Growth & Development

Growth

- **Definition:** Increase in the **size** & **number** of cells
- It can be assessed by measurements as Weight, Height (Length) & Skull circumference
- It is dependent on different factors at different ages:
  - Infancy: Nutrition (Substrate availability)
  - Childhood: Growth hormone
  - Puberty: Growth hormone & sex hormones

Development

- **Definition: Maturation** of function & skills
- It can be assessed by evaluation of mental , motor & sexual development

Growth Stages

A) **Intrauterine stage** (= Prenatal)

a. Embryonic period: 1st 8 weeks

b. Fetal period: 9-40 weeks

- Early fetal period: 9-24 weeks
- Late fetal period: 25-40 weeks

B) **Extrauterine stage** (= Postnatal)

a. Neonatal period: 1st 28 days

b. Infancy: 1st 2 years of life (after the neonatal period)

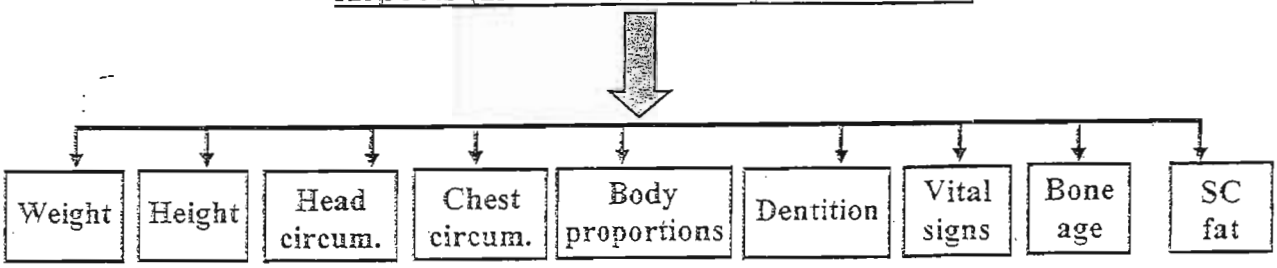
c. Childhood: 2 yrs-12 yrs

- Early childhood: 2-6 yrs [Preschool years]
- Late childhood: 6-12 yrs [School years]

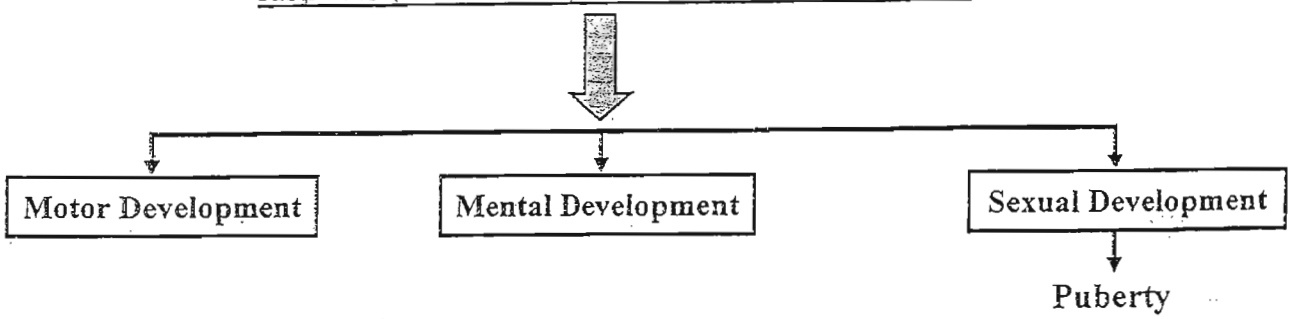
d. Adolescence: 10-20 yrs

Normal Growth & Development

Aspects (Indicators) of Physical Growth



Aspects (Indicators) of Normal Development



Normal Growth

Weight

Age	Weight	Comment
Birth	3	
1 month	3.750	1st 4 months 750 g/month
2 months	4.500	
3 months	5.250	
4 months	6	
5 months	6.500	2nd 4 months 500 g/month
6 months	7	
7 months	7.500	
8 months	8	
9 months	8.250	3rd 4 months 250 g/month
10 months	8.500	
11 months	8.750	
12 months	9	
2 years	12	Wt = (2 x age) + 8
3 years	14	
4 years	16	
5 years	18	
6 years	20	
7 years	22.5	2.5 Kg/yr
8 years	25	
9 years	27.5	
10 years	30	

Remember
Weight
- **Doubled** at 4 months
- **Tripled** at 12 months
- 8 Kg at 8 months

Height & Length

Age	Height	Comment
Birth	50	25 cm/ year
6 month	68	
1 years	75	
2 years	87	
3 years	94	
4 years	100	4-8 years 7 cm/year
5 years	107	
6 years	114	
7 years	121	
8 years	128	
9 years	135	9-12 years- 5 cm/year
10 years	140	
11 years	145	
12 years	150	

NB: Height (2-12 yrs)
Height = (6 x age) + 77

Height or Length??
- **Height:** Standing, in children > 2-3 yrs
- **Length:** Supine, in children < 2-3 yrs

Remember
Height
- **Doubled** at 4 years
- **Tripled** at 12 years
- 75 cm at 1 year

Head circumference

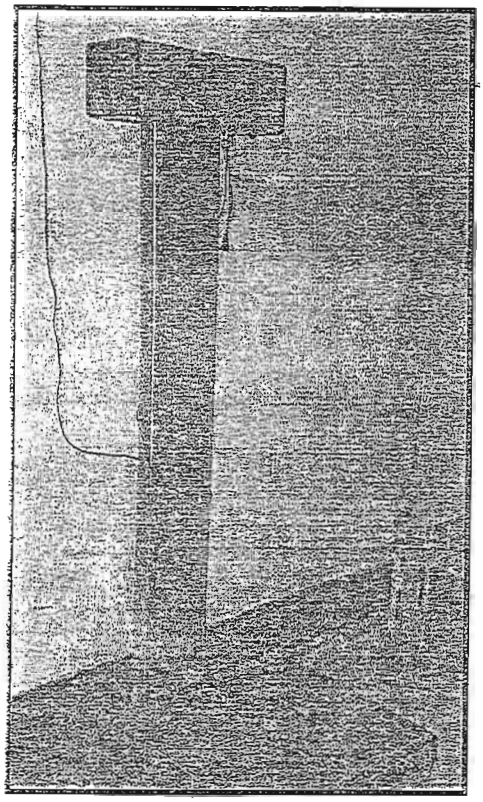
Age	H. Circ.	Comment
Birth	35	12 cm in the 1st year
6 months	43	
1 year	47	
2 years	49	6 cm in the next 11 years
6 years	51	
12 years	53	

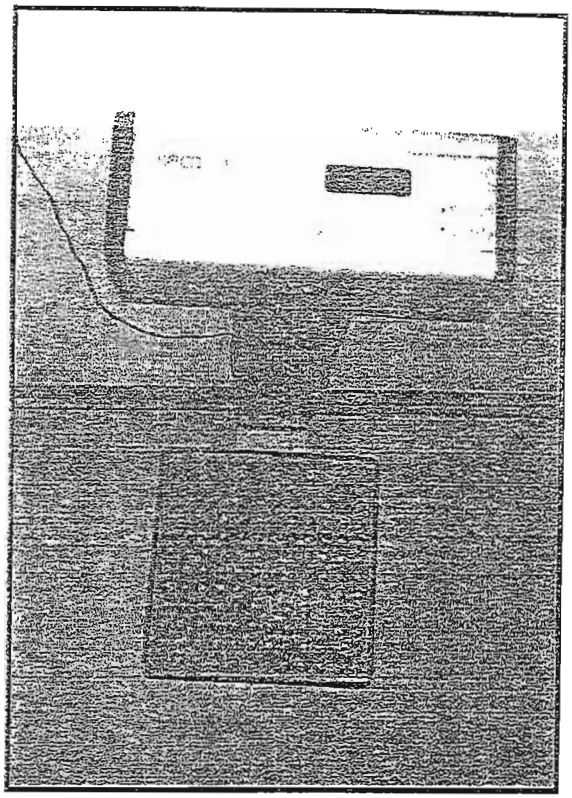
Fontanels

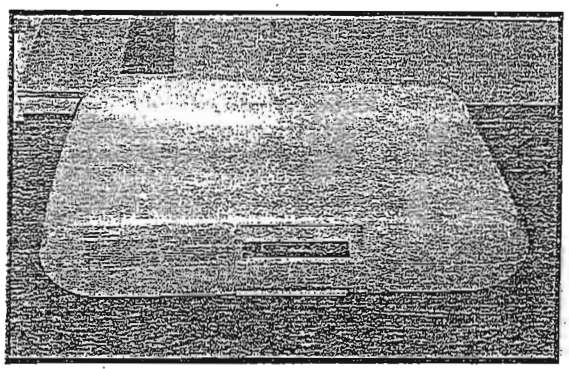
Age	Anterior	Posterior
Birth	3 fingers	Closed
6 months	2 fingers	Open in Congenital Hypothyroidism
1 year	1 fingers	
1.5 years	Closed	

Head Circumference (Thin plastic tape)
- **Anteriorly:** Midway between the hairline&eyebrows
- **Posteriorly:** Occipital prominence

Instruments for Weight & Height Measurement

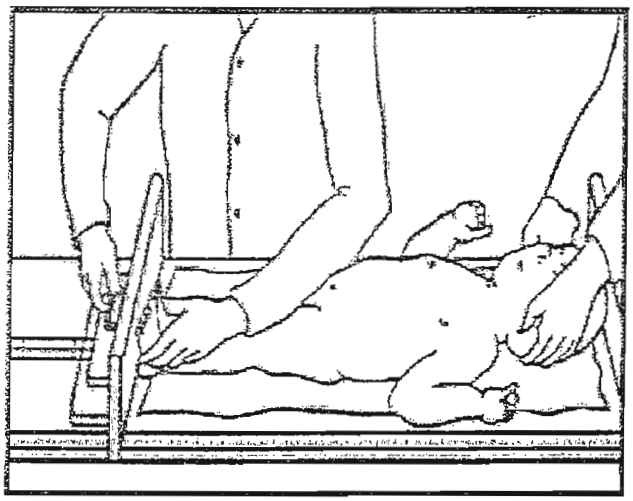




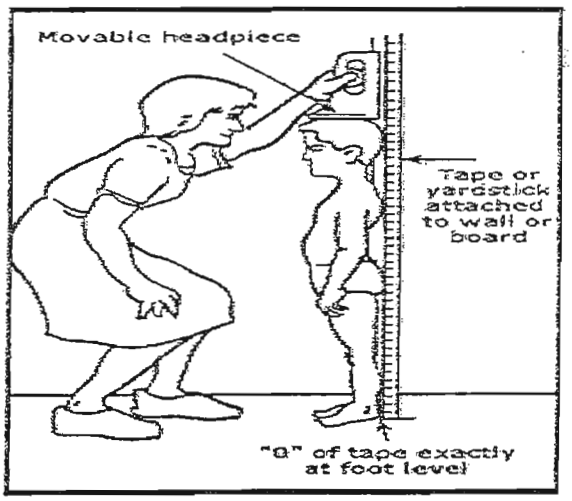


Weight is measured using a calibrated balance

- Infants should be naked
- Children should wear only underwear



Infantometer



Stadiometer

Length is measured using an infantometer
Height is measured using stadiometer

Body proportions

- **Height:** Should be measured against an appropriate vertical measure
- **Lower segment:** Measured from the upper border of the symphysis pubis to the floor
- **Upper segment:** Total height – lower segment (Top of the head & symphysis)
- **Span:** Distance between the tips of middle fingers when the arms are fully extended

Normal US/LS ratio:
- **At birth:** 1.7 (Umbilicus is in the middle)
- **At 3 yrs:** 1.3
- **At 7 yrs:** 1 (Symphysis is in the middle)

Normal Height/Span ratio:
- **< 7 yrs:** Span < Height
- **At 7 yrs:** Span = Height

Dentition

Primary (Deciduous) teeth

Tooth	Age (months)
Central incisor	6
Lateral incisor	9
1st Molar	12
Canine	18
2nd Molar	24

20

Teething in the lower jaw precedes the upper jaw by 1-2 months

Secondary (Permanent) teeth

32

Tooth	Age (yrs)
1st Molar	6
Central incisor	7
Lateral incisor	8
1st Premolar	9
2nd Premolar	10
Canine	11
2nd Molar	12
3rd Molar	18-24

Vital Signs

	Heart Rate (min)	Respiratory Rate (min)	Blood Pressure
Newborn	130	60	80/60
6 months	120	50	80/60
1 year	120	40	90/60
4 years	100	25	90/60
10 years	90	20	100/65

Chest Circumference

- **At birth:** Head circumference is > Chest circumference. Chest circumference = 33 cm
- **At 6 months:** Head circumference = Chest circumference. Chest circumference = 43 cm
- **After 1 yr:** Head circumference < Chest circumference
- **At 5 yrs:** Chest circumference = 56 cm

Skeletal Maturation (Bone age)

- Bone age is a measure of maturation of the epiphyseal centers (ossification)
- Normally, bone age corresponds to the chronological age
- Gives an idea of potential height & clue to the cause of short stature
- Bone age is determined by radiological assessment *(Gruelich-Pyle tables)*
- Reference atlases are available
- Site of assessment of bone age differ according to the age:
    a. **At birth & neonatal period:** Ossific centers around the knee joint
    b. **Early childhood:** Carpal bones (Roughly, one carpal bone appears/year)
    c. **Late childhood & adolescence:** Fusion of epiphyses

Age	Assessment of bone age
Birth	Lower end of femur Upper end of tibia
3 months	Head of humerus
6 months	Epiphysis of radius
9 months	Head of femur
12 months	Epiphysis of tibia
2-6 years	Appearance of carpal bones ▪ **6 months:** One carpal bone ▪ **1 year:** 2 carpal bones ▪ **2 years:** 3 carpal bones ▪ **3 years:** 4 carpal bones ▪ **4 years:** 5 carpal bones ▪ **5 years:** 6 carpal bones ▪ **6 years:** 7 carpal bones
Later on	Time of epiphyseal fusion

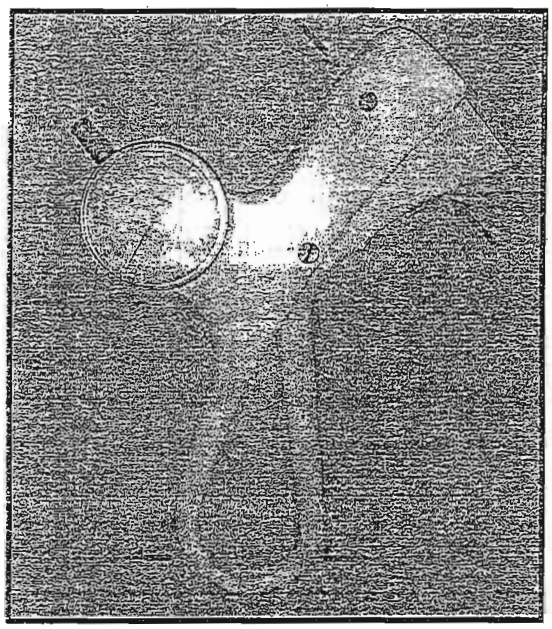
Left wrist or left knee X-ray are used if age < 2 yrs

Interpretation (Variation) of Bone age

Delayed bone age	Advanced bone age
Delayed puberty	Precocious puberty
Constitutional short stature	Excessive androgen production (CAH)
Hypothyroidism	Hyperthyroidism
GH deficiency	Exogenous obesity
Severe illness	
Prematurity	
Malnutrition	

Subcutaneous Fat Thickness

- **Normal variation of fat distribution**
  - **First year:** Excessive fat deposition
  - **From 2-3 years:** No more fat deposition
  - **Puberty:** Characteristic fat deposition in females (Buttocks & Breast)
- Site of assessment
  - **Limb fat:** Over the triceps
  - **Trunk fat:** Over ASIS
- **Abnormalities of SC fat thickness**
  - **Increased:** Obesity
  - **Decreased:** Malnutrition (Cachexia)
- Measured by special device ⇒



Factors affecting physical growth

Factors affecting Intrauterine Growth

A) Primary or Biological Factors (Inherent)

1. **Maternal nutrition & general condition**
2. **Maternal parity:** babies born to multiparous mothers **tend** to be larger
3. **Maternal size:** babies born to large mothers **tend** to be larger
4. **Maternal age:** babies born to young mothers (< 20 yrs) **tend** to be smaller
5. **Maternal environment:** babies born at high attitudes **tend** to be smaller
6. **Genetic & constitutional factors:** Fetal sex
   Male babies grow faster & are more muscular

B) Secondary Factors

a. Maternal factors

1. Teratoges

Definition: Teratogen is any environmental agent (drug, substance or exposure) that interferes with normal embryonic development (structure, growth or function)

Examples:

- Drugs: Thalidomide…
- Infection
- Maternal diseases DM & PKU
- Radiation (ionizing & non-ionizing)

Mechanism of teratogens:

- DNA damage
- Cell death
- Vascular insult
- Delayed differentiation

Mechanism of teratogens:
1. DNA damage
2. Cell death
3. Vascular insult
4. Delayed differentiation

2. **Congenital Infections**

Examples:

- Rubella, Toxoplasmosis
- CMV, HSV

Mechanism of teratogens:

3. **Severe malnutrition**
4. **Smoking**
5. **Chronic diseases:** Cardiac, renal, vascular, endocrinal…
6. **Pregnancy-related diseases:** PIH
7. **IU hypoxia**
8. **Placental & cord factors**
   - Placental insufficiency

b. Fetal factors

1. **Congenital anomalies**
2. **Genetic or chromosomal abnormalities**
3. **Congenital infections**
4. **Multiple pregnancies**
   - ➢ Till 29 wks of gestation ⟶ The same weight as singleton (of the same GA)
   - ➢ After 33 wks of gestation ⟶ The weight of each twin is less than the singleton
   - ➢ Average weight at term = 2.600 gm [average singleton = 3.200 gm]
5. **Metabolic diseases**

c. Endocrinal factors

1. **Insulin**
   - Insulin is an anabolic hormone (↑↑ protein synthesis)
   - It is well transmitted to the fetus (Transplacental) & produced in the fetus by the 3rd month of gestation
   - IDM are macrosomic due to fetal hyperinsulinemia
2. **IGF-II**
3. **Human placental lactogen (= Human chorionic somatomammotropin)**
   - Placental hormone
   - Its structure is similar to that of GH
   - Has a growth-stimulating activity (acts as maternal GH of pregnancy!)
   - Its amount is proportionate to the size of the placenta
4. **Other hormones**
   - ➢ Fetal pituitary GH: No role
   - ➢ Fetal thyroxine: No role
   - ➢ Androgens

Fetal overgrowth syndromes

1. IDM
2. Beckwith-Wiedemann $
3. Cerebral gigantism (Sotos)
4. IGF-II excess

Assessment of Growth

Definition of Growth

- **Definition:** Increase in the **size** & **number** of cells
- It can be assessed by measurements as Weight, Height & Skull circumference

General Features (= General Considerations)

- It is a **continuous** process
- It involves many aspects (*See before*)
- The age of development of different milestones is **variable** (= Wide normal range):
- Chronological age, physical growth & development usually evolve **hand in hand**
- Growth represents the **interaction** of heredity & environment
- It is **not a uniform** process
  - Rate: Fetal period is the fastest period of growth
  - Pattern: Head circumference increses mainly during the 1st 2 yrs of life

Growth Curves

Definition

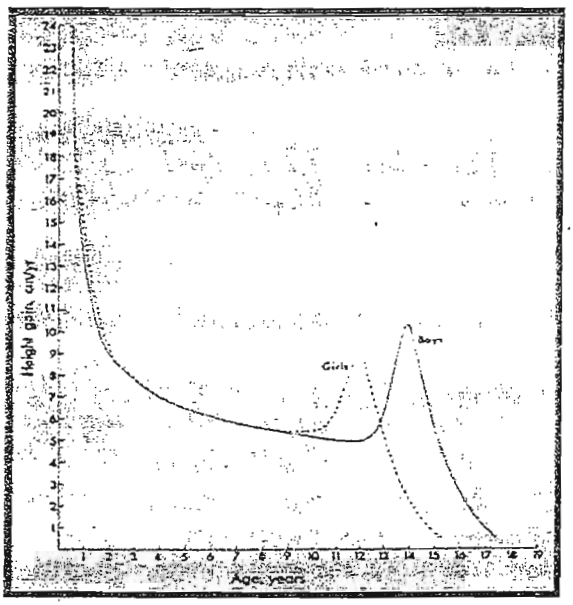
- Graphic method for assessment of physical growth
- By plotting various growth parameters against the age (e.g., Weight & height for age...)

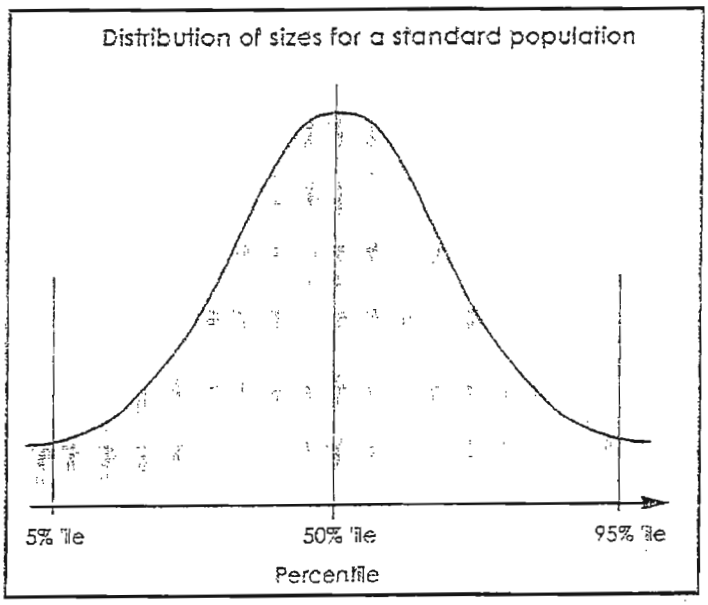
Rational (= Why should growth curves be used?)

- There is wide range of variation among **normal** children
- Growth curves are used to detect any **abnormal** growth pattern

Types

a. **Percentile** growth curves (Most **commonly** used)
b. **Velocity** growth curves: Most **accurate** *(Rate of increase per time)*
c. **Standard deviation** growth curves





Velocity Growth Curves

Definition

- Annual rate of growth velocity
- It is a measurement of gain from year to another
- It can detect any acceleration or deceleration from normal
- It is the most accurate type of growth curves (Gold standard for growth assessment)

How to create

- Two measurements are needed 4-12 months apart
- Divide the height difference by the time interval
- The result is expressed as cm/year growth velocity

Description of Normal Velocity Growth Curve

- Normally, Growth velocity deceases from birth afterward
- Early (up to 4-5 yrs), the deceleration is very rapid
- Then lessens in the prepubertal stage
- From the age of 3 yrs till start of puberty, difference > 2 cm/yr is unusul

Value (= Why most accurate?)

