Pathophysiology of development, growth, and aging

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Outline

- Prenatal development and growth defects
- Perinatal development defect
- Postnatal growth and development defect
- Aging

Development

- The progressive changes in size, shape, and function during the life of an organism by which its **genetic potentials** (genotype) are **translated** into functioning mature systems (phenotype).

- Prenatal development
- Perinatal development
- Postnatal development

What can influence development?

Main causes:

- Genetic factors (mutations)
  - inherited, acquired
- Environmental (physical, chemical, biological factors, malnutrition)

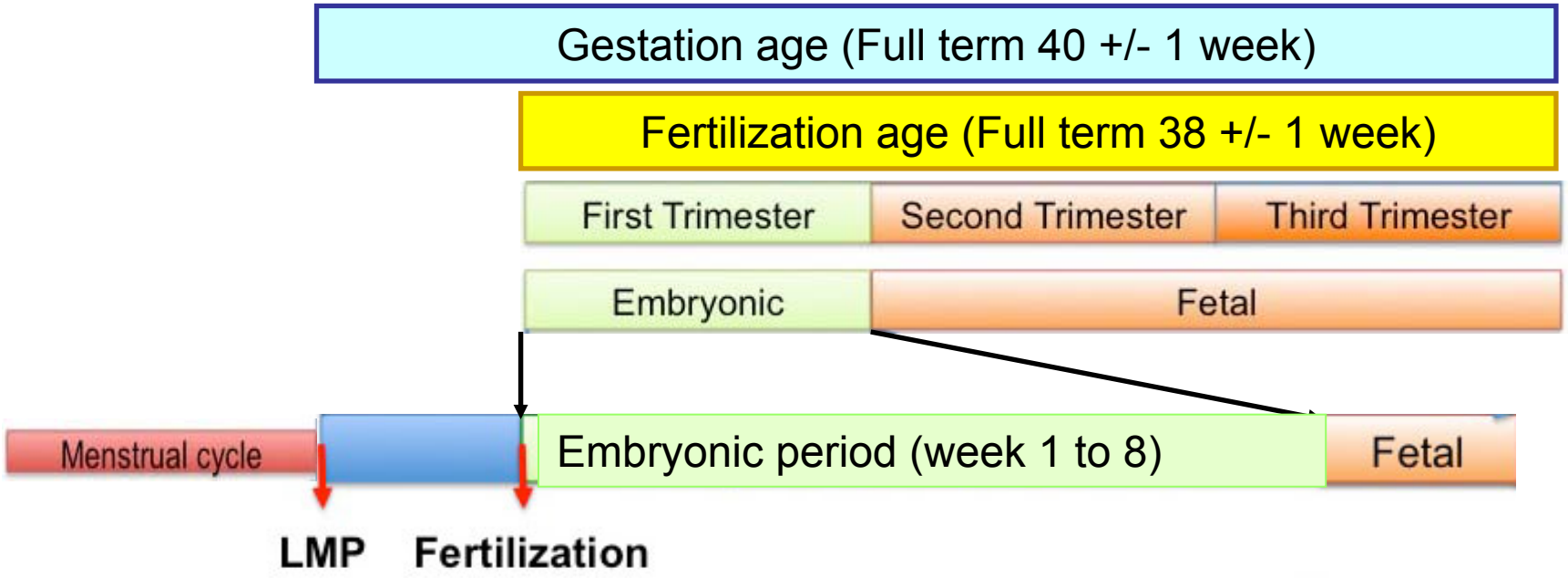
Mechanism:

- Cell damage
- Neuro-endocrine signaling and regulation disturbances
- Metabolism changes
- Unknown

Prenatal development and growth defects

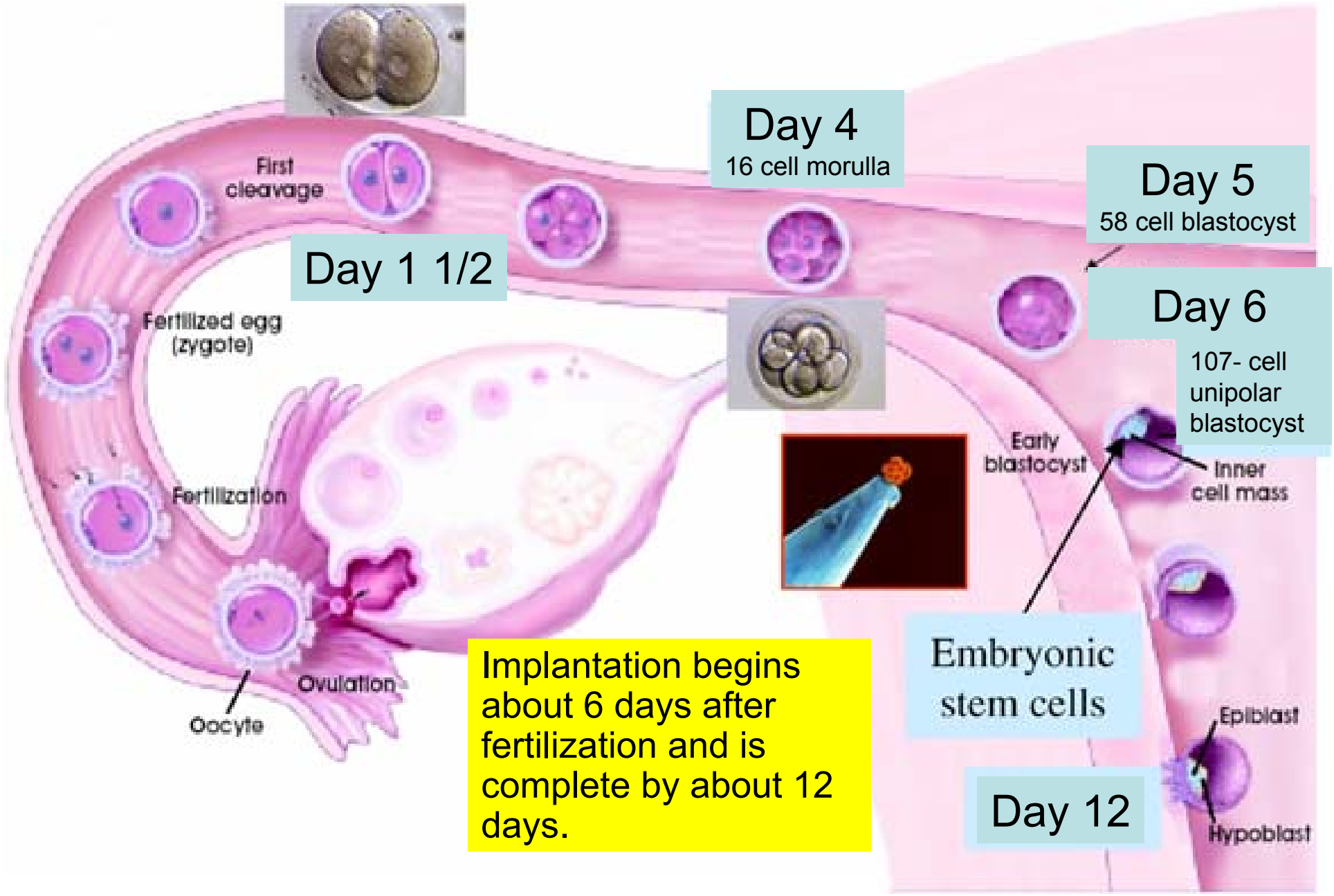
- Embryonal development defects
  - Chromosomal aberations
  - Mutations
  - Environmental factors (teratogens)
- Fetal growth and development defects
  - Development defects
  - Abnormal fetal growth
    - Fetal growth restriction
    - Accelerated fetal growth

Human development timeline



Gametopathy → Blastopathy → Embryopathy

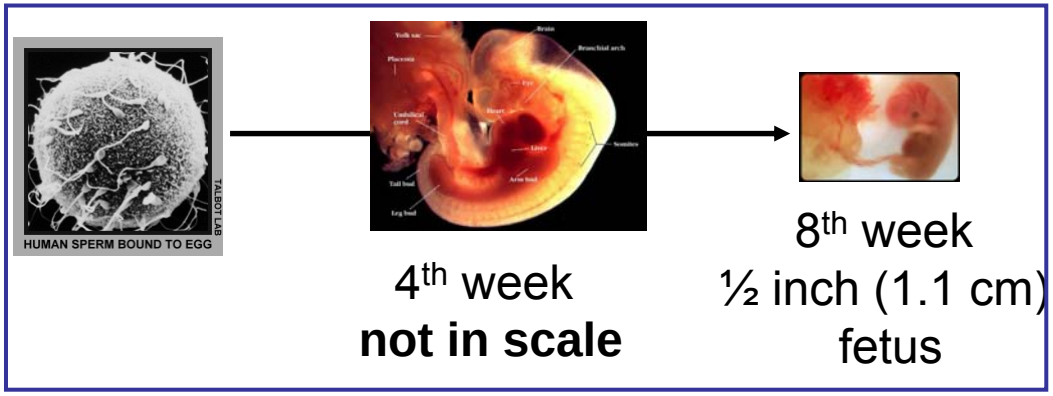
The first trimester is the most critical period for proper development



Approximately 8 days after fertilization, cells from the growing embryo begin producing human chorionic gonadotropin (hCG)

Embryonic Period

The first 8 weeks of human development

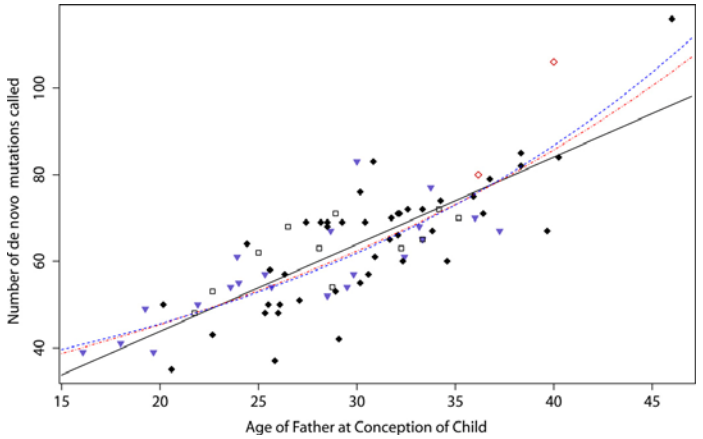


- Fertilization
- Gastrulation
- Implantation
  - critical process, about 50% of ebmryos does not implant properly and dies (many that die have chromosomal abnormalities)
- Placentation
  - development and growth of the placenta
- Organogenesis
  - Establish the basic structure of organs and tissues

Genetic factors in embryonic development

- Estimated 10% of sperm and 50% of eggs contain abnormal chromosomes (both numerical and structural).
- Every time human DNA is passed from one generation to the next it accumulates 100–200 new mutations, according to a DNA-sequencing analysis of the Y chromosome.

