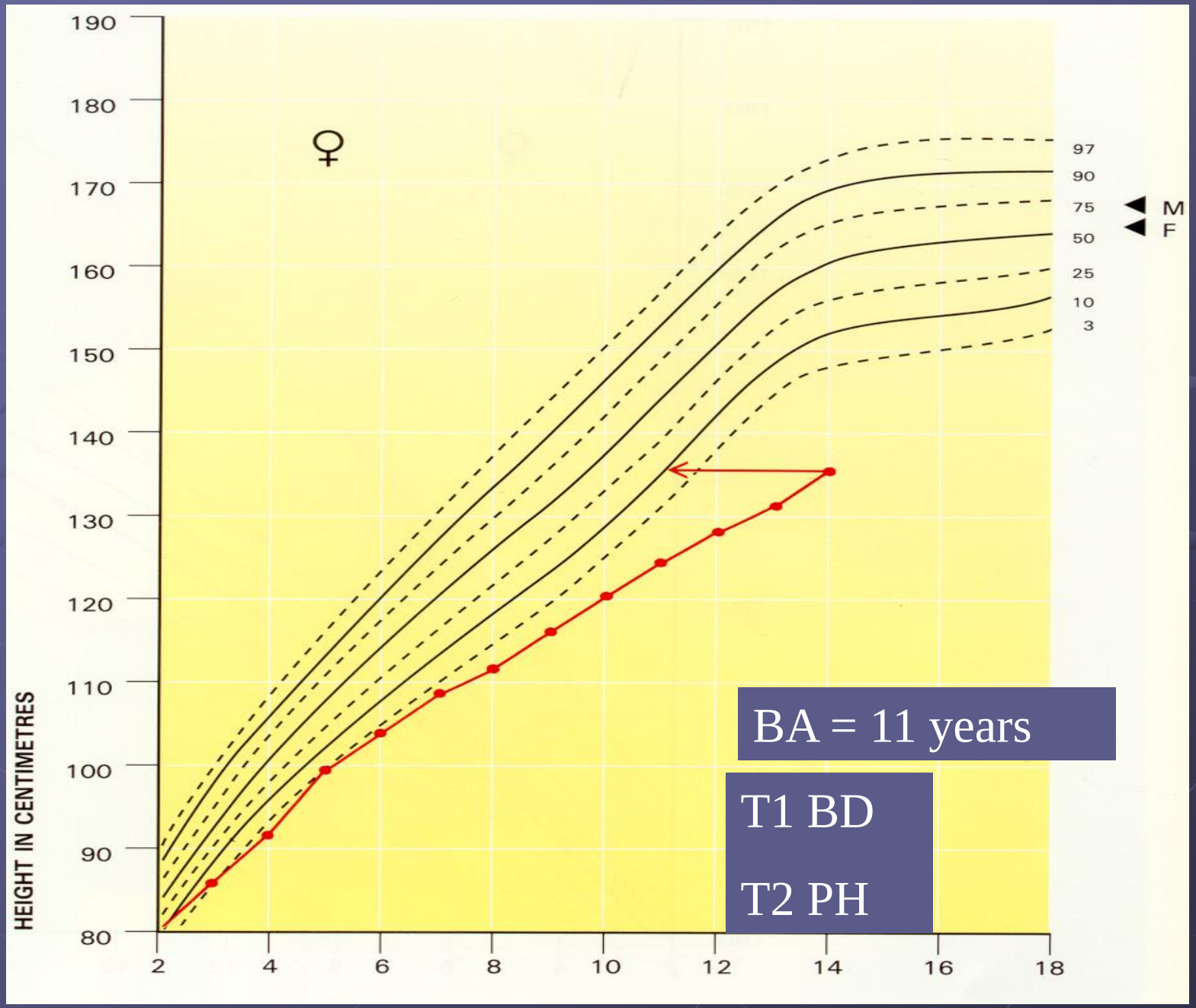
Growth Case - 5

Fourteen Year Old Girl

Shorter then Peers

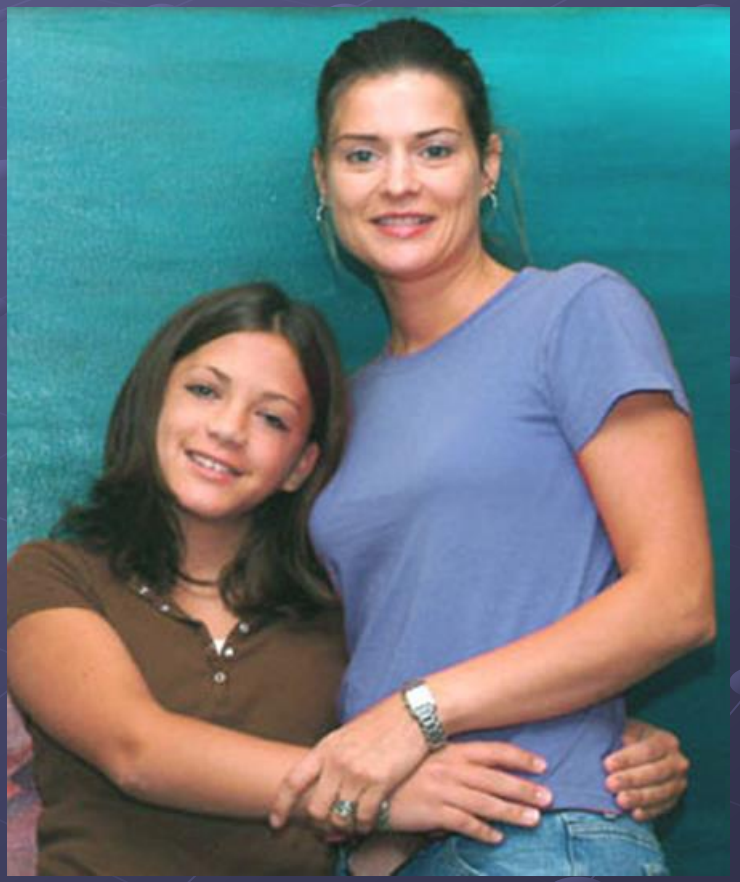
Not in Puberty

Puffy feet as a baby


190
180
170
160
150
140
130
120
110
100
90
80
HEIGHT IN CENTIMETRES
♀
97
90
75
50
25
10
3
M
F
2
4
6
8
10
12
14
16
18
BA = 11 years
T1 BD
T2 PH

