Developmental Disorders

General Principles

Causes:

Genetic

Environmental (Maternal, Physical, Chemical)

Mechanisms (Retinoic Acid)

General Principles

Teratology – "Study of Monsters"

Teratogen – agent that produces birth defects

2-3% of all newborns show at least one recognizable congenital malformation

4-6% after a few years – due to unrecognizable malformations at birth

Over 20% of infant mortality is linked to congenital malformations

Congenital Malformations

Range – Enzyme deficiency (point mutation) to gross anatomical malformations

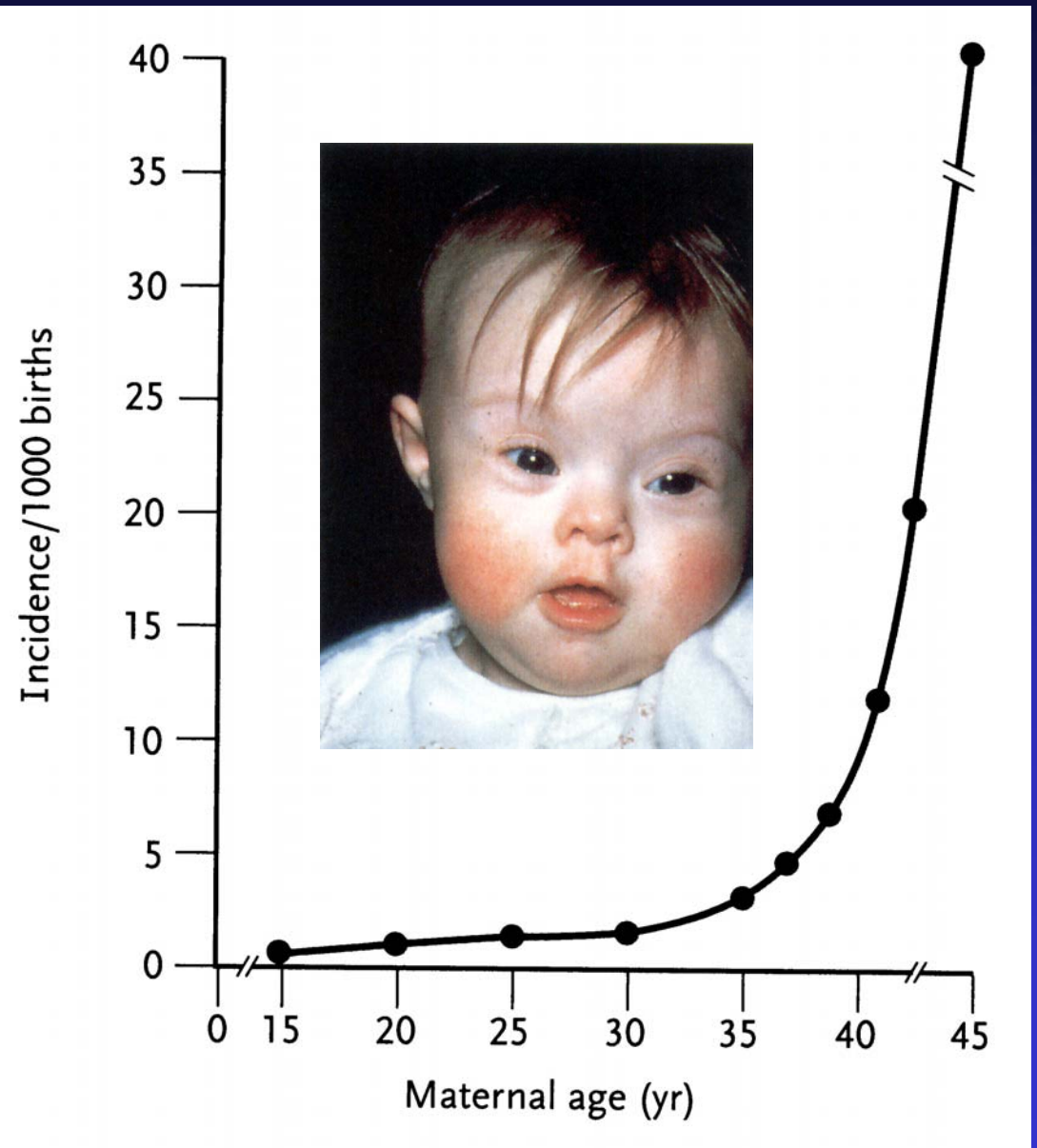
Interaction between genetic make-up and the environment

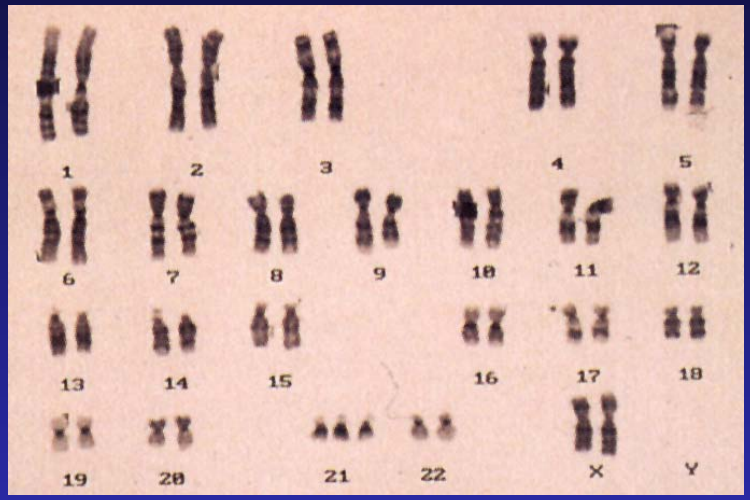
Penetrance – severity of a defect – influenced by genetic background: Different mice strains react differently to a specific teratogen.