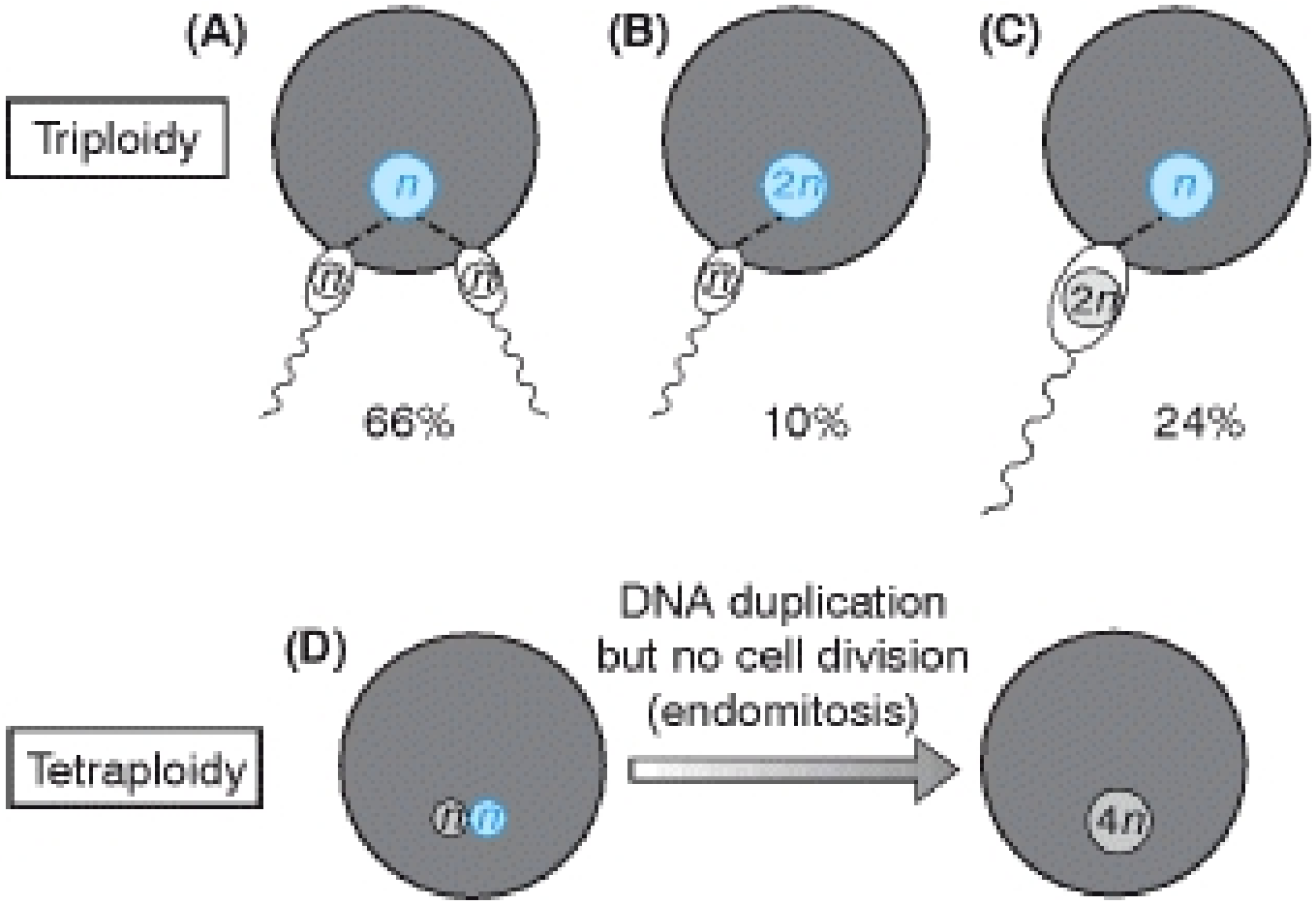
Father age and mutations



Numerical chromosomal abnormality

- 50% of spontaneous abortions have been estimated to be chromosomally abnormal
  - 95% of those are numerical abnormalities

Polyploidy

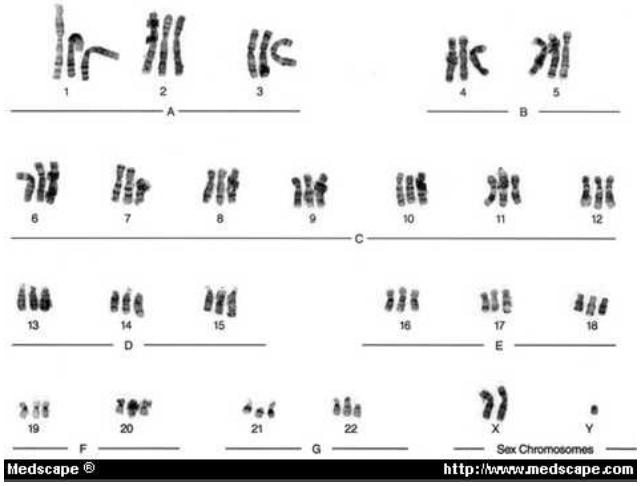


Between 1 and 3% of recognized human pregnancies are triploid

Triploidy

- 69,XXX, XXY or XYY
  - 1–3% of all conceptions
  - almost never liveborn
  - if born do not survive
  - Risk for chromosomal anomaly in subsequent pregnancy is not increased significantly

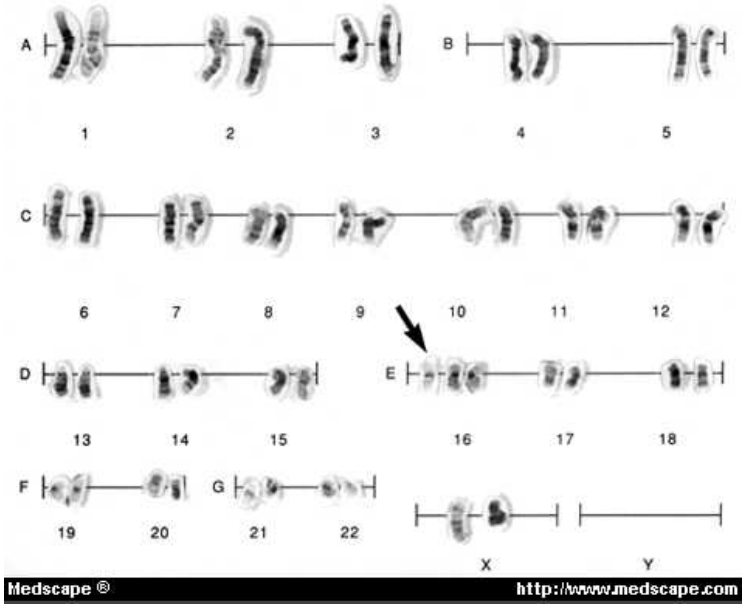
69, XXY



Aneuploidy

- one or more individual chromosomes extra or missing from a euploid set

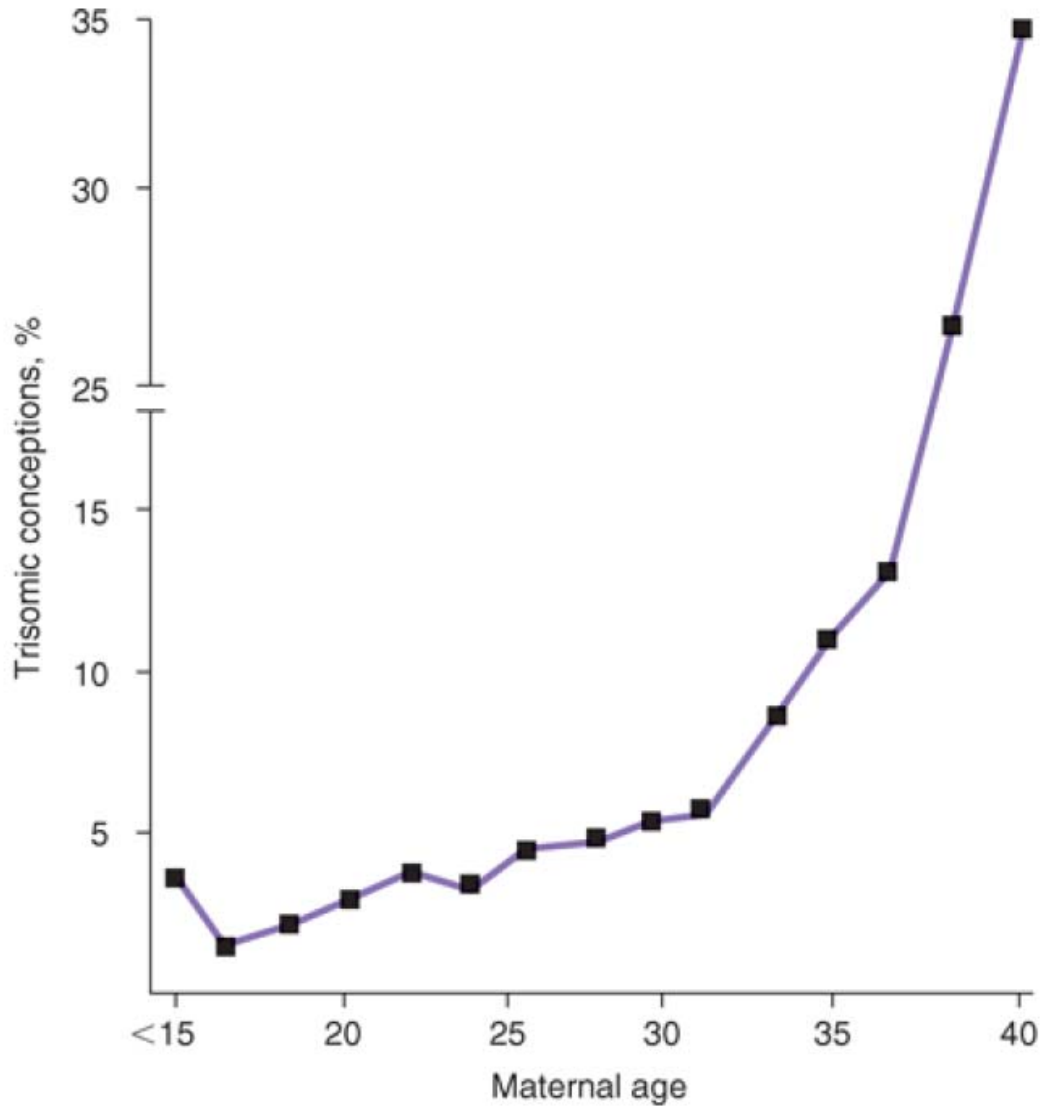
47,XX+16 (trisomy 16)
most common trisomy associated with spontaneous abortion



Consequences of autosomes aneuploidy

- nullisomy (missing a pair of homologs)
  - Preimplantation lethal
- monosomy (one chromosome missing)
  - Embryonic lethal
- trisomy (one extra chromosome)
  - Usually embryonic or fetal lethal
  - Trisomy 13 (Patau syndrome) may survive to term
  - Trisomy 18 (Edwards syndrome) may survive to term
  - Trisomy 21 (Down syndrome) may survive to age 40 or longer

MATERNAL AGE AND TRISOMY



Consequences of sex chromosomes aneuploidy

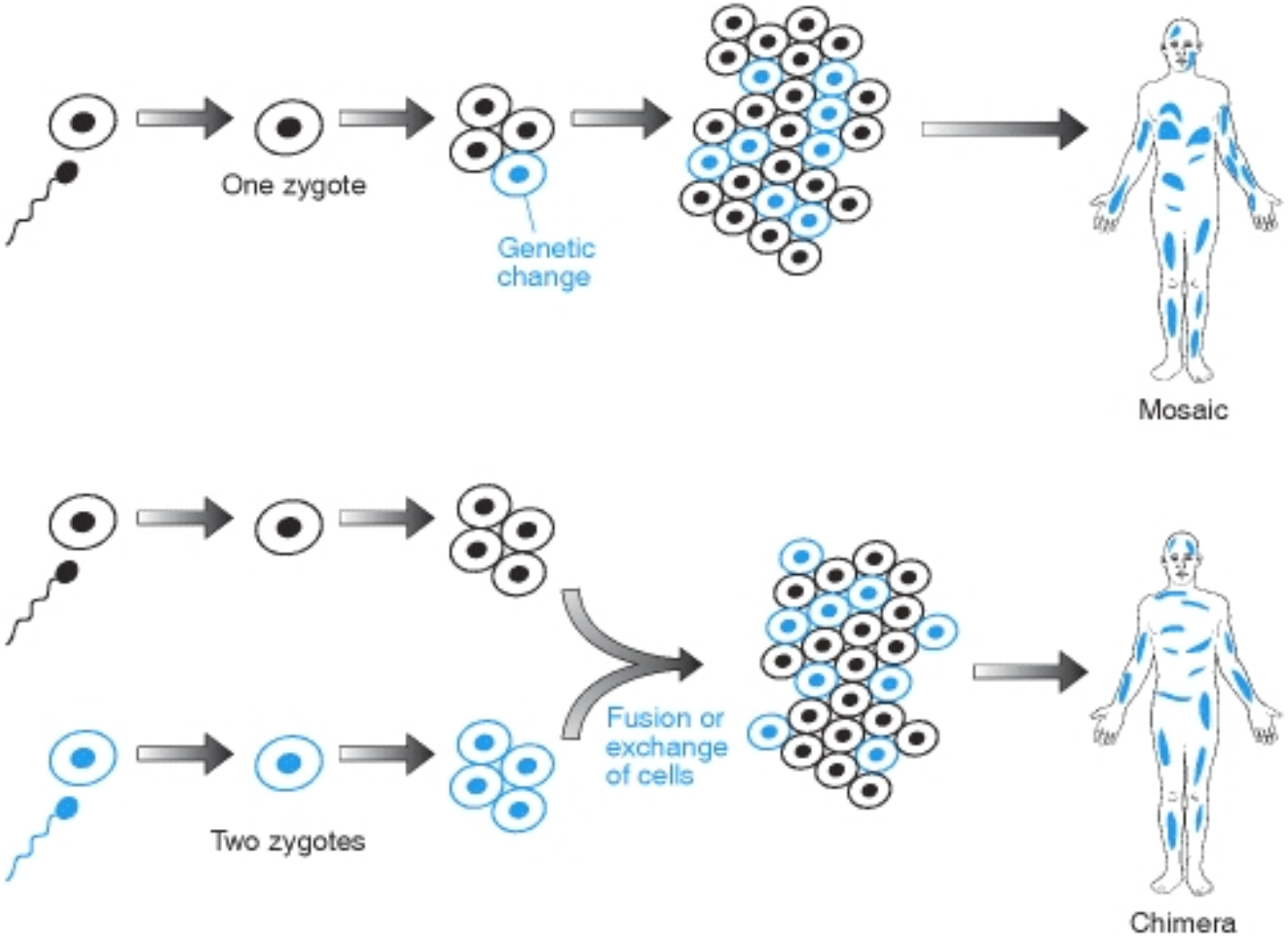
- 47, XXY (Klinefelter sy)
  - Male phenotype
  - hypogonadism and sterility
  - eunuchoid appearance
  - normal lifespan
  - possible language learning or reading impairmen