Investgations

- Karyotype 45 XO
- Turner syndrome
- LH 50
- Normal TFT

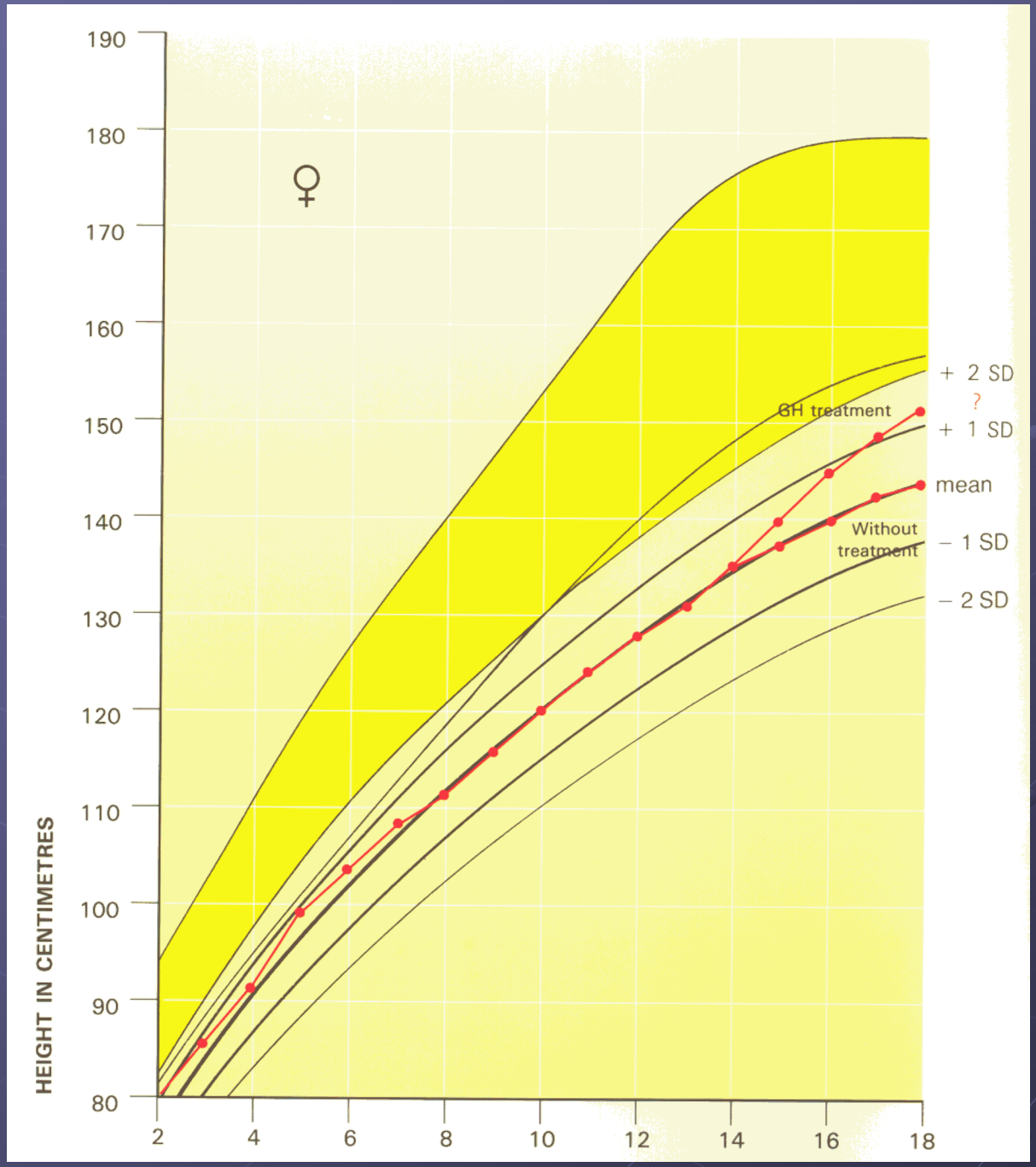


Investgations

- Karyotype 45 XO

- ? Other karyotypes
  - 55% 45 XO
  - 17% 46 X I (Xq)
  - 13% 45 X/ 46 XX

  - **Q? Why are they short**



Normal Girls

Turners

Untreated

With GH

Case 5

? What other treatment does she need and why

Case 5

? What other treatment does she need and why

She needs puberty!Oestrogen

Prevent Osteoporosis

Secondary sexual characteristics

Case 6

Thirteen year old girl

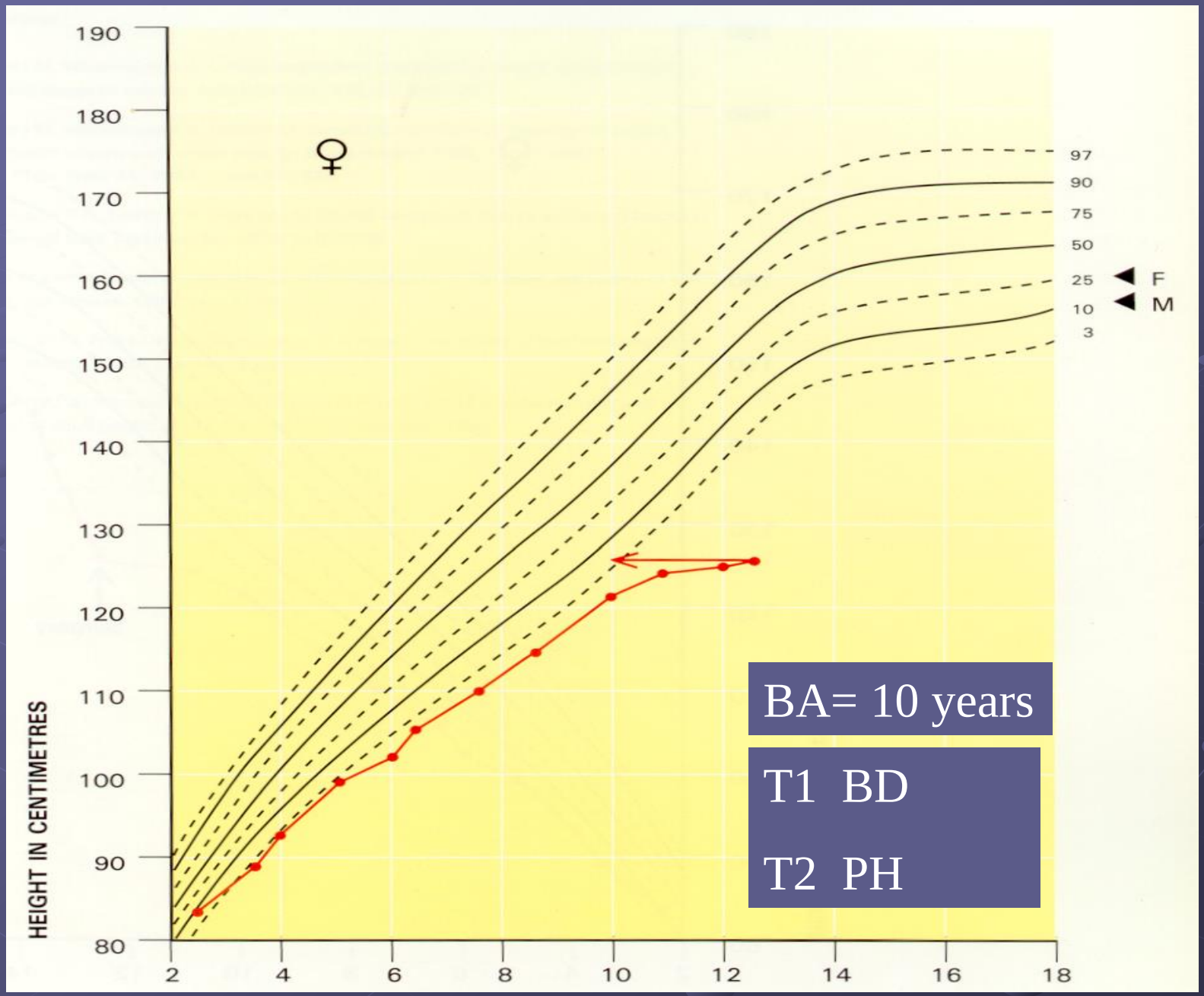
Always been short

Recently moved school

No pubertal development

Weight Loss

Chronic Abdominal Pain


HEIGHT IN CENTIMETRES
190
180
170
160
150
140
130
120
110
100
90
80
2
4
6
8
10
12
14
16
18
♀
97
90
75
50
25
10
3
F
M
BA= 10 years
T1 BD
T2 PH