1. It reflects the child status at any particular point (This year & **not** all preceding years)
2. It can detect any acceleration or deceleration from normal
3. Can monitor the effect of treatment e.g., GH therapy…

NB: Criteria for stopping GH therapy:

- Growth rate < 1 inch/year
- Bone age >14 yr in ♀& >16 yr in ♂

Percentile Growth Curves

Definition

- Available for different aspects of growth (Weight, Height, Head circumference)
- Available for different sexes (Males & Females)
- Should be available for each country (Egyptian growth curves are now available)

How to create

- Measure a certain parameter (e.g., height) in 100 healthy child
- Categorize them in 7 groups (*See below*)

Description of Normal Velocity Growth Curve

- Formed of 7 percentiles:
  - 50^{th} percentile is the average (= Median)
  - 25^{th} percentile is below average
  - 10^{th} percentile is low normal
  - 5^{th} percentile is lowest normal
  - 75^{th} percentile is above average
  - 90^{th} percentile is high normal
  - 95^{th} percentile is highest normal

Factors affecting Growth

1. Genetic factors

- Rate of growth depends on interaction between genetic & environmental factors
- It is a polygenic inheritance
- Children inherit their height & body frame from their parents
- Familial short stature is a good example

2. Race

- There is racial difference in growth rate, due to:
  - Genetic factors
  - Nutritional factors
  - Climate may have an impact
- **Negroes** grow faster than whites
- **Yellow race** tend to be short
- **Scandinavians** tend to be tall
- Therefore, Growth curves should be available for <u>each</u> country
- **Egyptian** growth curves are now available

3. Age

- Fetal: Fastest period of growth (*See factors affecting IU growth*)
- Infancy: Nutrition (Substrate availability)
- Childhood: Growth hormone (& Thyroxine)
- Puberty: Sex hormones (& Growth hormone)

4. Sex

- Females grow faster than boys from 7 months to 4 yrs
- Females start & complete pubertal changes before males (Age of puberty in ♀ & ♂)
- Growth curves should be available for different sexes (Males & Females)

5. Nutrition

- Under-nutrition leads to growth failure
- Over-nutrition leads to obesity
- Episodes of malnutrition is followed by catch-up growth

6. Socioeconomic factors (Education, food supply, housing...)

- Low socioeconomic level ⟶ Poor hygiene, poor nutrition & poor health
- High socioeconomic level ⟶ Better growth

7. Season

- There is seasonal variation in growth rate
- Height growth is fastest in Spring
- Weight growth is fastest in Autumn

8. Diseases

- Acute short illnesses: No affection of growth (Catch-up mechanism)
- Chronic illnesses (Cardiac, hepatic, renal diseases...): Marked affection of growth

9. Psychological factors

- Disturbed child-mother or family relation leads to functional hypopituitarism

10.Secular trend

- **Definition:** Deviation of the rate of growth through successive generations provided that all other factors affecting growth are constant
- **During the last 100 yrs,** there is a striking tendency for faster growth & maturation with successive generations (Earlier menarche, increased height potential...)
- **Importance:** Index of development of a community
- **Causes of + Ve secular trend:** Better nutrition & socioeconomic development
- **Causes of - Ve secular trend:** Wars, epidemics, famines...

11.Endocrinal Factors

a. Hormones with a Direct effect on growth

☒ Growth Hormone

- Protein hormone secreted by the anterior pituitary gland
- Pulsatile secretion more with sleep
- Action is **mediated** by insulin like growth factor-1 *(IGF-1)* or "Somatomedin C" formed by the liver
- Action:
  - **Growth:** ↑↑ Size of various tissues (bones, cartilage, muscles& viscera).
  - **Proteins:** Anabolic.
  - **CHO:** ↑↑ Gluconeogenesis.
  - **Lipids:** ↑↑ Lipolysis.
  - **Electrolytes:** ↑↑ Ca, ↑↑ Na, ↑↑ PO_4

☒ Thyroid Hormone

- Protein hormone secreted by the thyroid gland
- Action is **mediated** by insulin like growth factor-1 *(IGF-1)* or "Somatomedin C" formed by the liver
- Action:
  - Calorigenic
  - Protein: Anabolic in physiologic dose, catabolic in large dose
  - **Growth: Necessary for GH & IGF-1 synthesis & action**
  - Bone: ↑↑ Bone age
  - CNS: Important for the rapidly growing brain (synapses, myelination)
  - Sexual maturation: Delayed in hypothyroidism (? precocious puberty...)

☒ Sex Steroids

- Steroid hormones
- ↑↑ Bone age
- Concerned mainly with pubertal growth spurt
- Important for the development of 2ry sex characters
- Testosterone is important for virilization of the male fetus (CAH in a ♀...)

b. Hormones with an Indirect effect on growth

☒ Insulin

- Protein hormone secreted by the pancreas
- Anabolic hormone
- Has a growth-promoting effect through interaction with GH & IGF-1

☒ Glucocorticoids

- Steroid hormone secreted by the adrenal gland
- Required in physiological amount for optimum growth
- **Excessive** amount: Direct inhibition of epiphyses, ↓↓ GH, ↓↓ IGF-1



Normal child on percentile growth curves should:

- Lie between the 5th & 95th percentiles
- Follow his own percentile (Marked deviation should be investigated)
- All the growth parameters should follow the same percentile level

Abnormalities in percentile growth curves

- Values < 5th % are abnormal
- Values > 95th % are abnormal
- Sustained deviation from the child own percentile is abnormal

Value & Importance

- Demonstration of **normal** growth pattern (Each child has his own pattern of growth)
- **Educational** demonstration
- **Summary** of growth data over a long period
- **Statistical** value
- Diagnosis of **abnormal** growth:
  - **Single measurement:** Values < 5th % or > 95th % are abnormal
  - **Serial measurements:** Sustained deviation from the child own percentile is abnormal
- **A single growth parameter** should **not** be assessed in isolation from other growth parameters; e.g., a child's weight may be normal in proportion to his height if he is short, but low weight if tall **[Weigh for height curves are available]**
- **Weigh for height** < 5th percentile is the **single** best indicator of acute undernutrition
- **Catch-up growth:** Period of accelerated growth following a period of growth arrest
- Can monitor the effect of treatment e.g., GH therapy…
- Demonstration of drug side effects on growth e.g., steroids in SLE…
- Prediction of adult height

Errors in Interpretation of Growth Curves

- Obesity: Excess fat
- Kwashiorkor: Edema
- Interpretation of growth curves should be done together with proper clinical examination

Catch-up Growth

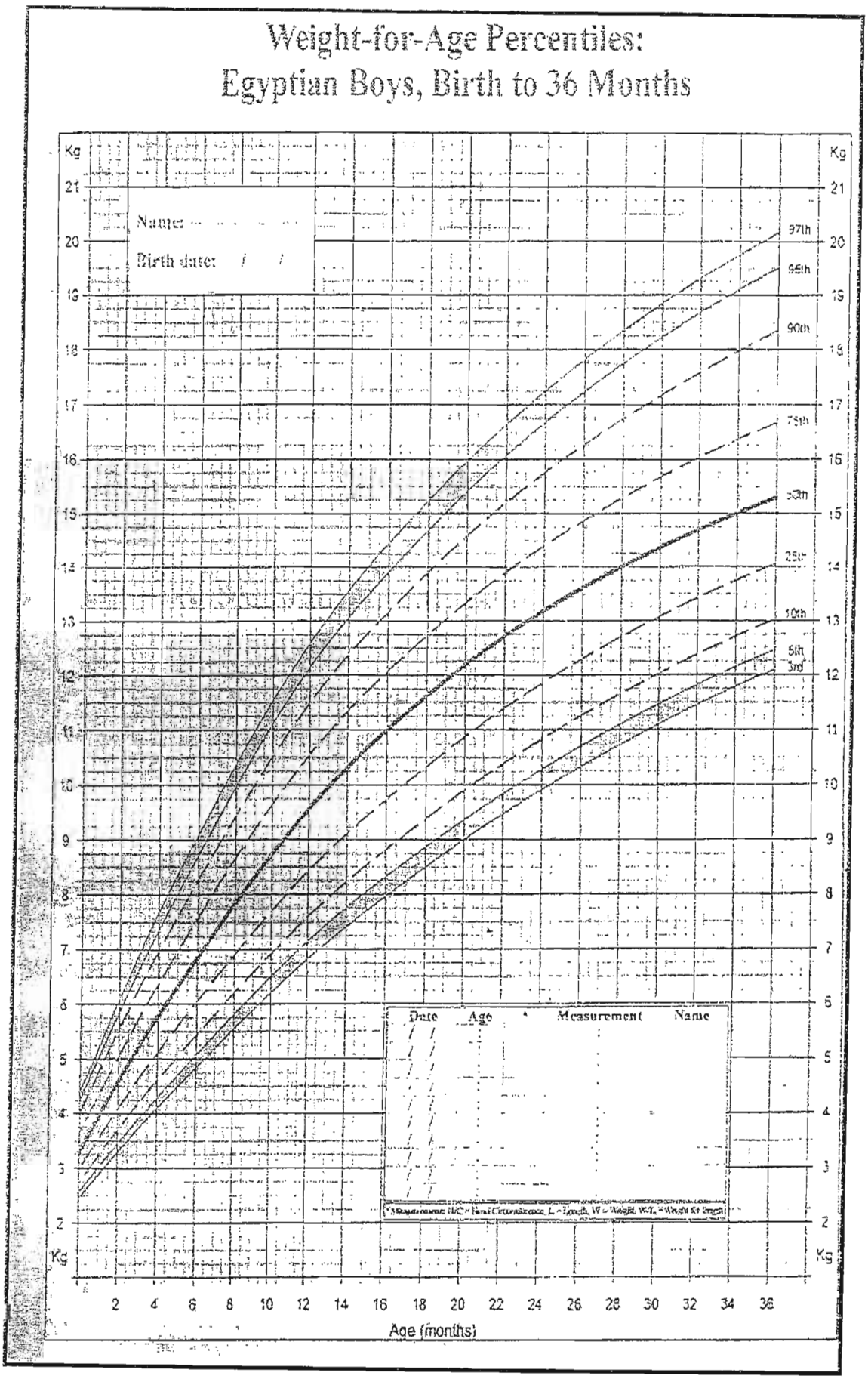
Definition: Period of accelerated growth following a period of growth arrest or restriction
Importance: Allows child to attain his target centile of growth
Types: Complete or incomplete
Examples:

- Gastroenteritis
- PEM
- GIT surgery (Atresia, CHPS…)

Factors affecting catch-up:

- **Onset:** The earlier, the more difficult to achieve a complete catch-up
- **Duration:** The longer the duration of the stress, the more difficult to achieve a complete catch-up
- **Sex:** Females show a more complete catch-up than males

Egyptian Growth Curves (Example)



Developmental Milestones

Definition of Development

- Definition: Maturation of function & skills
- It is due to: Functional maturation & myelination of the CNS

General Features (= General Considerations)

- It is a **continuous** process
- Chronological age, physical growth & development usually evolve **hand in hand**
- Motor development occurs in a **cephalocaudal** & **central-to-peripheral** direction: Truncal control ⇨ Arm control ⇨ Finger control
- Motor development is related to **brain development**. So, motor development is affected in children with MR
- Development represents the **interaction** of heredity & environment on the brain
- Environment provides physical & psychological needs:
  - Physical: Food, good health…
  - Psychological: Care, experiences…
- The age of development of different milestones is **variable** (= Wide normal range):
  - Median age: The age by which 1/2 standard population achieve a certain skill
  - Limit age: The age by which a certain skill should be achieved

Limit age is more useful as a guide to normal development than median age

> Example: **Walking unsupported**
> - Median age of walking unsupported is 12 months
> - Limit age of walking unsupported is 18 months

Monitoring of Development

a. Parents
b. Regular child health surveillance checks
c. Health care professional

Developmental Milestone (= Fields of Development)

A) **Gross Motor**
- Using large groups of muscle
- Examples: Sitting, standing, walking…

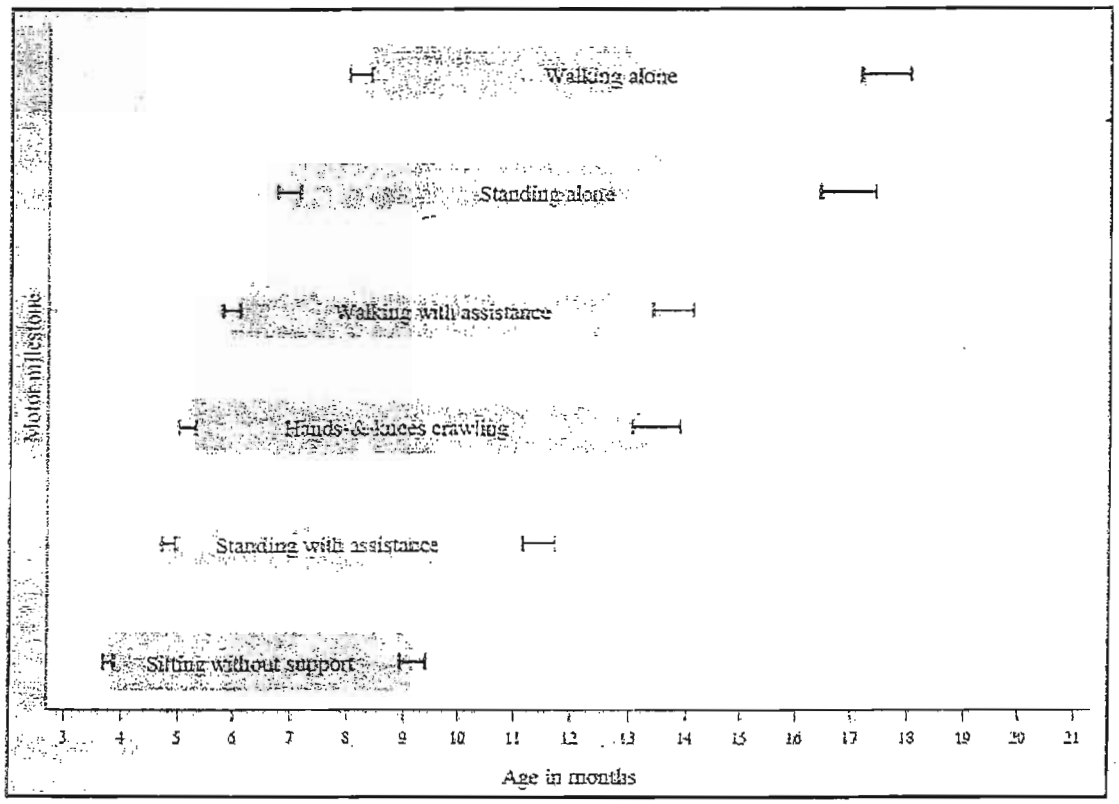
B) **Fine Motor** (& Vision)
- Using hands to do fine movements
- Examples: Eating, drawing, writing, dressing…

C) **Hearing, Speech & Language**

D) **Social, Emotional & Behavioral**

Gross Motor

Age	Gross Motor Development (Median Ages)
Newborn	Turns head from side to side
2 months	Raises head to 45°C
3 months	Head support Lifts head & chest (on prone position)
4 months	Pushes with feet
5 months	Sitting with trunkal support
6 months	Sitting with pelvic support
7 months	Sitting without support (1ST with round back then with straight back)
8 months	Turns from supine to prone (& reverse)
9 months	Creeping or Crawling
10 months	Standing
12 months	Walking (furniture)
15 months	Walking (alone)
1 ½ years	Ascends stairs (Child manner)
2 years	Descends stairs (Child manner) Kicks aball
3 years	Ascends stairs (Adult manner) Pedal tricycle
4 years	Descends stairs (Adult manner)
5 years	Can hop on one foot



Precocious Puberty

Definition

The appearance of 2ry sexual characters before 8 yrs in ♀ and 9 yrs in ♂

	True Precocious Puberty	Precocious Pseudopuberty
Synonyms	Central (intra-cranial) Gonadotropin dependent	Peripheral (extra-cranial) Gonadotropin independent
H-H-G	Active	Inactive
FSH & LH	↑↑	↓↓
Gonads	Active	Inactive
Gametogenesis	Present	Absent
2ry.sex characters	Isosexual ♀♂	Isosexual or heterosexual
GnRH stimulation	↑↑ LH & FSH	No ↑↑ LH & FSH

Precocious pseudopuberty ⟶ ↑↑ bone age ⟶ activation of HHG axis ⟶ True Precocious puberty (Combined Gonadotropin dependent & Gonadotropin independent Puberty)

Etiology

I) True Precocious Puberty:

A) Idiopathic (constitutional, functional)

B) Organic brain lesions
- Hypothalamic hamartoma
- Intracranial lesions
- Pineal region tumors

C) Radiotherapy

D) Hypothyroidism

> True precocious puberty:
> ♀ ⟶ 80% of cases are idiopathic
> ♂ ⟶ 80% of cases are pathologic

II) Precocious Pseudopuberty:

		Gonadal	Adrenal	Exogenous
Female	Isosexual (Feminizing)	• McCune-Albright $ • Autonomous ovarian cyst • Ovarian tumors ➢ Granulose cell tumor ➢ Teratoma	Feminizing adrenal tumor	Estrogens
	Heterosexual (Virilizing)	•Ovarian tumors e.g., Androblastoma	• Virilizing adrenal tumor • CAH	Androgens
Male	Isosexual (Virilizing)	• Leydig cell tumor • Familial male precocious P.	• Virilizing adrenal tumor • CAH	Androgens
	Heterosexual (Feminizing)	• Sertoli cell tumor	Feminizing adrenal tumors	Estrogens

In ♂, hCG secreting tumors (Hepatoblastoma, CNS, mediastinum) ⟶ Isosexual precocious pseudopuberty

III) Incomplete Precocious Puberty:
- Premature thelarche
- Premature adrenarche
- Premature menarche

IV) Combined Puberty:
- Congenital adrenal hyperplasia
- McCune-Albright $
- Familial male precocious puberty

Leoprolide: synthetic long-acting GnRH agonist
- *Pulsatile* GnRH is needed to ↑↑ FSH & LH
- *Continuous* GnRH stimulation: suppression

True Precocious Puberty

Idiopathic (Constitutional, functional)

Incidence (♀: ♂= 5-10:1)
It is the cause of PP in 90% of ♀
It is the cause of PP in *only* 25- 75% of ♂

Etiology
Sporadic (?? Familial) — True Isosexual

Clinical picture *(Synchronous as normal)*

☒ **Females:**
Breast enlargement → Pubic hair → Axillary hair → Menarche (+2ry sex characters)

☒ **Males:**
Testicular ↑↑ → Thinning & pigmentation of the scrotum → Penis ↑↑ → Pubic hair → Axillary hair (+2ry sex characters)

☒ **Both ♀ & ♂:**
Tall as children, Short as adults
Gametogenesis: present(Pregnancy & N.emissions)
Mentality: compatible with chronologic age

☒ **Course:**
Progressive (rapidly or slowly) or regressive

Investigations
1. **Gonadotrpins (FSH & LH)**
   - ↑↑ FSH& LH with detected pulsatile LH
   - GnRH stimulation: Brisk response ↑↑
2. **Sex hormones:** ↑↑ (consistent with bone age)
3. **Bone age:** Advanced bone age
4. **CT, MRI brain:** to exclude I.C. lesions (♂)*
5. **Pelvic U/S:** ↑↑ Ovaries, uterus ± ovarian cysts

Organic Brain lesion

Incidence
It is the cause of PP in 10% of ♀
It is the cause of PP in 25- 75% of ♂

Etiology
1. **Hypothalamic hamartoma**
2. **Intracranial lesions** (involving the hypothalamus)
   - TB meningitis
   - Encephalitis
   - Tumors (astrocytoma, ependymoma…)
   - Trauma
   - Tuber sclerosis
   - Neurofibromatosis (optic glioma)
3. **Pineal region tumors** (germinoma, astrocytoma)

True Isosexual

Clinical picture
☒ **Endocrinal:** may precede the IC lesion
☒ **Picture of the cause:** ↑↑ ICT, visual field…
☒ **Hypothalamic syndrome:**
- Hypothermia, hyperthermia, adipsia, DI
- Obesity, cachexia
- Hypersomnia
- Gelastic seizures (unnatural laughing)

Investigations as in constitutional precocious P.
Treatment GnRH analog *(Leoprolide)*
Rx of the cause

PP following Radiotherapy

Mechanism
Radiotherapy → True Precocious Puberty

True Isosexual

Clinical picture
1. **Precocious puberty:** ↑↑ growth
2. **GH & TSH deficiency:** ↓↓ growth
3. **Net result:** Normal growth

Treatment
- GnRH analog (Leoprolide): 0.25-0.3mg/Kg IM every 4 wks
- GH & Thyroid supplementation

Hypothyroidism& precocious puberty

Incidence
Hypothyroidism usually cause delayed puberty*
Precocious puberty may occur in severe, untreated 1ry hypothyroidism of long duration

Mechanism & C/P
TSH & GTH (LH & FSH) have identical α-chain
↓↓ T_3, T_4 → ↑↑ TSH → ↑↑ FSH receptors →

☒ **Females:**
↑↑ Estrogen → ↑↑ Breast& Bleeding (menses)
No ovulation

Incomplete Isosexual True

☒ **Males:**
↑↑ Sertoli cells→ ↑↑ Testicular size
No ↑↑ of Leydig cells → No ↑↑ testosterone
No virilization

Investigations
1. TSH & prolactin: ↑↑
2. Gonadotrpins (FSH & LH): ↓↓
3. CT, MRI brain: ↑↑ Sella
4. Pelvic U/S: Ovarian cysts

Treatment Thyroid supplementation (↓↓ TSH)

Treatment

GnRH analog *(Leoprolide)*: 0.25-0.3 mg/Kg IM every 4 wks (Other routes = intra nasal, SC)
Side effects: Recurrent sterile fluid collection at injection sites
Effects: ↓↓ GTH& sex hormones + ↓↓ growth rate to normal + ↑↑ adult height
Regression of 2 ry sex characters (breasts, menses, testicular size, pubic hair)

Precocious Pseudopuberty

Gonadotropin-Secreting Tumors	Familial male Precocious Puberty 1^{ry} Leydig cell hyperplasia	McCune-Albright Syndrome
I) Hepatoblastoma: **Mechanism** ▪ It secretes hCG ⟶ ↑↑ LH receptors ⟶ ↑↑ Leydig cells ⟶ ↑↑ Testosterone ▪ No spermatogenesis **Clinical picture** (Only in ♂ ≈ 2 yrs) ▪ Isosexual precocious pseudopuberty ▪ Hepatomegaly **Investigations** ▪ **hCG & α-fetoprotein:** ↑↑ ▪ **Plasma testosrerone:** ↑↑ ▪ **Gonadotrpins (FSH & LH):** ↓↓ [In the past, ↑↑ LH due to cross reactivity with hCG] ▪ **Testicular biopsy:** Leydig cell hyperplasia ▪ **Bone age:** Advanced bone age II) Other tumors: ▪ **Type:** Teratoma, teratoćarcinoma ▪ **Site:** CNS, mediastinum, gonads	**Etiology** (AD) **Mechanism** (Gonadotropin-independent) ▪ Activation mutation of LH receptors ⟶ ↑↑ Leydig cells⟶ ↑↑ testosterone ⟶ ↑↑ bone age ▪ No spermatogenesis **Clinical picture** (Only in ♂, 2 yrs) ▪ Isosexual precocious pseudopuberty ▪ True Isosexual precocious puberty may follow when bone age reaches pubertal age (combined) **Investigations** ▪ **Plasma testosrerone:** ↑↑ ▪ **Gonadotrpins (FSH & LH):** ↓↓ ▪ **Testicular biopsy:** Leydig cell hyperplasia ▪ **Bone age:** Advanced bone age **Treatment** ▪ Ketokonazole (# Testosterone synthesis) ▪ GnRH analog (Leoprolide): in true puberty	**Etiology** Autonomous hyperfunction of glands **Clinical picture** (Usually in ♀ ≈ 3 yrs) I) Skin: Pigmentation (Café-au-lait patches) II) Skeletal: Fibrous dysplasia III) Endocrinal: 1. **Gonads** ⟶ Precocious pseudopuberty [Functioning follicular cyst ⟶ ↑↑ Estrogen] True Isosexual precocious puberty may follow when bone age reaches pubertal age (combined) 2. **Thyroid** ⟶ Hyperthyroidism 3. **Adrenal** ⟶ Cushing syndrome 4. **Pituitary** ⟶ GH excess (gigantism or acromegaly) **Treatment** ☒ **Functioning ovarian cyst:** ▪ Surgery or aspiration ▪ Aromatase inhibitor *(Testolactone)* ▪ Anti-estrogen *(Tamoxifen)* ▪ GnRH analog (Leoprolide): (When??) ☒ **Hyperthyroidism** ☒ **Cushing** ☒ **GH excess:** *Octreotide*

Incomplete Precocious Puberty (Partial)

Definition

Isolated precocity of one of the 2 ry sexual characters before 8 yrs in ♀ and 9 yrs in ♂ without development of other signs of puberty. It is usually **transient**