- 45,X (Turner syndrome)
  - 99% abort spontaneously
  - survivors are of normal intelligence
  - Female phenotype
  - Infertile
  - physical signs
    - amenorrhea, absent secondary sex characteristics, short statue (~ 145 cm), rudimentary ovaries gonadal streak

Mixoploidy

- mosaicism
  - an individual possesses two or more genetically different cell lines all derived from a single zygote
- chimerism
  - an individual has two or more genetically different cell lines originating from different zygotes

Mosaics and chimeras



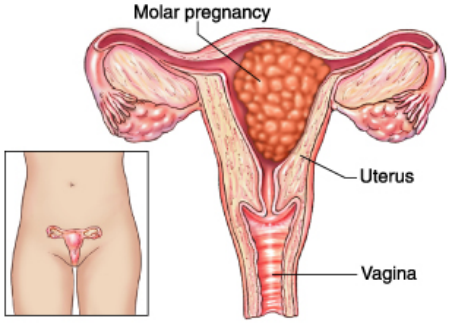
Causes of mosaicsm

- The zygote is chromosomally normal
  - Post-zygotic mitotic nondisjunction in some cells results in 2 types of cells with trisomy and monosomy
  - cells with monosomy are usually nonviable
  - only 2 cell lines will be retained in the tissue – with normal karyotype and with trisomy.
- The zygote is trisomic
  - chromosomal mosaicism may appear as a result of postzygotic nondisjunction or anaphase lagging of the additional chromosome in some cells (trisomic zygote rescue).
  - formation of 2 cell lines – with normal karyotype and trisomy

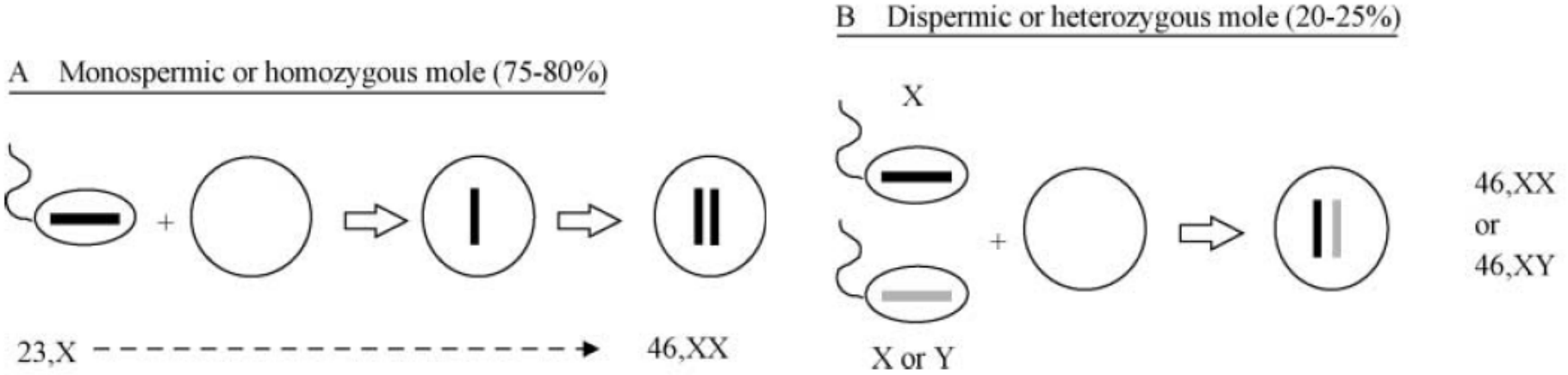
Wrong parental origin of genome
Uniparental diploidy

- Both genomes originate from the same parent

Uniparental diploidy
Hydatidiform moles

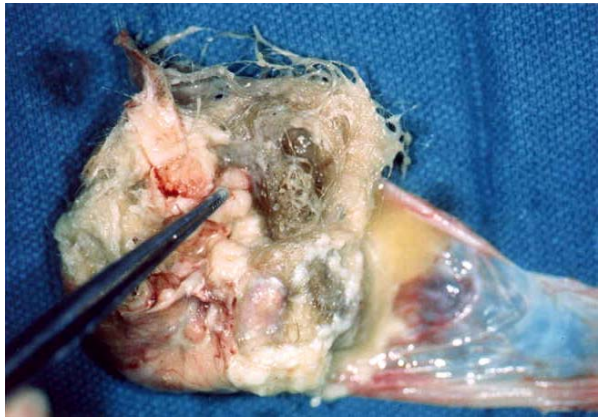


- 46,XX karyotype of exclusively **paternal origin**
- widespread hyperplasia of the trophoblast but no fetal parts
- significant risk of transformation into choriocarcinoma



Uniparental diploidy
Ovarian teratomas

- an embryo without sperm contribution (parthenogenesis)
  - maternal uniparental diploidy
- benign tumors of the ovary consist of disorganized embryonic tissues
- activation of an unovulated oocyte

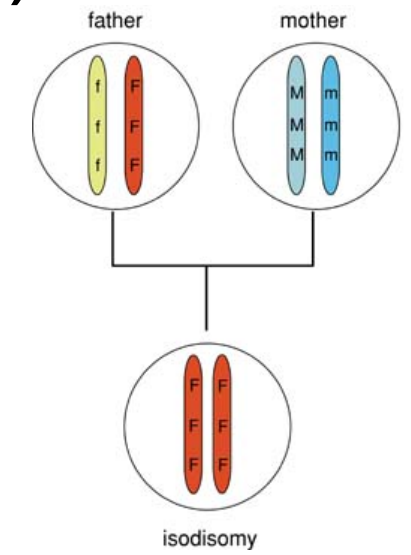


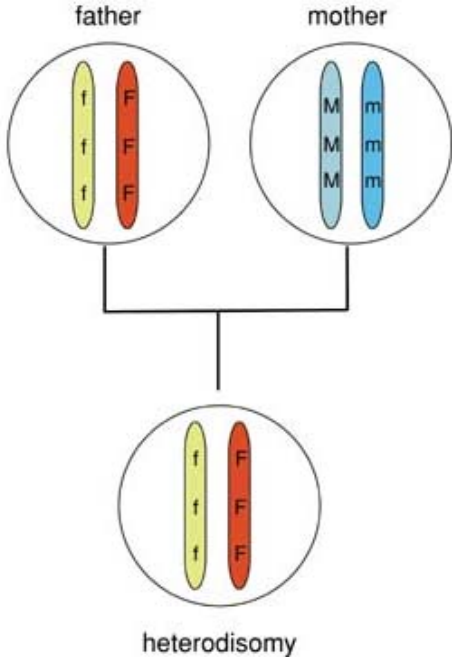
Wrong parental origin of chromosome Uniparental disomy (UPD)

- Affecting a single pair of homologs
- Undiagnosed if the result is not abnormal
- In some chromosomes characteristic syndromes

Uniparental disomy (UPD)

- Isodisomy
  - Both homologs are identical
  - Selective duplication of the monosomic chromosome
- Heterodisomy
  - Both homologs from one parent
  - Postzygotic trisomy rescue (repair mechanism):
    - Trisomic conceptus loses one chromosome by mitotic nondisjunction or anaphase lag of a totipotent cell
    - The euploid progeny of this cell form the embryo, while all the aneuploid cells die
    - One in three chance of uniparental disomy





Dysfunction of one or more imprinted genes

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Genetic imprinting suggested by maternal heterodisomy in non-deletion Prader-Willi syndrome

Robert D. Nicholls*†‡, Joan H. M. Knoll†, Merlin G. Butler§, Susan Karam‖ & Marc Lalande*†¶

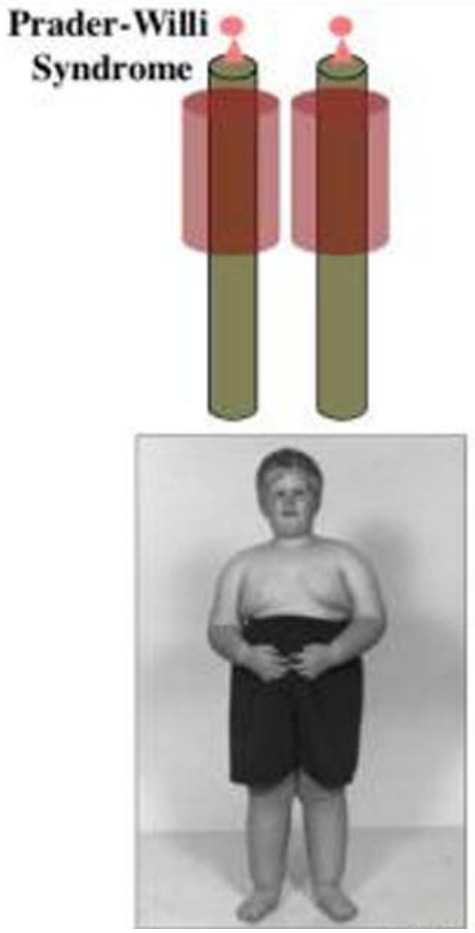
Origins of Prader-Willi and Angelman syndromes

Event	Proportion of PWS	Proportion of AS
Deletions	~75% 15q11q13 pat	~75% 15q11q13 mat
Uniparental disomy	~20%	~3%
Point mutations	not seen	~15% (in UBE3A gene)
Imprinting errors	~2%	~5%

Prader-Willi syndrome

- Mental retardation
- Hypotonia
- Gross obesity
- Male hypogenitalism

- Is caused by loss of function of genes that are expressed only from the paternal chromosome



Patient images: Medical Genetics, 2nd ed., Jorde LB, et al, ©2000

Angelman syndrome

- Mental retardation
- Lack of speech
- Growth retardation
- Hyperactivity
- Inappropriate laughter

- Is due to loss of function of a closely linked gene that is expressed only from the maternal chromosome