Investigations

- TFT Normal
- FBC Hb 97
- Platelets 600

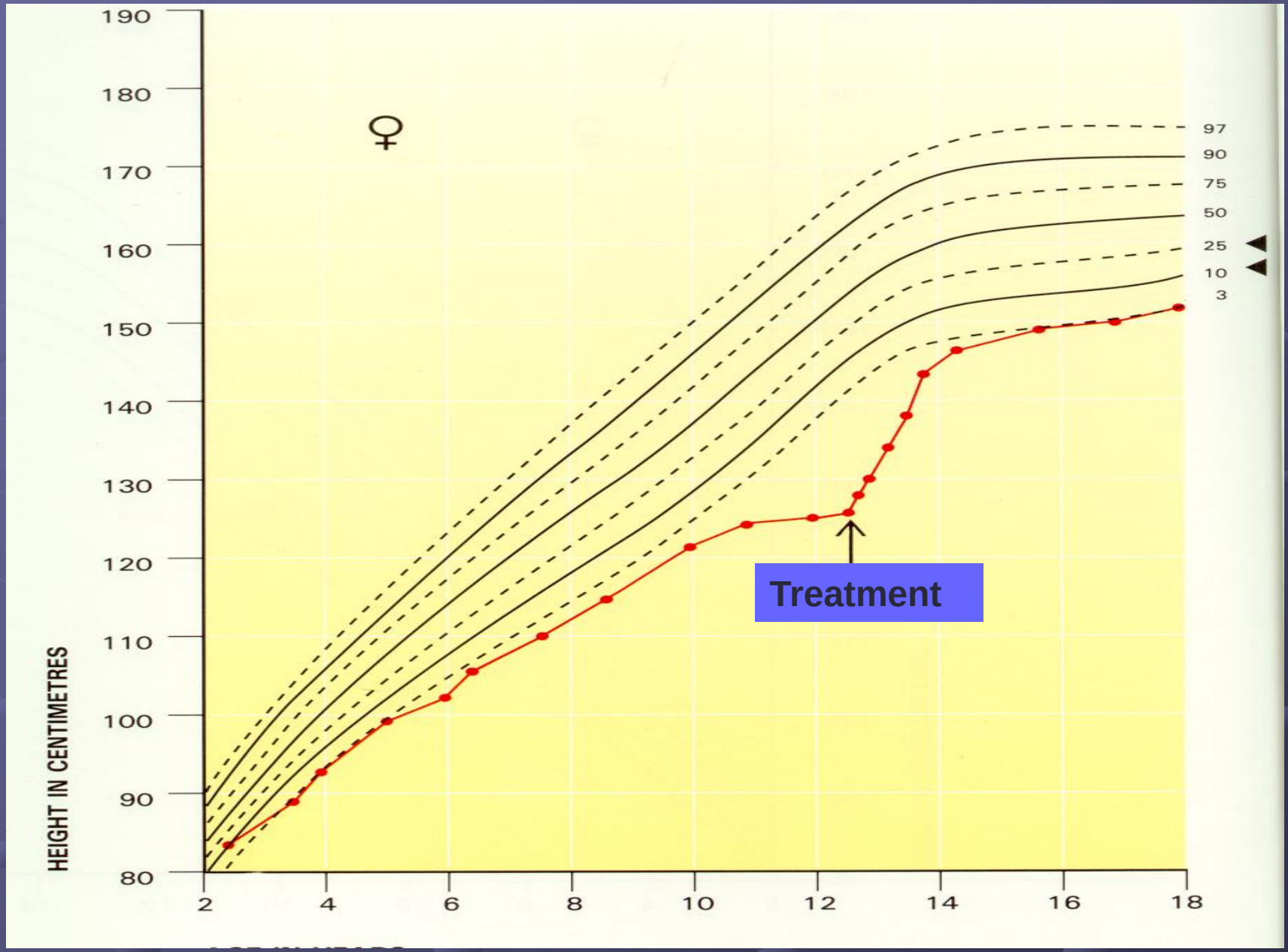
- ESR 60
- CT head normal

Further investigations

- Antigliaden antibodies N
- FOB Positive

- Abnormal Colonoscopy: UC

- Started on medical therapy

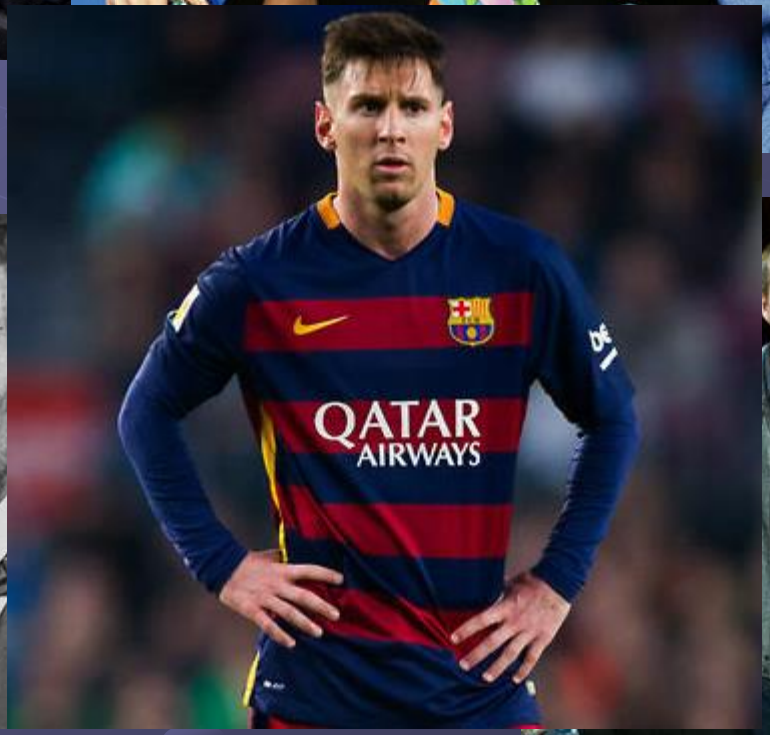

190
180
170
160
150
140
130
120
110
100
90
80
HEIGHT IN CENTIMETRES
♀
97
90
75
50
25
10
3
Treatment
2
4
6
8
10
12
14
16
18