Premature Thelarche	Premature Pubarche (Adrenarche)	Premature Menarche
Definition Isolated breast development **Etiology** Sporadic (? Familial) **Clinical picture** ▪Age of onset: During the 1st 2 yrs. May at birth ▪Course: Transient (3-5 yrs) Rarely progressive ▪Bilateral or unilateral ▪Atypical (exagerated) thelarche ↑↑ bone age, U/S ⟶ ↑↑ Ovaries **Investigations** ▪FSH, LH, Estrogen: Normal ▪Bone age: ± Advanced bone age ▪Pelvic U/S: ± Ovarian cysts **Treatment** Benign but F/U is needed as it may be 1st sign of precocious puberty	**Definition** Isolated appearance of sexual hair **Etiology** Premature ↑↑ adrenal androgens **Clinical picture** (♀ > ♂) ▪Sexual hair: pubic & axillary hair ▪ Atypical premature adrenarche: Systemic androgenic effects (acne, ↑↑ bone age…) ▪Course: Transient **Investigations** ▪FSH, LH, sex hormones: Normal ▪DHEA: ↑↑ ▪Bone age: ± Advanced bone age **Treatment** Benign but F/U is needed as it may be 1st sign of precocious puberty	**Definition** Isolated menses **Clinical picture** ▪1-3 attacks of menstrual bleeding ▪Course: Transient **Investigations** ▪FSH, LH, Estrogen: Normal ▪Pelvic U/S: ± Ovarian cysts **Treatment** Benign but F/U … **DD** (Vaginal bleeding) 1. Child abuse 2. FB 3. Vulvo-vaginitis 4. Uterine sarcoma

Precocious puberty in ♂:

A) **True precocious puberty**
B) **Precocious pseudopuberty**
   1. **Isosexual**
      - Gonadal: Leydig cell tumor, familial male precocious puberty
      - Adrenal: Virilizing adrenal tumor & CAH
      - Exogenous: Androgen
      - Gonadotropin-secreting tumors
   2. **Heterosexual**
      - Gonadal: Sertoli-cell tumor
      - Adrenal: Feminizing adrenal tumor
      - Exogenous: Estrogen
C) **Incomplete Precocious puberty**
   Premature adrenarche
D) **Combined Precocious puberty**
   - Familial male precocious puberty
   - CAH

Precocious puberty in ♀:

A) **True precocious puberty**
B) **Precocious pseudopuberty**
   1. **Isosexual**
      - Gonadal: McCune-Albright $
      Autonomous ovarian cyst, ovarian tumors
      - Adrenal: Feminizing adrenal tumor
      - Exogenous: Estrogen
   2. **Heterosexual**
      - Gonadal: ovarian tumors
      - Adrenal: Virilizing adrenal tumor& CAH
      - Exogenous: Androgen
C) **Incomplete Precocious puberty**
   Premature thelarche, Adrenarche, menarche
D) **Combined Precocious puberty**
   - McCune-Albright $
   - CAH

Fine Motor

Age	Fine Motor Development & Vision (Median Ages)
Newborn	Follows light & face in midline
1 month	Follows moving objects or light
4 months	Reaches out for objects
5 months	Sitting with trunkal support
6 months	Palmar grasp (Use of the **whole hand** to grasp objects)
7 months	Transfers objects from one hand to another
10 months	Pincer grasp (Use of the **index & thumb** to grasp objects)
12 months	Waves bye-bye
18 months	Builds tower of 3 cubes Scribbles
2 years	Builds tower of 6 cubes Draws a line
2½ years	Builds tower of 8 cubes
3 years	Bridge of 3 cubes Draws a circle
4 years	Makes steps by cubes Draws a cross
5 years	Draws a triangle
6 years	Draws a man with all features "Draw-A-man test"

Hearing, Speech & Language

Age	Hearing, Speech & Language (Median Ages)
Newborn	Cries Startle to loud noises
1 month	Follows moving objects or light
4 months	Laughs out loud Vocalization
5 months	Sitting with trunkal support
6 months	Babbling
9 months	Says Mama & Dada Mama & Dada (Specific to parents at 10-12 months)
12 months	Says 2-3 words (other than Mama & Dada)
18 months	Says 10 words Shows 2 parts of the body (Nose, ear…)
2 years	Says 3-word sentence (telegraphic)
3 years	Can tell name, age & sex
4 years	Counts up to 10 Recognizes 8 colors
5 years	Clear speech

Social, Emotional & Behavioral Development

Age	Social, Emotional & Behavioral Development (Median Ages)
Newborn	Follows face in midline
2 month	Social smile
3 months	Listens to music
4-6 months	Recognition of the mother
6 months	Puts food in mouth Prefers the mother
10 months	Respond to sound of name
12 months	Waves bye-bye Mimics Drinks from a cup with 2 hands
18 months	Symbolic play Feeds with spoon
2 years	Undresses
3 years	Has friends & interactive play "*Takes turn in play*"
4 years	Dressing

Vision Development

Age	Vision Development (Median Ages)
Newborn	Follows face in midline
2 month	Optokinetic nystagmus.
7 months	Colored vision

Hearing Development

Age	Vision Development (Median Ages)
Newborn	Startle to loud noise
4 month	Smiles to your voice (Or quietens)
7 months	Turns towards quiet sounds
10 months	Respond to sound of name & other familiar words (No, bye-bye…)

Primitive Neonatal Reflexes

Definition

- Group of reflexes mediated at the subcortical level as the cerebral cortex is still functionally deficient
- With maturation of the cerebral cortex, theses reflexes gradually disappear (≈ 4-6 ms)
- Moro reflex is the most important because it is reliable & easy to be elicited

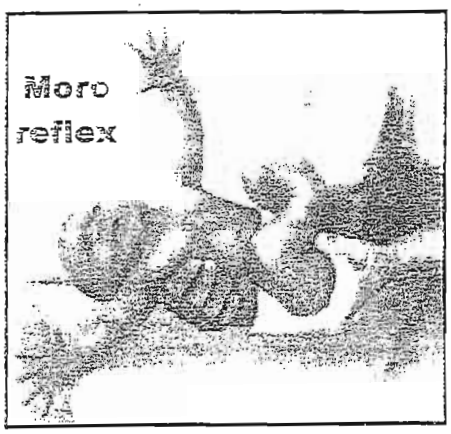
Significance

- **Normal** neonatal reflexes indicate Normal neurological condition
- **Asymmetrical** response indicate Focal neurological deficit
- **Persistence** of theses primitive reflexes indicate Cortical damage

Moro Reflex

Stimulus

- Sudden fall of supported head
- Sudden withdrawal of blanket
- Loud noise



Response

Abduction & extension followed by adduction & flexion

Timing

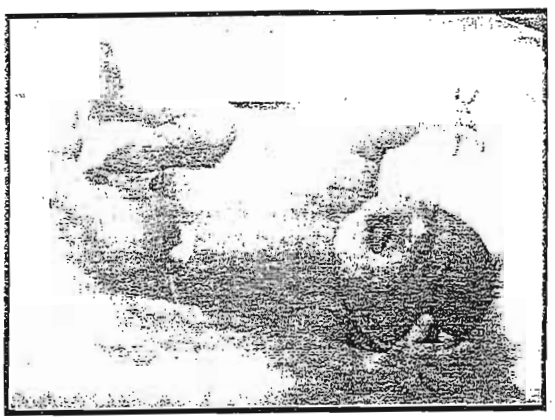
- Appearance: After 27 wks of gestation
- Disappearance: At the age of 4 months

Significance

a. **Normal response** Normal CNS

b. **Absent Moro reflex** (Serious)
- Marked prematurity (< 27 wks gestation)
- Intracranial hemorrhage (ICH)
- Asphyxia
- CNS depression (Maternal anesthesia or $MgSO_4$)

c. **Asymmetrical response**
- Fracture clavicle
- Erb's palsy



d. **Persistent Moro > 4-6 months**
- Cerebral palsy
- Mental retardation

e. **Exaggerated Moro**
- CNS irritation e.g., Kericterus

Primitive Neonatal Reflexes

Reflex	Stimulus	Response	Time of appearance	Time of dis-appearance
Placing reflex	Holding the baby with the dorsum of his feet touching the undersurface of the table	Foot elevation + Placement over the table	34	1.5 months
Stepping reflex	Holding the baby with his feet touching the table	Foot elevation + Walking movement	34	1.5 months
Rooting reflex	Touching the lips or the corners of the mouth	Opening of the mouth & Head turning towards the side of stimulus	27	4 months
Suckling reflex	Stimulation of the oral cavity (Nipple or finger	Suckling movements	27	4 months
Plantar reflex	Scratching of the outer aspect of the sole of the foot	Dorsiflexion of the big toe ± Fanning of other toes	34	1 year
Landau reflex	Holding the baby prone in a horizontal position	The body forms a convex arc + Flexion of the head, trunk & hips		
Palmar Grasp reflex	Putting a object in the palm of the hand	Flexion of the fingers & Grasping	27	4 months
Plantar Grasp reflex	Putting an object against the sole of the foot	Flexion of the toes & Grasping	27	8 months
Tonic neck reflex	Turning of the head to one side	Extension of the arm & leg on the same side + Flexion of the opposite side	34	5 months
Moro reflex	See before		27	4 months
Extrusion	Uses tongue to push foreign objects out of mouth		At birth	3 to 4 months
Parachute (forward) reflex	Holding in a position where he is dropped forward	Outstretching of the hands (Protection)	9 months of	Persists
Moro reflex	See before		27	4 months

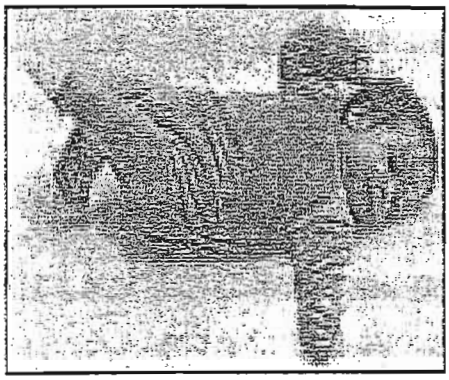
Primitive Neonatal Reflexes



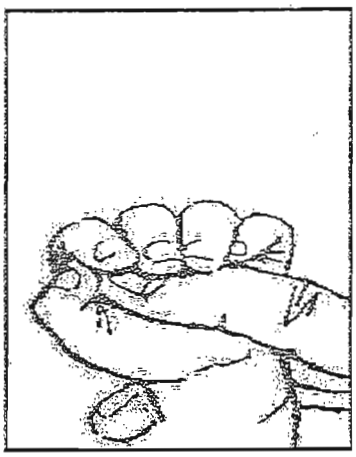
Placing reflex



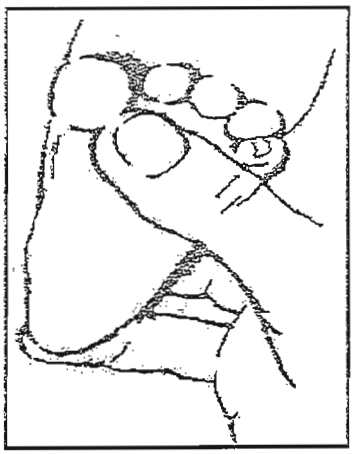
Stepping reflex



Tonic neck reflex



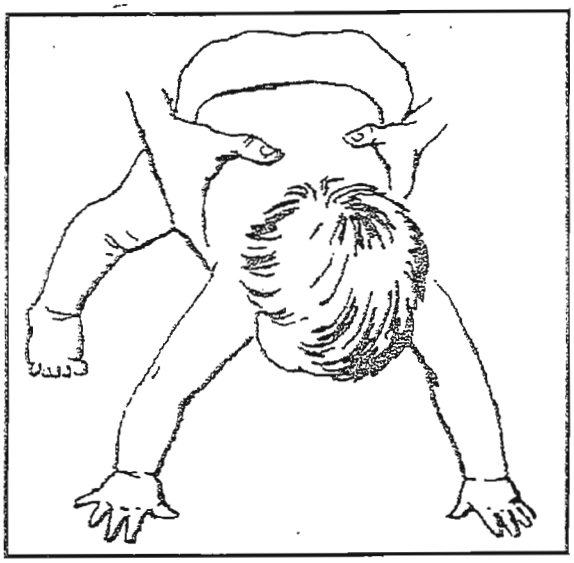
Palmar Grasp reflex



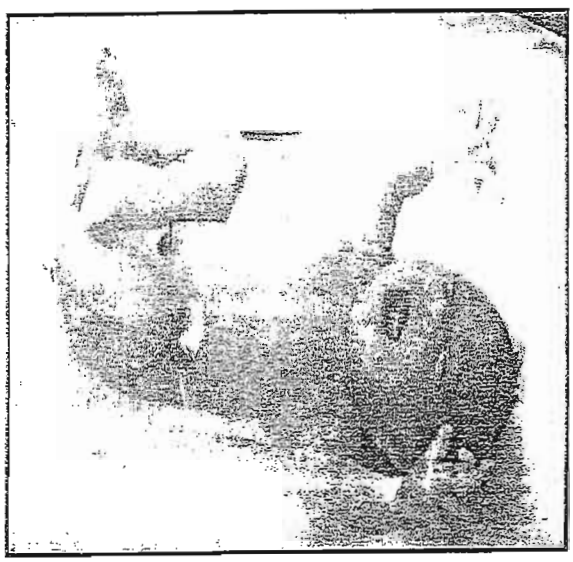
Plantar Grasp reflex



Rooting reflex



Parachute reflex



Moro reflex

Delayed walking

Introduction

Walking requires 3 factors:

- ☒ CNS
- ☒ Musculoskeletal system
- ☒ Training

Etiology

A) **Neurological causes** [Central & peripheral]

- Cerebral palsy
- Mental retardation
- Hydrocephalus
- Neuromuscular disorders
  - **AHC:** Weding-Hoffmann disease & Poliomyelitis
  - **Nerve:** Neuropathy (e.g., Guillain-Barré syndrome...)
  - **Neuromuscular junction:** Myasthenia gravis
  - **Muscle:** Myopathy

B) **Bone:** Rickets, trauma, fractures

C) **Training:** diagnosed by exclusion

Delayed Sphincteric Control

Etiology

1. **Neurological causes:** Mental retardation…
2. **Maturation delay**
3. **Mismanagement**
4. **Lack of training**
5. **Emotional**

Delayed Speech

Etiology

1. **Neurological causes:** Mental retardation…
2. **Familial**
3. Deafness:
   - ☒ Conductive: OM, Eustachian tube dysfunction (Cleft palate), Wax…
   - ☒ Sensorineural: Genetic, Alport, HIE, Kernicterus, Meningitis, Trauma, drugs (aminoglycosides, frusemide…), Neurodegenerative diseases
4. **Emotional**
5. **Lack of training**
6. **Autism**

Assessment of Gestational Age

Importance

a. Proper assessment of fetal growth, fetal well being & fetal functional maturity
b. Proper timing of antenatal diagnostic procedures (amniocentesis & CVS)
c. Proper timing of elective obstetric procedures (elective CS)
d. Identification of premature delivery (? neonatal management)

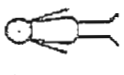
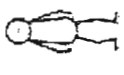
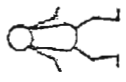
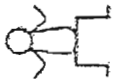
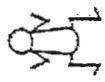
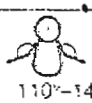
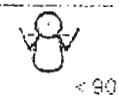
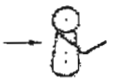
Methods

a. History: 1st day of the last menstrual period (LMP)
b. Examination: Fundal level
c. U/S
   - 1st trimester: Crown-rump length
   - 2nd trimester: Biparietal diameter & femur length
d. Neonatal reflexes
e. New Ballard score
   - Neuro-muscular maturation
   - Physical maturation
f. Laboratory & Radiological investigations
   - Ig
   - EMG, EEG, X ray
   - AF maturation, how?
   - Fetal Hb%

Neuro-muscular maturity	Physical maturity
Posture	Skin
Square window	Lanugo
Arm recoil	Plantar creases
Scarf sign	Breast
Polpliteal angle	Eye/ear
Heel to ear	Genitalia (♂ & ♀)

Assessment of gestational age—New Ballard score.

Neuromuscular Maturity

Score	-1	0	1	2	3	4	5
Posture							
Square window (wrist)	 >90°	 90°	 30°	 45°	 60°	 0	
Arm recoil		 180°	 140°–180°	 110°–140°	 90°–110°	 < 90°	
Popliteal angle	 180°	 160°	 140°	 120°	 100°	 90	 < 90°
Scarf sign							
Heel to ear							

Physical Maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40–50 mm: –1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior ⅔	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: –1 tightly: –2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Neuro-muscular maturity	Physical maturity
Posture	Skin
Square window	Lanugo
Arm recoil	Plantar creases
Scarf sign	Breast
Polpliteal angle	Eye/ear
Heel to ear	Genitalia (♂ & ♀)

Pituitary Gland

(The master gland)

Anterior Pituitary

Somatotropes → GH (191 aa)
Lactotropes → Prolactin (199 aa)
Thyrotropes → TSH (Thyrotropin)
Coticotropes → ACTH (Corticotropin)
Gonadotropes → FSH, LH

These hormones are under the control of:

- Hypothalamic neurohormones: via the hypothalamo-hypophyseal portal circulation
- Feedback control

Posterior Pituitary (Neural hormones)

ADH (arginine vasopressin)
Oxytocin

These hormones are **synthesized** in supraoptic & paraventricular nuclei of the hypothalamus and **transmitted** via the axoplasm to be **stored** in the posterior pituitary.

Growth Hormone

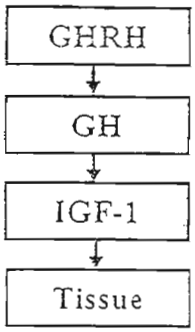
- **Pulsatile** secretion more with sleep
- Action is **mediated** by insulin like growth factor-1 *(IGF-1)* or "somatomedin C" formed by the liver
- **Action:**
  1. **Growth:** ↑↑ Size of various tissues (bones, cartilage, muscles& viscera).
  2. **Proteins:** Anabolic.
  3. **CHO:** ↑↑ Gluconeogenesis.
  4. **Lipids:** ↑↑ Lipolysis.
  5. **Electrolytes:** ↑↑ Ca, ↑↑ Na, ↑↑ PO_4
- **Control of GH secretion:**

Increase	Decrease
GHRH (GH-releasing hormone)	Somatostatin (also ↓↓ insulin, glucagon, gastrin, VIP)
Synthetic GHRH	Synthetic somatostatin analog *(Octreotide)*
Hypoglycemia (Insulin)	Hyperglycemia
↑↑ aa (e.g., arginine)	
Clonidine, L-dopa, Glucagon	
Stress, Sleep, Exercise, Fasting	

Hypopituitarism

Definition

It is deficiency of GH with or without other pituitary hormones



Etiology

I) Isolated GH deficiency:

A) Genetic

- GHRH receptor gene mutation
- GH gene mutation (AR, AD or X-linked)
- Biologically inactive GH
- GH receptor gene mutation *(Laron syndrome)*: Autosomal recessive [↑↑ GH, ↓↓ IGF-1, No response to exogenous GH]
- IGF-1 gene mutation



B) Acquired

- Radiotherapy (leukemia)
- Idiopathic

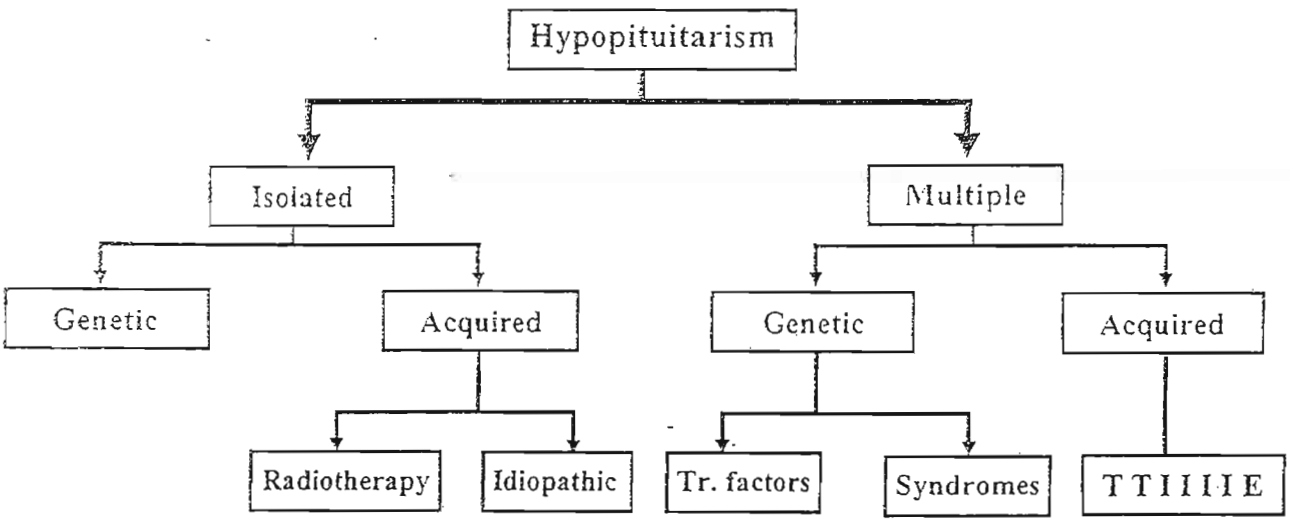
II) Multiple pituitary hormone deficiency:

A) Genetic

- Mutations of transcription factors ⟶ Failure of transcription e.g. PROP1, LHX3, LHX4 gene mutation
- Congenital absence of the pituitary gland
- Anencephaly, encephalocele& hydrocephalus
- Septo-optic dysplasia (optic n. dysplasia& maldevelopment of septum pellucidum)
- Holoprosencephaly

B) Acquired

- Trauma: birth injury, child abuse, fracture base of skull, surgery
- Tumors: Craniopharyngioma, adenoma, germinoma, optic glioma
- Irradiation (GH deficiency precedes other hormones)
- Infection: meningitis & encephalitis
- Infiltration: histiocytosis X, hemochromatosis, sarcoidosis, TB, Toxoplasmosis
- Immune hypophysitis
- Empty-sella syndrome: congenital or following surgery or irradiation



Clinical picture

A) **Congenital Hypopituitarism:**

1. **At Birth:**
   - Normal weight & height
   - Neonatal emergencies: apnea, cyanosis, hypoglycemia, seizures
   - Prolonged neonatal jaundice (Conjugated)
   - Microphallus in male is an important **diagnostic** clue

2. **Infancy& childhood:**
   - Profound proportionate postnatal growth failure (>2 SD below the mean for age & sex)
   - Facies: rounded head, short face, prominent forehead, depressed nasal bridge, small nose, underdeveloped mandible, teeth (Delayed eruption & crowded)
   - Intelligence: usually normal
   - Sexual maturation: may be delayed
   - Hypoglycemia (10%)

B) **Acquired Hypopituitarism:**

1. **Hormonal manifestations:**
   - The child is normal initially
   - Gradual onset& progressive course of growth failure
   - Hypofunction of thyroid, adrenals and gonads
   - Diabetes insipidus

2. **C/P of the cause:**
   - Pressure symptoms: ↑↑ ICT, optic atrophy, visual field defects, seizures
   - Trauma, infection…

Investigations

Thyroid hormones are necessary for GH synthesis & action; so must be assessed before GH studies.

A) **Laboratory:**

1. **GH plasma level**

   GH level < 10 ng/ mL after 2 provocative tests is diagnostic
   - Physiologic stimulation: Sleep (60 min), Exercise (20 min) ??
   - Provocative agents: Insulin, clonidine, arginine, glucagon, L-dopa

Measuring GH level every 20 min over (12-24 hr) is used to diagnose *GH neurosecretory dysfunction.*

2. **IGF-1:** ↓↓ in all cases but ↑↑ with GH administration (except in Laron syndrome)
3. **Other pituitary hormones:** ACTH, TSH, ADH, Cortisol, T_3, T_4 (Not FSH & LH)
4. **Prolactin:** Hyperprolactinemia strongly suggests hypothalamic lesion.
5. **TRH stimulation test:** ↑↑TSH& prolactin suggests hypothalamic lesion.
6. **GHRH stimulation test:** ↑↑GH suggests hypothalamic lesion.