Patient images: Medical Genetics, 2nd ed., Jorde LB, et al, ©2000

Environmental factors - Teratogens

Agents and conditions which can impair prenatal development

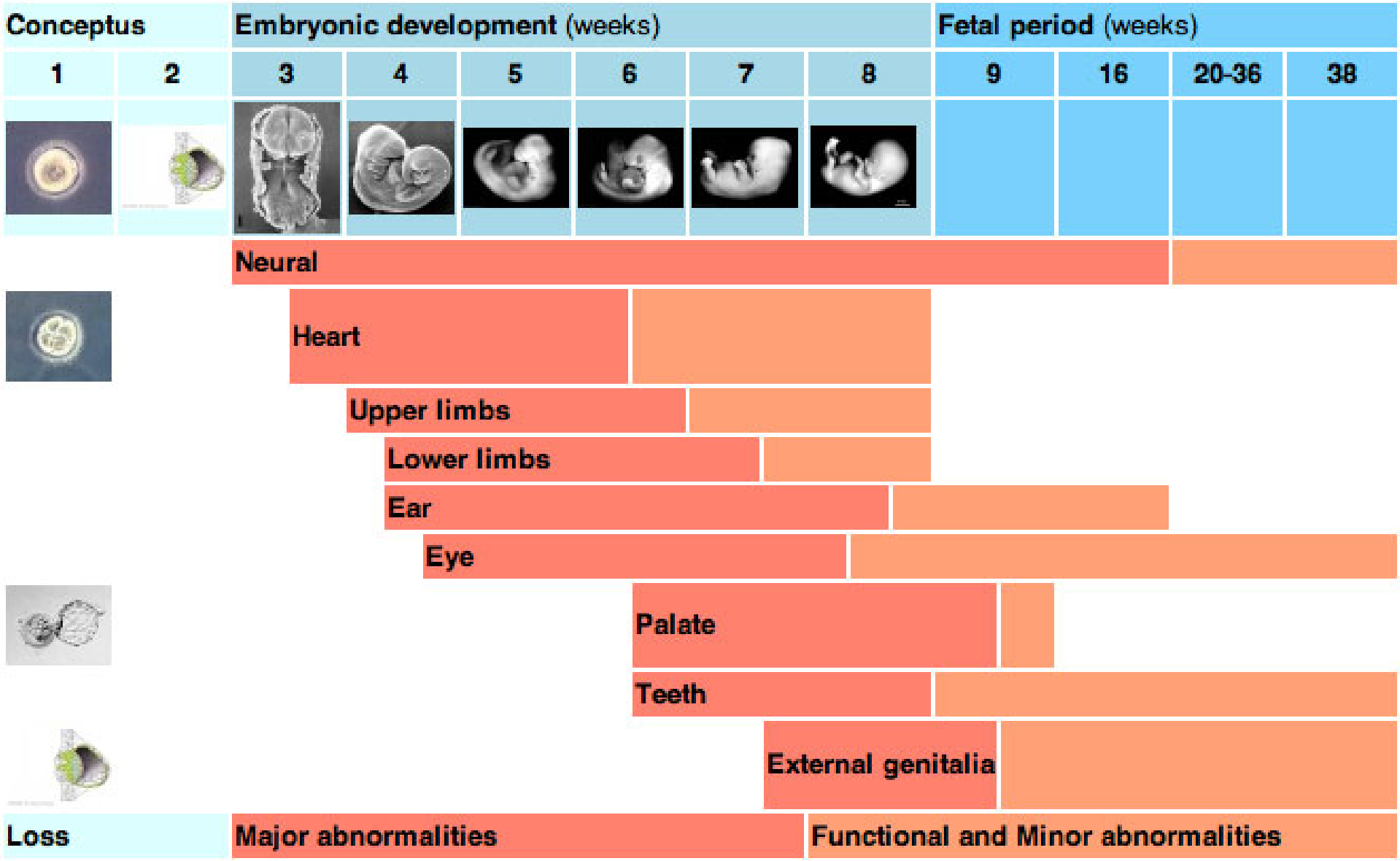
- Physical
- Chemical
- Biological
- Stress
- Malnutrition

- Timing – critical period
- Exposure – treshold efect , interaction
- Genetic variability

Mechanism of teratogen action

- Direct effect on genetic information
  - (E.g. ionizing irradiation, nucleotide analogs, viral infections….)
- Direct effect on signaling or cell survival
  - E.g. mimicking of estrogen effect, anti-angiogenic effect, malnutrition, inflammation, cell damage …)
- Indirect effect
  - Restriction of nutrient supply
  - e.g. blood supply (e.g. vasoconstriction – cocaine, nicotine), malnutrition

Critical periods for teratogen exposure



Thalidomide

- Europe 1956-1962 (was not approved in US)
- Approved and taken to reduce pregnancy associated morning sickness
- Interferes with blood vessel growth
- Underdeveloped limbs. WHY?
- Morning sickness coincides with limb growth

Physical and Chemical Teratogens

- Ionizing radiation
- Environmental toxins (solvents, dioxin, some phthalates)
- Pharmaceuticals and drugs (anti-cancer drugs, alcohol, nicotin)

Maternal-fetal transmission of infection in pregnancy

- Transplacentally
- Perinatally (from vaginal secretions or blood)

Infections associated with congenital defects

- TORCH
  - Toxoplasma
  - Others (parvovirus B19 (B19V), VZV, West Nile virus, measles virus, enteroviruses, adenovirus, and human immunodeficiency virus (HIV).
  - Rubella
  - Cytomegalovirus (CMV)
  - Herpes(HSV)

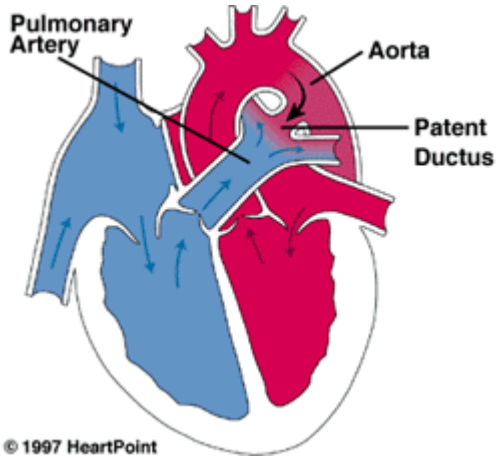
Congenital toxoplasmosis

- Transplacental or perinatal infection
- Infections that occur within 6 months prior to conception or during pregnancy may result in transplacental transmission
  - The risk of infection to the fetus in the first trimester is ~ 14-17% (usually severe)
  - The risk of infection to the fetus in the third trimester is ~ 59-65% (usualy mild)

Congenital toxoplasmosis

- Typical manifestation
  - chorioretinitis, hydrocephalus, and intracranial calcifications
  - subclinical (67-80%)
- Consequences
  - abortion or neonatal death (~10% of infections)
  - mental retardation, seizures, visual defects, spasticity, hearing loss
  - ~ 85% of live infants with congenital infection appear normal (may develop clinical symptoms and deficiencies later in life)

Rubella



- Transplacental infection
- The classic of congenital rubella synd
  - Sensorineural hearing loss (58%)
  - Ocular abnormalities (cataract, infantile glaucoma, and pigmentary retinopathy; 43%)
  - Congenital heart disease (patent ductus arteriosus, and pulmonary artery stenosis; 30-50%)
- Other findings:
  - Intrauterine growth retardation, prematurity, stillbirth, and abortion

Most of the complications develop in infants born to mothers who acquire rubella infection during the first 16 weeks of pregnancy

Mechanism of rubella teratogenic effect

- ?:
  - secondary to vasculitis resulting in tissue necrosis
  - direct viral damage of infected cells
    - cells infected with rubella in the early fetal period have reduced mitotic activity. This may be the result of chromosomal breakage or due to production of a protein that inhibits mitosis

Cytomegalovirus

- Transplacental infection
  - 85%-90% are asymptomatic at birth
  - ~10% intrauterine growth restriction

Congenital CMV

- can occur at any stage of pregnancy
  - sensorineural hearing loss
  - intracranial calcifications
  - microcephaly
  - hydrocephalus
  - hepatosplenomegaly
  - delayed psychomotor development
  - optic atrophy

Mechanism of rubella teratogenic effect

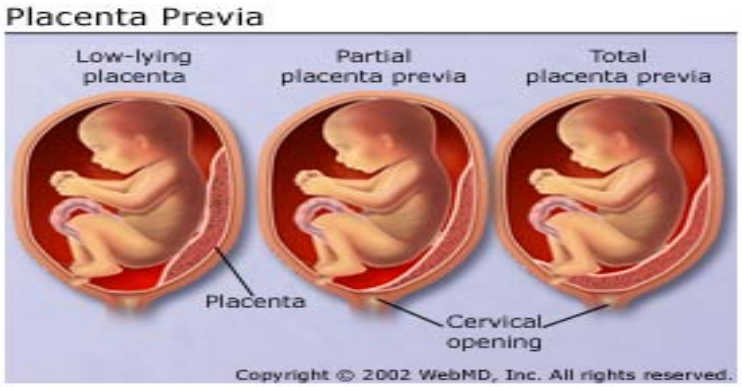
- ?:
  - secondary to vasculitis resulting in tissue necrosis without inflammation
  - direct viral damage of infected cells - cells infected with rubella in the early fetal period have reduced mitotic activity. This may be the result of chromosomal breakage or due to production of a protein that inhibits mitosis.

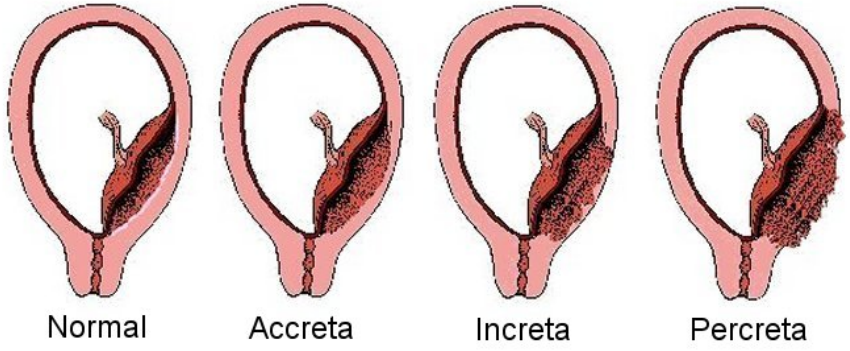
Cytomegalovirus (CMV)

- Transplacental infection
  - 85%-90% are asymptomatic at birth
  - ~10% intrauterine growth restriction
  - can occur at any stage of pregnancy
  - 10%-15% of infected eventually present with developmental, visual, hearing, or dental abnormalities in the first years of life
- Severe sequelae are more common with infection in the first trimester
- The overall risk of infection is greatest in the third trimester

Abnormal Implantation

- Defective receptivity, implantation, and/or decidualization
  - External surface of uterus, ovary, bowel, gastrointestinal tract, mesentery, peritoneal wall
  - Tubal pregnancy (most common ectopic)
  - Placenta previa - inferior implantation - placenta overlies internal os of uterus
  - Placenta Accreta - placenta to grow beyond the lining of the uterus (endometrium) into or through the myometrium
  - Placental insufficiency (IUGR)

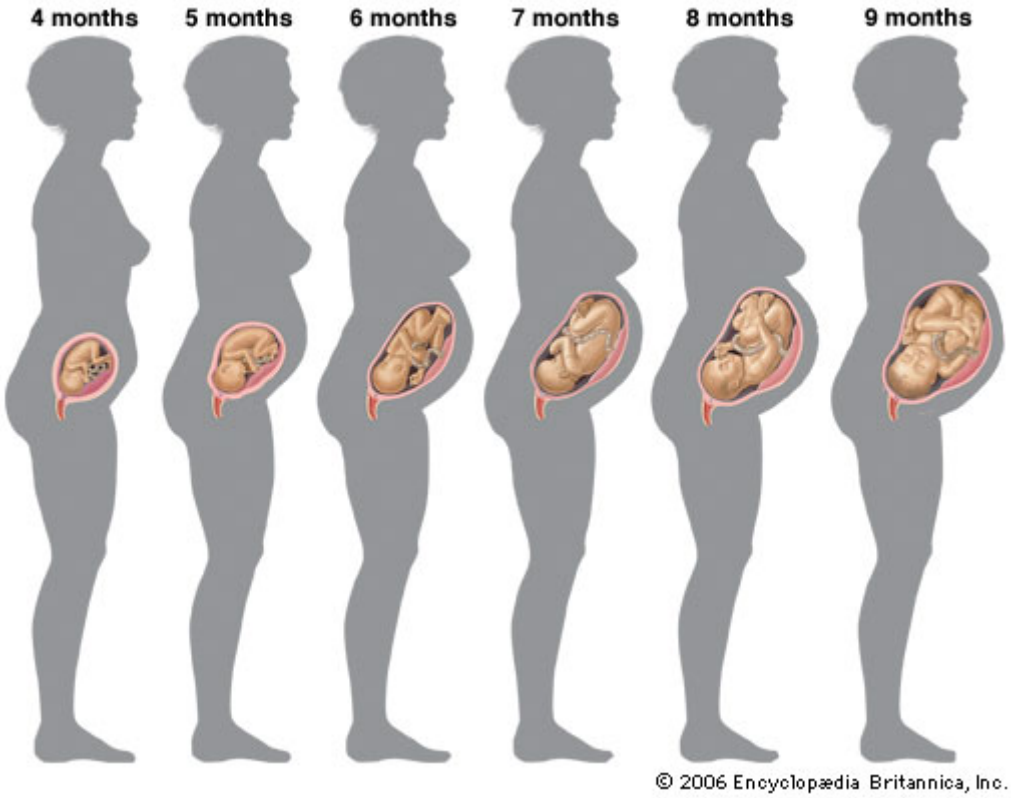




Tubal pregnancy

- 94% of ectopic pregnancies
  - if uterine epithelium is damaged (scarring, pelvic inflammatory disease)
  - if zona pellucida is lost too early, allows premature tubal implantation
  - embryo may develop through early stages, can erode through the uterine horn and reattach within the peritoneal cavity