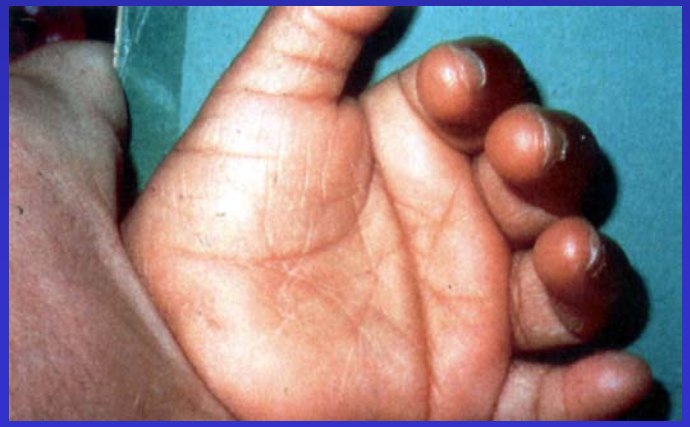
Factors:

- Parental Age
- Race
- Country of Residence
- Time of the year
- Familial Tendencies

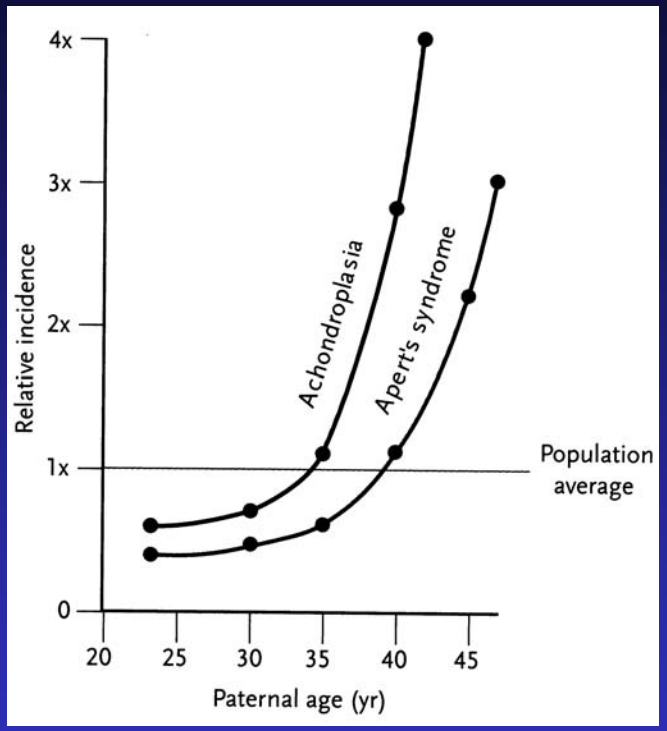
Maternal Age

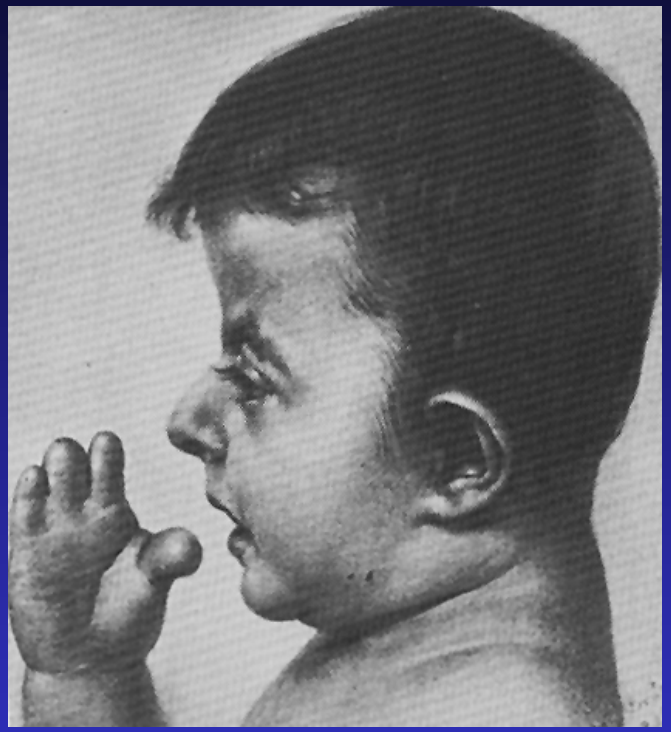






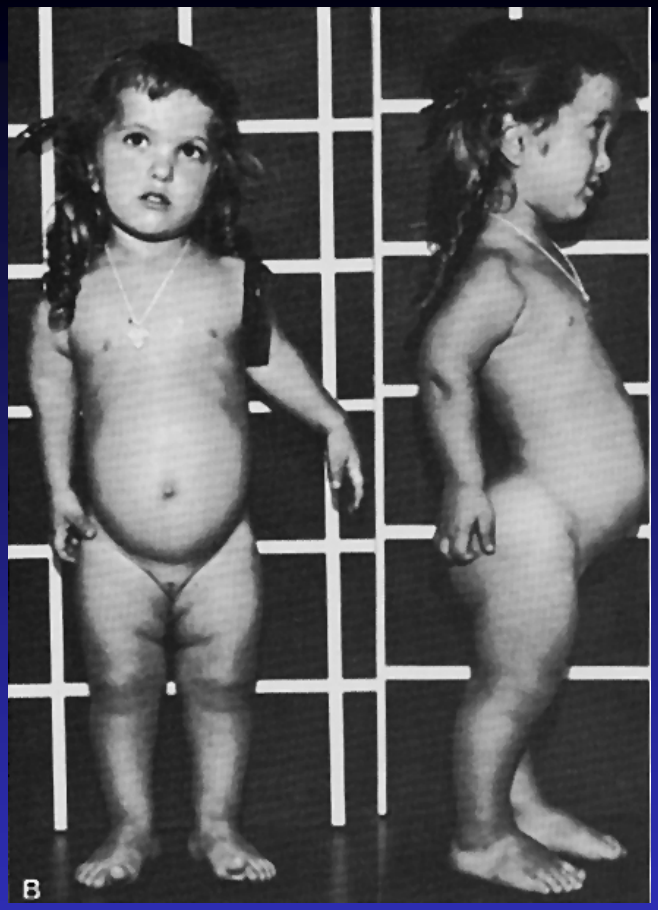
Paternal Age

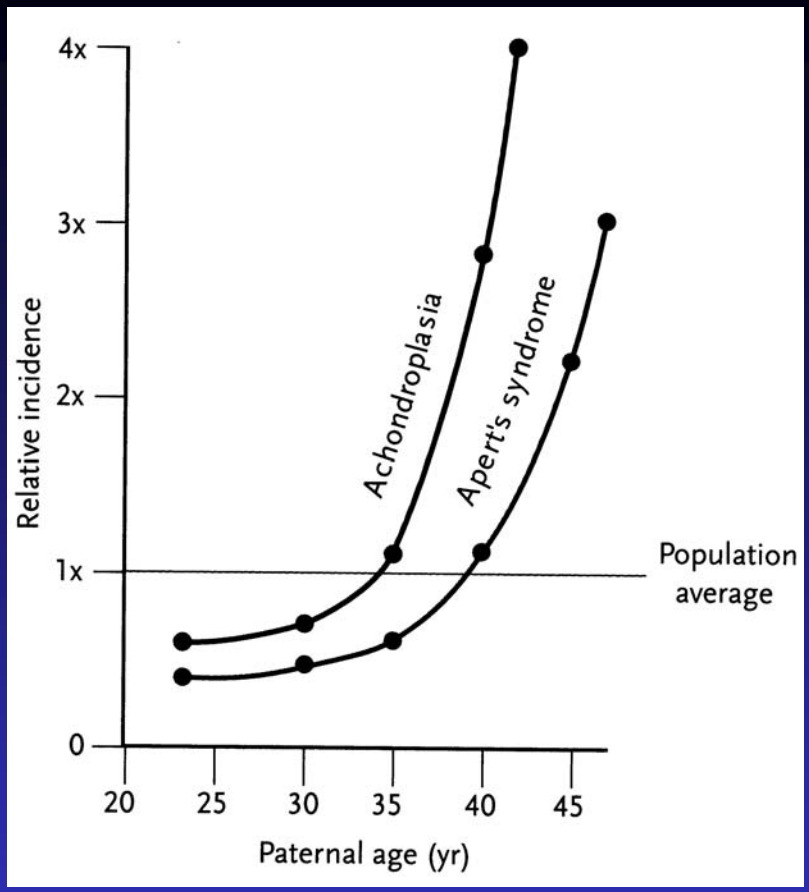




Apert's syndrome (Acrocephalosyndactyly)

- Premature suture closure → Abnormal head shape
- Webbed fingers and toes
- Mutation: Chromosome 10
- FGFR2 gene (Fibroblast Growth Factor Receptor 2)





Achondroplasia (Short-limbed dwarfism)