B) **Imaging:**
- Skull X-ray: beaten silver appearance, separation of sutures, enlargement of sella. destruction of clinoid processes& IC calcification (bone defects in histiocytosis)
- **Long bones:** delayed bone age.
- CT& MRI

In hypothalamic lesions: ↓↓ all anterior pituitary hormones except prolactin

Treatment

1. Treatment of the cause: Surgery for tumors.
2. **Replacement of pituitary hormones:** Thyroid, hydrocortisone & late sex hormones.
3. **Recombinant human GH (rHuGH)**
   - *Dose:* 0.18-0.3 mg/kg/week, SC in 6-7 divided doses.
   - *Duration:* continuous till closure of epiphyses (NB: *leoprolide* may be used to delay puberty).

Criteria for stopping Rx:

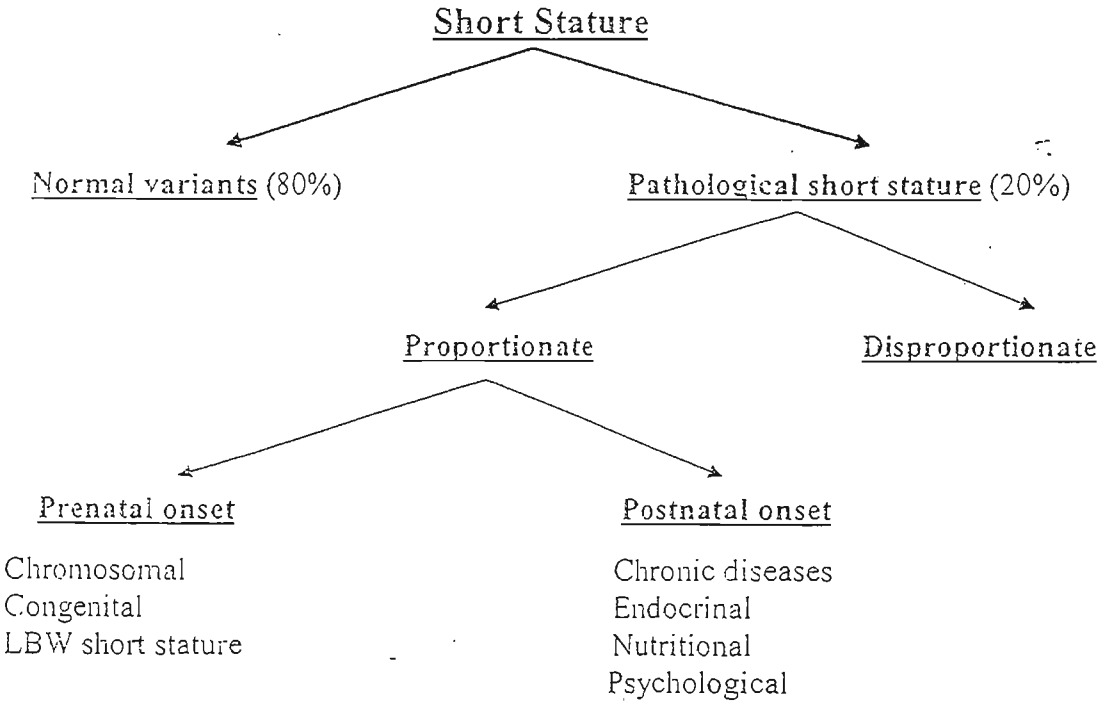
- Growth rate < 1 inch/year
- Bone age >14 yr in ♀ & >16 yr in ♂

- *Side effects:*
  - Leukemia.
  - Hypothyroidism
  - Pseudotumor cerebri
  - Gynecomastia
  - Slipped capital femoral epiphyses, worsening of scoliosis.
  - Development of anti-GH antibodies (Rx with IGF-1)

- *Other indications of hGH:*
  - Turner syndrome
  - Noonan syndrome
  - ESRD
  - Prader-Willi $
  - Silver-Russel $
  - IUGR
  - Skeletal dysplasia
  - Juvenile rheumatoid arthritis.
  - Familial short stature (some patients may benefit)

4. **GHRH in hypothalamic causes.**
5. **Recombinant IGF-1:** in Laron $ & with the development of anti-GH antibodies

DD Short stature.



Short Stature

Definition

Height more than 2 SD below the mean height for age & sex or < 5th percentile.
Pathologic short stature: Height >3 SD below the mean height for age& sex.

Nomenclatures

Lower segment: Measured from the upper border of the symphysis pubis to the floor.

Upper segment: Total height – lower segment.

Arm span: Distance between the tips of middle fingers when the arms are fully extended.

Supine length: (birth to 2-3 yrs).The child is measured on his back by 2 individuals with appropriate equipment with fixed headboard & movable footboard. The head should be in the "Frankfurt plane" (ear hole to lower border of eye socket).

Standing height: measured against an appropriate vertical measure with the heels together and buttocks & shoulder plates touching the vertical and the head in "Frankfurt plane".

U/L ratio:

- At birth: 1.7 (Umbilicus is in the middle)
- At 3 yrs: 1.3
- At 7 yrs: 1 (Symphysis is in the middle)

Arm span – height:

- 1st 7 yrs: –3
- 8 -12 yrs: Zero

Classification

A) **Proportionate or Disproportionate**

1. **Proportionate short stature:** normal values are obtained
2. **Disproportionate short stature:** abnormal values are obtained

B) **Type of short stature**

1. Short limbs
2. Short trunk

Ratio	Short Limbs	Short Trunk
U/L	High	Low
Arm span/Height	Low	High

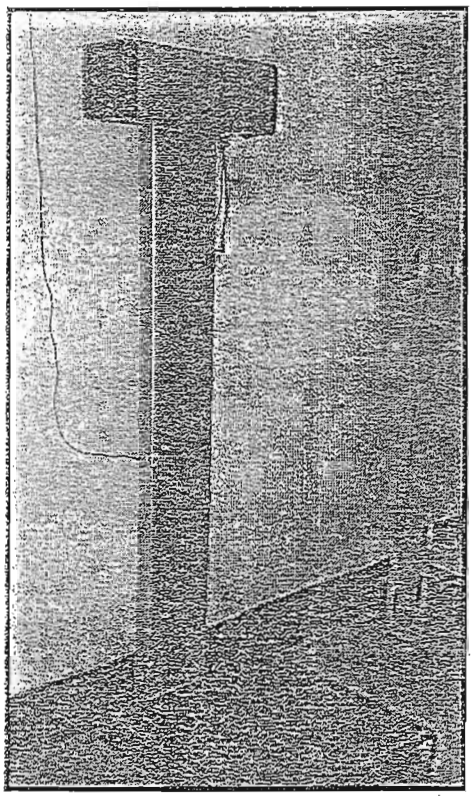
C) **Classification of short limbs**

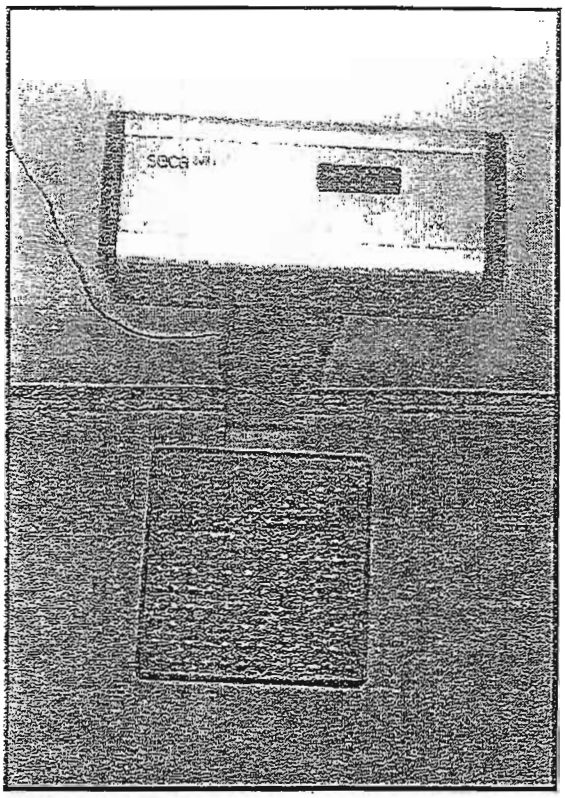
1. Rizomelic: proximal shortening of humerus & femur (e.g., achondroplasia)
2. Mesomelic: middle segment shortening of radius& ulna, tibia& fibula.
3. Acromelic: terminal shortening of fingers.

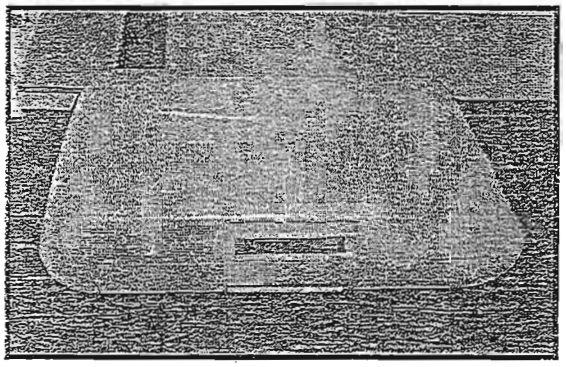
MPH & TCR

Mean parental height = (Father's height + Mother's height) / 2
Mid Parental Height (MPH) for ♂ = Mean parental height + 7
Mid Parental Height (MPH) for ♀ = Mean parental height - 7
Target Centile Range (TCR) for ♂ = MPH ± 12
Target Centile Range (TCR) for ♀ = MPH ± 11

Instruments for Weight & Height Measurement

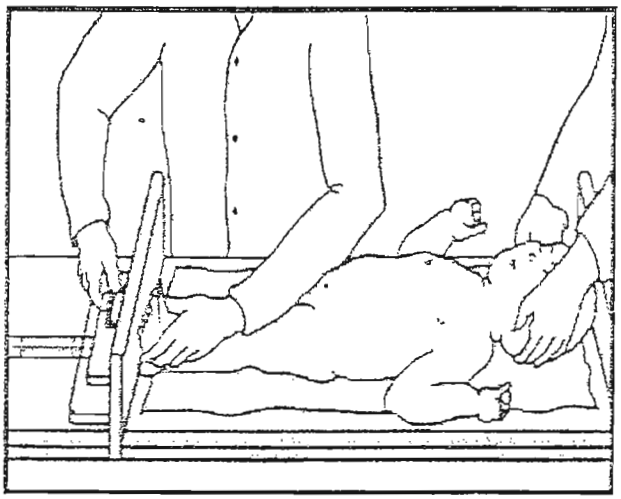




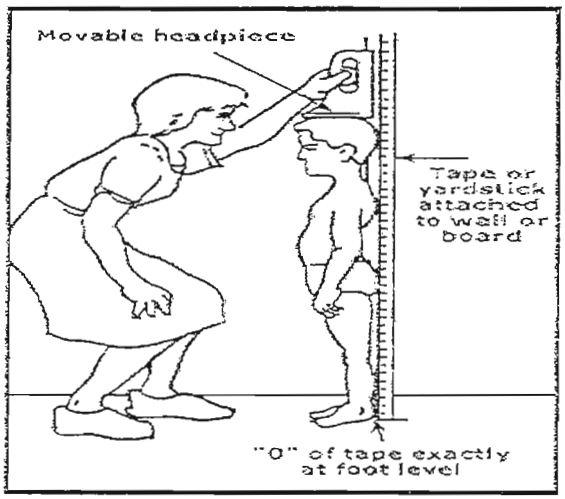


Weight is measured using a calibrated balance

- Infants should be naked
- Children should wear only underwear



Infantometer



Stadiometer

Length is measured using an infantometer
Height is measured using stadiometer

Etiology

A) Normal variants (80%)

	1. Familial (genetic)	2. Constitutional growth delay
Family history	Positive (parents are short)	Positive
Growth velocity	Normal	Period of transient decelerated growth
Bone age	Normal	Delayed
Puberty	Normal	Delayed
Adult height	Short adult height	Normal adult height
Treatment	GH may be useful	Reassurance

B) Pathological (20%)

1. **Endocrinal**
   - Hypothalamus: Laurance-Moon Biedl
   - Pituitary: Hypopituitarism
   - Thyroid: Congenital hypothyroidism
   - Suprarenal: Cushing, CAH
   - Gonads: Precocious puberty
   - Pancreas: DM
2. **Chronic debilitating diseases**
   - CVS: CHD, RHD
   - Resp.: TB, Cystic fibrosis, asthma
   - Renal: CRF, RTA, DI
   - GIT: Malabsorption, IBD
   - Immunodeficiency
   - Hepatic: Cirrhosis, Wilson's
   - Collagen: JRA
   - Blood: Chronic hemolytic anemia
   - Infection: TB, suppurative lung S.
   - Metabolic: aa, organic acidemias
3. **Chromosomal**
   - Turner
   - Down
   - Trisomy 18
4. **Congenital syndromes**
   - Prader-Willi
   - Silver-Russel
   - Cornelia De Lange (microcephaly,synophrys...)
   - Progeria
5. **Metabolic**
   - Aminoacidopathies
   - Organic acidemias
   - Storage diseases (Gaucher, NP...)
   - Minerals: Cu, Fe...
6. **Psychological (deprivation) dwarfism**
   - Disturbed child-mother or family relation → ↓↓ GH release (Unknown mechanism)
   - Growth will be resumed if the child is provided with love & care (i.e., Catch-up)
   - Bone age is delayed
7. **Malnutrition:** Malnutrition → ↓↓ Synthesis of GH mediators (Growth factors)
8. **Skeletal (=Causes of Disproportionate short stature)**
   - Rickets
   - Achondroplasia (large head, short limbs& normal trunk) + Normal mentality
   - Hypochondroplasia (normal head - Features are not prominent as achondroplasia)
   - Osteogenesis imperfecta (osteoporosis + multiple fractures + blue sclera + hearing ↓)
   - Mucopolysaccharidoses
   - Chondroectodermal dysplasia (short limbs+ectodermal dysplasia+polydactyly+CHD)
9. **Primordial short stature(LBW short stature)**
   - IUGR (Congenital infections, Congenital malformation, placental insufficiency)
   - Silver-Russel syndrome (triangular face, incurved 5th finger, hemihypertrophy)
   - Seckel syndrome (Bird-headed dwarfism)
10. **Drugs:** Steroids

Approach to a case of short stature

(A) History:

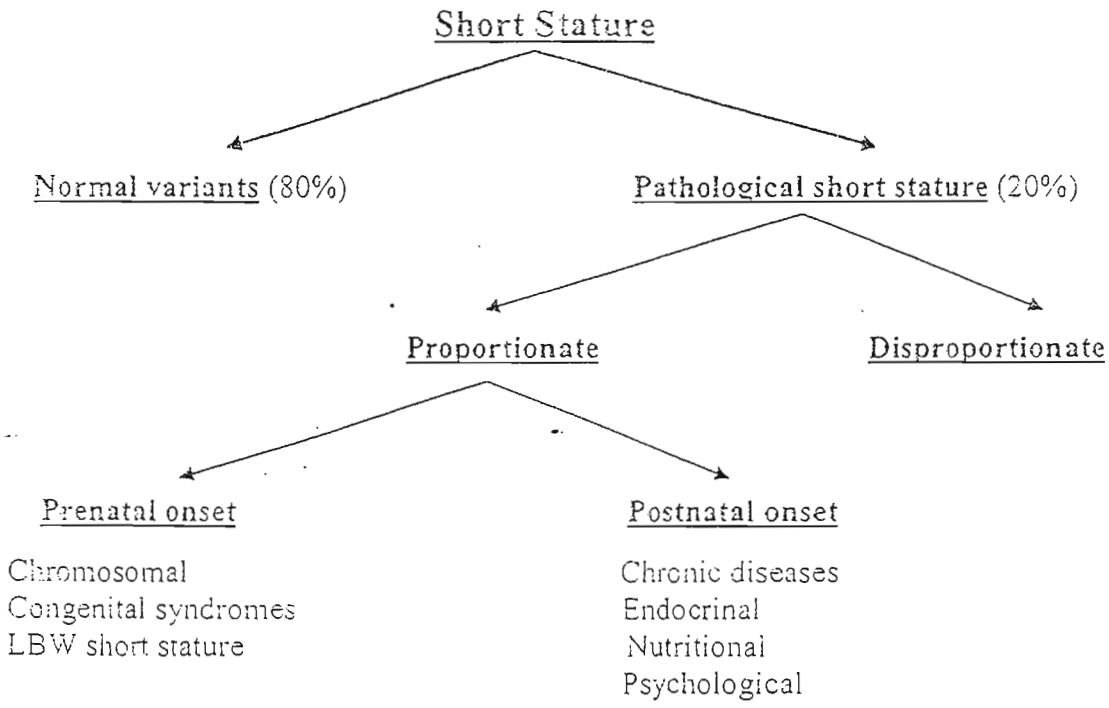
- Symptoms of different system affection
- Nutritional history
- Perinatal history: Birth length& weight, causes of IUGR
- Psychological assessment
- Parental heights & TCR

(B) Physical examination:

- Measure height/length, US& LS, arm span ⟶ Proportionate or disproportionate
- Manifestations of chromosomal abnormalities (e.g., Turner…), congenital syndromes (e.g., Prader-Willi), hypopituitarism (microphallus)
- Complete system examination.

(C) Investigations:

- CBC, ESR, UA, electrolytes, KFTs, LFTs
- Karyotyping is routine in all ♀ with short stature
- Bone age (Lt wrist X-ray): normal in familial cases& skeletal dysplasia
- Imaging: CT, MRI
- Investigations of endocrinal causes (start with thyroid): *See before*



Tall Stature

Definition

Height more than 2 SD above the mean height for age & sex or > 97th percentile.

Etiology

1. **Familial (genetic or constitutional)**
   - +Ve family history.
   - Normal bone age
   - Normal puberty
   - Tall adult height.
2. **Exogenous obesity** ⟹ -Advanced bone age
3. **Precocious puberty** ⟹ -Tall child height
4. **Hyperthyroidism** ⟹ -Normal adult height
5. **Marfan:** ↑↑ arm span, ↓↓ US/LS
6. **Homocystinuria:**
7. **Klinefelter (XXY)& XYY syndrome**
8. **McCune-Albright syndrome**
9. **Cerebral gigantism (Sotos syndrome):**
   - Growth rate: -At birth ⟶ Macrosomic -1-5 yrs: accelerated rate of growth
     - >5 yrs ⟶ Normal growth rate - Normal adult height
   - Physical: Large head, dolicocephaly, hypertelorism, prominent jaw, large hands & feet
   - Mental: MR
   - Sexual: Normal
   - ↑↑ Risk of malignancy (Wilms, liver)
   - Normal endocrinal studies.
10. **GH excess** ⟶ Open epiphyses ⟶ Gigantism
    ⟶ Closed epiphyses ⟶ Acromegaly
    (Skull, coarse facies hands, feet, jaw, tongue, kyphosis, IGT)

Etiology:

- ☒ Hyperplasia
- ☒ Adenoma (GH-secreting)

Investigations:

- ↑↑ GH (No ↓↓ with hyperglycemia)
- ↑↑ IGF-1
- ↑↑ Prolactin (in case of pituitary adenoma secreting both GH& prolactin)
- ↓↓ Pituitary hormones (compression by adenoma)
- Skull X-ray, CT & MRI brain

Treatment:

- Surgical removal of adenoma
- Irradiation (hypopituitarism)
- Somatostatin analogues *(Octreotide)*
- Bromocriptine (dopamine agonist) in cases with ↑↑ prolactin
- GH receptors antagonist *(Pegvisomant)*

Dopamine = Prolactin-inhibiting factor

Fetal overgrowth syndromes

1. IDM
2. Beckwith-Wiedemann $
3. Cerebral gigantism (Sotos)
4. IGF-II excess

Treatment of familial tall stature

♂ ⟶ Testosterone enanthate

♀ ⟶ Ethinyl estradiol

When: Predicted adult height >3 SD.
Severe psychological impairment

Puberty

Definition

It is the period of life during which the endocrine & gametogenic functions of the gonads have developed to the point where reproduction is possible [physical & sexual maturation]

Adolescence

It is the period of life during which child becomes an adult [Physical, sexual, psychological & social maturation].So, puberty is 1st part of adolescence.

Physiology of Puberty

Sex hormones = Testosterone & Estrogen

- Prepubertal stage:
  - Hypothalamo-hypophyseal-gonadal axis is dormant (upper neuronal inhibition)
  - ↑↑ Sensitivity of H-H-G axis to sex hormones
  - LH & sex hormones: undetectable
- 1-3 yrs before puberty:
  - GnRH & LH *pulsatile* secretion start to occur first during sleep
  - Gradual ↑↑ in amplitude & frequency of GnRH & LH pulses
  - Adrenarche: ↑↑ adrenal androgens (responsible for pubic hair, acne, voice...)
- During puberty:
  - GnRH & LH *pulsatile* secretion occur at 90-120 min intervals
  - No more diurnal variation
  - In ♀, +Ve feedback effect of estrogen causing LH surge in midcycle (ovulation)

Age of Onset of Puberty *(Variable)*

♀ = 8-13 yrs ♂ = 9-14 yrs

Factors affecting the age of Onset of Puberty

1. **Osseous maturation (bone age):**
- The onset of puberty is more closely related to osseous maturation than to chronological age
- Estrogen is responsible for bone maturation & epiphyseal closure in both ♀& ♂
2. **Genetic factors**
3. **Nutrition:** Good nutrition ⟶ earlier puberty
4. **Body build:** Moderate obesity ⟶ earlier puberty, Morbid obesity ⟶ delayed puberty
5. **Physical activity(energy balance):** ♀athletes (ballet dancers & swimmers) ⟶ delayed puberty

Physical changes of Puberty

☒ Females:
- First sign of puberty is **breast** enlargement
- Followed by ⟶ Pubic hair ⟶ Axillary hair ⟶ Menarche
- Average age of menarche in Egyptian ♀ is 12.5 yrs
- Less obvious changes: ↑↑ Ovaries, uterus, labia & thickening of vaginal mucosa

☒ Males:
- First sign of puberty is **testicular** enlargement (Prader orchidometer)
- Followed by ⟶ Thinning & pigmentation of the scrotum ⟶ ↑↑ Penis ⟶ Pubic hair ⟶ Axillary hair
- Less obvious changes: ↑↑epididymis, seminal vesicles, prostate & gynecomastia (65%)

- **Prader orchidometer (12-ellipsoids):** 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 25 ml
- **Testicular volume:** Preadolescence = 1-3 ml
- **Testicular length** (exclude epididymis): Preadolescence = 1.5-3 cm

Stages of Puberty (= Tanner staging)

☒ Females:

Stage	1. Pubic Hair	2. Breasts
1	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast & papilla elevated as small mound ↑↑ areolar diameter
3	Darker, start to curl	Breast & areola enlarged, no contour separation
4	Coarse, Curly, abundant, but amount less than adult	Areola and papilla form 2ry mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

3. **Axillary hair** (3 stages)
   - No
   - Appearance
   - Adult type

☒ Males:

Stage	1. Pubic Hair	2. Penis	3. Testes
1	Pre-adolescent	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, at the base of the penis	Slight enlargement	Enlarged scrotum- Pink
3	Darker, start to curl	Longer	Larger
4	Coarse & Curly	Larger (glans & breadth)	Larger- Dark scrotum
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

4. **Axillary hair** (as in females)

Secondary Sex Characters

2ry Sex Ch.	Male	Female
Voice	Deep	High pitched
Hair distribution	Beard, frontal baldness. chest, pubic hair (triangle with apex up)	Less body hair, ↑↑ scalp hair, pubic hair (triangle with base up)
Body shape	Masculine	Fat distribution (breast & buttocks)
skeleton	Wide shoulders, Narrow hips	Narrow shoulders, wide hips
Libido	↑↑ Libido	↑↑ Libido