Fetal growth and development



Second and Third Trimester

Fetal Period

- Continuing growth and differentiation of organs formed in embryonic period
  - some organs have a later development and continue to develop after birth - neural, genital, respiratory, bones
- growth in size, length (Second Trimester)
- growth in weight (Third Trimester)

Fetal growth is dependent on:

- Genetic disposition
- Nutrient and oxygen availability
- Endocrine factors (insulin, IGF-1, thyroid hormones…)
- Other environmental factors which may influence functioning of the developing systems

Fetal growth restriction (FGR)

Definition

- growth below the 10th percentile with abnormal maternal and/or fetal Doppler studies

Early-onset disease

  - the fetus may not reach a viable weight and maturity
  - Severe placental insufficiency

Late-onset disease

  - may lead to intra-uterine death (early delivery may be indicated)

Causes of FGR

- Maternal
  - Malnutrition, Infection (e.g. CMV, Toxoplasmosis...), Chronic diseases (cardiovascular, renal, autoimmune…)
- Placental
  - Abnormal placentation, inflammation
- Environmental
  - Drug use, toxins, high altitude, irradiation
- Fetal
  - chromosomal aberations and mutation, Intrauterine infection, Multiple pregnancy

Intrauterine programming

- The intrauterine conditions in which the mammalian fetus develops have an important role in regulating the function of its physiological systems later in life.

Clinical manifestations of FGR in newborn

- Insuficient nutrition
- Hypoxia
- Hypercapnia
- Hyperlacticemia (metabolic acidosis)

Fetal growth acceleration

- Macrosomia (Large for gestational age fetuses)
  - Defined in several different ways
    - birth weight of 4000-4500 g (8 lb 13 oz to 9 lb 15 oz)
    - greater than 90% for gestational age after correcting for neonatal sex and ethnicity
  - Based on these definitions, macrosomia affects 1-10% of all pregnancies

Pathophysiology of macrosomia

- Intermittent periods of hyperglycemia
  - poorly controlled diabetes
  - maternal obesity
  - excessive maternal weight gain
- Genetic, racial, and ethnic factors influence birth weight and the risk of macrosomia

- Hyperglycemia in the fetus results in:
  - the stimulation of insulin, insulinlike growth factors, growth hormone, and other growth factors

Diabetic macrosomia

- Accelerated growth starts in the second trimester (from as early as 18 weeks)
- Glucose control did not appear to have a direct effect on growth of babies

Consequences of macrosomia

- Increased risk of intrauterine and perinatal death
- Birth trauma for the neonate
- Birth canal lacerations
  - eg, perineal, vaginal, and cervical, or cesarean delivery for the mother.
- In the neonate of a diabetic mother
  - poor glucose control

Perinatal Period

- The period of time around birth, from week 28 of pregnancy until 7 days after birth
- Critical period

Perinatal period

- Newborn needs to activate many systems and establish independent regulation (homeostasis)
  - Lung function - Fluid drainage, Gas exchange, muscular activity
  - Circulatory changes - Closure of 3 vascular shunts
  - Thermoregulation - metabolic rate, fat metabolism
  - Nutrition - gastrointestinal tract function, peristalsis
  - Waste - kidney function
  - Endocrine function - loss of placenta, maternal hormones

Funcional respiration

- 24-week fetuses lung development
  - **Terminal sacs** now appear which will eventually become **alveoli**
  - Lung cells begin to produce surfactant
  - Survival possible w/o surfactant therapy

Apgar newborn scoring system (since 1953)

APGAR SCORING SYSTEM

	0 Points	1 Point	2 Points	Points totaled
Activity (muscle tone)	Absent	Arms and legs flexed	Active movement	
Pulse	Absent	Below 100 bpm	Over 100 bpm	
Grimace (reflex irritability)	Flaccid	Some flexion of Extremities	Active motion (sneeze, cough, pull away)	
Appearance (skin color)	Blue, pale	Body pink, Extremities blue	Completely pink	
Respiration	Absent	Slow, irregular	Vigorous cry	

Severely depressed	0-3
Moderately depressed	4-6
Excellent condition	7-10

Virginie Apgarová (1909-1974)

Thyroid hormone

- Have most profound effects on the terminal stages of brain differentiation
  - synaptogenesis, growth of dendrites and axons, myelination and neuronal migration

- 3rd trimester, perinatal and early postnatal periods

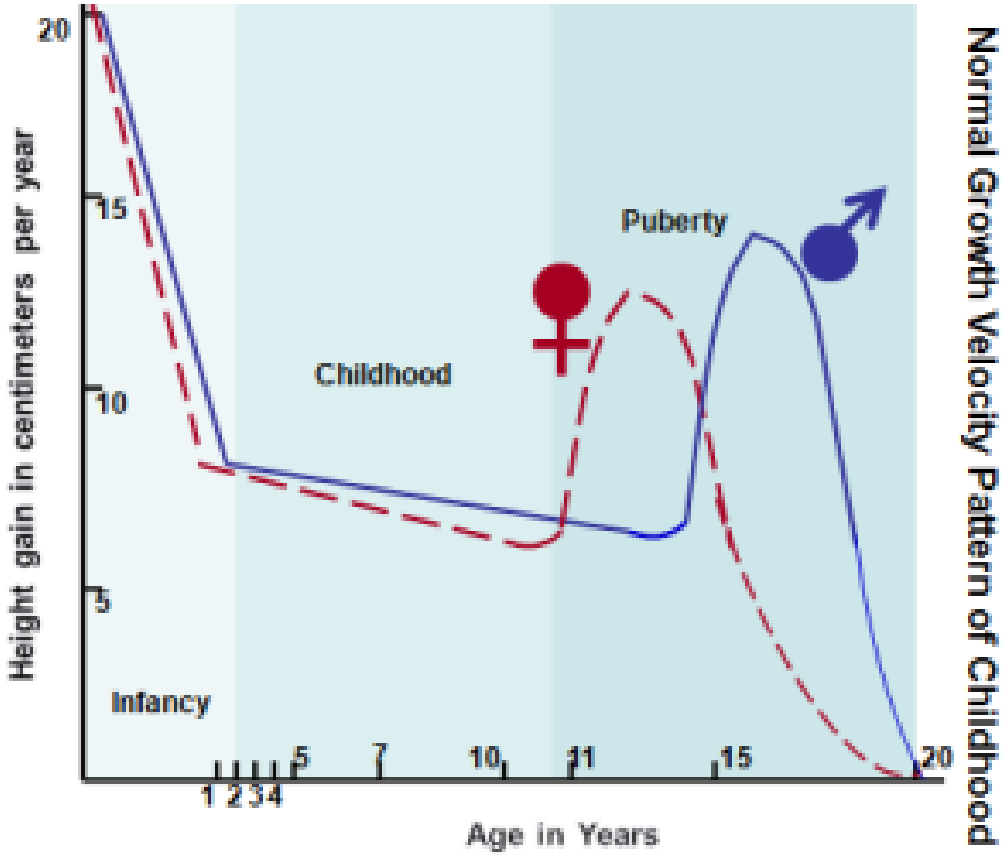
Fetal and perinatal thyroid deficiency

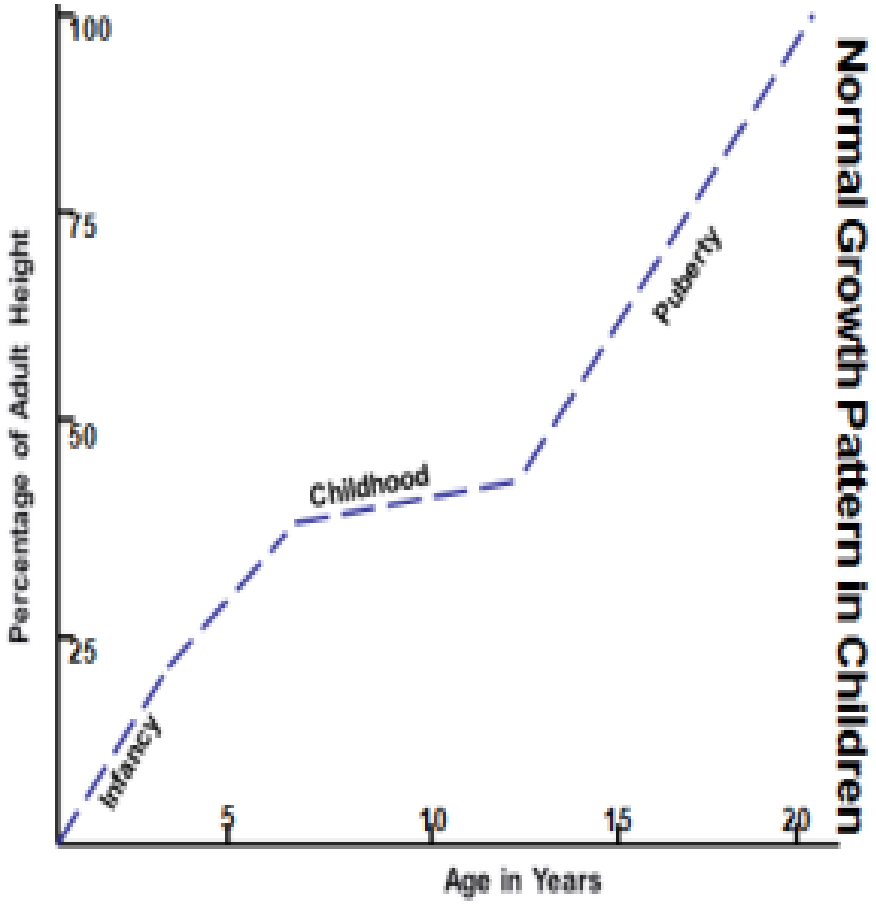
- Maternal hypothyroidism
  - typically is associated with infertility
  - Subclincial hypothyroidism may adversely affect the fetus development
- Fetal hypothyroidism
  - Children are normal at birth (maternal thyroid hormones)
  - If untreated the child will become permanently mentally and growth retarded - cretinism
- Iodine deficiency
  - Combined maternal and fetal hypothyroidism
  - Mental retardation - cretinism with deaf-mutism and spasticity

Postnatal growth and development

Growth

- The increases in cell size and number that take place during the life history of an organism





Growth

- Genetic and epigenetic factors
- Endocrine control of growth
- Nutrition
- Environmental factors (temperature, hypoxia, sleep, polutants)
- Other factors (eg. socioeconomic, stress)

Short statue

- Height below the 5-th percentile (alternatively: height less than 2 standard deviations below the mean, which is near the 3-rd percentile)
  - 3-5% of all children are considered short
- Many of these children actually have normal growth velocity:
  - familial short stature
  - Constitutional delay in growth and maturation