- Normal trunk – Short arms and legs
- Disproportionately large head
- Mutation: Chromosome 4
- FGFR3 gene (Fibroblast Growth Factor Receptor 3)

Race/Country of Residence

TABLE 7-1 Incidence of Neural Tube Defects

Site	Incidence*
India	0.6
Ireland	10
United States	1
Worldwide	2.6

*Per 1000 live births

Neural Tube defects correlate with Maternal Folic Acid (vitamin B complex) deficiency

Possible Cause: Poor nutrition

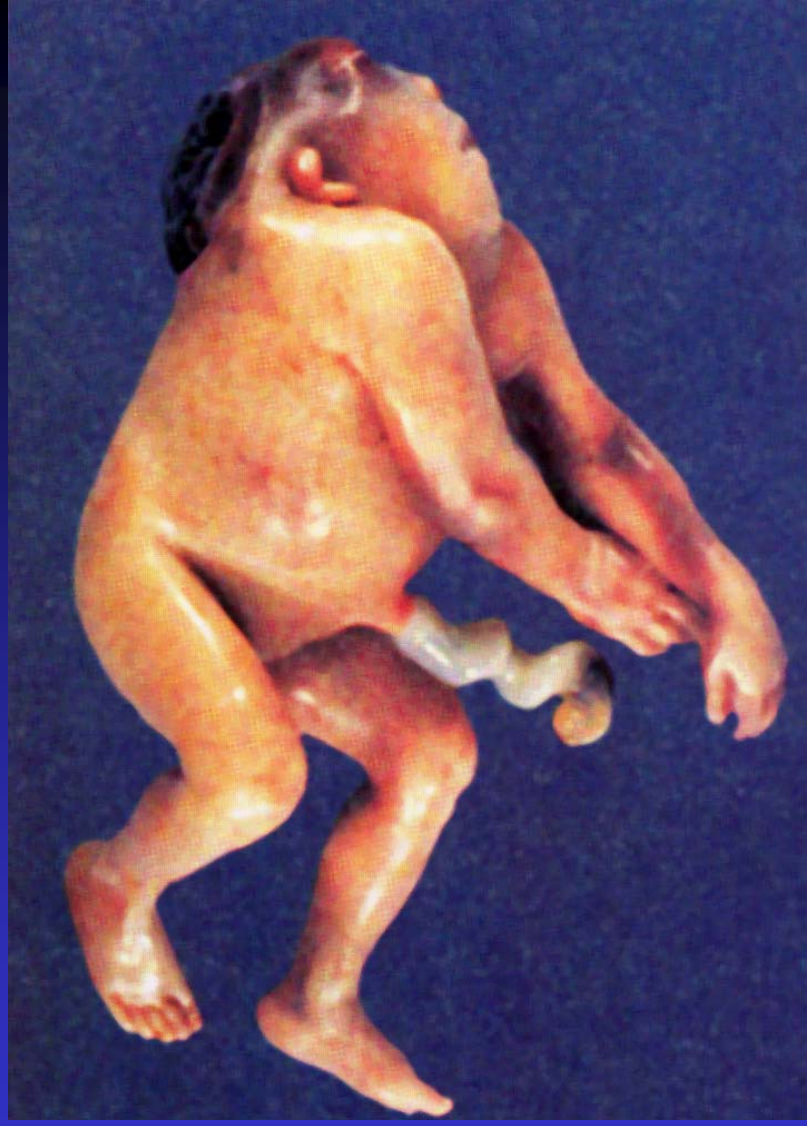
BIRTH DEFECTS INFANT MORTALITY RATES, BY STATE, FOUR-YEAR AVERAGES, U.S., 1988–1991