Growth

- **Definition:** Increase in the size & number of cells
- It can be assessed by measurements as Weight, Height (Length) & Skull circumference
- It is dependent on different factors at different ages:
  - Fetal: Fastest period of growth (*See factors affecting IU growth*)
  - Infancy: Nutrition (Substrate availability)
  - Childhood: Growth hormone (& Thyroxine)
  - Puberty: Sex hormones (& Growth hormone)

Pubertal growth spurt

It is divided into 3 phases:

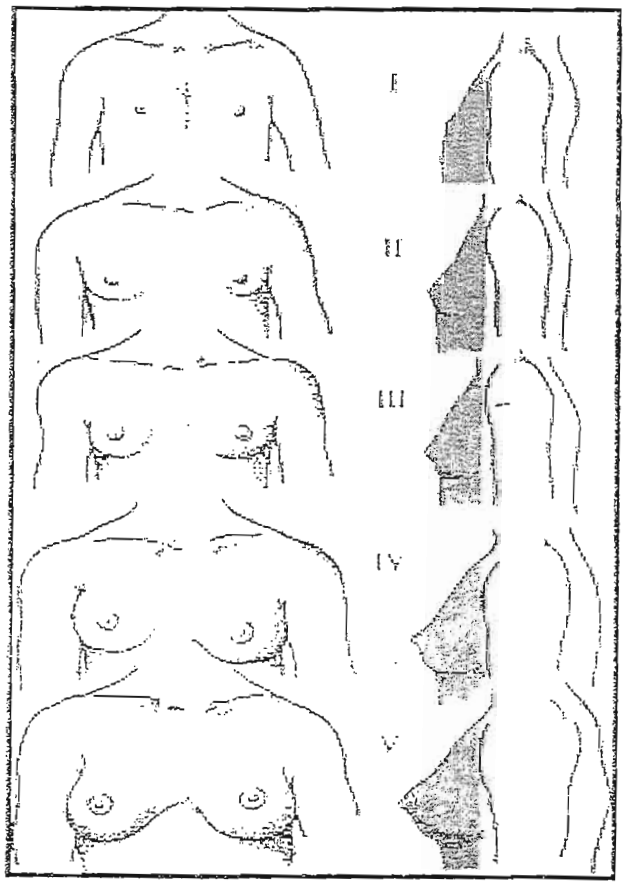
- Take-off = Minimum growth velocity
- Peak height velocity = Maximum growth velocity
- Decelerated phase

☒ Females:

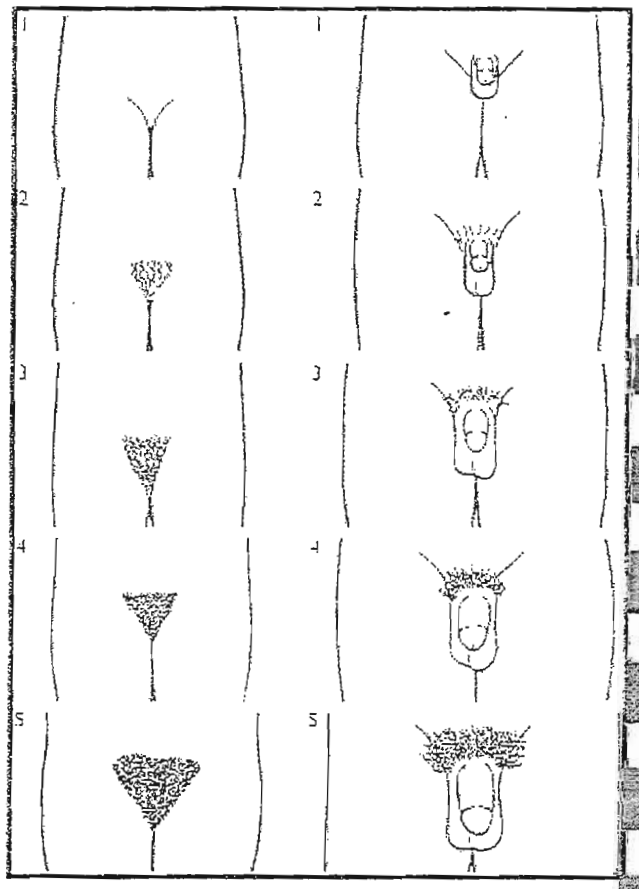
- Onset of peak height velocity = pubertal stage 2-3 [i.e., pre-menarcheal event]
- Height gain = 25 cm

☒ Males:

- Onset of peak height velocity = pubertal stage 3-4 [2 yrs after females]
- Height gain = 28 cm [Mean height difference between ♂ & ♀ = 13 cm, why??]



Tanner staging of female breast changes



Tanner staging of pubic hair

Cushing Syndrome

Definition

Increased level of cortisol with **hypertension** and characteristic pattern of **obesity**

Etiology

A) Exogenous Cushing Syndrome (Cushinoid Syndrome)*:

Prolonged therapy with:

- ACTH
- Steroid

B) Endogenous Cushing Syndrome:

☒ ACTH dependent:

a. Cushing disease: ACTH secreting pituitary adenoma (microadenoma)
→ Bilateral adrenal hyperplasia (most common in children > 7 yrs)

b. Ectopic ACTH: Pancreatic islet cell carcinoma, neuroblastoma, Wilms tumor

☒ ACTH-independent (adrenal):

a. Functioning adrenocortical tumor: in infancy (Malignant* or benign)
b. Primary pigmented nodular adrenocortical disease: multiple, small pigmented nodules
c. McCune-Albright syndrome (autonomous hyperfunction)
d. Multiple Endocrine Neoplasia (MEN) type I

Clinical picture

- Characteristic obesity: Moon face, flushed plethoric face, doubled chin, trunkal, buffalo hump, thin limbs, striae rubra (abdomen& thigh).
- Delayed healing of wounds
- Osteoporosis → pathologic fractures and kyphosis
- Muscle weakness & myopathy
- Hyperglycemia
- Short stature
- Increased susceptibility to infection

- Hypertension → Heart failure
- Hypokalemia → Polyuria, polydipsia, muscle weakness, paralysis, constipation & tetany

- Androgen excess → Hirsutism, acne, deep voice, accelerated growth & clitoromegaly
- Adolescent female → Amenorrhea & hirsutism

Investigations

A) Diagnosis of Cushing Syndrome:

Laboratory:

- ↑↑ Na, ↓↓ K, ↓↓ H^+ (metabolic alkalosis)
- ↑↑ Glucose, OGTT
- CBC → ↑↑ RBC, ↑↑ PNLs, ↓↓ Lymphocytes, ↓↓ eosinophils

Hormonal:

- Cortisol level: loss of circadian rhythm then persistent elevation
- ↑↑ Salivary cortisol level (screaning)
- ↑↑ Urinary cortisol & 17(OH) corticosteroids
- Single dose dexamethasone suppression test (25 μg/Kg) → No ↓↓ in Cortisol level

B) Diagnosis of the etiology of Cushing syndrome:

Hormonal:

- Plasma ACTH
  - a. ACTH dependent → ↑↑ ACTH
  - b. Non-ACTH dependent → ↓↓ ACTH
- CRH stimulation test:
  - a. ACTH dependent → ↑↑ ACTH & cortisol
  - b. Non-ACTH dependent → No response (Pituitary is suppressed)
- Dexamethasone suppression test [D_1 30 µg/Kg/day qid, D_2 120 µg/Kg/day qid]
  - a. ACTH dependent → ↓↓ Cortisol
  - b. Non-ACTH dependent → No response

Imaging:

- X-ray: Osteoporosis, advanced bone age, ↓↓ thymic shadow
- Brain CT, MRI: Pituitary microadenoma
- Abdominal US, CT, MRI: adrenal adenoma

Treatment

1. Adrenal tumors: surgical removal
   - a. Benign → Subtotal adrenalectomy
   - b. Malignant → Total adrenalectomy

   } + Replacement therapy (Cortisol & ACTH)
2. Pituitary adenoma (Cushing disease):
   - a. Pituitary irradiation (?? Hypopituitarism)
   - b. Surgical removal (Transphenoidal approach)
   - c. Total adrenalectomy: may be followed by the development of locally invasive pituitary tumor → ↑↑ ACTH → Hyperpigmentation *(= Nelson syndrome)*
   - d. Cyproheptadine (Centrally acting serotonin antagonist → # ACTH release)

Obesity & Overweight

Definition

- Obesity: BMI > 95th% for age& sex. (In adults BMI>30 Kg/m^2)
- Overweight: BMI = 85-95th% for age& sex
- Body mass index (BMI) = Weight (Kg)/ Height^2 (meters)
- BMI also ↑↑ in body builders due to ↑↑ muscle bulk
- More than 22 millions children < 5 years are overweight

Classification

A) Exogenous obesity: [Most common]

Etiology: Multifactorial

a. **Gene-environment interaction**

b. **Genetic control of energy expenditure** (specific set point for body weight)
↓↓ Energy expenditure → ↑↑ Risk of obesity

c. **Environmental**
Type of food: ↑↑calories, ↑↑ CHO, ↑↑ Fat, highly processed
Physical activity: TV watching, games, computers

d. **Heredity** (parental obesity specially maternal, familial)

e. **Leptin deficiency or resistance:** (↑↑ food intake& ↓↓ energy expenditure)

Clinical picture:

- Tall stature (Adult height is normal or low)
- Advanced bone age & early puberty
- Acanthosis nigricans (hyperpigmented hyperkeratotic skin lesion usually in the post. neck or axilla). It is a clinical marker of insulin resistance & ↑↑ risk of type 2 DM

Prevention:

1. Change dietary habits & ↑↑ physical activity
2. Breast feeding ⟶ ↓↓ risk of obesity

Treatment:

1. Dietetic: ↓↓ CHO, ↓↓ fat, ↓↓ calories, ↑↑ fibers
2. Life style: ↓↓ TV watching, ↑↑ physical activity
3. Drugs "Not very promising"
   - ↓↓ *Food intake* ⟶ Sympathomimetics, MAO inhibitors
   - ↑↑ *Energy expenditure* ⟶ Ephedrine, caffeine
   - ↓↓ *Fat absorption* ⟶ Orlistat
4. Recombinant leptin: ↓↓ weight, ↑↑ energy expenditure
5. Surgical: gastroplasty

B) Endocrinal:

- Hypothalamic lesions: Encephalitis, tumors (craniopharyngioma, optic glioma)
- Frolich syndrome: Dwarfism, polyphagia, obesity, DI, hypersomnia
- Cushing syndrome
- Hypothyroidism
- Pseudohypoparathyoidism
- Stein-Leventhal $: Obesity, hirsutism, amenorrhea, infertility, polycystic ovaries, inverted FSH / LH ratio (Normally FSH > LH)

C) Congenital syndromes:

- Laurance-Moon-Biedle $: Obesity, short stature, mental retardation, polydactyly, syndactyly, retinitis pigmentosa, hypogonadism
- Beckwith-Wiedemann $: Fetal overgrowth, macrosomia, macroglossia, polycythemia, visceromegaly (HSM& nephromegaly), omphalocele, hemihypertrophy, hypoglycemia, characteristic ear lobe crease, ↑↑ risk of neoplasms (Wilms tumor)
- Prader-Willi $: Hypotonia, hypogonadism, mental retardation, short stature, small hands& feet, early FTT followed by rapid weight gain (1-6 yrs), polyphagia & obesity

  Genetics of Prader-Willi:
  - Deletion of paternally acquired segment of chromosome 15
  - Maternal disomy (Both chromosomes 15 are from the mother)

    (NB: Paternal disomy of chromosome 15 ⟶ Angelman syndrome)

C) Chromosomal:

- Turner (XO)
- Down (Trisomy 21)
- Klinefelter syndrome (XXY)
- XXXXY syndrome

Complications of obesity

1. CVS ⟶ HTN, ischemic heart disease, hyperlipidemia& atherosclerosis
2. Respiratory ⟶ Sleep apnea, Pickwickian $, restrictive hypoventilation
3. CNS ⟶ Pseudotumor cerebri, social& behavioral problems
4. GIT ⟶ Fatty liver, cholesterol gall stones, GERD
5. Endocrine ⟶ Insulin resistance, type 2 DM, early puberty, Stein-Leventhal $
6. Joints ⟶ Slipped femoral epiphyses
7. Social & behavioral problems

Approach to a case of obesity:
Dietetic history, Stature, BP, Mentality, Syndromic

Hypogonadism

Definition

- Delayed sexual development with no evidence of puberty by the age 13 in ♀& 14 in ♂
- Causes include: Constitutional, hypogonadotropic& hypergonadotropic hypogonadism

Male Hypogonadism	Female Hypogonadism
(A) Primary hypogonadism (= Hypergonadotropic-hypogonadism) Testicular defect ↑↑ Gonadotropins	(A) Primary hypogonadism (= Hypergonadotropic-hypogonadism) Ovarian defect ↑↑ Gonadotropins
(B) Secondary hypogonadism (= Hypogonadotropic-hypogonadism) Hypothalamic/pituitary defect ↓↓ Gonadotropins (FSH & LH)	(B) Secondary hypogonadism (= Hypogonadotropic-hypogonadism) Hypothalamic/pituitary defect ↓↓ Gonadotropins (FSH & LH)

Male Hypergonadotropic-Hypogonadism

Etiology

1. **Congenital anorchia:** Testicular damage after sexual differentiation
2. **Defects of androgen production:** see before (46 XY-DSD)
3. **Rudimentary testes:** (AR or XLR) "Very small testes"
4. **Germ cell aplasia (Del Castillo $ or Sertoli cell only$):**
   - Leydig cells: normal ⟶ normal testosterone ⟶ normal sexual differentiation
   - Seminiferous tubules (absent Sertoli cells) ⟶ Small testes, azoospermia, infertility
   - No inhibin (normally secreted by Sertoli cell) ⟶ ↑↑ FSH with normal LH
5. **Klinefelter (47, XXY male):** (1/1000)
6. **45, X male:** Yp segment is translocated to another chromosome
7. **XX male:** Paternal X-Y Crossing over involving SRY gene
8. **XXX male:** Paternal X-Y Crossing over AND maternal X-X non-disjunction
9. **Noonan Syndrome:** (1/1000)
10. **Testicular damage**
    - Bilateral torsion (Vascular)
    - Surgical trauma during correction of cryptorchidism
    - Radiotherapy & chemotherapy
    - Acute orchitis: Mumps in pubertal ♂

Noonan Syndrome:

- Etiology: AD (variable expression)
- Features of Turner $ + Normal karyotyping + affecting ♀& ♂
- Short stature, neck webbing, cubitus valgus
- CHD: PS
- Facies: Hypertelorism, epicanthus, ptosis, micrognathia, antimongloid slant, ear anomalies
- Hypogonadism: Delayed puberty (2 yrs later)
  - ♂: Small testes, cryptorchidism
  - ♀: Premature ovarian failure
- Mental retardation: 25%
- Rx: hGH

Klinefelter Syndrome:

Genetic types:

- Non-disjunction (most common)
- Mosaicism (better prognosis)
- Variants: XXXY, XXXXY (↑↑ Severity)

C/P: as in ♂1ry hypogonadism + some MR + learning disability + behavioral disorders

Investigations:

Complications:

Breast cancer, mediastinal germ cell tumors

Rx:

Poly-Y male (47, XYY male):

No Hypogonadism

Aggressive antisocial behavior& violence

Clinical picture



1. **Onset:** Usually present as delayed puberty
   May be suspected at birth (Micropenis & small testes)
2. **Measurements:** Tall stature; span > height, LS > US *(Eunuchism)*
3. **Testes:** Absent or small (Prader Orchidometer)
4. **Secondary sex characters fail to develop:**
   - **Hair (facial, axillary, pubic):** scanty
   - **Acne:** absent
   - **Voice:** high pitched
   - **Fat distribution:** feminine (buttocks, breast)
   - **Penis& scrotum:** infantile
5. **Gynecomastia**
6. **Infertility** (Azoospermia)
7. **Picture of the cause**

Investigations

1. Testosterone level: ↓↓
2. Gonadotropins "FSH & LH": ↑↑ (specially > 11 yrs)
3. hCG stimulation test: No response [Normally hCG ⟶ ↑↑ Testosterone at *any* age]
4. AMH & Inhibin level
5. Karyotyping (XXY...)
6. Azoospermia
7. Testicular biopsy (In Klinefelter $: Hyalinized seminiferous tubules)

Side Effects of sex steroids
- Lipid abnormalities
- Thromboembolism
- Acne
- HTN

Treatment

- Long-acting **testosterone enanthate**, starting at 11-12 yrs (Why?)
  Dose: 50 mg IM/3-4 wks, ↑↑ by 50 mg every 6-9 months till 200 mg/3-4 wks
- **Intracytoplasmic sperm injection (ICSI):** ?? fertility

Male Hypogonadotropic-Hypogonadism

Etiology

1. **Hypopituitarism:** Transcription factors & TTIIIIE
2. **Isolated deficiency of gonadotropins:**
   - Sporadic
   - Familial
3. **Genetic defects:**
   - Kallmann $ (XLR, AR, AD) " hypogonadism, **anosmia**, mid-facial & renal defects"
   - DAX-1 gene mutation causing adrenal hypoplasia & impaired GnRH secretion
4. **Congenital syndromes**
   - Laurance-Moon Biedl
   - Prader-Willi

Clinical picture

- As C/P of primary hypogonadism
- Picture of the cause (Microphallus in hypopituitarism, anosmia in Kallmann $)

Investigations

1. Testosterone level: ↓↓
2. Gonadotropins "FSH& LH": ↓↓ with absence of nocturnal pulsatile LH secretion
3. hCG stimulation test: ↑↑ Testosterone
4. GnRH stimulation test: Blunt GTH response (DD: Constitutional delayed puberty)
5. Other pituitary hormones (GH, ACTH) & imaging
6. DNA probes for different mutations (Kallmann $)

Differential Diagnosis

- Constitutional delayed puberty: "Not uncommon = 3 %"

Diagnosis: If no puberty (Testicular volume < 4 mL) by the age of 14-15 yrs & testosterone level < 50 ng/dL. It should be differentiated from hypogonadotropic-hypogonadism;

- o **Family history:** +Ve
- o **Single 8 A.M. Testosterone level:** is a good predictor of impending puberty
- o **Nocturnal pulsatile LH secretion:** may be detected
- o **GnRH stimulation test:** ↑↑ LH
- o **Treatment:** Testosterone enanthate, 100 mg IM/4 wks, for 4-6 months

Value:

- Increase 2ry sex characters (relieves anxiety)
- May initiate puberty (↑↑ Growth & ↑↑ Bone age)
- DD: from Hypogonadotropic-hypogonadism (Diagnostic therapeutic test)

Treatment

- Constitutional delayed puberty should be **ruled out**
- Established cases (pubertal changes regress after discontinuation of testosterone):

a. **Testosterone enanthate**, starting at 11-12 yrs
Dose: 50 mg IM/3-4 wks, ↑↑ by 50 mg every 6-9 months till 200 mg/3-4 wks ⟶
Development of 2ry sex characters but with *small sized testes*

b. hCG (*Pregnyl*): IM 500-1000 IU, 3 times weekly ⟶ stimulates testicular growth & spermatogenesis. If testicular ↑↑ is not sufficient after 6-12 months, add:

c. **Human menopausal gonadotropin (HMG)"*Humegon*"**: IM 37.5-150 IU, 3 times/ wk

d. **Episodic administration of GnRH:** programmable infusion pump (Very expensive)

Prognosis

Spermatogenesis can be achieved after proper Rx (up to 2 yrs)

Female Hypergonadotropic-Hypogonadism

Etiology

1. **Turner syndrome (45, XO):** (1/2000)
2. **Noonan $:** Differences??
3. **XX Gonadal dysgenesis (Pure gonadal dysgenesis):** Gonads as Turner, No somatic features
4. **Mixed gonadal dysgenesis:** see before
5. **XXX female:** Non disjunction, No hypogonadism, learning& behavioral disorders
6. **XXXX & XXXXX female:** Hypogonadism + MR
7. **Resistant ovary syndrome:** FSH receptor defect
8. **Ovarian damage**
   - . Radiotherapy& chemotherapy
   - . Galactosemia
   - . Denys-Drash syndrome
   - . Ataxia telangiectasia
   - . Immune ovarian failure

	Turner	Noonan
Sex	Only ♀	♀& ♂
Genetics	Non-disjunction	AD
Cardiac	CoA / bicuspid aotic valve	PS
Mentality	MR in 18%	MR more common
Sexual Development	Hypogonadism	Delayed (2yrs)

Turner Syndrome

Genetic Types

- ☒ Non-disjunction (most common): The X chromosome is usually of maternal origin
- ☒ Mosaicism (better prognosis): 45, X / 46, XX

Clinical picture

(A) **At birth:** Edema of dorsum of hands & feet

(B) **Childhood:**

- Short stature (mean = 143 cm)
- Webbing of the neck
- Widely spaced nipples
- Cubitus valgus (↑↑ carrying angle)
- Low posterior hair line
- Normal mentality (MR in 18%)
- Cardiac: Coarctation, bicuspid aortic valve
- Renal: Hoarseshoe, ectopic kidney…
- Thyroiditis (30%)
- IGT, Type II DM

(C) **Puberty:**

- Secondary sex characters fail to develop

Investigations

1. Estrogen level: ↓↓
2. Gonadotropins "FSH& LH": ↑↑ (specially > 11 yrs)
3. Karyotyping (45, X)
4. U/S, Echocardiography, Thyroid profile

Treatment

- **hGH**
- **Estrogens:** To induce the development of 2ry sex characters. Start at 11-12 yrs (Why?)
- **Estrogen + Progesterone cyclic therapy:**
  - Estrogen D1- D23
  - Progestrone D10- D23
  - No Rx D23-D30 ⟶ Withdrawal bleeding
- **Ovum donation + IVF:** ?? Fertility

Female Hypogonadotropic-Hypogonadism

Etiology

1. **Hypopituitarism:** Transcription factors& TTIIIIE
2. **Isolated deficiency of gonadotropins:**
   - Sporadic
   - Familial
3. **Genetic defects:**
   - Kallmann $ (XLR, AR, AD) " hypogonadism, anosmia, mid-facial& renal defects"
4. **Congenital syndromes**
   - Laurance-Moon Biedl
   - Prader-Willi
5. **Anorexia nervosa**

Clinical picture

- As C/P of primary hypogonadism
- Picture of the cause (anosmia in Kallmann syndrome)

Investigations (as in 2ry.♂ hypogonadism)

Treatment Constitutional delayed puberty should be **ruled out**

Gynecomastia

Definition

Enlargement of the male breast due to hypertrophy of the glandular tissue

Etiology

1. Physiological
   a. Neonatal: Transplacental passage of maternal estrogens
   b. Pubertal (65% of all ♂): ↑↑ aromatase activity. Bilateral or unilateral & tender
2. Pathological
   a. Endocrinal: Male hypoganadism (Klinefelter syndrome)
   b. Liver cell failure (↓↓ estrogen metabolism)
   c. Neoplastic: Feminizing tumors (testicular & adrenal)
      Prolactinoma
      Bronchogenic carcinoma (Paramalignant syndrome)
   d. Drugs: Estrogens, spironolactone, digitalis, cimetidine, ketoconazole
   e. Idiopathic

Cryptorchidism

DD of empty scrotum:
1. Absent testes
2. Retractile testes
3. Undescended testes

Definition

Failure of descent of one or two testes

Incidence

Term = 3.4% Preterm = 30% Spontaneous descent occurs in the majority
If No descent by the age of 4 months, the testis will remain undescended

Factors affecting testicular descent

1. Hormonal
   Testosterone, DHT & AMH
2. Mechanical
   Gubernaculum, epididymis & abdominal pressure

Retractile testis:
Brisk cremastric reflex
Testes can be brought down to the scrotum

Classification

1. Abdominal
2. Inguinal
3. Gliding
4. Ectopic (Superficial inguinal, perineal)

Investigation

1. Testosterone before & after hCG stimulation: to detect functioning testicular tissue & exclude anorchia
2. U/S, CT, MRI abdomen
3. Laparoscopy

Complications

1. Infertility (Testicular pathological changes start to occur by 6-12 months)
2. Malignancy (1/40-80)
3. Psychological

Treatment *(Before 9-15 months, ideally at 6 months)*

1. **Hormonal**
   a. **hCG (Pregnyl):** IM 3000 IU/ wk for 4 weeks; or
   b. **GnRH**
2. **Surgical** (*Orchidopexy)*

Cairo University Faculty of Medicine — Time Allowed 1.5 hrs

Pediatric Department — Total Marks 25

M.Sc Pediatrics

Second part

Genetics

Answer the following questions:

1- Enumerate 5 characters of X-linked dominant mode of inheritance. (5 marks)
2- Enumerate 5 clinical features that are suggestive of Turner syndrome (5 marks)
3- Non invasive investigations for prenatal diagnosis of Down syndrome. (5 marks)

Problem solving (5 marks)

Five year old child with pectus exacavatum ,dislocated lenses of the eyes and a heart murmur his uncle developed aortic diltation and insufficiency at age 41.