Case 6

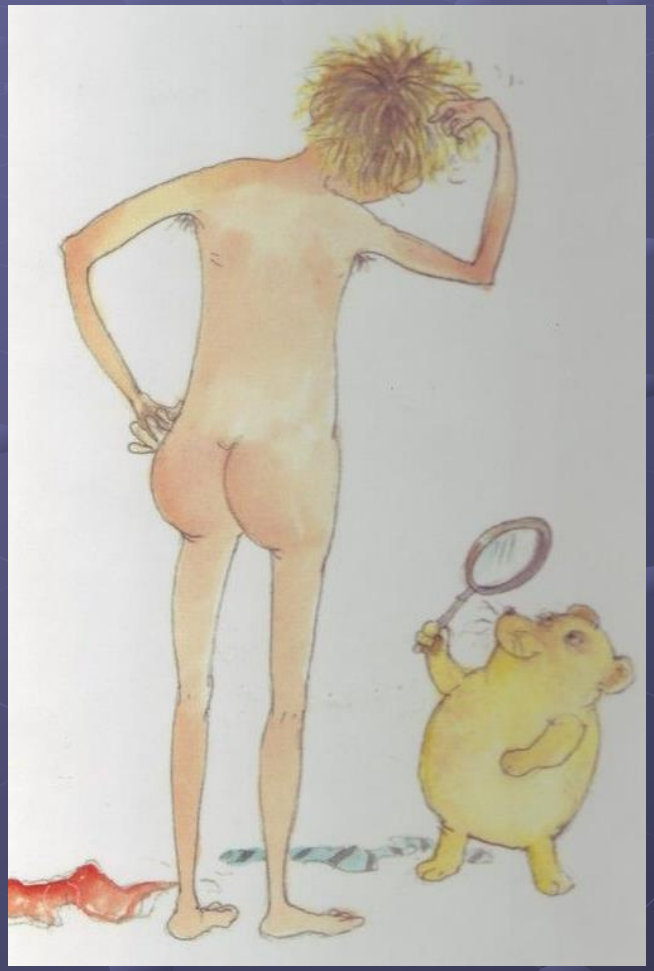
IBD

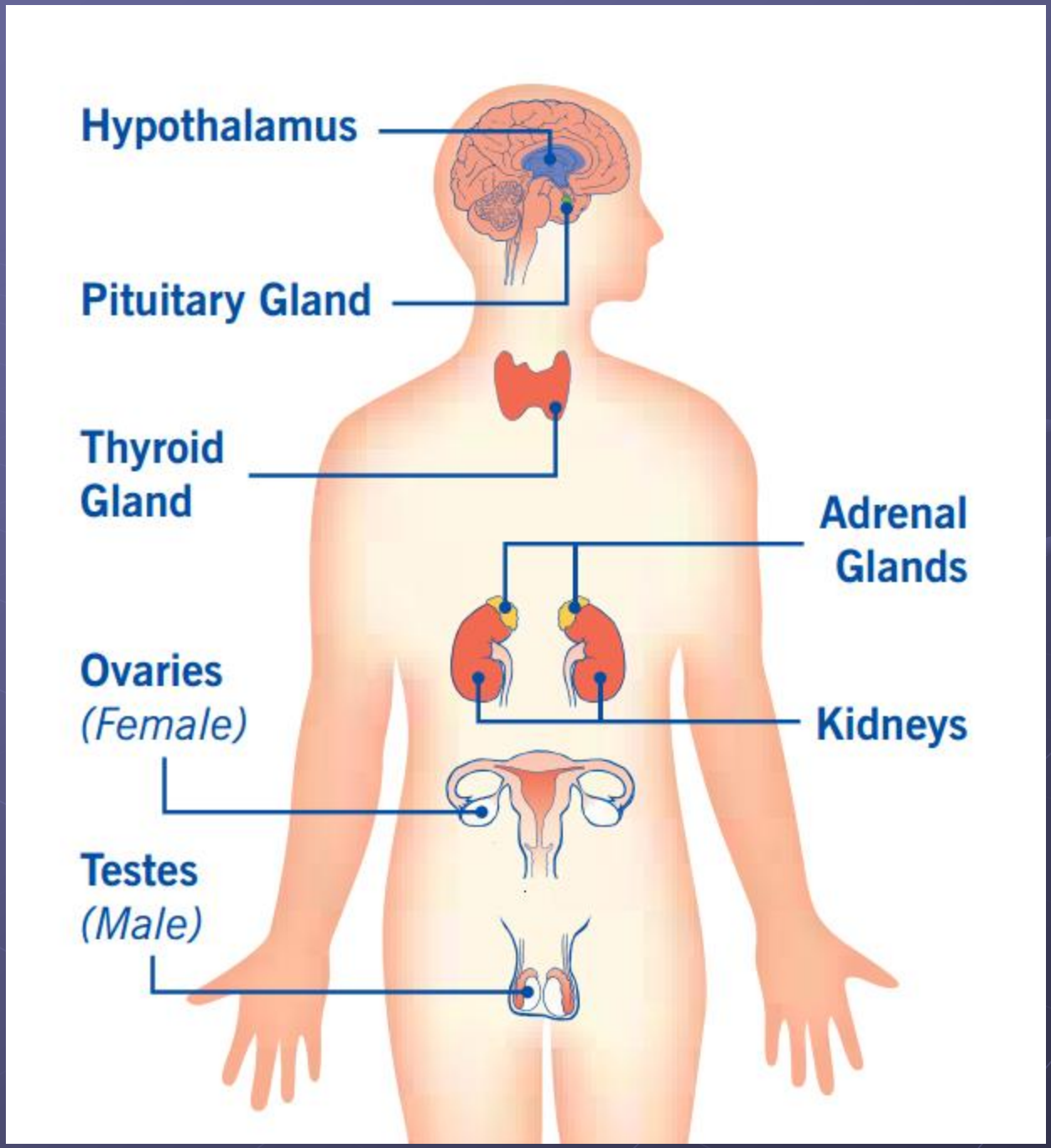
And

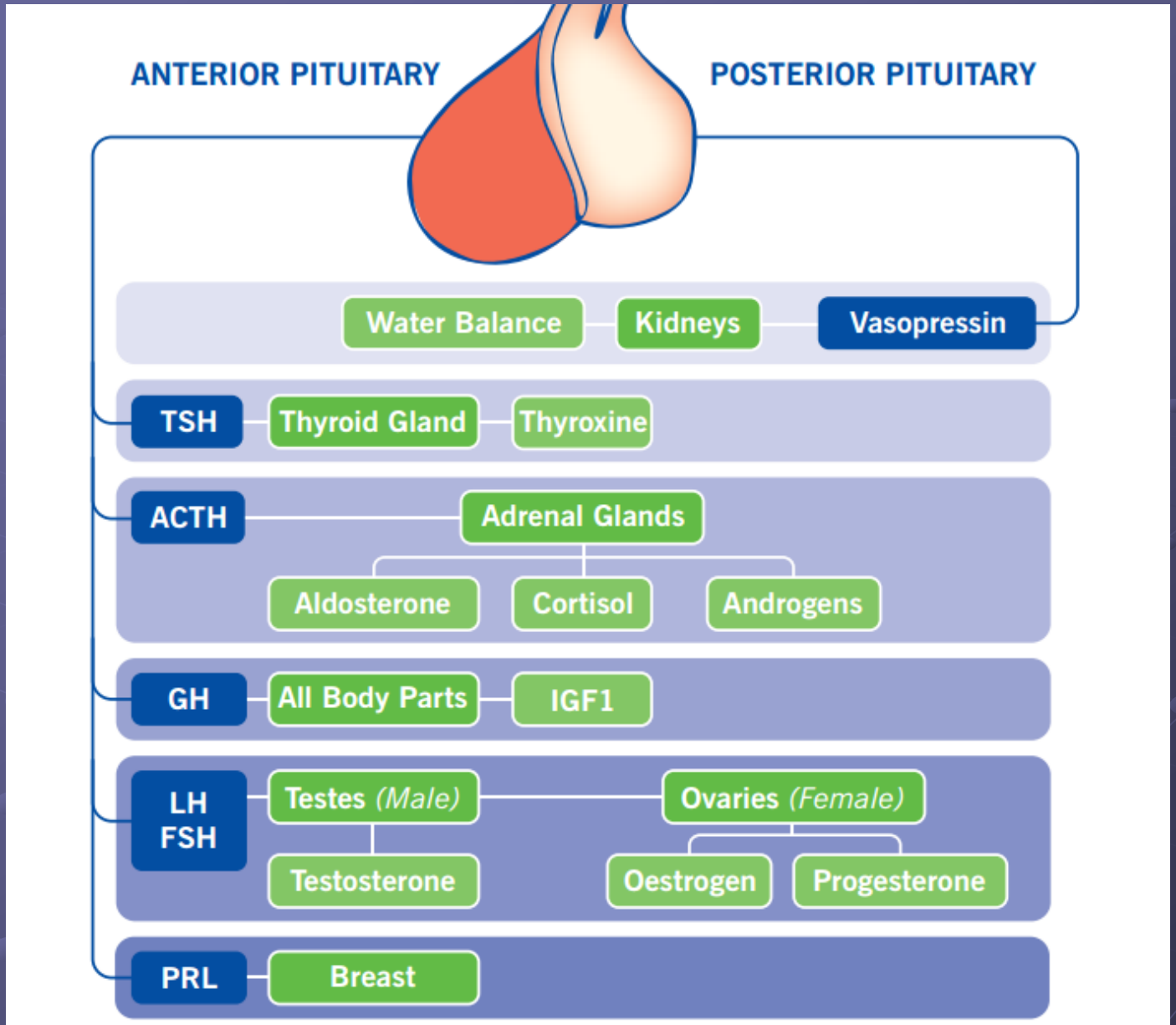
Familial Short Stature


QATAR
AIRWAYS

There are puberty hormones after this point!




Hypothalamus
Pituitary Gland
Thyroid Gland
Adrenal Glands
Ovaries (Female)
Kidneys
Testes (Male)

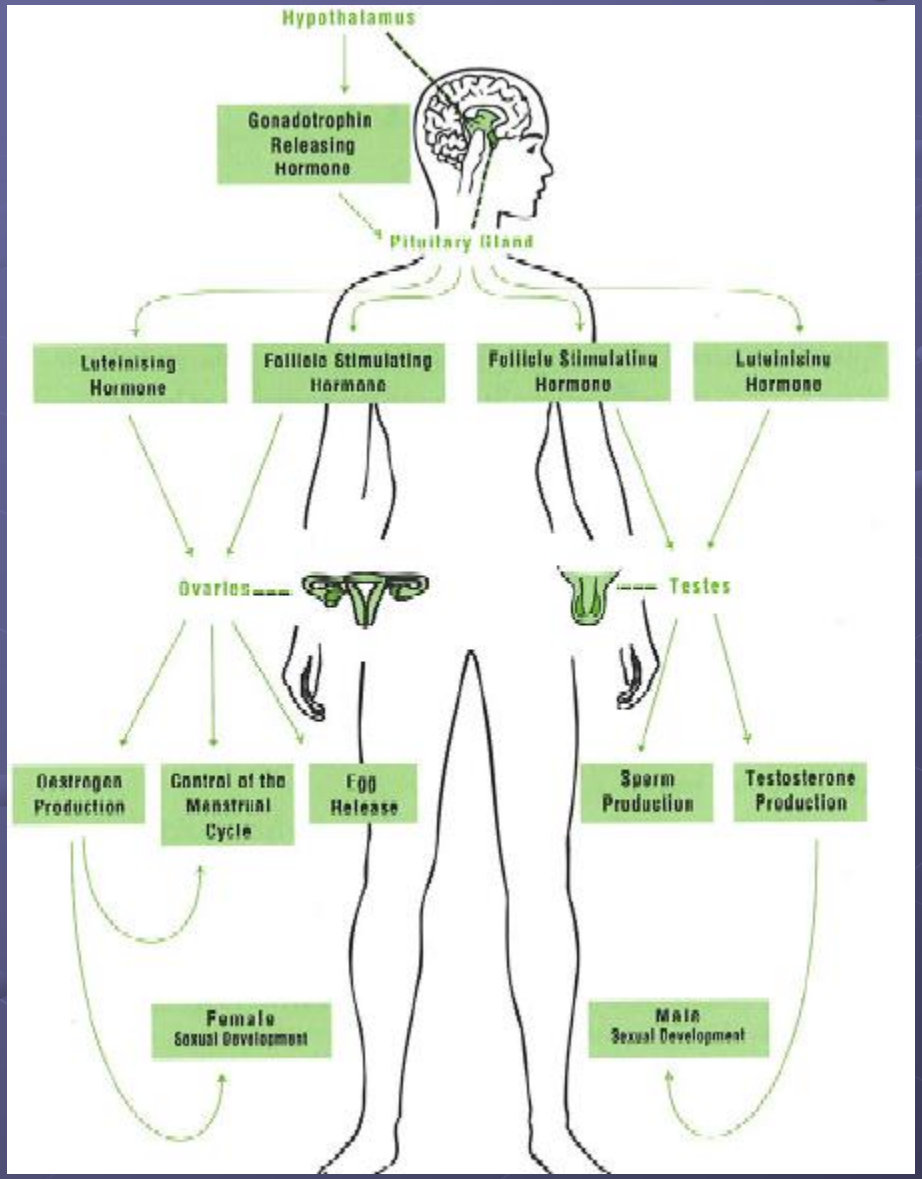


TSH Thyroid Stimulating Hormone
ACTH Adrenocorticotrophic Hormone
GH Growth Hormone
IGF1 Insulin Growth Factor 1
LH Luteinising Hormone
FSH Follicle Stimulating Hormone
PRL Prolactin