The causes of short stature

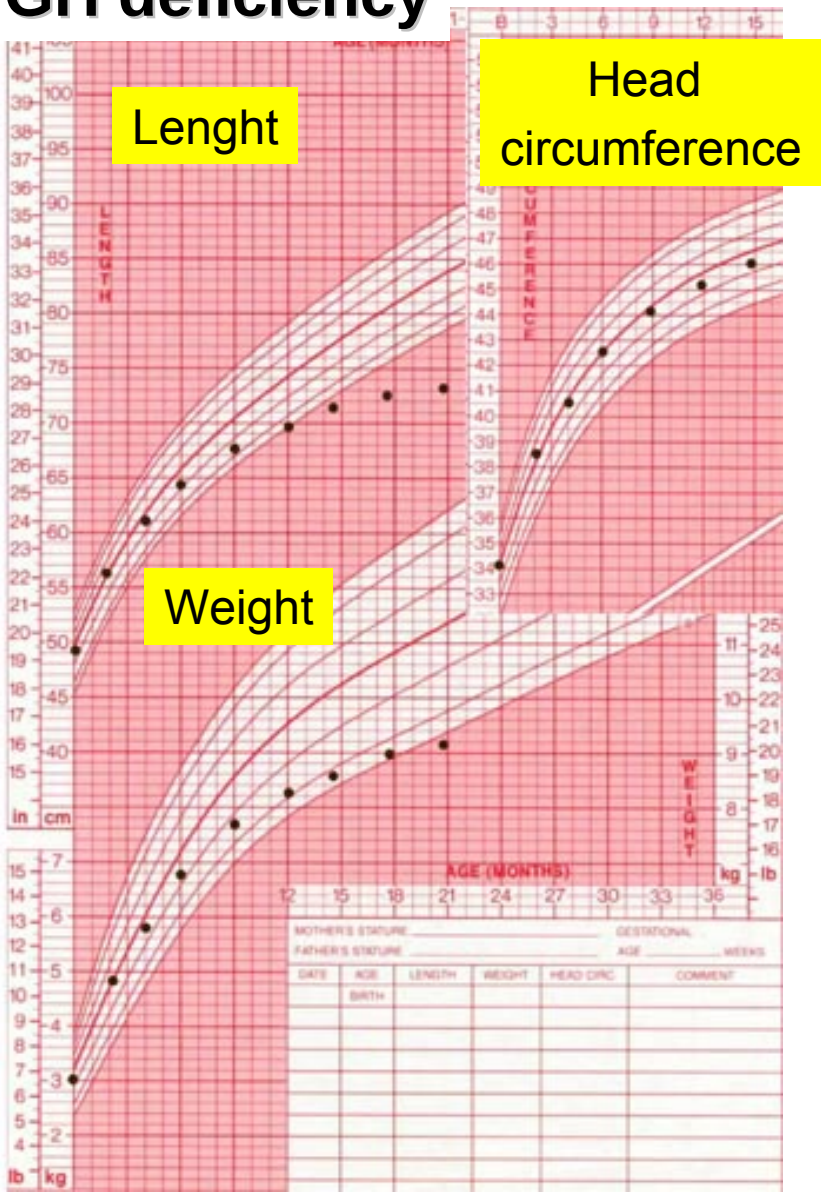
- Malnutrition
- Chronic disease
- Familial short stature
- Constitutional delay of growth and development
- Social
  - e.g. participation in sports that require weight control
- **Endocrine diseases (~ 5% of children with short statue and poor growth rate)**

Growth hormone function defects

- Disruption of the growth hormone production
  - higher brain
  - hypothalamus
  - pituitary
- Growth hormone resistance
  - Insulin-like growth factor I (IGF-I) deficiency

Growth Failure

GH deficiency



- Lower-than-normal growth rate

Congenital growth hormone deficiency

- A mutation in a transcription factor (POUF-1, also known as PIT1)
  - Also prolactin deficiencies and variable thyroid-stimulating hormone (TSH) deficiencies)
- Inactivating mutations of the PROP1 (Prophet of PIT-1) transcription factor
  - Also do not produce luteinizing hormone (LH) or follicle-stimulating hormone (FSH) and thus, do not spontaneously progress into puberty.
  - They may also have TSH deficiency.
- Septooptic dysplasia (SOD) (de Morsier syndrome)
  - may include other pituitary deficiencies, optic nerve hypoplasia, and absence of the septum pellucidum (incidence 1 in 50,000 births).
  - mutation in the gene for transcription factor HESX1 (but not only)

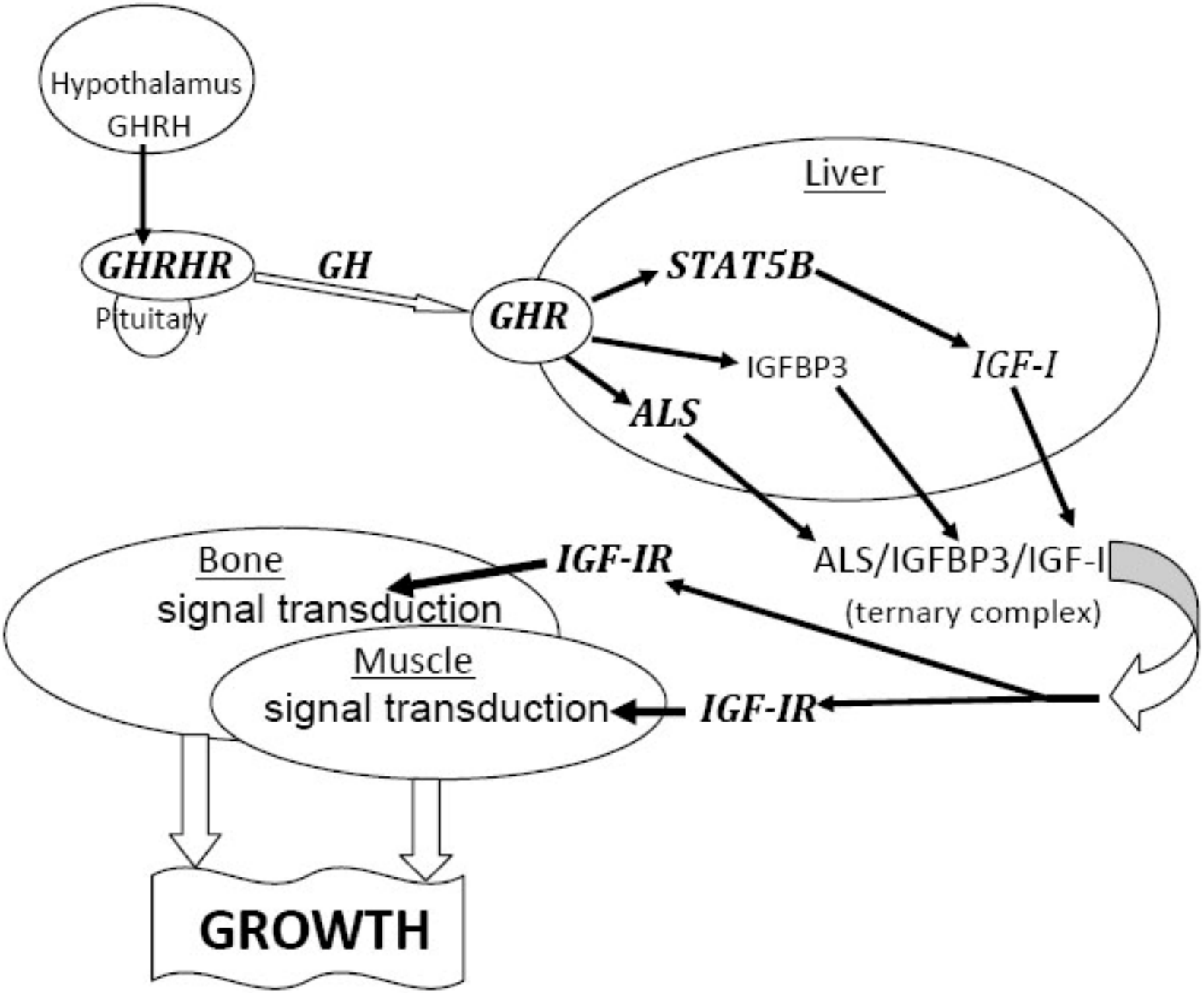
Acquired growth hormone deficiency

- trauma
- infections (eg, encephalitis, meningitis)
- cranial irradiation
  - somatotrophs appear to be the most radiation-sensitive cells in the pituitary
- systemic diseases (particularly histiocytosis).
- Most instances of isolated growth hormone deficiency are idiopathic

Congenital growth hormone resistance

- GH receptor deficiency (**Laron syndrome**)
- Postreceptor defects
  - transduction molecule defects STAT5b
  - the IGF-I/IGFBP3 stabilizer acid labile subunit (ALS) defects
  - IGF-I gene or the IGF-I receptor defects

IGF-1 deficiency


Hypothalamus
GHRH
GHRHR
Pituitary
GH
GHR
Liver
STAT5B
IGFBP3
IGF-I
ALS
ALS/IGFBP3/IGF-I
(ternary complex)
IGF-IR
Bone
signal transduction
Muscle
signal transduction
IGF-IR
GROWTH

- GHRD due to homozygosity for the GH receptor
- Children lined up according to descending age from 15 years to 2 years, with 3 normal children standing behind age mates.

Arlan L Rosenbloom, MD; Chief Editor: Stephen Kemp, MD, PhD more
http://emedicine.medscape.com/article/922902-overview#a0104

Postreceptor GH resistance

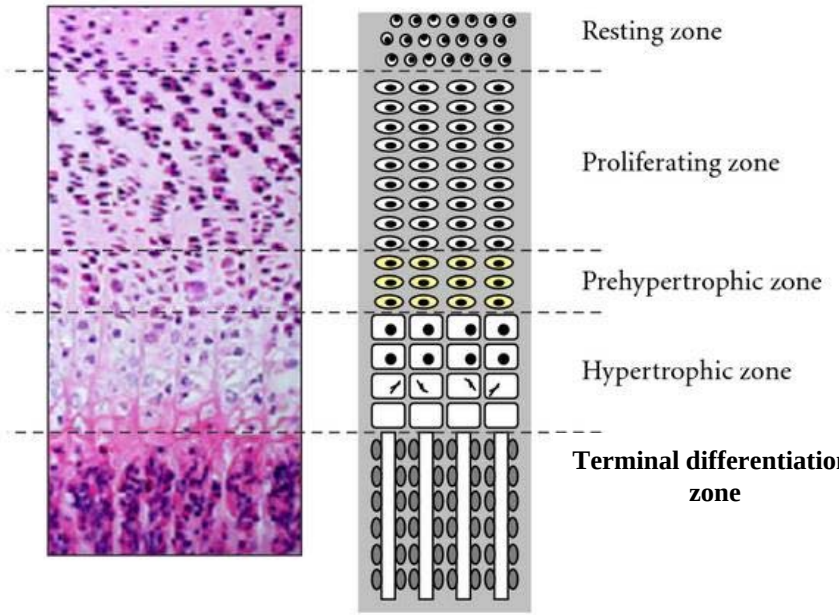
- Individuals with homozygouse *IGF-I* gene mutations
  - sever mental retardation (brain development)
  - intrauterine growth retardation (somatic growth) and micrognathia
  - deafness
- Heterozygous mutations of the IGF-I receptor
  - moderate intrauterine growth retardation
  - microcephaly
  - inconsistent mental retardation (cognitive impairment)
- Mutations of STAT5b
  - do not appear to have intrauterine growth retardation or impaired brain development
  - immunodeficiency problems (role of STAT5b in multiple cytokine transduction/transcription pathways)
- ALS deficiency
  - modest effect on growth, without any other phenotypic features

Acquired growth hormone resistance

- Malnutrition
- Hepatic disease
- Renal disease
- Diabetes
- GH mutation in which GH inhibiting antibodies develop after a few months of replacement therapy with recombinant GH

Sceletal dysplasia
Osteochondrodysplasias

- Many of the genes mutated in skeletal dysplasias encode proteins that play critical roles in the growth plate