What is the most likely diagnosis ?

What is the mode of inheritance ?

What is the diagnostic confirmatory test ?

Multiple choice questions :

1.A baby born with pulmonary hypoplasia secondary to oligohydraminos caused by renal agenesis would be classified as having

a-An association
b- A dysplasia
c-A sequence
d-A syndrome

2-The pattern of inheritance shown by malignant hyperthermia is

a-autosomal dominant
b-autosomal recessive
c- X-linked dominant
d-X-linked recessive

3-The DiGeorge/Shprintzen syndrome is caused by deletion in which chromosome

a. 4
b. 7
c. 15
d. 22

Cairo University Faculty of Medicine — Time Allowed 1.5 hrs

Pediatric Department — Total Marks 25

M.Sc. Pediatrics

Second part

Genetics

Answer the following questions:

1- Enumerate 5 characters of X-linked dominant mode of inheritance. (5 marks)
2- Enumerate 5 clinical features that are suggestive of Turner syndrome. (5 marks)
3- Non invasive investigations for prenatal diagnosis of Down syndrome. (5 marks)

Problem solving (5 marks)

Five year old child with pectus exacavatum ,dislocated lenses of the eyes and a heart murmur his uncle developed aortic diltation and insufficiency at age 41.

What is the most likely diagnosis ?

What is the mode of inheritance ?

What is the diagnostic confirmatory test ?

Multiple choice questions :

1.A baby born with pulmonary hypoplasia secondary to oligohydraminos caused by renal agenesis would be classified as having

a-An association
b- A dysplasia
c-A sequence
d-A syndrome

2-The pattern of inheritance shown by malignant hyperthermia is

a-autosomal dominant
b-autosomal recessive
c- X-linked dominant
d-X-linked recessive

3-The DiGeorge/Shprintzen syndrome is caused by deletion in which chromosome

a. 4
b. 7
c. 15
d. 22

Cairo University Faculty of Medicine — Time Allowed 1.5 hrs

Pediatric Department — Total Marks 25

M.Sc. Pediatrics

Second part

Genetics

Answer the following questions:

1- Enumerate 5 characters of X-linked dominant mode of inheritance. (5 marks)
2- Enumerate 5 clinical features that are suggestive of Turner syndrome. (5 marks)
3- Non invasive investigations for prenatal diagnosis of Down syndrome. (5 marks)

Problem solving (5 marks)

Five year old child with pectus exacavatum ,dislocated lenses of the eyes and a heart murmur his uncle developed aortic diltation and insufficiency at age 41.

What is the most likely diagnosis ?

What is the mode of inheritance ?

What is the diagnostic confirmatory test ?

Multiple choice questions :

1.A baby born with pulmonary hypopiasia secondary to oligohydraminos caused by renal agenesis would be classified as having

a-An association.
b- A dysplasia
c-A sequence
d-A syndrome

2-The pattern of inheritance shown by malignant hyperthermia is

a-autosomal dominant
b-autosomal recessive
c- X-linked dominant
d-X-linked recessive

3-The DiGeorge/Shprintzen syndrome is caused by deletion in which chromosome

a. 4
b. 7
c. 15
d. 22

Cairo University Faculty of Medicine

Time Allowed 1.5 hrs

Pediatric Department

Total Marks 25

M Sc. Pediatrics

Second part

Genetics

Answer the following questions:

1- Enumerate 5 characters of X-linked dominant mode of inheritance. (5 marks)
2- Enumerate 5 clinical features that are suggestive of Turner syndrome. (5 marks)
3- Non invasive investigations for prenatal diagnosis of Down syndrome. (5 marks)

Problem solving (5 marks)

Five year old child with pectus exacavatum ,dislocated lenses of the eyes and a heart murmur his uncle developed aortic diltation and insufficiency at age 41.

What is the most likely diagnosis ?

What is the mode of inheritance ?

What is the diagnostic confirmatory test ?

Multiple choice questions :

1.A baby born with pulmonary hypoplasia secondary to oligohydraminos caused by renal agenesis would be classified as having

a-An association
b- A dysplasia
c-A sequence
d-A syndrome

2-The pattern of inheritance shown by malignant hyperthermia is

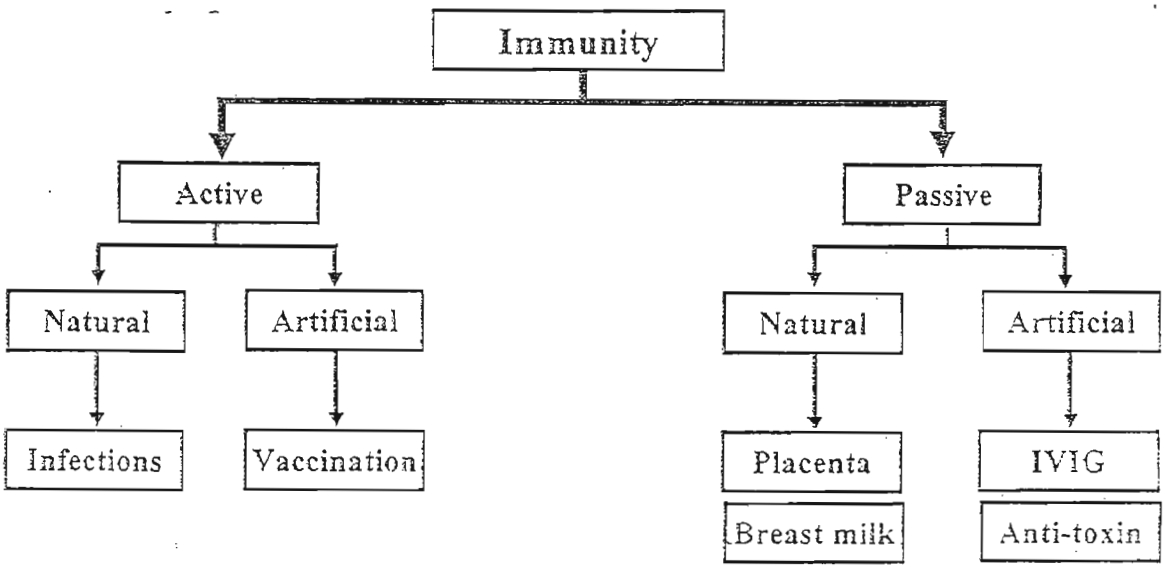
a-autosomal dominant
b-autosomal recessive
c- X-linked dominant
d-X-linked recessive

3-The DiGeorge/Shprintzen syndrome is caused by deletion in which chromosome

a. 4
b. 7
c. 15
d. 22

Immunization

Classification



A) Active Immunity

a. Natural

- ☒ Infections: Clinical or subclinical
  - ➢ Solid long-term immunity: Measles, Mumps, Rubella, Varicella
  - ➢ Transient short-term immunity: Influenza (Antigenic shift & drift)
  - ➢ Polioviruses: Lifelong immunity for each type, however, there is No cross immunity between the 3 types of polioviruses

b. Artificial

- ☒ Vaccination: Administration of vaccines or toxoids for prevention of diseases
  - ➢ Vaccines: Part of the pathogen used to produce specific immunity
  - ➢ Toxoids: Toxin with lost toxicity & retained antigenicity

B) Passive Immunity

a. Natural

- ☒ Placenta: Transplacental passage of antibodies (IgG). Protective for 3-6 months
- ☒ Breast milk: IgA

b. Artificial

- ☒ Antitoxin: Diphtheria & tetanus (TIG & TAT)
- ☒ Immune globulin for measles
- ☒ Immune globulin for rubella
- ☒ VZIG
- ☒ Hepatitis A Immunoglobulin (IG)
- ☒ IVIG

No transplacental immunity to pertussis (IgM)

Types of Vaccines

1. Killed (Inactivated): Salk (IPV), Hepatitis A
2. Living attenuated: Sabin (OPV), MMR, BCG, Varicella, Infuenza
3. Toxoids: Diphtheria, Tetanus
4. Bacterial fraction: Capsular polysaccharide (Hemophilus influenza, meningococcal, pneumococcal vaccines), acellular pertussis
5. Recombinant vaccines: Hepatitis B

Compulsory Vccines in Egypt

Age	Vaccine	Type	Dose
1st 3 months	▪ BCG	Live attenuated	0.05 ml ID
2 months	▪ OPV ▪ DPT ▪ Hepatitis B	Live attenuated D&T=toxoid, P=inactivated Recombinant	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml IM
4 months	▪ OPV ▪ DPT ▪ Hepatitis B	Live attenuated D&T=toxoid, P=inactivated Recombinant	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml IM
6 months	▪ OPV ▪ DPT ▪ Hepatitis B	Live attenuated D&T=toxoid, P=inactivated Recombinant	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml IM
9 months	▪ OPV	Live attenuated	▪ 2 drops PO
12 months	▪ MMR	Live attenuated	▪ 0.5 ml SC
18 months	▪ OPV ▪ DPT ▪ MMR	Live attenuated D&T=toxoid, P=inactivated Live attenuated	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml SC
4-6 years	▪ OPV ▪ DT ▪ MMR	Live attenuated Toxoid Live attenuated	▪ 2 drops PO ▪ 0.5 ml IM ▪ 0.5 ml SC

Non-Compulsory Vccines

1. Hemophilus influenza vaccine
2. Pneumococcal vaccine
3. Meningococcal vaccine
4. Hepatitis A vaccine
5. Varicella vaccine
6. Rota vaccine
7. Influenza vaccine
8. Rabies vaccine

General Contraindications to Vaccination

1. Serious allergic reaction e.g., anaphylaxis after a previous vaccine dose
2. Allergy to vaccine components
3. Moderate or severe acute illness with or without fever
4. Immunodeficiency: Live-attenuated vaccines; Sabin (OPV), MMR, BCG, Varicella
5. Immunosuppressive drugs: Live-attenuated vaccines...
6. Pregnancy: Live-attenuated vaccines

Vaccines can be administered in

1. Mild acute illness with or without fever
2. Mild or moderate local reaction or fever after previous vaccine
3. Current antimicrobial therapy

Remember

- **Bacterial Vaccines:** BCG, Hemophilus influenza, Pneumococcal, Meningococcal, Typhoid
- **Viral Vaccines:** OPV, MMR, Hepatitis B, Hepatitis A, Varicella, Rota, Rabies, Yellow fever

Vaccines

	Oral Polio Vaccine (Sabin)	Inactivated Polio Vaccine (Salk)	DPT	Hepatitis B Vaccine
Nature	Live-attenuated	Inactivated (Killed)	Toxoids (D & T) + Killed whole cell pertussis	Recombinant DNA vaccine
Against	Poliovirus (3 strains)	Poliovirus (3 strains)	D-P-T	HBV
Dose	2 drops	0.5 ml	0.5 ml	0.5 ml
Route	Oral	IM	IM	IM
Schedule	▪ 2, 4, 6, 9 months ▪ Boosters: 18 months & 4-6 yrs	▪ 2, 4, 6 months ▪ Boosters: 18 months & 4-6 yrs	▪ 2, 4, 6 months ▪ 1st Booster: 18 months ▪ 2nd Booster: 4-6 yrs **(DT)**	▪ 0, 1, 6 months (WHO) ▪ 2, 4, 6 months (Egypt), why?
Precautions	Cold chain Breastfeeding? (No significant reduction of immune response)			
Advantages	☒ Cheap ☒ Gives local GIT & systemic humoral immunity ☒ Effective (95%)	☒ No risk of VAPP	☒ Effective	☒ Effective (95%)
Disadvantages	Easily inactivated (Cold chain)	No local GIT immunity		
Contra-indications (+ General CI)	☒ Immunocompromised patients ☒ Healthy household contacts of immunocompromised patients		☒ Children > 6 yrs ☒ Neurological conditions ☒ Convulsions or high fever after previous DPT dose	
Side effects	☒ Vaccine-associated paralytic poliomyelitis (= VAPP) is very rare (1 every 2 millions) ☒ Loose stools	☒ Local: Pain & redness ☒ Systemic: Mild fever	☒ Local: Pain & redness ☒ Systemic: Fever ☒ Convulsions	☒ Local: Pain & redness ☒ Systemic: Fever

	Measles vaccine	MMR	BCG	Hemophilus influenza type b (Hib)
Nature	Live-attenuated	Live-attenuated	Live-attenuated	Polysaccharide vaccine
Against	Measles virus	M-M-R	TB bacilli	Hib
Dose	0.5 ml	0.5 ml	0.05 ml	0.5 ml
Route	SC	SC	Intra-dermal (**Lt** deltoid area)	IM
Schedule	▪ 9 months ▪ Booster: as MMR (15 months) ▪ Booster: as MMR (4-6 yrs)	▪ 1st dose: 12-15 months ▪ 2nd dose: at 18 months (or later at 4-6 yrs)	▪ At birth or 1st 3 months ▪ Booster: 5 & 11 yrs	▪ 2, 4, 6 months ▪ Booster: 12-15 month
Precautions			**Tuberculin test** is indicated if the vaccine is given beyond 6-12 months of age	
Advantages	☒ Effective (95%) ☒ Post-exposure prophylaxis: within 3 days after exposure	☒ Effective (99% after 2nd dose)	☒ The only available vaccine for TB ☒ ↓↓ Pulmonary TB (≈ 50% effectiveness) ☒ ↓↓ TB meningitis & disseminated disease (≈ 50-80% effectiveness)	☒ Effective in prevention of meningitis, epiglottitis…
Contra-indications (+ General CI)	☒ Immunocompromised ☒ Pregnancy or expected pregnancy (within 3 ms) ☒ TB ☒ Age < 8 months	☒ Immunocompromised ☒ Pregnancy or expected pregnancy (within 3 ms) ☒ TB ☒ Age < 12 months	☒ Immunocompromised ☒ Pregnancy	
Side effects	☒ Local: Pain & redness ☒ Systemic: Fever	☒ Local: Pain & redness ☒ Systemic: Fever ☒ Arthritis	☒ Erythema, papule ± ulceration in 3-6 wks ☒ Scar formation: 2-6 months ☒ Regional LN: Anti-TB Rx may be needed ☒ Disseminated infections: in immunocompromised individuals	☒ Local: Pain & redness ☒ Systemic: Fever

	Meningococcal vaccine	Varicella Vaccine	Hepatitis A Vaccine	Pneumococcal Conjugate Vaccine (PCV)
Nature	Polysaccharide vaccine	Live-attenuated	Inactivated vaccine	Polysaccharide vaccine
Against	A, C, Y, W135	VZV	HAV	Heptavalent (7 types)
Dose	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Route	SC	SC	IM	IM
Schedule	▪ Single dose at the age of ≥ 2 yrs ▪ Indications: - Before splenectomy - Sickle cell anemia - Outbreaks - Travelers (Haj & Omra)	▪ 1st dose: ≥ 12 months ▪ 2nd dose: 4-6 yrs or earlier provided (≥ 3 m interval)	▪ 1st dose: ≥ 12 months ▪ 2nd dose: 6-12 m interval	▪ 2, 4, 6 months ▪ Booster: 12-15 month
Advantages	☒ Protection starts 7-10 days after vaccination			☒ Effective in prevention of meningitis, pneumonia…
Disadvantages	▪ Protection for 2-3 yrs only			
Contra-indications (+ General CI)	☒ < 2 yrs	☒ Immunocompromised ☒ Pregnancy or expected pregnancy (within 3 ms)		
Side effects	☒ Local: Pain & redness ☒ Systemic: Fever	☒ Local: Pain & redness ☒ Systemic: Fever ☒ Rash (< 5% of cases)	☒ Local: Pain & redness ☒ Systemic: Fever	☒ Local: Pain & redness ☒ Systemic: Fever

Influenza Vaccine

- Inactivated vaccine
- Dose: 6 months-3 yrs = 0.25 ml
  > 3 yrs = 0.5 ml
- Route: IM
- Schedule: 2 doses (4 wks interval) then annual
- Indications: Asthma, CHD…

Rota Vaccine

- Live-attenuated vaccine
- Dose: 1 ml
- Route: Oral
- Schedule: 2 doses (2 & 4 months)
- Indications: Protection against Rotavirus GE

Rabies Vaccine

- Inactivated vaccine
- Dose: 0.5 ml
- Route: IM
- Schedule: 5 doses (0, 3, 7, 14, 28 days)
- Indications: Post-exposure immunization

	Meningococcal vaccine	Pneumococcal Conjugate Vaccine (PCV)	Pneumococcal Polysaccharide Vaccine (PPV)	Hemophilus influenza type b (Hib)
Nature	Polysaccharide vaccine	Polysaccharide vaccine	Polysaccharide vaccine	Polysaccharide vaccine
Against	A, C, Y, W135	7 types of bacteria (Heptavalent)	23 types of bacteria	Hib
Route	SC (0.5 ml)	IM (0.5 ml)	IM (0.5 ml)	IM (0.5 ml)
Schedule	▪ Single dose ▪ > 2 yrs of age ▪ Protection for 2-3 yrs ▪ Protection starts after 10 days	☒ 2-6 months ▪ 3 doses: 2, 4, 6 months ▪ 4th dose: 12-15 month ☒ 6-12 months ▪ 2 doses: with 2 ms interval ▪ 3rd dose > 12 months ☒ 12-24 months ▪ 2 doses with 2 ms interval ☒ 2-5 yrs: One dose ☒ > 5 yrs: Not needed	▪ Single dose ▪ > 2 yrs of age ▪ Protection for 2-3 yrs ▪ Protection starts after 10 days ▪ interval ☒ 2-5 yrs: One dose ☒ > 5 yrs: Not needed	☒ 2-6 months ▪ 3 doses: 2, 4, 6 months ▪ Booster: 12-15 month ☒ 6-12 months ▪ 2 doses: with 2 ms interval ▪ Booster > 12 months ☒ 12-24 months ▪ 1 + booster (2 ms interval) ☒ 2-5 yrs: One dose (Only) ☒ > 5 yrs: Not needed
Indications	☒ Epidemics ☒ Before splenectomy ☒ Sickle cell anemia ☒ Complement deficiency	☒ All children < 2 yrs (Routine) ☒ Children 2-5 yrs (Not immunized) ▪ Before splenectomy ▪ Sickle cell anemia ▪ Complement deficiency ▪ Immunosuppressives ▪ Heart or lung diseases ▪ NS, CRF ▪ AIDS	☒ Children > 2 yrs ▪ Before splenectomy ▪ Sickle cell anemia ▪ Complement deficiency ▪ Immunosuppressives ▪ Heart or lung diseases ▪ NS, CRF ▪ AIDS	☒ All children < 2 yrs (Routine)
Side effects	☒ Local: Pain & redness ☒ Systemic: Fever	☒ Local: Pain & redness ☒ Systemic: Fever	☒ Local: Pain & redness ☒ Systemic: Fever	☒ Local: Pain & redness ☒ Systemic: Fever

Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2009

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼ Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB		see footnote 1	HepB						
Rotavirus[2]			RV	RV	RV[2]						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP	see footnote 3	DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	Hib[4]	Hib					
Pneumococcal[5]			PCV	PCV	PCV	PCV				PPSV	
Inactivated Poliovirus			IPV	IPV		IPV					IPV
Influenza[6]					Influenza (Yearly)						
Measles, Mumps, Rubella[7]						MMR		see footnote 7			MMR
Varicella[8]						Varicella		see footnote 8			Varicella
Hepatitis A[9]						HepA (2 doses)				HepA	
Meningococcal[10]										MCV	

Range of recommended ages

Certain high-risk groups

This schedule includes the recommended ages for routine administration of currently licensed vaccines, as of December 1, 2008 for children aged through 6 years. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at http://www.vaers.hhs.gov or by telephone, 800-822-7967.

Hepatitis B vaccine (HepB). *(Minimum age: birth)*

At birth:

- Administer monovalent HepB to all newborns before hospital discharge.
- If mother is hepatitis B surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
- If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG (no later than age 1 week).

After the birth dose:

- The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1 or 2 months. The final dose should be administered no earlier than age 24 weeks.
- Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg (anti-HBs) after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).

4-month dose:

- Administration of 4 doses of HepB to infants is permissible when combination vaccines containing HepB are administered after the birth dose.

Rotavirus vaccine (RV). *(Minimum age: 6 weeks)*

- Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks 0 days or older (i.e., 15 weeks 0 days or older).
- Administer the final dose in the series by age 8 months 0 days.
- If Rotarix® is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). *(Minimum age: 6 weeks)*

- The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
- Administer the final dose in the series at age 4 through 6 years.

***Haemophilus influenzae* type b conjugate vaccine (Hib).** *(Minimum age: 6 weeks)*

- If PRP-OMP (PedvaxHIB® or Comvax® [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
- TriHiBit® (DTaP/Hib) should not be used for doses at ages 2, 4, or 6 months but can be used as the final dose in children aged 12 months or older.

Pneumococcal vaccine. *(Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])*

- PCV is recommended for all children aged younger than 5 years. Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- Administer PPSV to children aged 2 years or older with certain underlying medical conditions (see *MMWR* 2000;49[No. RR-9]), including a cochlear implant.

6. Influenza vaccine. *(Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])*

- Administer annually to children aged 6 months through 18 years.
- For healthy nonpregnant persons (i.e., those who do not have underlying medical conditions that predispose them to influenza complications) aged 2 through 49 years, either LAIV or TIV may be used.
- Children receiving TIV should receive 0.25 mL if aged 6 through 35 months or 0.5 mL if aged 3 years or older.
- Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.

7. Measles, mumps, and rubella vaccine (MMR). *(Minimum age: 12 months)*

- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.

8. Varicella vaccine. *(Minimum age: 12 months)*

- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
- For children aged 12 months through 12 years the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.

9. Hepatitis A vaccine (HepA). *(Minimum age: 12 months)*

- Administer to all children aged 1 year (i.e., aged 12 through 23 months). Administer 2 doses at least 6 months apart.
- Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
- HepA also is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).

10. Meningococcal vaccine. *(Minimum age: 2 years for meningococcal conjugate vaccine [MCV] and for meningococcal polysaccharide vaccine [MPSV])*

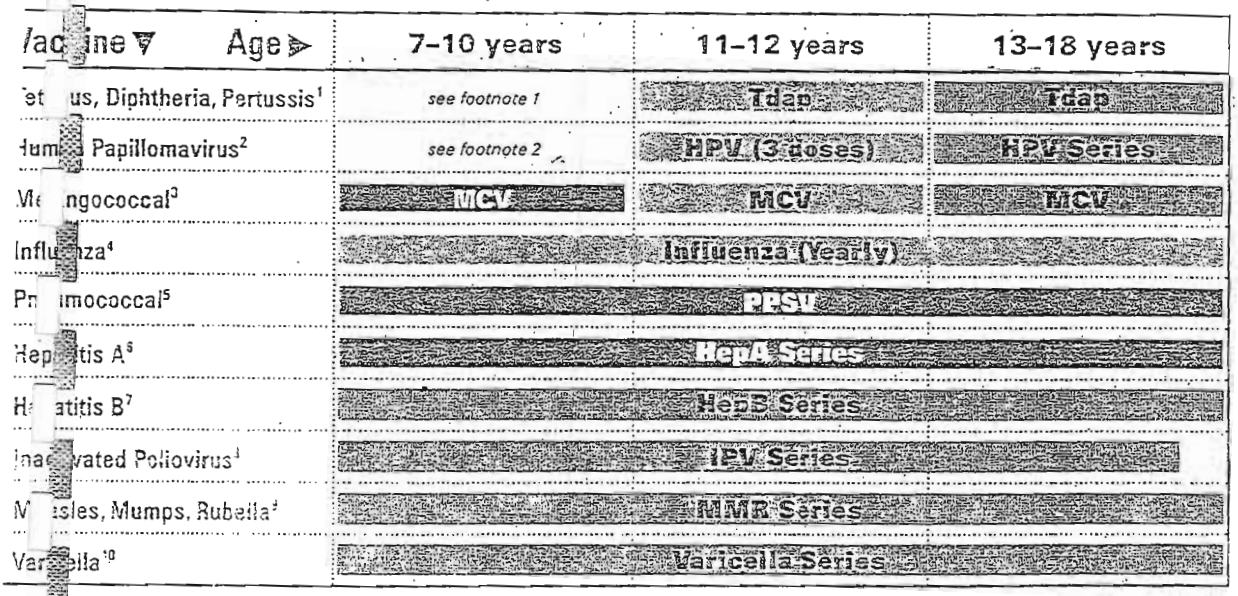
- Administer MCV to children aged 2 through 10 years with terminal complement component deficiency, anatomic or functional asplenia, and certain other high-risk groups. See *MMWR* 2005;54(No. RR-7).
- Persons who received MPSV 3 or more years previously and who remain at increased risk for meningococcal disease should be revaccinated with MCV.