State	*Rate*	*RR*	*95% CI*	*Rank*
Alabama	242.4	1.22	(1.13–1.32)	49
Alaska	189.3	0.95	(0.77–1.18)	15
Arizona	227.1	1.14	(1.06–1.24)	45
Arkansas	211.4	1.07	(0.95–1.19)	38
California	190.4	0.96	(0.93–0.99)	17
Colorado	199.1	1.00	(0.91–1.10)	23
Connecticut	160.0	0.81	(0.72–0.90)	4
Delaware	232.5	1.17	(0.96–1.42)	47
District of Columbia	180.6	0.91	(0.73–1.13)	9
Florida	194.4	0.98	(0.93–1.03)	21
Georgia	209.0	1.06	(0.99–1.13)	35
Hawaii	153.5	0.77	(0.65–0.92)	1
Idaho	218.9	1.10	(0.94–1.30)	39
Illinois	208.6	1.05	(1.00–1.11)	33
Indiana	209.8	1.06	(0.98–1.14)	36
Iowa	221.8	1.12	(1.01–1.24)	40
Kansas	200.1	1.01	(0.90–1.13)	26
Kentucky	242.5	1.22	(1.12–1.33)	50
Louisiana	226.1	1.14	(1.05–1.23)	43
Maine	186.2	0.93	(0.79–1.11)	11
Maryland	171.0	0.86	(0.79–0.94)	6
Massachusetts	153.9	0.78	(0.71–0.84)	2
Michigan	190.8	0.96	(0.91–1.02)	18

Minnesota	200.1	1.01	(0.93–1.10)	25
Mississippi	222.8	1.12	(1.02–1.24)	41
Missouri	208.1	1.05	(0.97–1.13)	32
Montana	225.8	1.14	(0.94–1.38)	42
Nebraska	207.2	1.04	(0.91–1.20)	29
Nevada	169.9	0.86	(0.72–1.01)	5
New Hampshire	189.6	0.96	(0.81–1.15)	16
New Jersey	179.6	0.91	(0.85–0.97)	7
New Mexico	240.9	1.21	(1.08–1.37)	48
New York	183.9	0.93	(0.89–0.97)	10
North Carolina	207.8	1.05	(0.98–1.12)	31
North Dakota	251.3	1.27	(1.04–1.55)	51
Ohio	199.2	1.00	(0.95–1.06)	24
Oklahoma	192.4	0.97	(0.87–1.07)	19
Oregon	179.9	0.91	(0.81–1.02)	8
Pennsylvania	195.8	0.99	(0.93–1.04)	22
Rhode Island	188.4	0.81	(0.67–0.98)	13
South Carolina	227.0	1.14	(1.05–1.25)	44
South Dakota	205.8	1.04	(0.84–1.27)	28
Tennessee	194.3	0.98	(0.90–1.06)	20
Texas	208.8	1.05	(1.01–1.10)	34
Utah	211.2	1.06	(0.95–1.19)	37
Vermont	158.3	0.80	(0.61–1.05)	3
Virginia	188.8	0.95	(0.88–1.02)	14
Washington	188.1	0.95	(0.87–1.03)	12
West Virginia	229.0	1.15	(1.01–1.32)	46
Wisconsin	207.4	1.05	(0.96–1.13)	30
Wyoming	205.4	1.04	(0.80–1.34)	27
United States	**198.4**			

Time of Year

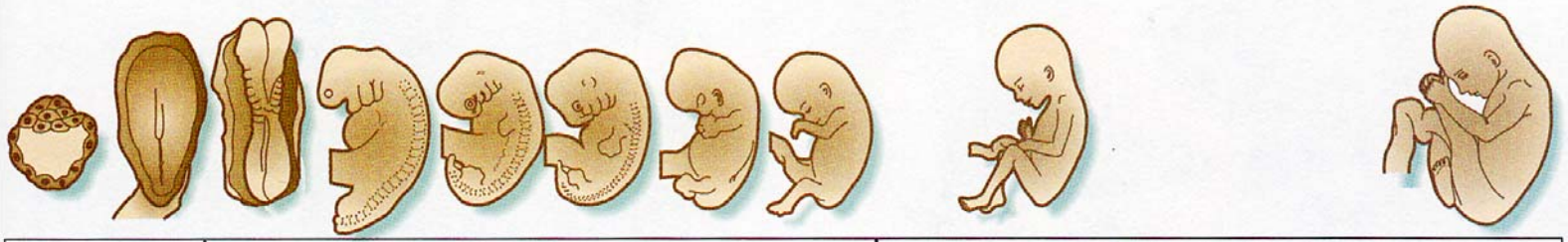
Anencephaly – High incidence of January births – Late winter / Early Spring conceptions