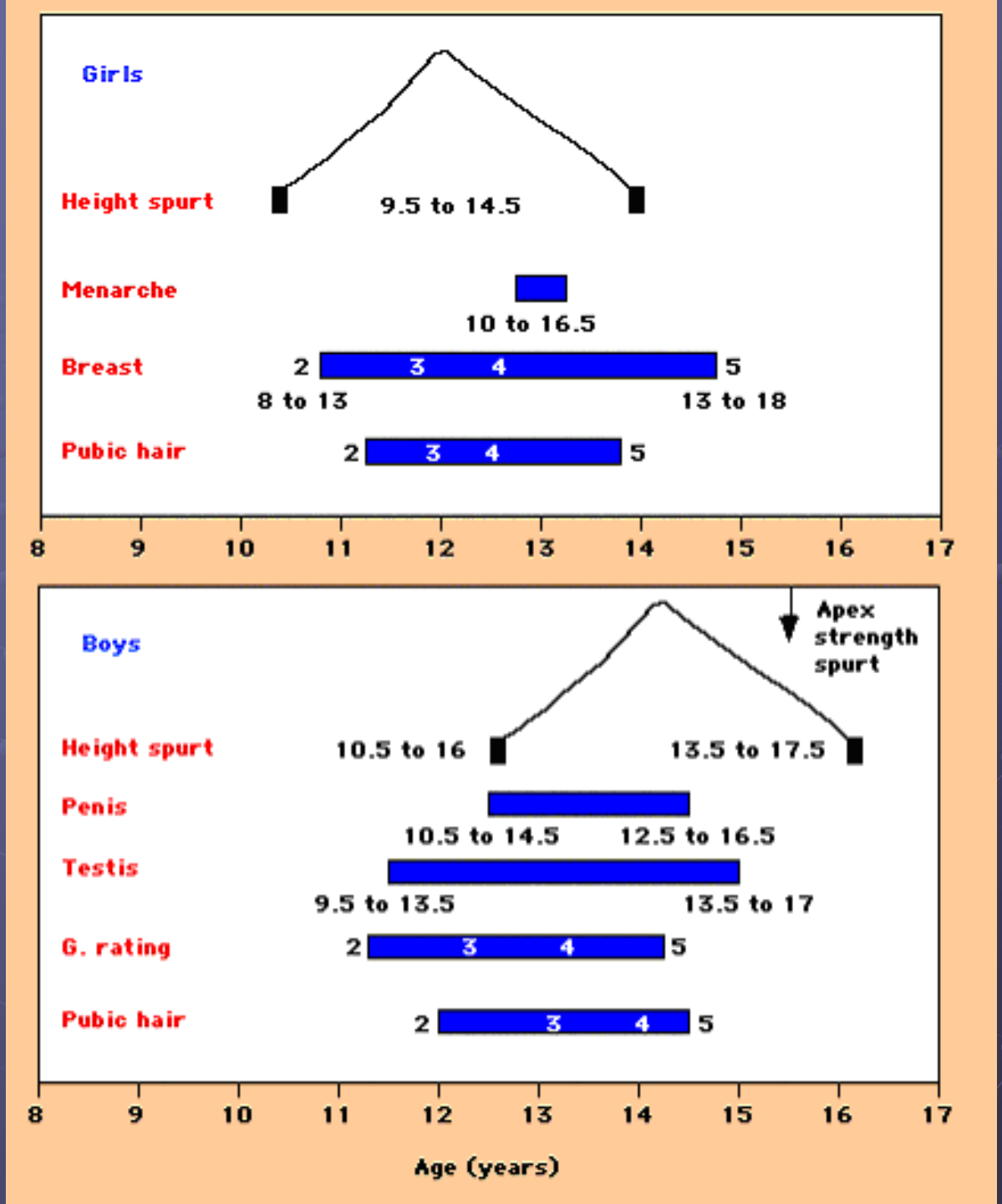
Definitions- Normal Puberty

- **Normal Puberty (All in tempo)**
  - Central activation of the H-P-Gonadal axis
  - Progressive sequential changes
  - Appropriate rate (over 3-4 years)
- **Girls (First Sign)**
  - Breast development before
  - Growth Spurt
- **Boys (First Sign)**
  - Increased testicular enlargement
  - >4ml (orchidometer)
  - Growth spurt later

Normal puberty



- www.apeg.org.au
- See Booklets in PDF format


Girls
Height spurt
9.5 to 14.5
Menarche
10 to 16.5
Breast
2
3
4
5
8 to 13
13 to 18
Pubic hair
2
3
4
5
8
9
10
11
12
13
14
15
16
17
Boys
Apex strength spurt
Height spurt
10.5 to 16
13.5 to 17.5
Penis
10.5 to 14.5
12.5 to 16.5
Testis
9.5 to 13.5
13.5 to 17
G. rating
2
3
4
5
Pubic hair
2
3
4
5
8
9
10
11
12
13
14
15
16
17
Age (years)

Late Puberty:
When is it time to grow up?

15 year old boy presents with NO puberty

What is the differential diagnosis?
What history is relevant?
Important exam findings?

What investigations are appropriate?
What are your treatment options?

Delayed Puberty

Definition

No signs of puberty within 2 SD of the mean age of onset.

- Males >14 years
- Females >13 years

ALbanese et al, Clin Endocrinol 1995;43:105

What is the differential diagnosis?

- **Normal variant**

  Constitutional delay in growth and development (CDGD)

  By far the most common

- **Primary Gonadal Failure**

  Hypergonadotropic Hypogonadism

  Raised LH and FSH

- **Secondary/Central Gonadal Failure**

  Hypogonadotropic Hypogonadism

  Low FSH and LH

Hypergonadotropic Hypogonadism Raised LH/FSH

Males

Klinefelters (47XXY or variants)
Vanishing testis syndrome
Trauma/Infection
Noonan Syndrome

Females

Turner Syndrome or X deletions
Radiation
Chemotherapy
Noonan Syndrome
Autoimmune ovarian failure

Hypogonadotropic Hypogonadism
Low LH/FSH

- **CDGD (>85%)**
- **Chronic illness**
- **Anorexia nervosa/ malnutrition**
- **Excessive physical training**
- **Pituitary/Hypothalamic disease**
- **Isolated (Kallmann)**
- **Multiple pituitary abnormality**
- **(tumours, congenital hypopituitarism)**
- **Syndromes**

What hx is relevant?