The Recommended Immunization Schedules for Persons Aged 0 Through 18 Years are approved by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/recs/acip), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).

DEPARTMENT OF HEALTH AND HUMAN SERVICES • CENTERS FOR DISEASE CONTROL AND PREVENTION

ecommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States • 2009

For those who fall behind or start late, see the schedule below and the catch-up schedule



This schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 1, 2008, for children aged through 18 years. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at http://www.vaers.hhs.gov or by telephone, 800-822-7967.

1. Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap). *(Minimum age: 10 years for BOOSTRIX® and 11 years for ADACEL®)*
- Administer at age 11 or 12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a tetanus and diphtheria toxoid (Td) booster dose.
- Persons aged 13 through 18 years who have not received Tdap should receive a dose.
- A 5-year interval from the last Td dose is encouraged when Tdap is used as a booster dose; however, a shorter interval may be used if pertussis immunity is needed.

2. Human papillomavirus vaccine (HPV). *(Minimum age: 9 years)*
- Administer the first dose to females at age 11 or 12 years.
- Administer the second dose 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).
- Administer the series to females at age 13 through 18 years if not previously vaccinated.

3. Meningococcal conjugate vaccine (MCV).
- Administer at age 11 or 12 years, or at age 13 through 18 years if not previously vaccinated.
- Administer to previously unvaccinated college freshmen living in a dormitory.
- MCV is recommended for children aged 2 through 10 years with terminal complement component deficiency, anatomic or functional asplenia, and certain other groups at high risk. See *MMWR* 2005;54(No. RR-7).
- Persons who received MPSV 5 or more years previously and remain at increased risk for meningococcal disease should be revaccinated with MCV.

4. Influenza vaccine.
- Administer annually to children aged 6 months through 18 years.
- For healthy nonpregnant persons (i.e., those who do not have underlying medical conditions that predispose them to influenza complications) aged 2 through 49 years, either LAIV or TIV may be used.
- Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.

5. Pneumococcal polysaccharide vaccine (PPSV).
- Administer to children with certain underlying medical conditions (see *MMWR* 1997;46(No. RR-8)), including a cochlear implant. A single revaccination should be administered to children with functional or anatomic asplenia or other immunocompromising condition after 5 years.

6. Hepatitis A vaccine (HepA).
- Administer 2 doses at least 6 months apart.
- HepA is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).

7. Hepatitis B vaccine (HepB).
- Administer the 3-dose series to those not previously vaccinated.
- A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB® is licensed for children aged 11 through 15 years.

8. Inactivated poliovirus vaccine (IPV).
- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

9. Measles, mumps, and rubella vaccine (MMR).
- If not previously vaccinated, administer 2 doses or the second dose for those who have received only 1 dose, with at least 28 days between doses.

10. Varicella vaccine.
- For persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007;56(No. RR-4)), administer 2 doses if not previously vaccinated or the second dose if they have received only 1 dose.
- For persons aged 7 through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
- For persons aged 13 years and older, the minimum interval between doses is 28 days.

The Recommended Immunization Schedules for Persons Aged 0 Through 18 Years are approved by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/recs/acip), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).

DEPARTMENT OF HEALTH AND HUMAN SERVICES • CENTERS FOR DISEASE CONTROL AND PREVENTION

CS103164

Catch-up Immunization Schedule for Persons Aged 4 Months Through 18 Years Who Start Late or Who Are More Than 1 Month Behind—United States • 2009

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 6 YEARS					
Hepatitis B[1]	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Rotavirus[2]	6 wks	4 weeks	4 weeks[2]		
Diphtheria, Tetanus, Pertussis[3]	6 wks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[4]	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12-14 months No further doses needed if first dose administered at age 15 months or older	4 weeks[4] if current age is younger than 12 months 8 weeks (as final dose)[4] if current age is 12 months or older and second dose administered at younger than age 15 months No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months	
Pneumococcal[5]	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older or current age 24 through 59 months No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for high-risk children who received 3 doses at any age	
Inactivated Poliovirus[6]	6 wks	4 weeks	4 weeks	4 weeks[6]	
Measles, Mumps, Rubella[7]	12 mos	4 weeks			
Varicella[8]	12 mos	3 months			
Hepatitis A[9]	12 mos	6 months			
CATCH-UP SCHEDULE FOR PERSONS AGED 7 THROUGH 18 YEARS					
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis[10]	7 yrs[10]	4 weeks	4 weeks if first dose administered at younger than age 12 months 6 months if first dose administered at age 12 months or older	6 months if first dose administered at younger than age 12 months	
Human Papillomavirus[11]	9 yrs	Routine dosing intervals are recommended[11]			
Hepatitis A[9]	12 mos	6 months			
Hepatitis B[1]	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Inactivated Poliovirus[6]	6 wks	4 weeks	4 weeks	4 weeks[6]	
Measles, Mumps, Rubella[7]	12 mos	4 weeks			
Varicella[8]	12 mos	3 months if the person is younger than age 13 years 4 weeks if the person is aged 13 years or older			

1. Hepatitis B vaccine (HepB).
- Administer the 3-dose series to those not previously vaccinated.
- A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB® is licensed for children aged 11 through 15 years.

2. Rotavirus vaccine (RV).
- The maximum age for the first dose is 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks or older (i.e., 15 weeks 0 days or older).
- Administer the final dose in the series by age 8 months 0 days.
- If Rotarix® was administered for the first and second doses, a third dose is not indicated.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).
- The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.

4. *Haemophilus influenzae* type b conjugate vaccine (Hib).
- Hib vaccine is not generally recommended for persons aged 5 years or older. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults. However, studies suggest good immunogenicity in persons who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy; administering 1 dose of Hib vaccine to these persons is not contraindicated.
- If the first 2 doses were PRP-OMP (PedvaxHIB® or Comvax®), and administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer 2 doses separated by 4 weeks and a final dose at age 12 through 15 months.

5. Pneumococcal vaccine.
- Administer 1 dose of pneumococcal conjugate vaccine (PCV) to all healthy children aged 24 through 59 months who have not received at least 1 dose of PCV on or after age 12 months.
- For children aged 24 through 59 months with underlying medical conditions, administer 1 dose of PCV if 3 doses were received previously or administer 2 doses of PCV at least 8 weeks apart if fewer than 3 doses were received previously.
- Administer pneumococcal polysaccharide vaccine (PPSV) to children aged 2 years or older with certain underlying medical conditions (see *MMWR* 2000;49[No. RR-9]), including a cochlear implant, at least 8 weeks after the last dose of PCV.

6. Inactivated poliovirus vaccine (IPV).
- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

7. Measles, mumps, and rubella vaccine (MMR).
- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.
- If not previously vaccinated, administer 2 doses with at least 28 days between doses.

8. Varicella vaccine.
- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
- For persons aged 12 months through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
- For persons aged 13 years and older, the minimum interval between doses is 28 days.

9. Hepatitis A vaccine (HepA).
- HepA is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).

10. Tetanus and diphtheria toxoids vaccine (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).
- Doses of DTaP are counted as part of the Td/Tdap series
- Tdap should be substituted for a single dose of Td in the catch-up series or as a booster for children aged 10 through 18 years; use Td for other doses.

11. Human papillomavirus vaccine (HPV).
- Administer the series to females at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals for series catch-up (i.e., the second and third doses should be administered at 2 and 6 months after the first dose). However, the minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks, and the third dose should be given at least 24 weeks after the first dose.

Nutritional Disorders

Classification

Pediatric nutritional disorders can be classified into:

A) **Severe childhood undernutrition (Protein-energy malnutrition)**
B) **Overweight & obesity**
C) **Specific vitamin & mineral deficiency:** e.g., iron, vitamin D & A deficiency

Protein-Energy Malnutrition

Definition

- Group of related disorders characterized by **protein & energy** deficiency
- PEM is almost always associated with other nutritional deficiencies, therefore the term **"severe childhood undernutrition"** is preferred
- They have variable clinical & biochemical presentations (but overlap may occur)

Contributing factors to PEM

1. Poverty, Ignorance, Illiteracy
2. Infection: Recurrent GE, measles, TB...
3. Urbanization
4. Disasters
   - Natural: Earthquakes
   - Human-related: Wars
5. Environmental degradation

Clinical Spectrum

	Definition	Features
Marasmus	Severe form of chronic undernutrition	Wasting
Kwashiorkor	Severe form of chronic protein deficiency	Edema
Marasmic-KWO	Mixed marasmus & Kwashiorkor	Wasting + Edema
Mixed forms	Mixed	Mixed

NB: Nutritional dwarfism Mild to moderate form of chronic undernutrition
Short stature & Underweight (**No** wasting & **No** edema)
Commonest form of undernutrition (Recurrent infections)

Remember

Main Features





Marasmus





Kwashiorkor

Kwashiorkor

Definition

- Severe form of chronic malnutrition caused by **protein deficiency** with adequate caloric intake in the form of excess CHO

Incidence

- 6 months-2 years (Age of weaning)

Etiology

A) **Dietetic**

- ☒ Wrong compensation of scanty breast milk or over-diluted formula by excess CHO
- ☒ Weaning: Substitution of milk with high CHO diet (without proteins) e.g., potatoes, rice water, starch...

B) **Infections**

- ☒ Post-GE: anorexia, vomiting, diarrhea, wrong dietary restriction
- ☒ Post-measles

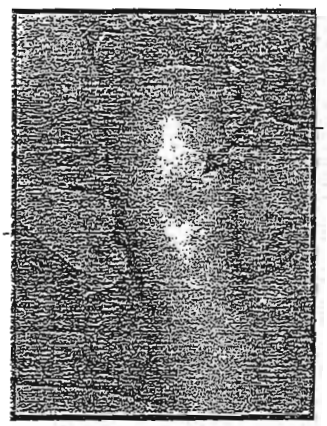
C) **Maternal deprivation**

Clinical Picture

4 Constant

A) **Constant manifestations**

1. **Edema** (Diagnosis can **not** be made in absence of edema)
   - ☒ Cause:
     - Hypoalbuminemia (↓↓ Oncotic pressure)
     - ↑↑ ADH & aldosterone (2ry to ↓↓ effective plasma volume)
   - ☒ C/P
     - Site of **onset:** Dorsum of the feet
     - **March:** Then becomes generalized;
       - ➢ LL edema
       - ➢ Dorsum of hands
       - ➢ No Ascites
     - **Character:** Pitting



Pitting Edema

2. **Mental changes**
   - ☒ Cause:
     - ↓↓ Amino acids (Neurotransmitters)
     - ↓↓ Niacin (& NAD, NADP)
     - Maternal deprivation
   - ☒ Manifestations
     - Apathy
     - Lethargy
     - Disinterested in the surroundings
     - Miserable
     - No mental retardation (These changes are reversible with Rx)



Apathy

3. **Disturbed muscle/fat ratio**
   - **Muscle:** Wasting (↓↓ Proteins)
   - **Fat:** Excess SC fat (↑↑ CHO)

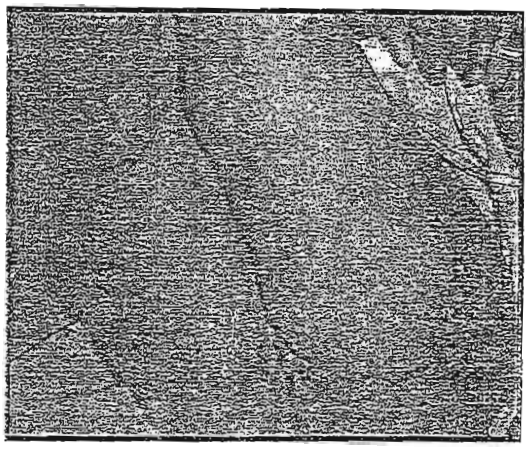
Skin fold thickness

4. **Growth failure:** Detected by skin fold thickness (May be masked by edema & excess SC fat)

B). Variable manifestations

7 Variable

1. Hair changes
   - ☒ Cause:
     - ↓↓ Sulfur-containing amino acid
     - ↓↓ Tyrosine (↓↓ Melanin)
     - ↓↓ Copper
   - ☒ Manifestations
     - Sparse, soft & easily detached
     - Light in color
     - Flag sign: With recovery (Alternating light & dark bands)



2. Skin changes
   - ☒ Cause:
     - ↓↓ Vitamin A
     - ↓↓ Zinc
     - ↓↓ Niacin
     - Disturbed amino acid metabolism
   - ☒ Manifestations
     - Site: Buttocks, perineum
     - Lesions: Cracking, fissuring, ulceration, hypo- & hyperpigmentation ± infection

3. Hepatomegaly
   - ☒ Cause:
     - Accumulation of fat & glycogen
   - ☒ Manifestations
     - Liver: Enlarged & soft

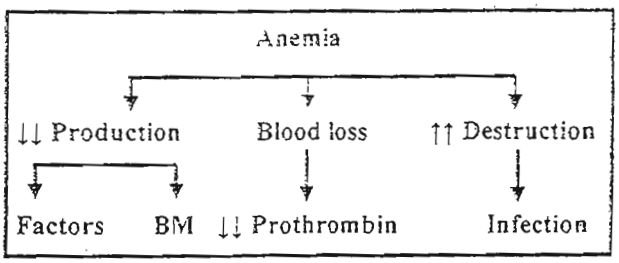
Remember
- Hepatomegaly is Variable
- Fatty infiltration is Constant

4. GIT
   - a. **Anorexia:** Mental changes & infection
   - b. **Vomiting:** GE
   - c. **Diarrhea:** Mucosal damage, GE

5. **Vitamin deficiency**
   - a. **Vitamin A:** Keratomalacia, xerophthalmia, blindness, bitot spots, infections
   - b. **Vitamin B:** Stomatitis & glossitis
   - c. **Vitamin C:** Scurvy
   - d. **Vitamin K:** Bleeding (Hypoprothrombinemia)
   - e. **Vitamin D:** Rickets does not occur *(Rickets is a disease of growing bones)*

6. **Infections**
   - a. Gastroenteritis (GE)
   - b. Bronchopneumonia
   - c. Skin infection
   - d. Septicemia

7. **Anemia** *(See Hematology)* ⇨



Complications

1. Infection: Pneumonia, GE…
2. Hypothermia & Hypoglycemia
3. Bleeding
4. Shock: Hypovolemic or septic

Investigations

A) Laboratory

- CBC: Anemia, leukocytosis (Infection)
- Serum albumin: ↓↓ (N = 3.5-5.5 g/dl)
- Serum globulins: ↓↓ α & β-globulins (↑↑ γ-globulins due to infections)
- Dilutional hyponatremia
- Hypokalemia
- Hypoglycemia (Due to disturbed glucose metabolism)

Total body Na is ↑↑

B) Imaging

- CXR: Pneumonia

Differential Diagnosis

1. Other causes of **generalized edema**

	Mechanism	C/P
Nephrotic	Hypoalbuminemia (↓↓ OP)	Nephrotic syndrome (Describe)
Nutritional	Hypoalbuminemia (↓↓ OP)	Kwashiorkor (Ascites is very rare)
Hepatic	Hypoalbuminemia (↓↓ OP)	Jaundice, hepatomegaly…
Cardiac	↑↑ Venous pressure	Tachycardia, Tachypnea, Tender hepatomegaly
Allergic	↑↑ Capillary permeability	History (exposure) + Itching – Urticaria (wheals)

2. **Skin diseases:**
   a. **Pellagra:** 3Ds (Dermatitis, Dementia, Diarrhea)
   b. **Diaper dermatitis**

3. Other causes of **PEM:** *See classification table*
   a. **Marasmus**
   b. **Marasmic- Kwashiorkor**
      ☒ Etiology
      - Kwashiorkor patient: with CHO restriction
      - Marasmic patient: treated with CHO diet (without adequate proteins)

      ☒ C/P
      - Kwashiorkor patient (Edema) + Loss of SC tissue
      - Marasmic patient (Wasting) + Edema

      Wasting + Edema

   c. **Nutritional dwarfism** (Most common form of childhood undernutrition)
      - Mild to moderate form of chronic undernutrition
      - Short stature, Underweight & Recurrent infections (No wasting & No edema)

Prevention

1. **General measures:** Environmental sanitation, Socioeconomic development
   Adequate food supply, prevention of infection
2. **Promotion of breastfeeding:** It is the simplest, cheapest & most effective method
3. **Heath education**
4. **Nutritional education:** Value of breastfeeding, proper weaning…
5. **Regular assessment of child health & growth pattern:** Growth curves
6. **Regular assessment of nutritional state:** Early manifestations of nutritional disorders
7. **Proper management of childhood infections:** Especially GE…
8. **Proper antenatal care**

Marasmus

Definition

- Severe form of chronic malnutrition caused by **insufficient caloric intake**

Incidence

- Nutritional marasmus: 6 months-2 years
- Non-nutritional marasmus: Depends on the etiology



Etiology (↓↓ Calories)

A) **Nutritional marasmus**

☒ Dietetic
- Scanty breast milk
- Over-diluted formula

☒ Infection (Recurrent GE):
- ↓↓ Intake: Anorexia & vomiting
- ↑↑ Losses: Diarrhea
- Wrong medical advice

B) **Non-nutritional marasmus**

- CVS: CHD, RHD
- Resp.: TB, Cystic fibrosis
- Renal: CRF, RTA
- Hepatic: Chronic liver disease (Cirrhosis)
- Blood: Chronic hemolytic anemia
- GIT: Malabsorption (Parasites , Celiac…)
- Others: Cleft palate, CHPS, malignancy, starvation, anorexia nervosa

Clinical Picture

A) **Loss of weight:** Growth curves (Quite below the expected weight for age i.e., < 5th %)
B) **Muscle wasting**
C) **Loss of SC fat:** Thin wrinkled skin with marked bony prominences

Degrees of Marasmus

	Weight loss	Loss of SC fat
1st degree	15-25% of the expected weight	Abdominal wall
2nd degree	25-35% of the expected weight	Buttocks & thighs
3rd degree	> 35% of the expected weight	Face (Senile facies)

D) **Vitamin deficiency:** A, D, K, C, B *(See kwashiorkor for manifestations)*
E) **Mineral deficiency:** Iron deficiency anemia
F) **Dehydration**
G) **Other manifestations Hunger**
- Anxious look, irritability & crying *(DD: Kwashiorkor)*
- Hunger diarrhea: Scanty dry greenish stools



2nd degree marasmus

Investigations

- CBC: Anemia, leukocytosis (Infection)
- Serum proteins: Not markedly ↓↓
- Hypoglycemia
- Investigations of non-nutritional marasmus

Complications

1. Infection: Pneumonia, GE…
2. Hypothermia & Hypoglycemia

Management of PEM

A) Hospital Management

☒ **Indications**

- Moderate or severe Kwashiorkor
- Marasmic kwashiorkor
- 3rd degree marasmus
- Complications

☒ **Management plan (Stabilization & Rx of complications)**

- Infection (GE, pneumonia…): Proper antibiotics
- Shock: Shock therapy (Lactated ringer's 20 ml/Kg over 1 hr), FFP can be used
- Dehydration: IV fluid therapy (Deficit therapy)
- Electrolyte disturbances: should be corrected
- Anemia: Packed RBCs
- Hypoglycemia
- Hypothermia: External heating

B) Nutritional Management (Home or hospital)

	Marasmus	Kwashiorkor
Rational (Target)	↑↑ Calories 150-200 Kcal/Kg/day	↑↑ Proteins 4-6 gm/Kg/day
Type of foods	According to the age: ▪ Milk-fed: Milk (Lactose-free may be used initially) then standard… ▪ Weaned infants: Balanced diet [CHO=50%, Lipids=35 %, Ptns=15%]	According to the age: ▪ Milk-fed: Milk (Lactose-free may be used initially) then standard… ▪ Weaned infants: High-protein diet - Egg, meat, chicken, beans - Vegetables, fruits
Amount	Start with ≈ 75 Kcal/Kg/day ↑↑ Amount & concentration according to the child **tolerance** (Rate of ↑↑ ≈ 5-10 Kcal/Kg/day)	Start with ≈ 1 gm/Kg/day ↑↑ Amount & concentration according to the child **tolerance**
Route	Oral or Nasogastric tube	Oral or Nasogastric tube More difficult, why? Anorexia
Vitamins	➢ Vitamin A - 6-12 months: 100.000 IU/day - > 12 months: 200.000 IU/day ➢ Vitamin B, C, D, Folic acid	
Minerals	➢ Iron (4-6 mg/kg/day) ➢ Potassium ➢ Zinc	

Complications of Rx

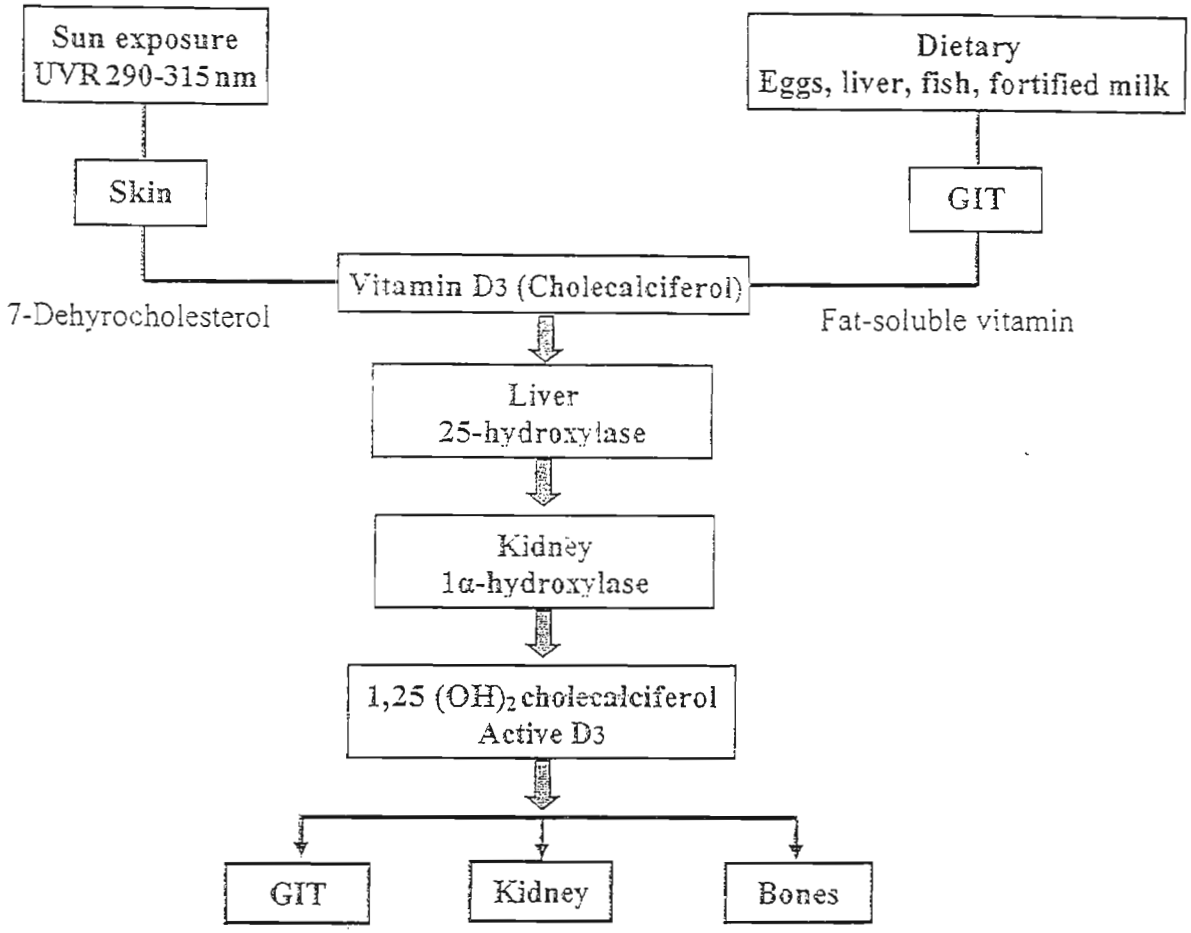
1. **Diarrhea:** Due to transient CHO intolerance (Lactose)
2. **Nutritional recovery syndrome:** Firm enlarged liver