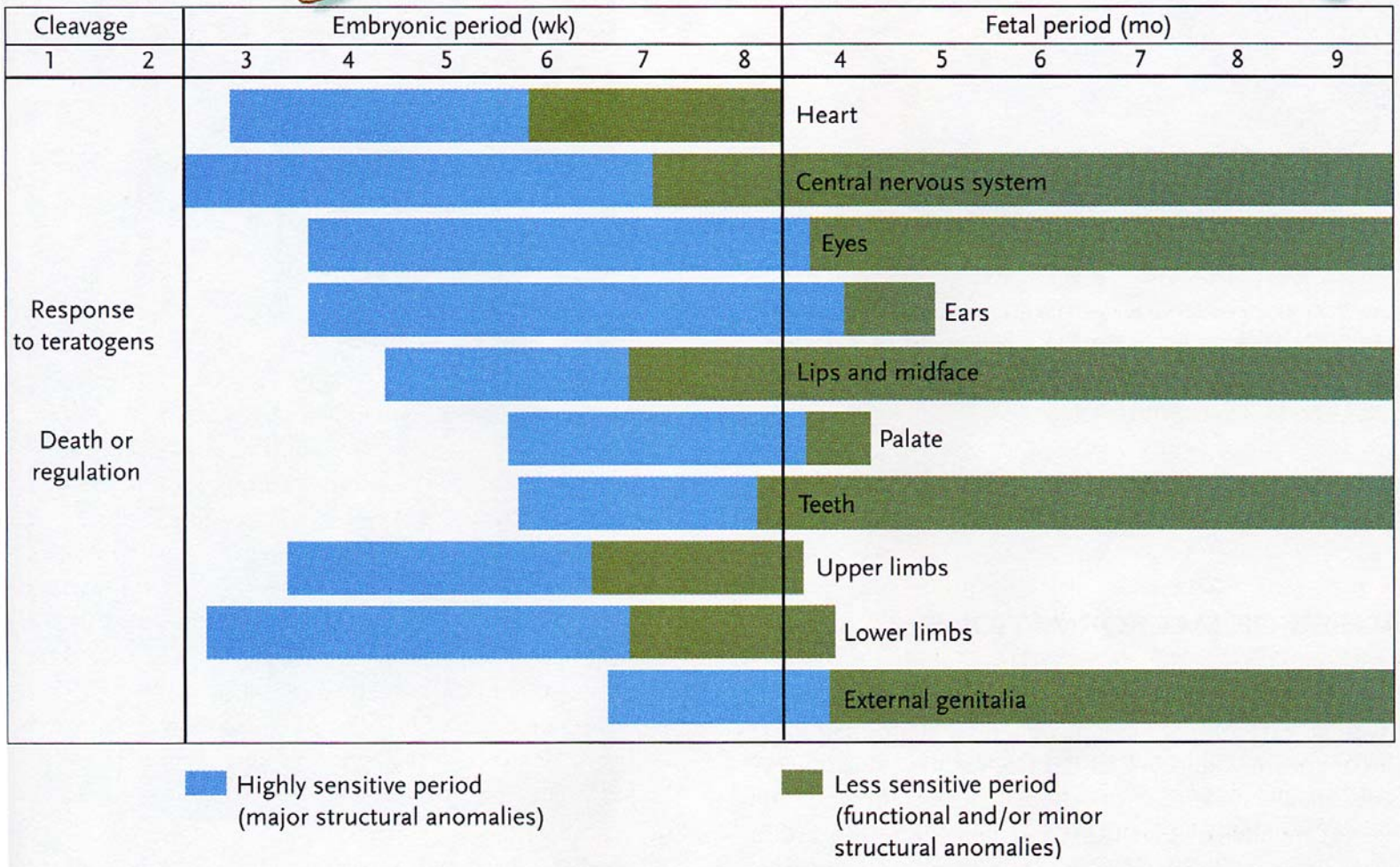


Maternal Folic Acid deficiency

Related to nutritional deficits during winter

Windows of Susceptibility





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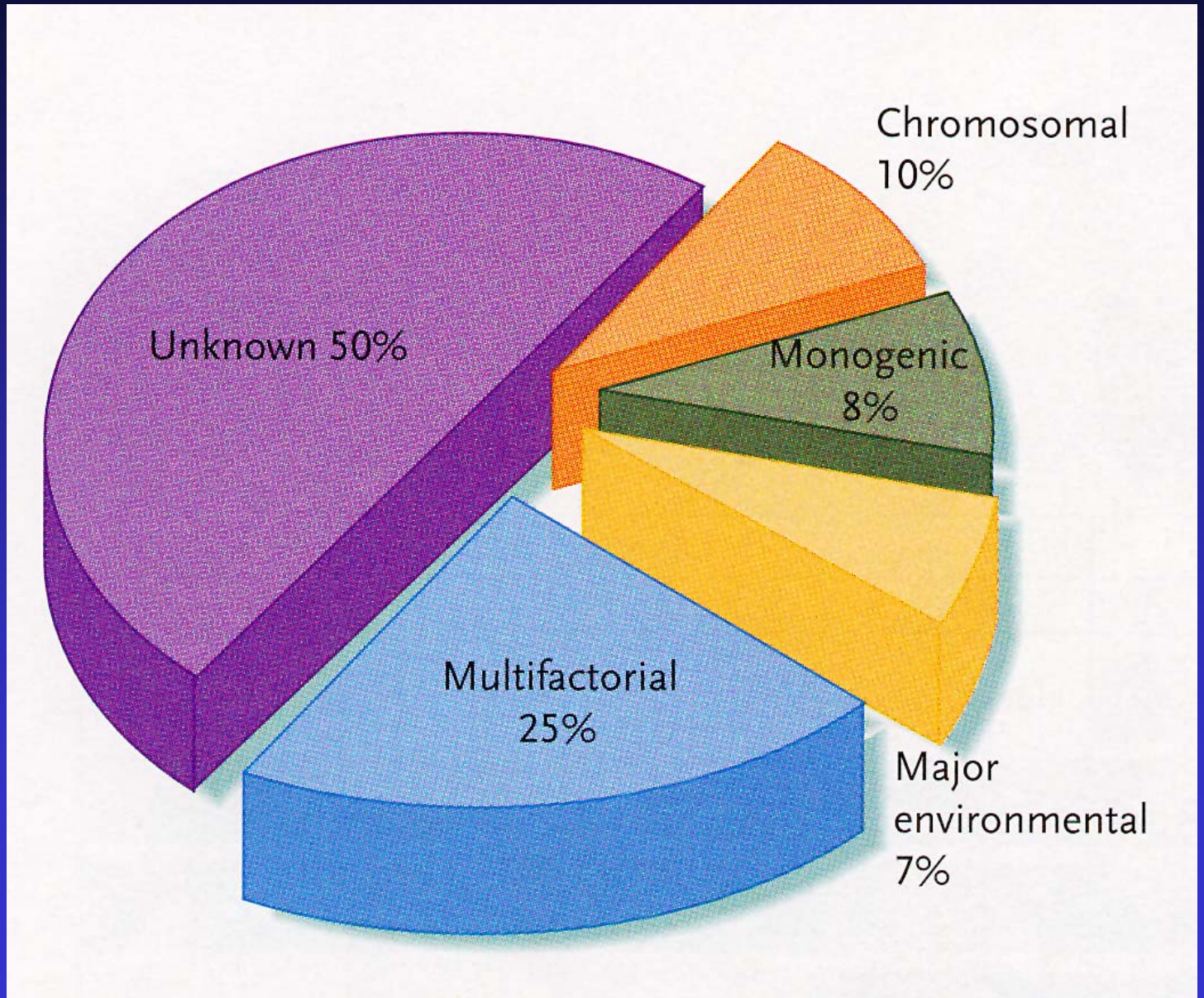
Causes