Birth/ postnatal trauma
Chronic illness/ medications (esp: steroids)
Malignancy

Growth pattern
Dental eruption
Weight/ physical activity

Family history of CDGD
Heights of sibs and parents

Delayed Puberty Treatment Goals

Promote virilisation

Promote growth

Precipitate puberty

Not compromise final height

DP and Testosterone

N=15 boys

14.1 +/-1.0 yrs

TE 50 mg monthly for 1.2 yrs

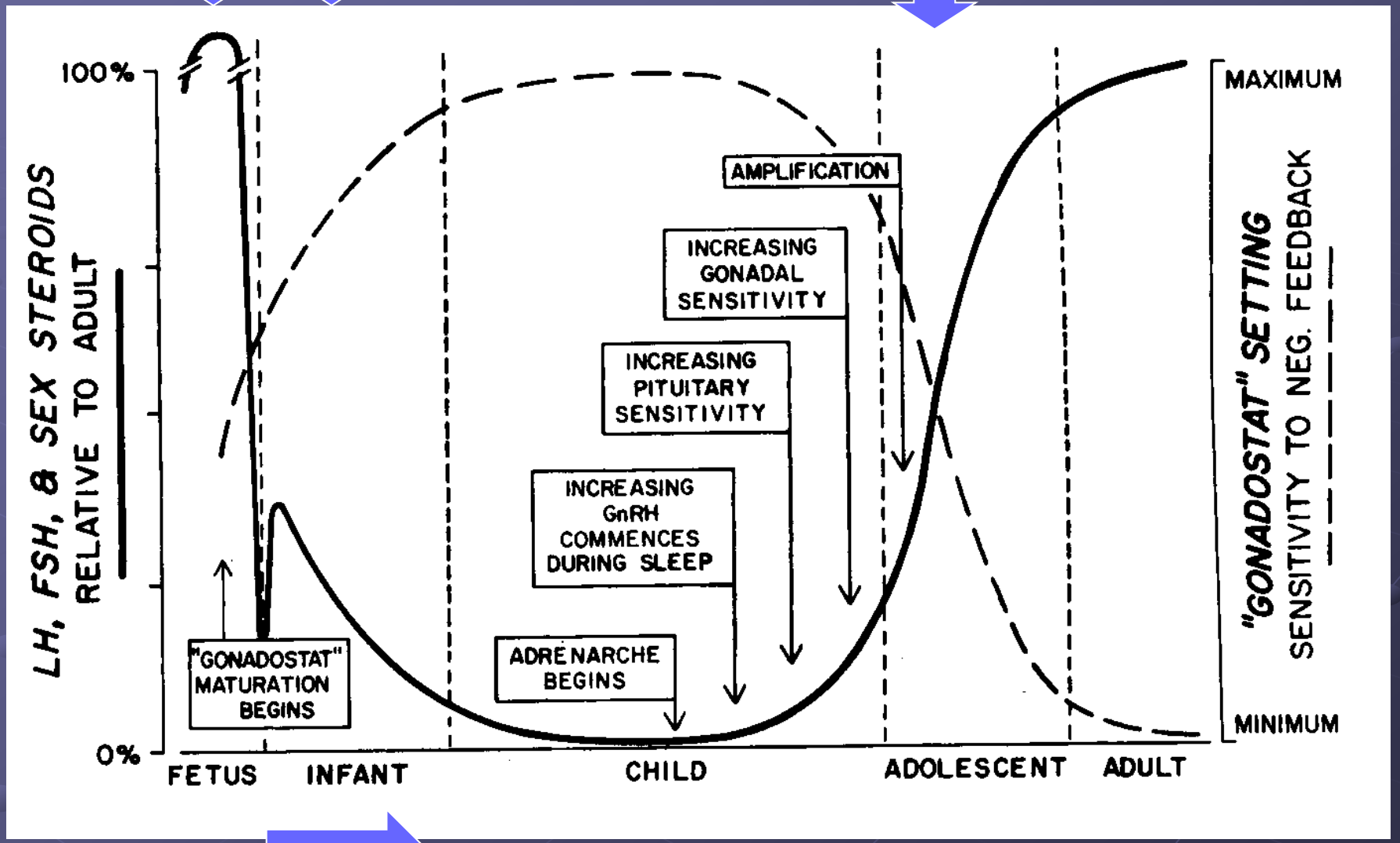
HV from 3.8 to 10.0 cm/yr

Testes from 5.9 to 11.3 ml

Final ht = pretreatment predicted ht

Richman and Kirsch, N Engl J Med, 1988;319:1563

Early Puberty



The three puberties of life

The Arche's

- Gonadarche
- Pubarche
- Thelarche
- Menarche
- Spermache
- Adrenarche

Precocious Puberty -Definition

- Pathological process
  - Too early
  - Too fast
  - Pathological hormonal milieu
- Arbitrary
  - Females <8 years (menarche <9 years)
    - This will be 2% of healthy girls
  - Males <9 years
- Clinical confirmation
  - Clinical signs (and USS in females)
  - Hormonal evaluation
  - Bone age advancement
  - Rate of acceleration

Clinical signs of sustained sex steroids exposure

- Growth height velocity
  height compared to mid parental height

- Breasts progressive development
- Androgen Pimples/acne/body odour

- Introitus pink-red epithelium pre oestrogen
  white-pink with sustained oestrogen exposure
  (cornification of epithelium)

Investigation (First line)

- Bone Age (X-ray L hand and wrist)
- USS pelvis
  - Uterine size, endometrial thickness
  - sometimes useful info on ovaries
- Thyroid functions
- Done but not always that useful tests
  - FSH and LH
  - Testosterone
  - Oestradiol

Differential Diagnosis

Endogenous

Central
GnRH dependent

Peripheral
GnRH independent

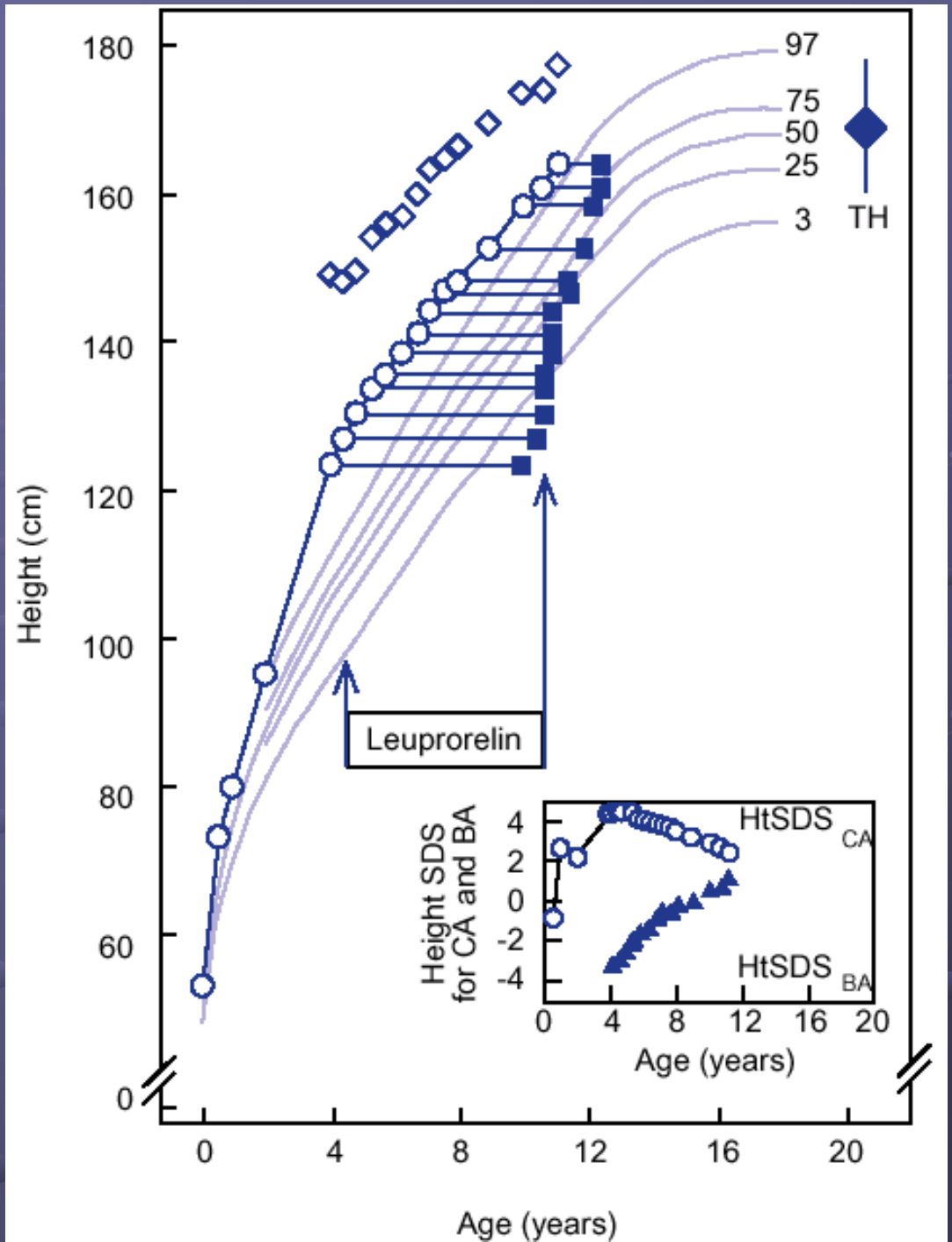
Exogenous
- O/C
- HRT
- E2 creams
- Soy?
- ‘Natural remedies’

GnRH (LHRH) stimulation test

Pubertal response	LH dominant
Prepubertal	FSH dominant

Causes of Central PP

- **Idiopathic**
- More common to find abnormality on males than females
- Structural Abnormality
  - Hypothalamic Hamartoma
  - Meningomyleocoele
  - Hydrocephalus
  - NF-1
- CNS insult
  - Neonatal Encephalopathy
  - Cranial Irradiation
  - Trauma/Surgery