SOX9 mutation - short and curved bone

FGFR3 mutation - achondroplasia, hypochondroplasia

PTHR1 mutation - metaphyseal dysplasia

RUNX2 mutation - cleidocranial dysplasia

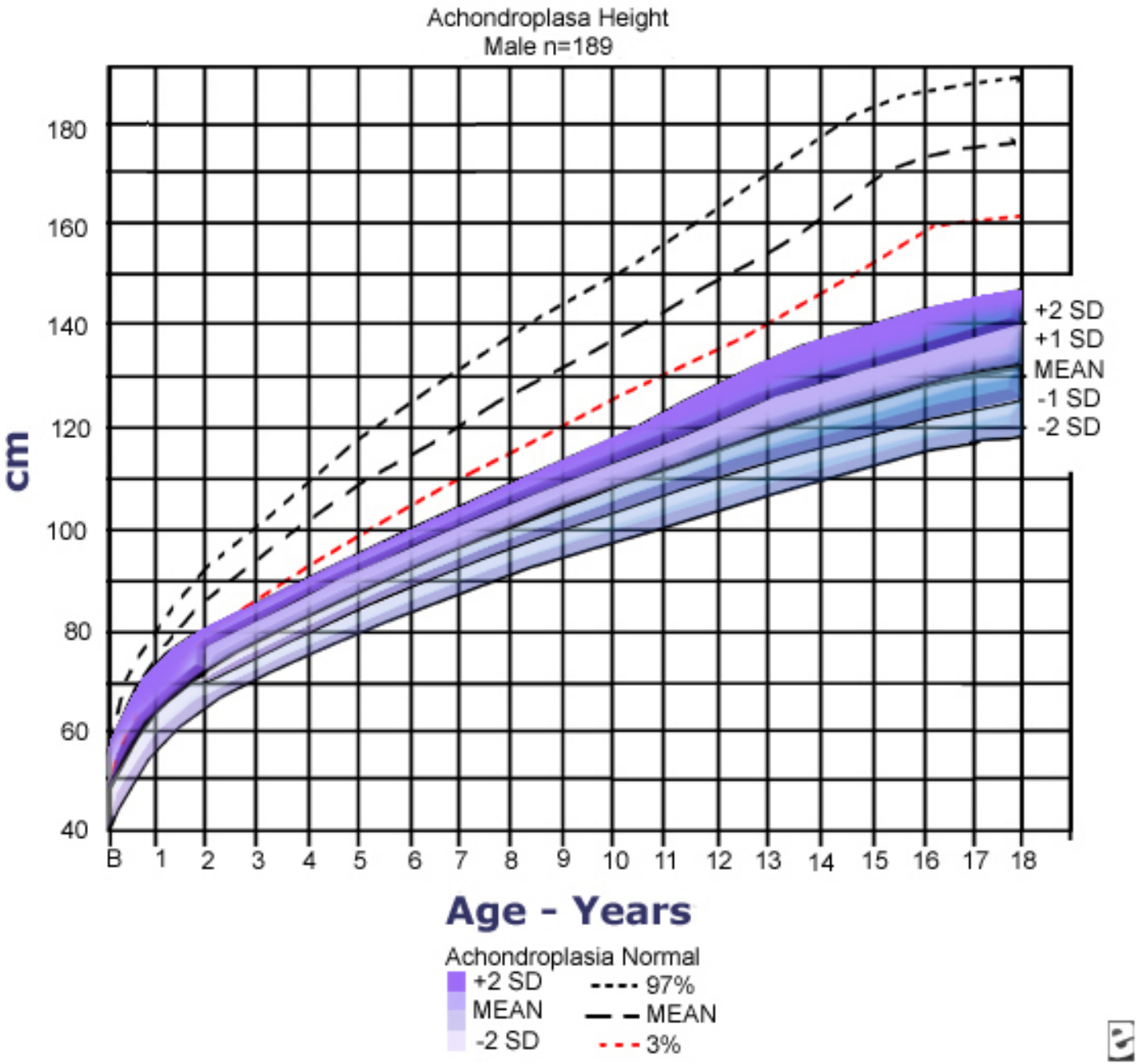
Mutations in type II collagen - large number of disorders classified as spondyloepiphyseal dysplasia

Achondroplasia

- Skeletal dysplasia most common type of short-limb disproportionate dwarfism
- Mendelian autosomal dominant trait with complete penetrance
- 80% of cases are due to new or de novo mutations
- 1 in every 40,000 children (~150 000 worlwide)
- intrinsic abnormalities in the growth and/or remodeling of cartilage and bone.
- affect the skull, spine, and extremities in varying degrees

Genetic basis for achondroplasia

- Autosomal dominant
  - 4p16.3
  - 80% of cases result from a random new mutation
- Molecular basis of achondroplasia
  - Mutation in *FGFR3* causes enhancement in the *FGFR3* function of limiting endochondral ossification.
- decreased endochondral ossification
  - inhibited proliferation of chondrocytes in growth plate cartilage, decreased cellular hypertrophy, and decreased cartilage matrix production


Achondroplasa Height
Male n=189
180
160
140
120
100
80
60
40
cm
B 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Age - Years
+2 SD
+1 SD
MEAN
-1 SD
-2 SD
Achondroplasia Normal
+2 SD
MEAN
-2 SD
97%
MEAN
3%

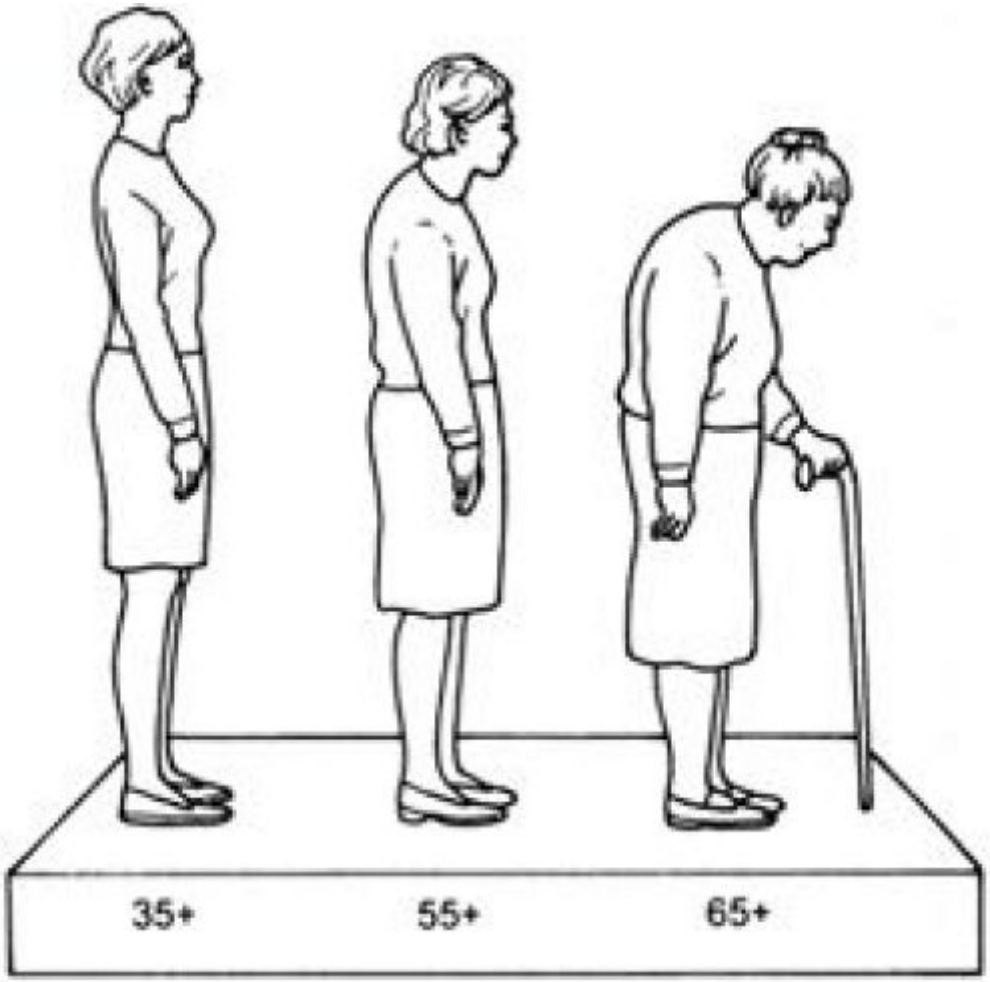
Pathophysiology of achondroplasia

- Short-limb dwarfing condition
- Patients' sitting height is within normal range
- The arms and thighs more severely involved than the forearms, legs, hands, and feet
  - Abnormal endochondral ossification
  - Periosteal and intramembranous ossification is normal

Morbidity associated with achondroplasia

- Recurrent otitis media (hearing loss)
- Neurologic complications due to cervicomedullary compression (
  - eg, hypotonia, respiratory insufficiency, apnea, cyanotic episodes, feeding problems, quadriparesis, sudden death
- Obstructive and restrictive respiratory complications
  - eg, upper airway obstruction, pneumonia, apnea
- Hydrocephalus
- Spinal deformities
  - eg, kyphosis, lordosis, scoliosis, spinal canal stenosis
- Obesity
- Genu varum
- Cardiovascular complications

Aging



Aging outline

- What is aging?
- What causes aging?
  - Aging of the cells
  - Aging of the organism
- Genes that control aging
  - Mutations that cause accelerated aging
  - Mutations that prolog lifespan

What is aging?

- Progressive physiological changes in an organism that lead to senescence, or a decline of biological functions and of the organism's ability to adapt to metabolic stress.
- Aging takes place in a cell, an organ, or the total organism with the passage of time.
- It is a process that goes on over the entire adult life span of any living thing.

Encyclopaedia Britannica, 2014

Aging, 2014, Encyclopaedia Britannica Online, Retrieved 07 February 2014, from http://www.britannica.com/EBchecked/topic/9171/aging

Cell aging

- Gradual changes in the molecular physiology of the cell that causes a decline in the normal function of cells

- Most aging models are based on the idea that gradual change in the original structure of DNA is a major underlying cause

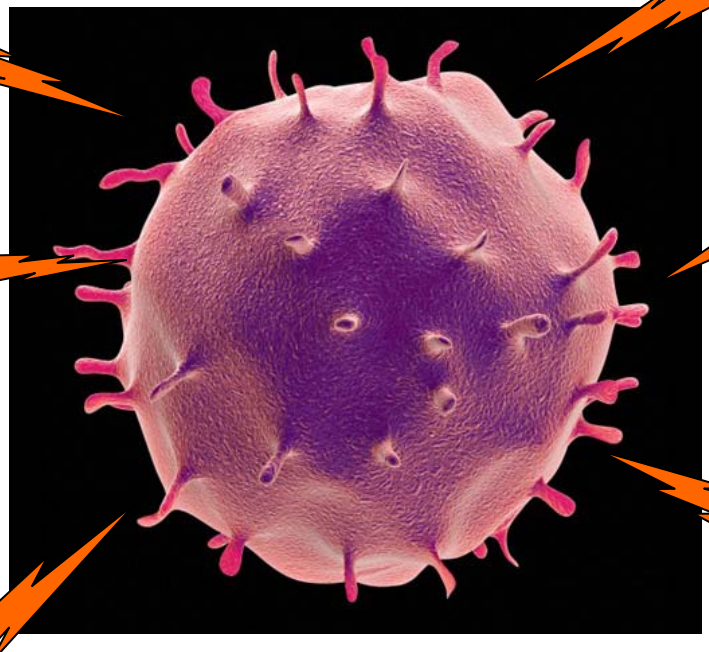
What Causes Aging?