Chromosomal
10%
Unknown 50%
Monogenic
8%
Multifactorial
25%
Major
environmental
7%

Genetic - Chromosomal

Sex chromosome complement	Incidence	Phenotype	Clinical factors
XO	1:3000	Immature female	Turner syndrome: short stature, webbed neck, high and arched palate
XX		Female	Normal
XY		Male	Normal
XXY	1:1000	Male	Klinefelter syndrome: small testes, infertility, often tallness with long limbs
XYY	1:1000	Male	Tall, normal appearance; reputed difficulty with impulsive behavior
XXX	1:1000	Female	Normal appearance, mental retardation (up to one third of cases), fertility (in many cases)

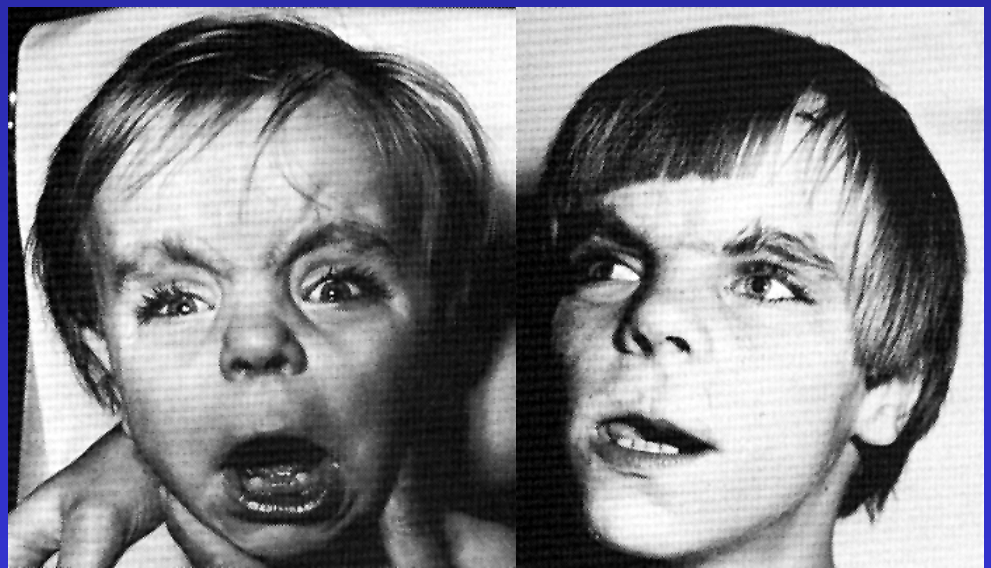
Polypoidy

Monosomy

Trisomy 8, 9, 13, 18, 21

Abnormal Structure – deletions, duplications, translocations, etc.