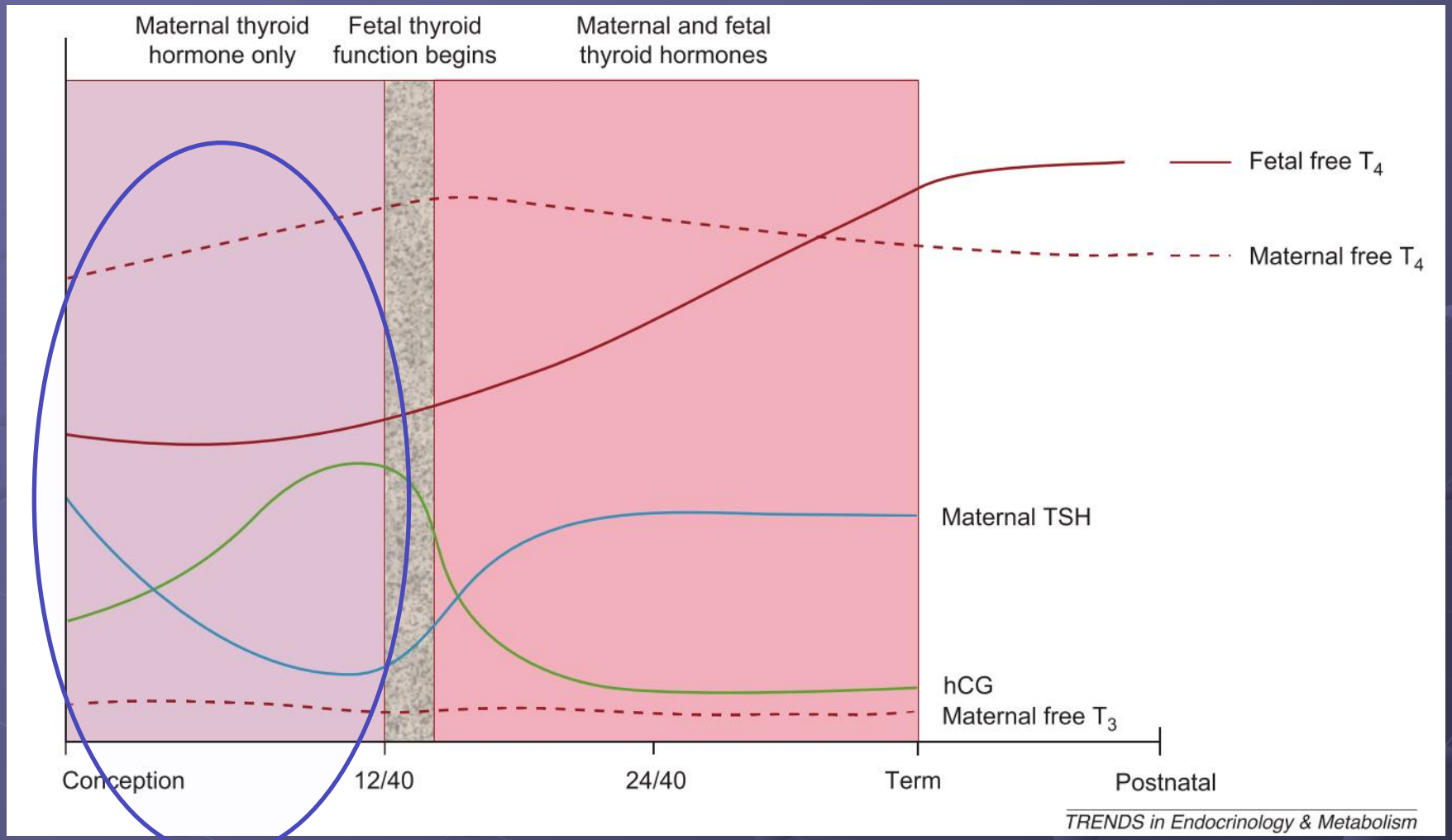


Example of idiopathic Precocious puberty

Advanced Bone age

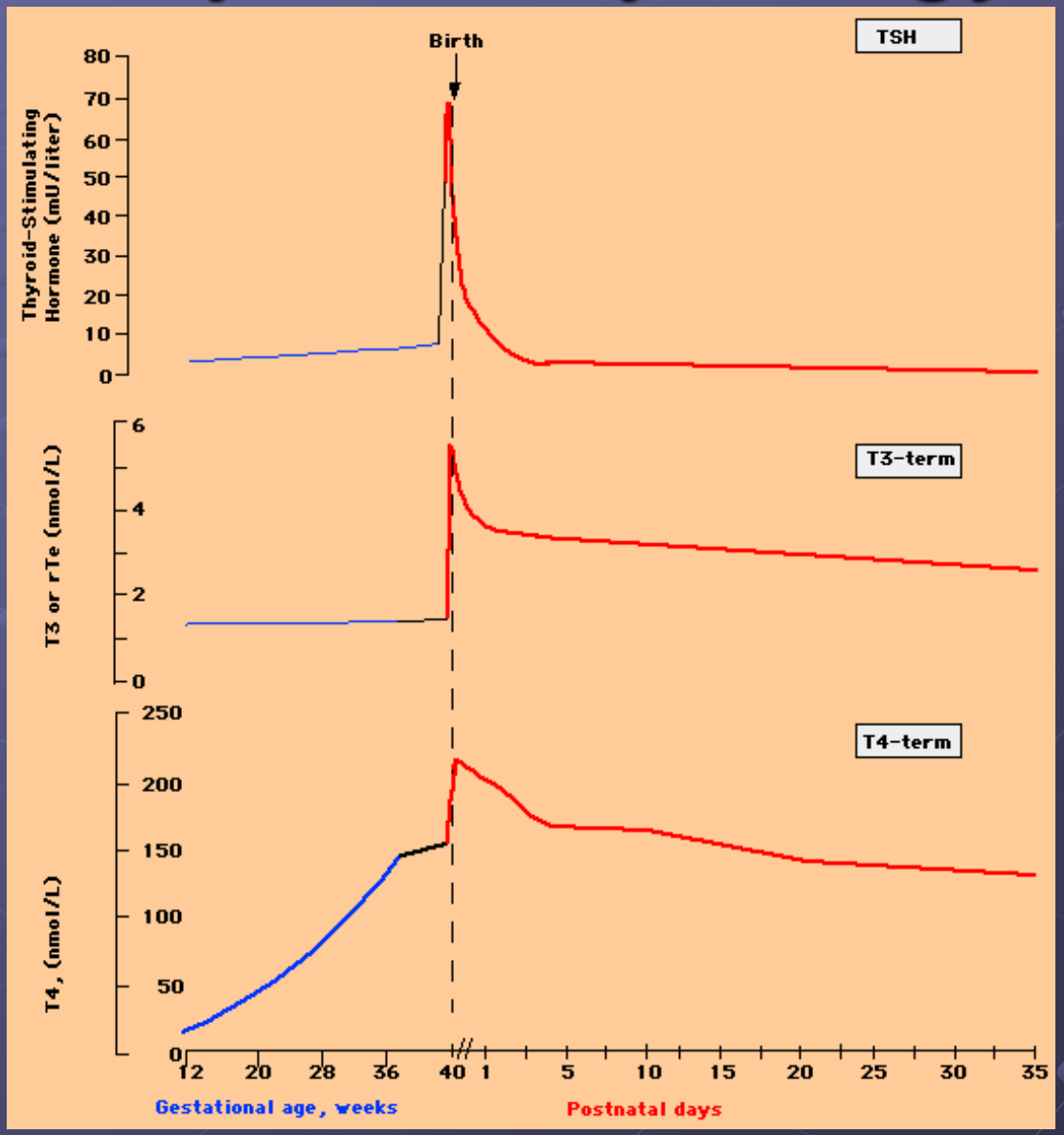
Effect of treatment with Lucrin

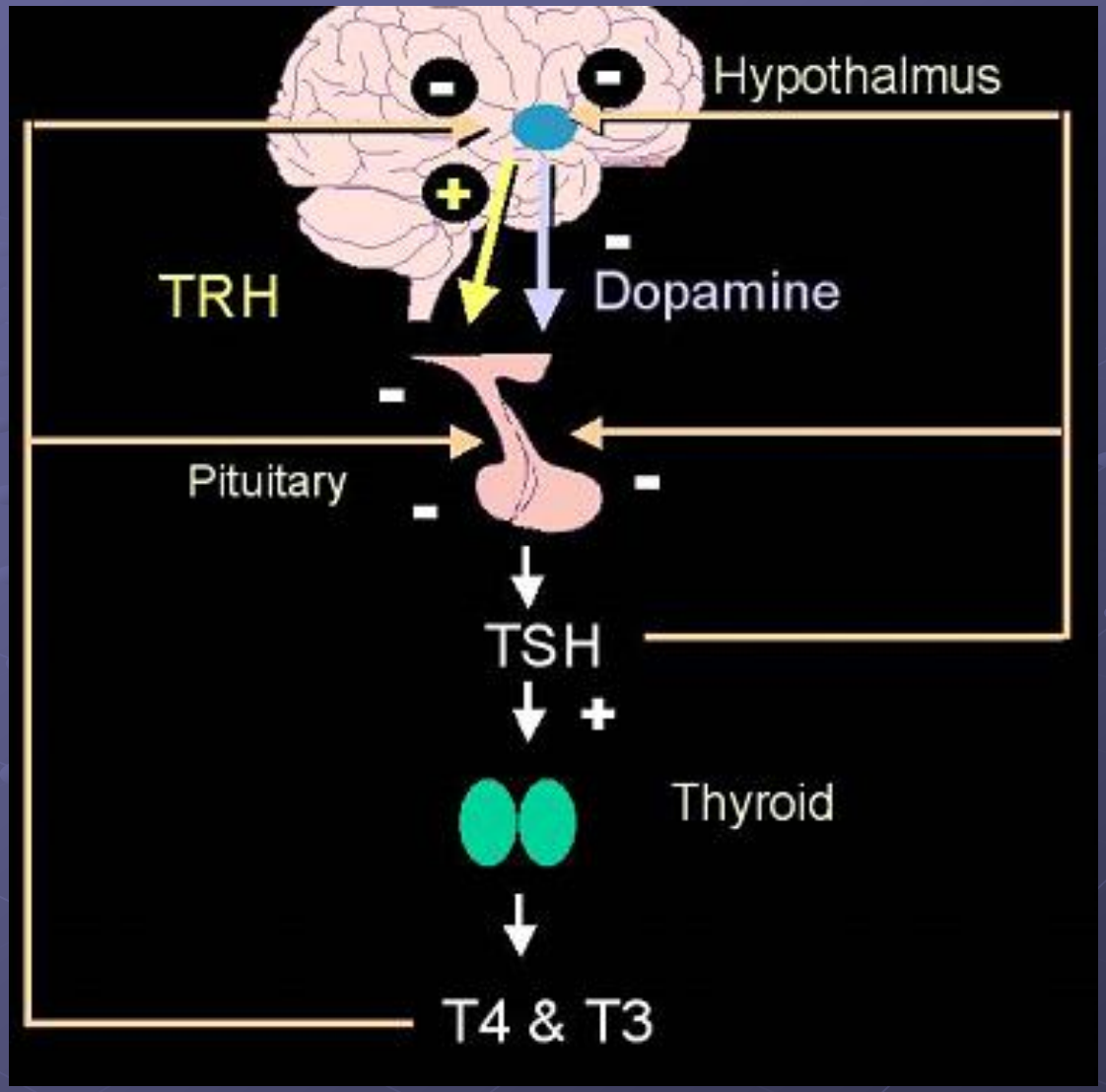
Past this point are thyroid cases!