Auto-immunity (1964)

Genetic control

Loss of telomeres (1961/1973)

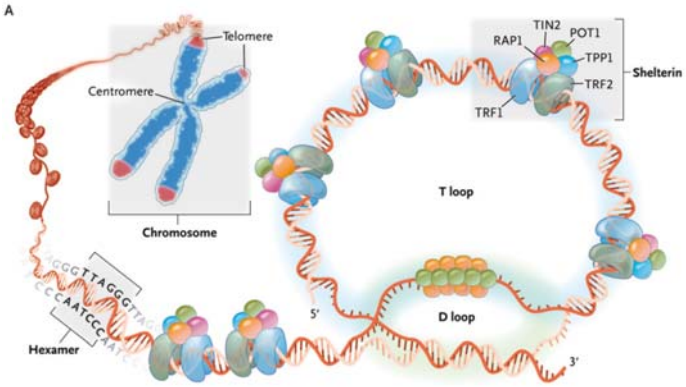
Reactive oxygen species DNA and mitochondria damage (1956/1972)



Reduced stem cell function

Wear and tear (1881)

Telomeres



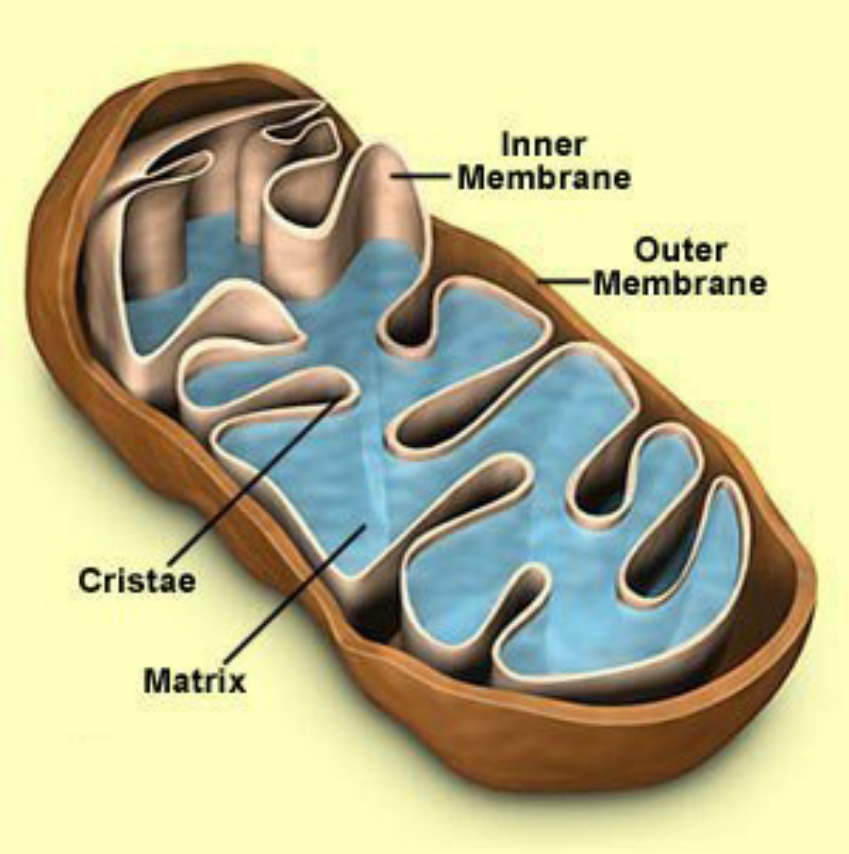
N Engl J Med 361;24, 2009

- Repetitive DNA sequences avoiding the loss of genetically encoded information at the end of linear chromosomes during mitosis
- When they are too short, telomeres signal the arrest of cell proliferation, senescence, and apoptosis

Telomeres and Aging

- Telomere attrition leads to cell senescence and the Hayflick phenomenon
- Telomere shortening is not uniform among tissues (e.g., the brain and heart show little shortening) or among the various cells within a tissue.
- Telomerase gene therapy increases the lifespan of mice by 10-20 %.

MITOCHONDRIA and AGING

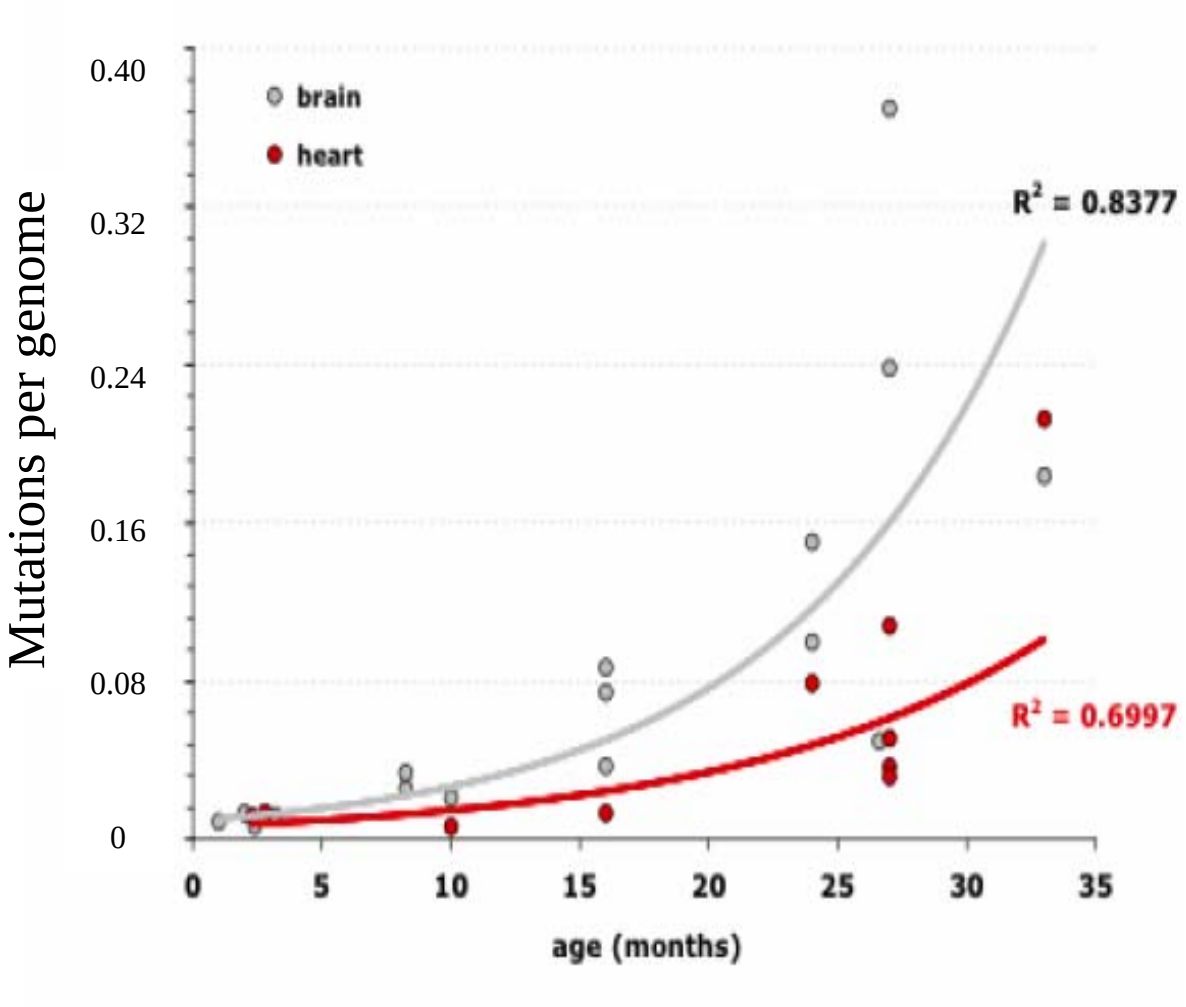


- Mitochondria play central roles in at least 4 processes related to aging:

1. Energy production
2. Generation of reactive oxygen species (ROS)
3. Apoptosis
4. Metabolism

mtDNA point mutations increase with age

(a very similar graph is available for mtDNA deletions)



Vermulst et al.
Nature Genetics
April 2007

Tissue aging

- Cell apoptosis
  - programmed cell death
- Cell senescence (Hayflick and Moorfield 1961)
  - Irreversible cell cycle arrest
  - Cells maintain metabolic activity and can remain viable essentially indefinitely

Aging of the organism?

- The loss of tissue homeostasis through stem, progenitor, and functional tissue cell attrition

Progeroid syndromes

- Progeria: "before old age“ (Greek)
- „Premature aging disorders“
- Most are associated with defects in genome maintenance
  - Mutations in two classes of DNA repair proteins
    - RecQ protein-like helicases (RECQLs)
    - Nucleotide excision repair (NER) protein

Examples

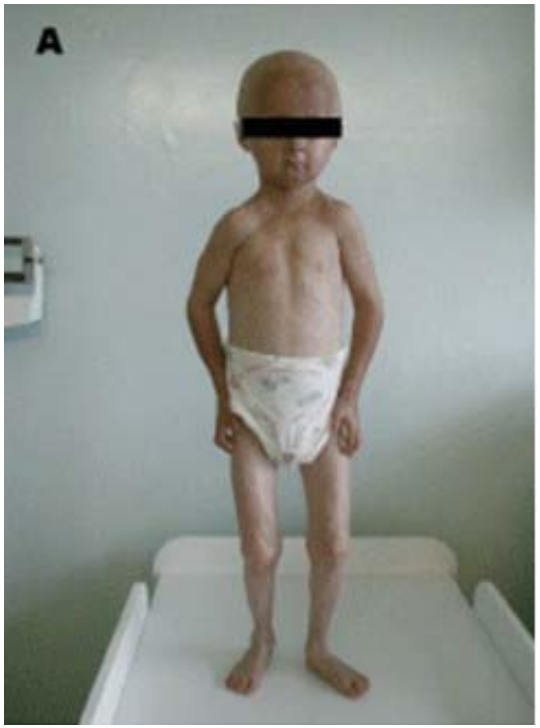
- Werner syndrome (WS)
- Bloom syndrome (BS)
- Rothmund–Thomson syndrome (RTS)
- Cockayne syndrome (CS)
- Xeroderma pigmentosum (XP)
- Trichothiodystrophy (TTD)

Werner syndrome or progeria adultorum (1904)

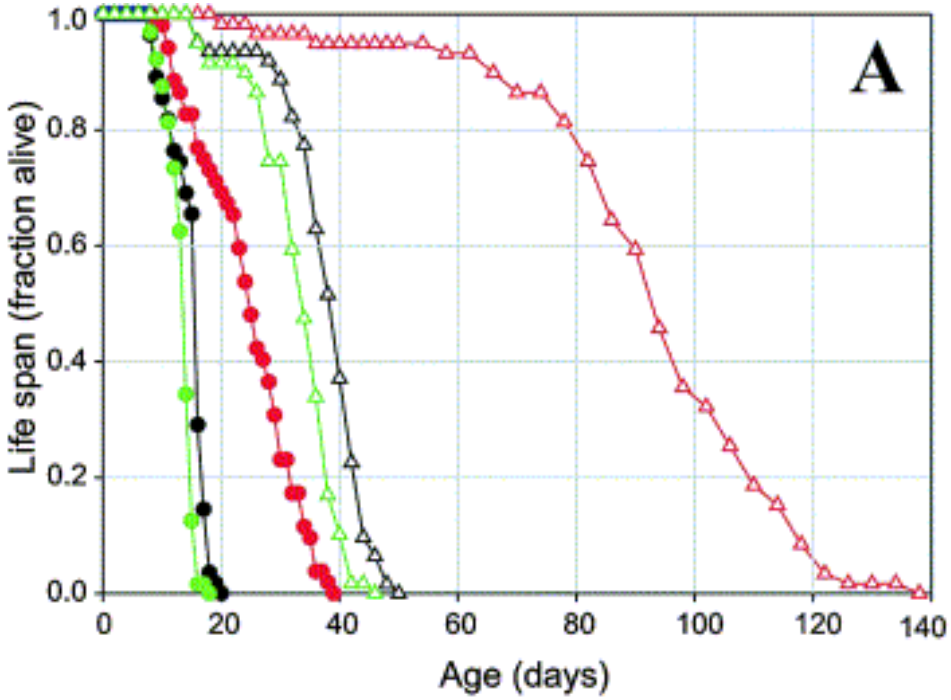
- Autosomal recessive
- Scleroderma-like, thin, tight skin and bilateral cataracts
  - affects connective tissue throughout the body
  - caused by null mutations at the WRN locus, which codes for a member of the RecQ family of DNA helicases (response to DNA damage)
- premature aging with onset in the third decade of life

Hutchinson-Gilford syndrome

- Lamin A protein defect (LMNA gene) that provides the molecular scaffolding of cell nuclei
  - Leads to nuclear instability from cell division and early death of every body cell
- Has onset early in life (2 yr of age)
  - Growth failure
  - Craniofacial abnormalities
  - Physical changes of aging
- Median age at death is 12 yr
  - cause is coronary artery and cerebrovascular disease
  - insulin resistance and atherosclerosis
  - Increased cancer risk, degenerative arthritis are not present



Healthy Worms With Extreme Longevity



black = wild type
red = defective insulin signaling
• = normal diet
Δ = caloric restriction

- Caloric restriction can extend worm lifespan 2.5-fold.
- Reduced insulin signaling extends lifespan 1.7-fold.
- Combined lifespan extension is 6 to 7-fold, equivalent to ~500 year old humans.

Fig. 1A, Houthoofd, *et al.,* Exp. Gerontol. **38:**947-954, 2003

- end -

The placenta and intrauterine programming