Partial Trisomy 13



Mutations

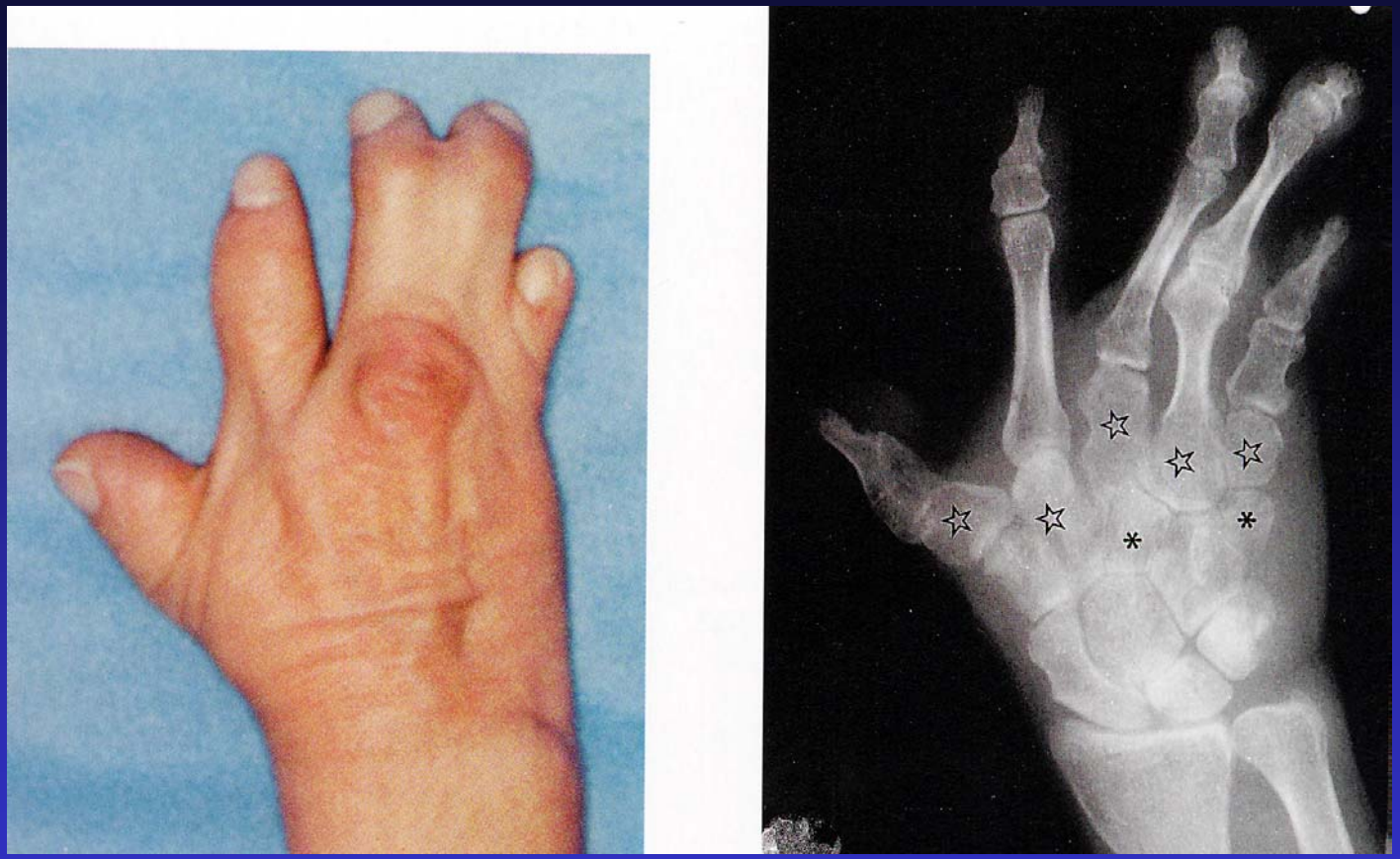
Most genetic mutations are known based on morphological abnormalites – Specific gene is unknown

Recent advances in molecular genetics have uncovered the molecular basis for some disorders.

Many morphological abnormalities involve mutations of transcription factors or cell-cell signals

One example is Synpolydactyly caused by a mutation in the HOXD13 gene.