Maternal thyroid hormone only
Fetal thyroid function begins
Maternal and fetal thyroid hormones
Fetal free T_4
Maternal free T_4
Maternal TSH
hCG
Maternal free T_3
Conception
12/40
24/40
Term
Postnatal
TRENDS in Endocrinology & Metabolism

Patel 2011

Thyroid Physiology

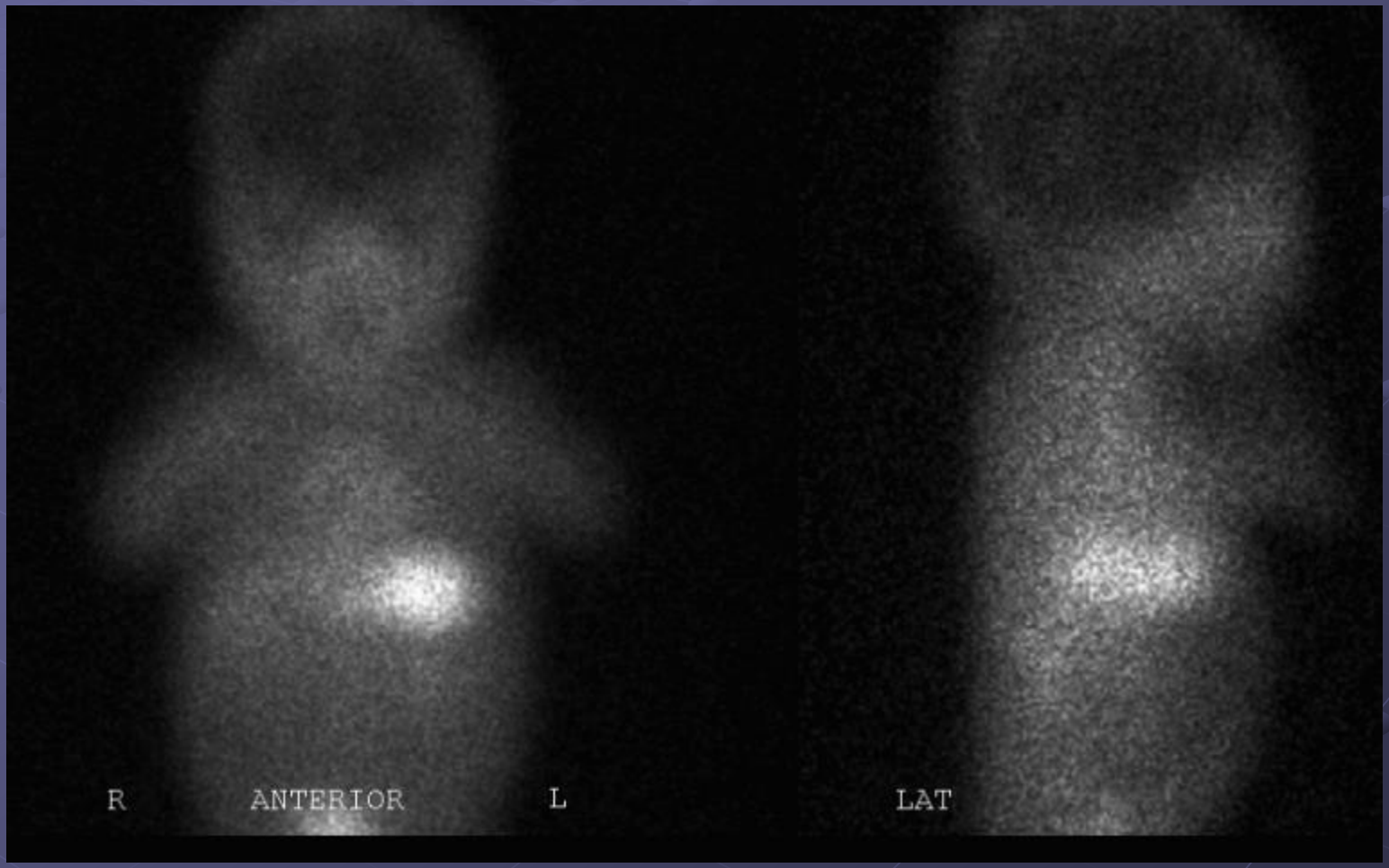



Hypothalmus
TRH
Dopamine
Pituitary
TSH
Thyroid
T4 & T3

Case

- 6 day old neonate has an elevated TSH on neonatal screening >100 mIU/L
- Pretx FT4 3.8pmol/l (15-35)
- TSH 135 mIU/L (0.5-6.0)
- No features of hypothyroidism or hx or examination.

Thyroid scintiscan – athyreosis



Case

- Treated with L-Thyroxine 15mcg/day with normalization of FT4 by 2 weeks.
- Monthly TFTs over the first 12 months were normal
- At 13 months of age the mother ran out of L-thyroxine and failed to fill further prescriptions!

Case

- But she continued with monthly TFTs.

- 4 months after stopping L thyroxine
  - FT4 16 pmol/l (15-35)
  - FT3 5 pmol/l (3.9-9.0)
  - TSH 2.5 mIU/l (0.5-6.0)

Case

- What is the likely cause for this presentation?

- A) Mum tested her other child
- B) The thyroid has grown
- C) The father is giving the T4 and the mother doesn’t know
- D) Something has gone away
- E) Mother has hashimotos
- F) D and E

Case

- What is the likely cause for this presentation?

- A) Mum tested her other child
- B) The thyroid has grown
- C) The father is giving the T4 and the mother doesn’t know
- D) Something has gone away
- E) Mother has hashimotos
- **F) D and E**

Case

- Transient hypothyroidism secondary to TSH blocking antibodies.
- A normally formed gland can be missed on thyroid scintiscan in the presence of blocking antibodies.
- Thyroid USS can detect thyroid glands in neonates

Case 2

- Mother with Grave's disease on PTU during pregnancy.

2.9 Kg term male,

- On Day 2 of age:

FT4 = 7.0 pmol/l (15-35)

FT3 = 3.5 pmol/l (3.9-9.0)

TSH = 50 mIU/l (0.5-6.0)

- Do these TFTs reflect the normal neonatal changes?

Case 2

On Day 8:

FT4	=48 pmol/l	(15-35)
FT3	=19.0 pmol/l	(3.9-9.0)
TSH	<0.01 miU/l	(0.5-6.0)

Q: As this is a self limiting problem, is therapy needed?

Case 5

- On Day 8:

- FT4 =48 pmol/l (15-35)
- FT3 =19.0 pmol/l (3.9-9.0)
- TSH <0.01 miU/l (0.5-6.0)

- **A: This is neonatal graves**

Neonatal Thyrotoxicosis

- **INCIDENCE**
- Grave's is 0.2 percent of women,
- Neonatal Graves is 2% of these. (approximately 1:25,000 neonates).
- males = females
- Severity consistent in future pregnancies.
- Severe neonatal thyrotoxicosis has up to a 20% mortality untreated.

- Evolves rapidly, evident by D7

Neonatal graves

- What is quickest options to treat
  - A) Nothing
  - B) Carbimazole
  - C) Lugol's iodine
  - D) Propranolol
  - E) Do a CT and Put in a long line
  - F) All are similarly effective

Neonatal graves

- What is quickest options to treat
  - A) Nothing
  - B) Carbimazole
  - **C) Lugol's iodine**
  - D) Propranolol
  - E) Do a CT and Put in a long line
  - F) All are similarly effective

Treatment

- Lugol's iodine 1 drop tid Blocks T4 release, synthesis and I uptake (Wolf Chaikoff effect).
- Propranolol Within hours
- Carbimazole will take several days to have an effect on T4 release from the thyroid.