Rickets

Definition

- Defective mineralization of the growing bones (Disease of childhood)

Physiologic Considerations



Hormonal Regulation of Ca Homeostasis

	Vitamin D	Parathyroid hormone
Intestine	↑↑ Ca absorption	↑↑ Ca absorption (through ↑↑ Vit. D)
Kidneys	↑↑ Ca reabsorption	↑↑ PO_4 excretion (Phosphaturia)
Bones	Normal mineralization of bones	Bone resorption (↑↑ Osteoclasts)

Structure of Normal Bone Formed of **matrix** (Osteoid tissue) & **minerals** (Ca & P)

Bone Lavers (in the epiphyseal region)

1. Zone of resting cartilage: 1 layer
2. Zone of proliferating cartilage: 6-8 layers
3. Zone of degenerating cartilage (= Zone of provisional calcification): Deposition of Ca & P
4. Zone of ossification: Invasion of the ZPC by BV & osteoblasts with mineralization

Bone Pathology in Rickets Proliferation without degeneration

Remember

- **Osteomalacia:** ↓↓ Mineralization of bones (any age)
- **Osteoporosis:** ↓↓ Bone volume & ↓↓ Bone minerals

Types of Rickets (= Classification)

A) Ca deficiency rickets with 2ry ↑↑ PTH
- Vitamin D deficiency
- Malabsorption of vitamin D
- Hepatic disease
- Renal osteodystrophy

B) Primary PO_4 deficiency (No 2ry ↑↑ PTH)
- XL-D Hypophosphatemic rickets
- Fanconi syndrome: PCT dysfunction [Glucosuria, phosphaturia, aminoaciduria]

C) End-organ resistance to 1,25 $(OH)_2$

D) Cases resembling rickets: Hypophosphatasia

Another Classification

	Vitamin D deficiency rickets	Non-Vitamin D deficiency rickets
Incidence	More common	Less common
Age	6 months-2 years	Any age
Response to Vit D therapy	Good	Poor

Vitamin D-Deficiency Rickets

Definition

Defective mineralization of the **growing** bones (Disease of childhood

Incidence

- 6 months-2 years (Age of weaning)

Etiology

A) **Lack of vitamin D**

a. Inadequate intake of vitamin D
- ☒ Prolonged exclusive breast milk
- ☒ Rachitogenic diet ⟹

b. Inadequate sun exposure
- ☒ Wrapping
- ☒ Winter-time
- ☒ Windows

B) Other causes: Malabsorption, renal or hepatic diseases

Remember

Rachitogenic diet is any of:
- Deficient in vitamin D
- Deficient in Ca & PO_4
- Non-optimum Ca:P ratio
- ↑↑ Content of phytate or oxalates

Clinical Picture

A) Skeletal

1. Head
   - Frontal bossing
   - Macrocephaly (Cranial cause)
   - Delayed closure of AF
   - Delayed dentition

   NB: Craniotabes is Ping-Pong ball sensation detected on pressing over the occiput (= Bone thinning)



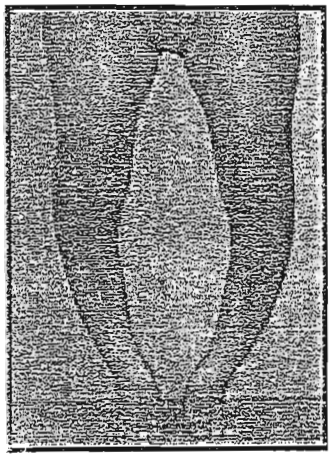
2. Limbs
   - Broadening of the ends of long bones
   - Marfan sign: Transverse groove across medial malleolus
   - Deformities of the UL: Convexity of the forearm (in creeping infants)
   - Deformities of the LL
     - Genu varum: Bow legs
     - Genu valgum: Knock knees
     - Genu recurvatum: Overextension of the knees



Broadening (At the wrist)



Genu valgum



Genu varum

3. Chest
   - Rosary beads: Cartilage proliferation at the costochondral junctions
   - Pigeon chest: ↑↑ AP diameter of the chest (Protrusion of the sternum + rib flaring)
   - Harrison sulcus: Horizontal groove along the costal insertion of the diaphragm
   - Longitudinal sulcus: Vertical groove behind rosary beads



Rosary beads

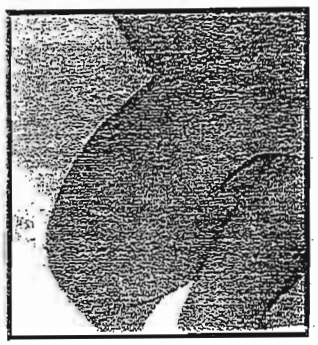


Pigeon chest (Harrison sulcus)



Pigeon

4. Spine: Due to laxity of ligaments
   - Kyphosis (Correctable) "DD: Pott's disease"
   - Scoliosis
   - Kyphoscoliosis
   - Lumbar lordosis



5. Pelvis: Contracted pelvis (important in ♀)

B) Muscles & Ligaments: Hypotonia due to hypophosphatemia leading to:

1. Delayed motor milestones (Sitting, crawling, standing, walking…)
2. Downward displacement of liver & spleen (Visceroptosis)
3. Abdominal Distension due to:
   - Hypotonia
   - Visceroptosis (Not true enlargement)
   - Constipation

C) Neurological

1. Anorexia, Irritability, sweating
2. Hypocalcemic tetany:

> **Remember**
> Ca is usually **normal** in rickets due to 2ry **hyperparathyroidism**

a. Causes of hypocalcemia
   - Parathyroid gland exhaution
   - Bone depletion (prolonged untreated cases)
   - Vitamin D (IM massive dose) due to rapid mobilization of Ca from blood to bone

b. Manifestations

☒ Latent tetany (Serum Ca = 7-9 mg %)

Asymptomatic, only elicited by provocation

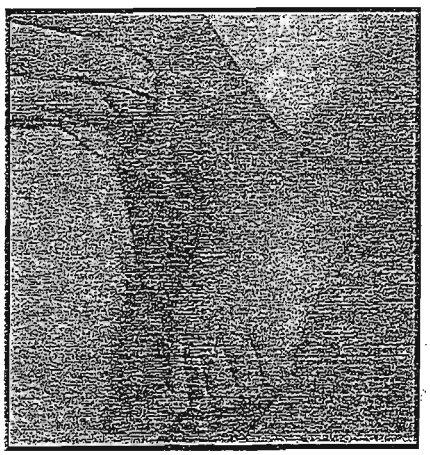
- ➢ Chvostek sign: Tapping of the Facial nerve ⟶ Twitches of facial muscles
- ➢ Trousseau sign: Constriction of the UL by sphygmomanometer (Carpal spasm)
- ➢ Peroneal sign: Tapping of the peroneal nerve ⟶ Pedal spasm

☒ Manifest tetany (Serum Ca < 7 mg %)

- ➢ **Carpopedal spasm**
- ➢ **Laryngospasm**
- ➢ **Convulsions**



Carpal spasm



Pedal spasm

Complications of Rickets

> Causes of chest infection:
> - Hpotonia (weak cough)
> - Chest deformities

1. Respiratory: Chest infections, atelectasis (collapse), why?
2. Neurological: Tetany, convulsions, laryngospasm
3. Short stature (disproportionate)
4. Bone fractures & deformities
5. Iron deficiency anemia (Breast milk is deficient in both vitamin D & iron)
6. Contracted pelvis (Obstructed labor in ♀)
7. Complications of treatment (Vitamin D): Hypervitaminosis D

Differential Diagnosis

1. Delayed closure of anterior fontanel
2. Delayed Dentition

Delayed closure of AF	Delayed Dentition
▪ Rickets	▪ Rickets
▪ Osteogenesis imperfecta	▪ Osteogenesis imperfecta
▪ Down syndrome	▪ Down syndrome
▪ Hypothyroidism	▪ Hypothyroidism
▪ Intracranial causes of macrocephaly	

3. Delayed walking
   a. Neurological causes [Central & peripheral]
      - Cerebral palsy
      - Mental retardation
      - Hydrocephalus
      - Neuromuscular disorders
        - **AHC:** Weding-Hoffmann disease & Poliomyelitis
        - **Nerve:** Neuropathy (e.g., Guillain-Barré syndrome...)
        - **Neuromuscular junction:** Myasthenia gravis
        - **Muscle:** Myopathy
   b. Bone: Rickets, trauma, fractures
   c. Training: diagnosed by exclusion

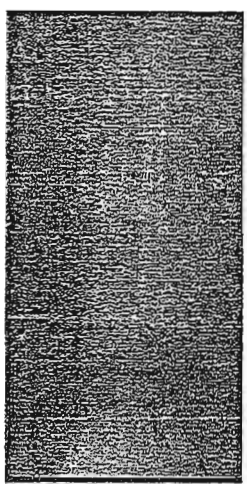
Investigations

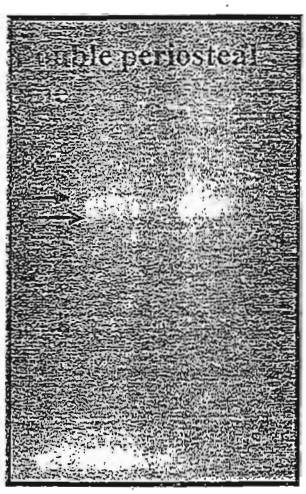
A) **Laboratory**

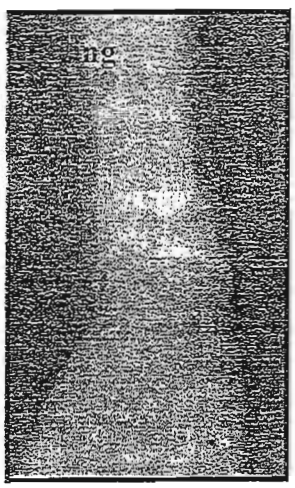
- Serum calcium: Normal or ↓↓, When? (N = 9-11 mg/dl)
- Serum phosphorus: ↓↓ (N = 4.5-6.5 mg/dl)
- Serum alkaline phosphatase: ↑↑ (Early manifestation)

B) **Imaging** *(Radiological improvement start to occur after <u>2 wks</u> of vitamin D therapy)*

	Active	Healing	Healed
Metaphysis	Broadening, Cupping & Fraying	Dense **<u>concave</u>** white line of calcification	Dense **<u>straight</u>** white line of calcification
Diaphysis	↓↓ Bone density Fractures (Green-stick) Double periosteal line	Still there is manifestations of active rickets (but less severe)	Improved bone density
Epiphysis	↑↑ Joint space Bone age (Carpal bones)		









Prevention

1. **Nutritional education:** Value of breastfeeding, proper weaning…
   - ➢ Diet rich in vitamin D: eggs, liver, oily fish, fortified milk
   - ➢ Avoid rachitogenic diet *(See before)*
2. **Vitamin D supplementation [40 IU = 1 µg]**
   - ➢ Full-term: 400-800 IU/day (as early as the 3rd month)
   - ➢ Preterm: 1000-1500 IU/day (as early as the 1st month)
3. **Sun exposure** (UVR)
4. **Regular assessment of nutritional state:** Early manifestations of rickets

Treatment

A) **Vitamin D therapy**

a. Oral therapy
- Dose
  - Vitamin D3: 3000-5000 IU/day
  - Active form of vitamin D: 0.5-2 µg/day (1-α preparation of Vit. D can be used)
- Duration: 2-4 weeks

b. Parentral therapy
- Dose
  - Vitamin D3: 600.000 IU (Shock therapy)
- Duration: **Single IM dose**
- Advantages
  - More rapid
  - No need for parents compliance
  - Diagnosis of non-vitamin D deficiency rickets
- Disadvantages (Side effects)
  - Tetany
  - Hypervitaminosis D

Monitoring of HR is essential
Stop if bradycardia occurs

B) **Treatment of complications**

a. **Tetany:** IV Ca gluconate 10% "1 ml/Kg" (Slowly while monitoring heart rate, why?)
b. **Deformities & Fractures:** Orthopedic care (After complete bone healing)
c. **Infections:** proper antibiotics
d. **Iron deficiency anemia:** Iron (6 mg/Kg/day)

Hypervitaminosis D

Etiology

- Prolonged oral vitamin D therapy
- Parenteral vitamin D therapy (Shock therapy)

Clinical Picture

- GIT: Anorexia, nausea, vomiting, constipation
- Renal: Polyuria, polydipsia, renal stones (Dysuria, colics, UTI…)

Prevention

Careful vitamin D therapy

Investigations

- Laboratory: ↑↑ serum Ca, ↑↑ Urinary Ca
- Imaging: X-rays, US (Nephrocalcinosis, stones)

Treatment

Stop vitamin D & Ca therapy, IV fluids, Steroids

Non-Vitamin D Deficiency Rickets

Classification

A) Renal rickets

a. Renal glomerular
- CRF: Due to defective vitamin D activation (1α-hydroxylation)
- CRF should be suspected in patients with non-nutritional rickets

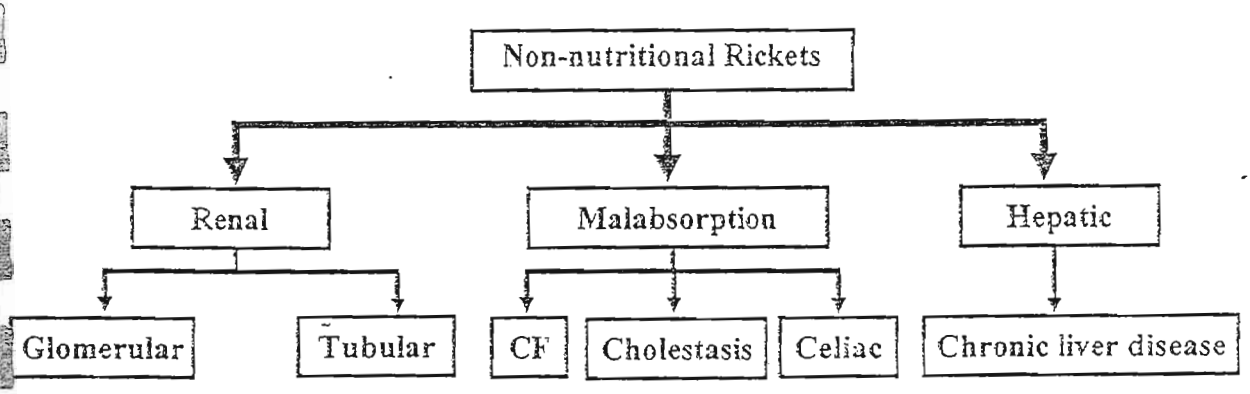
b. Renal tubular
- Vitamin D resistant Hypophosphatemic rickets (XL-D)
- Vitamin D resistant Hypocalcemic rickets (Vitamin D dependent rickets)
- Fanconi syndrome: PCT dysfunction [Glucosuria, phosphaturia, aminoaciduria]
- Cystinosis: Fanconi syndrome + Corneal cystine crystal *(Pathognomonic)*
- Lowe syndrome: Oculo-cerebro-renal syndrome [Glucoma & cataract-MR- Fanconi]
- Lightwood: Infantile renal tubular acisdosis
- Lignac

B) Malabsorption

a. Cystic fibrosis
b. Celiac disease
c. Chronic Cholestasis

C) Hepatic rickets
- Chronic liver disease
- Due to defective vitamin D activation (25-hydroxylation) & defective bile secretion

Remember



Vitamin A Deficiency

Clinical Picture

- Eye: Keratomalacia, xerophthalmia, blindness, bitot spots (= Conjunctival plaques)
- Skin: Dry, scaly skin
- Increased susceptibility to infections: GE & pneumonia

Prevention

- Diet: Eggs, liver, fruits, vegetables
- Supplementation:
  - At the age of 12 months (with MMR vaccine): 100.000 IU
  - At the age of 18 months (with OPV, DPT & MMR vaccines): 200.000 IU

Nutritional Requirements

Balanced Diet should contain:

1. Adequate water
2. Adequate calories
   - ➢ CHO = 50 %
   - ➢ Lipids = 35 %
   - ➢ Proteins = 15 %
3. Adequate macronutrients [CHO, Lipids, Proteins]
4. Adequate micronutrients [Vitamins, minerals, trace elements]
5. Adequate amount of fibers "Fruits, vegetables, cereals" (Bulking effect, prevention of constipation)

High biological value proteins	Low biological value proteins
Animal origin (milk, meat, eggs)	Vegetable origin (cereals, legumes)
Contain all essential amino acids	Not all essential amino acids

Energy, Water, Macronutrients

	Energy (Kcal/Kg/day)	Water (ml/Kg/day)	Proteins (gm/kg/day)	Lipids	CHO
Infancy	100	120	2-2.5	1 gm/Kg/day	10 gm/Kg/day
2-6 years	90	100	1.6-1.8		
6-12 years	70-80	80-90	1.2		
12-20 years	50-60	70-80	1		
Adults	40	40-50	0.8		
Function	Energy is needed for: - Basal metabolism (50%) - Physical activity (25%) - Growth (12%) - Fecal losses (8%) - Specific dynamic action of food (5%)	- Water constitutes: ▪ Infants: 75-80% of BW ▪ Adults: 60 % of BW **Remember** - Breast milk = 87 % H_2O - Infants are more liable to dehydration (see GE)	- Growth of tissues - Cellular elements - Enzymes & hormones - Blood proteins: ▪ Hemoglobin ▪ Coagulation factors ▪ Oncotic pressure ▪ Immunity (Ig) ▪ Buffers ▪ Viscosity	- Energy (1 gm = 9 Kcal) - Essential FA - Fat soluble vitamins - CNS development - Insulation (Temperature control) - Support of viscera - Makes food palatable	- **Main** source of energy
Related disorders	- Marasmus (↓↓ Calories) - Obesity (↑↑ Calories)	- Dehydration	- Kwashiorkor (Edema)		

Vitamins & Minerals

	Vitamin A	Vitamin D	Vitamin C	Iron	Calcium
Requirements	2000 IU/day	400-800 IU/day	50 mg/day	10-15 mg/day	500 mg/day
Function	- Epithelial health ▪ Skin ▪ Mucous membrane (GIT & respiratory) - Retinal pigments	- Normal bone mineralization - Ca, PO_4 metabolism	- BV integrity - Antioxidant - Iron absorption - Hemostasis	- Hb synthesis - Intracellular enzymes	- Normal bone mineralization - Nerve conduction - Hemostasis
Related disorders	▪ Keratomalacia ▪ Xerophthalmia ▪ Corneal ulcers ▪ Blindness	▪ Rickets ▪ Osteomalacia	Scurvy	Iron deficiency anemia	Rickets

	Vitamin B1	Vitamin B2	Vitamin B6	Vitamin B12	Folic acid
Requirements	0.5-1 mg/day	0.5-1 mg/day	0.5-1 mg/day	1-2 µg / day	200 µg /day
Function	- Cofactors in metabolic pathways Skin integrity	- Cofactors in metabolic pathways	- Coenzyme - Hb synthesis	- CNS metabolism - Hb synthesis	- DNA synthesis
Related disorders	Beri-beri	▪ Cheilosis ▪ Glossitis ▪ Fissuring of mouth	▪ Neuropathy ▪ Convulsions ▪ Anemia	▪ Neuropathy ▪ Megaloblastic Anemia	Megaloblastic Anemia

Mineral Metabolism

Classification

Minerals are classified into 2 groups:

1. **Macrominerals** (= Principal elements): Calcium, Magnesium, Phosphorus, Sodium, Potassium, Chloride & Sulfur
2. **Microminerals** (= Trace elements): Iron, Copper, Manganese, Iodide, Fluoride, Cobalt, Molybdenum, Selenium & Chromium

	1. Macrominerals	2. Macrominerals (Trace elements)
Body content	Grams / Kg body weight	Milligrams / Kg body weight
Daily requirement	> 100 mg	< 100 mg

Vitamins

Definition

- Organic nutrients required in minute amounts for normal growth & health
- They can not be synthesized in the body
- Not involved in tissue structure & not oxidized for energy production
- They are classified into 2 groups:
  1. **Fat-soluble vitamins:** A, D, E, K
  2. **Water-soluble vitamins:** B complex & vitamin C

Micronutrients

Vitamins | **Trace elements**

Trace Elements

	Source	Physiology	Effects of deficiency	Effects of excess
Iron	- Red meat - Organ meat - Egg yolk - Whole cereals - Vegetables	- Hemoglobin - Myoglobin - Cytochromes - Enzymes (MAO)	See iron-deficiency anemia: Hematological, neurological, epithelial…	A) **Acute poisoning:** - Nausea, vomiting - Diarrhea - Abdominal pain Hypotension - Hypoglycemia - ↑↑ Liver enzymes B) **Chronic excess** Chronic hemolytic anemia
Copper	- Oysters - Nuts - Liver	- Essential component of: ➢ Superoxide dismutase ➢ Cytochrome oxidase ➢ Tyrosinase (*Melanin*) - Iron absorption & mobilization - Normal function of the CNS	- Microcytic anemia - Neurological symptoms - Depigmentation - Neutropenia - Osteporosis	A) **Acute poisoning:** - Nausea, vomiting - Abdominal pain - ↑↑ Liver enzymes B) **Chronic excess** Wilson disease
Fluoride	- Toothpaste - Fluorinated water	- Essential component of: ➢ Bone ➢ Teeth	- Dental caries	- Fluorosis: Brittle teeth Teeth mottling
Iodine	- Iodized table salt - Near sea - Saltwater fish	- Formation of thyroid hormones	- Hypothyroidism	- Hypothyroidism, goiter - Maternal Iodine excess: congenital hypothyroidism
Manganese	- Nuts - Tea	- Essential component of: ➢ Superoxide dismutase ➢ Arginase, choline estrase	- Hypercholesterolemia	- Neurological symptoms - Cholestasis

Selenium	- Seafood - Meat - Garlic	- Enzyme cofactor of: ➢ Glutathione peroxidase	- Cardiomyopathy - Myopathy	- Neurological symptoms - Nausea, diarrhea - Garlic odor
Zinc	- Shellfish - Meat - Cheese	- Essential component of: ➢ Superoxide dismutase ➢ Carbonic anhydrase - Insulin storage	- Circumoral & perianal rash - Poor wound healing - Alopecia, chronic diarrhea	- Nausea, vomiting - Diarrhea - Abdominal pain
Chromium	- Brewer's Yeast - Meat	- Potentiates insulin action	- Impaired glucose tolerance - Peripheral neuropathy - Encephalopathy	- Unknown?
Molybdenum	- Brewer's Yeast - Meat	- Essential component of: ➢ Xanthine oxidase	- Impaired glucose tolerance - Peripheral neuropathy - Encephalopathy	- Unknown?