Synpolydactyly / HOXD13

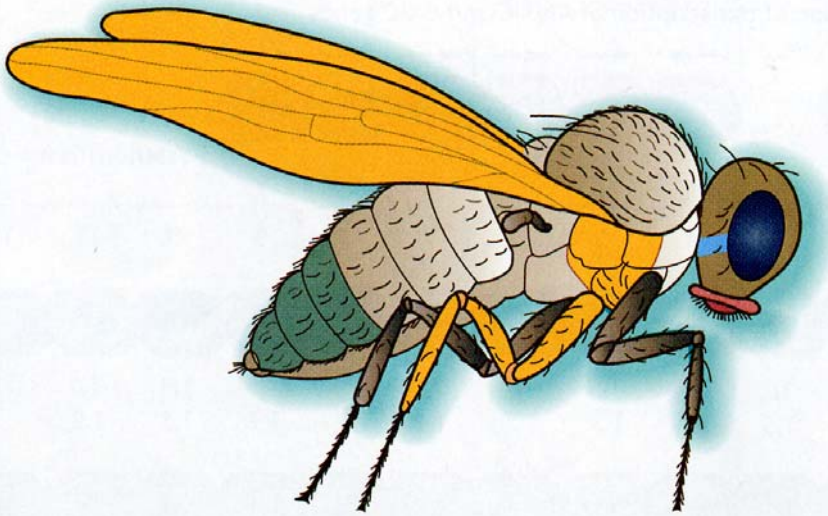


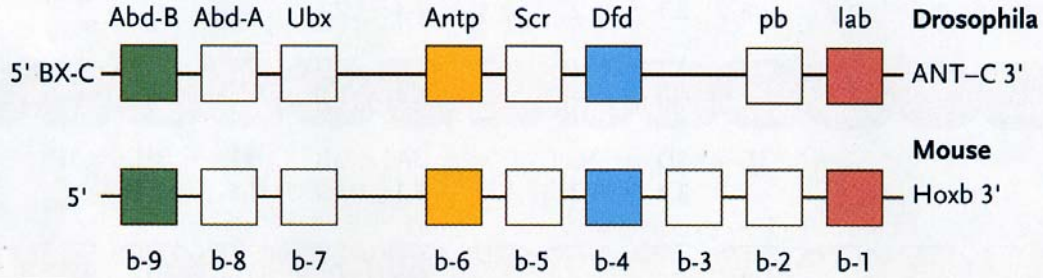
Digit fusions

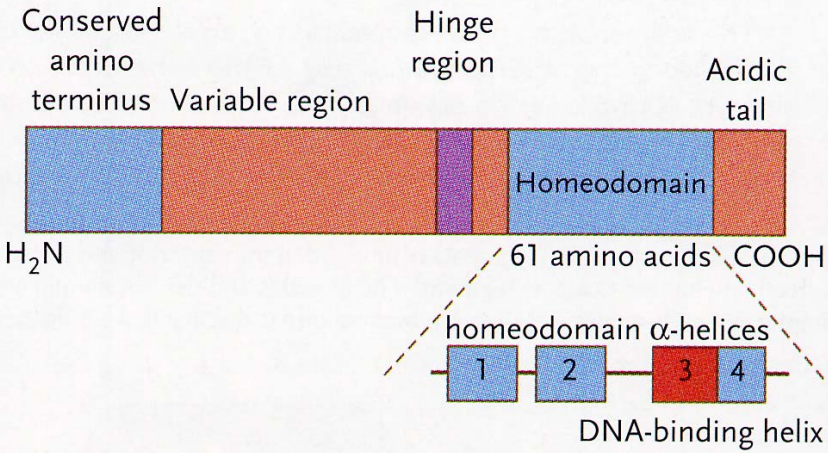
Supernumerary carpals

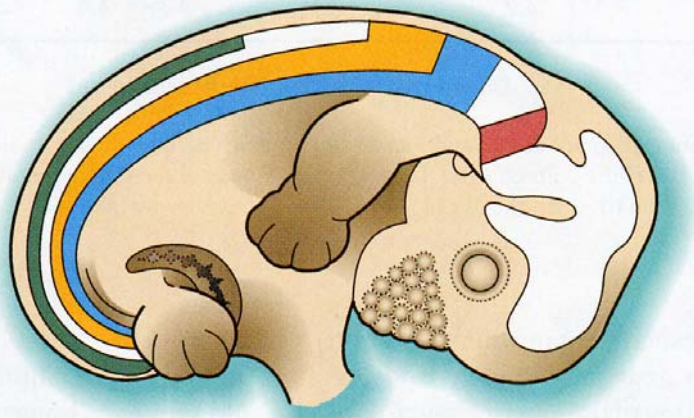
Transformation of metacarpal to carpals

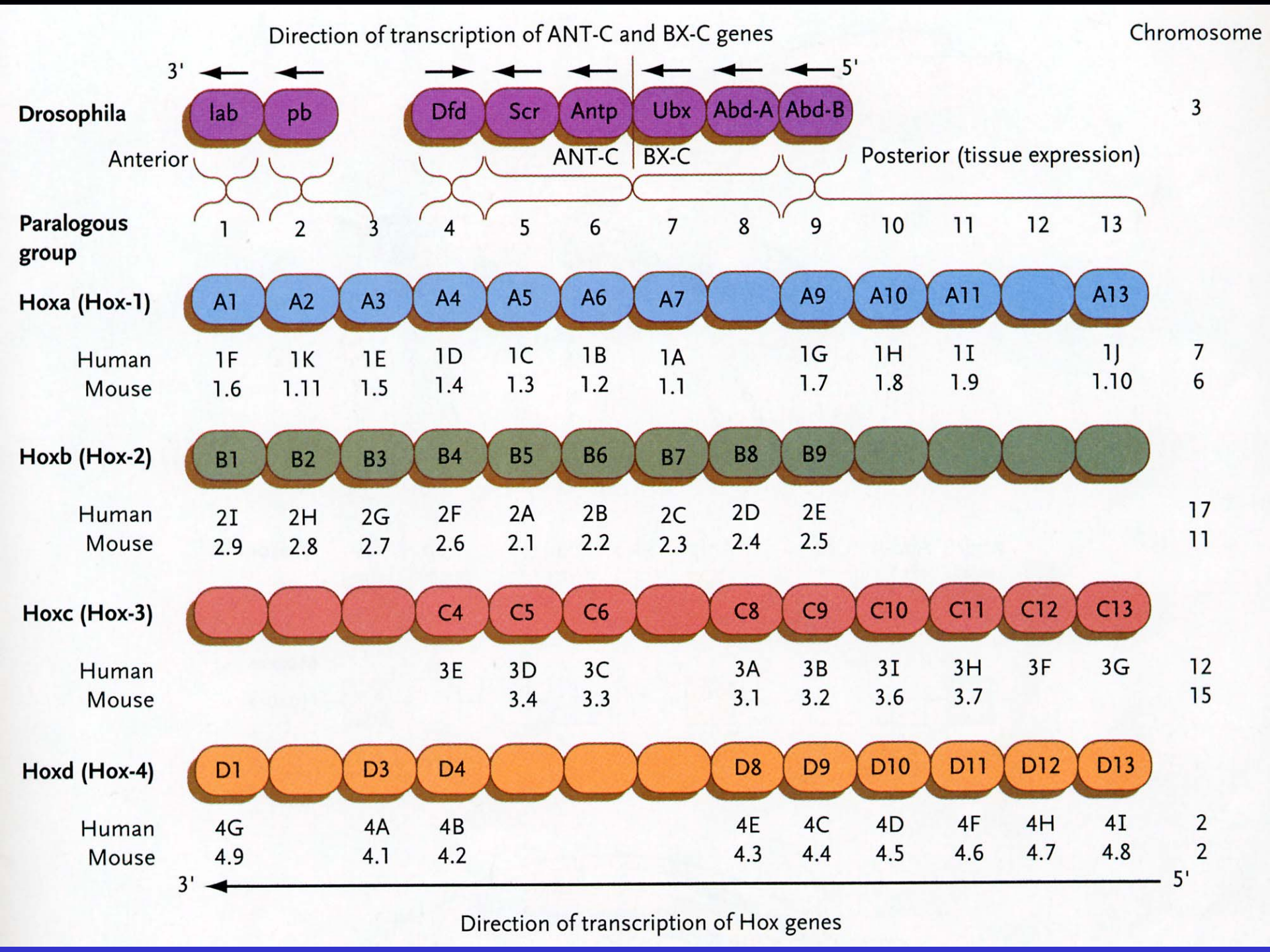
Homeobox Genes

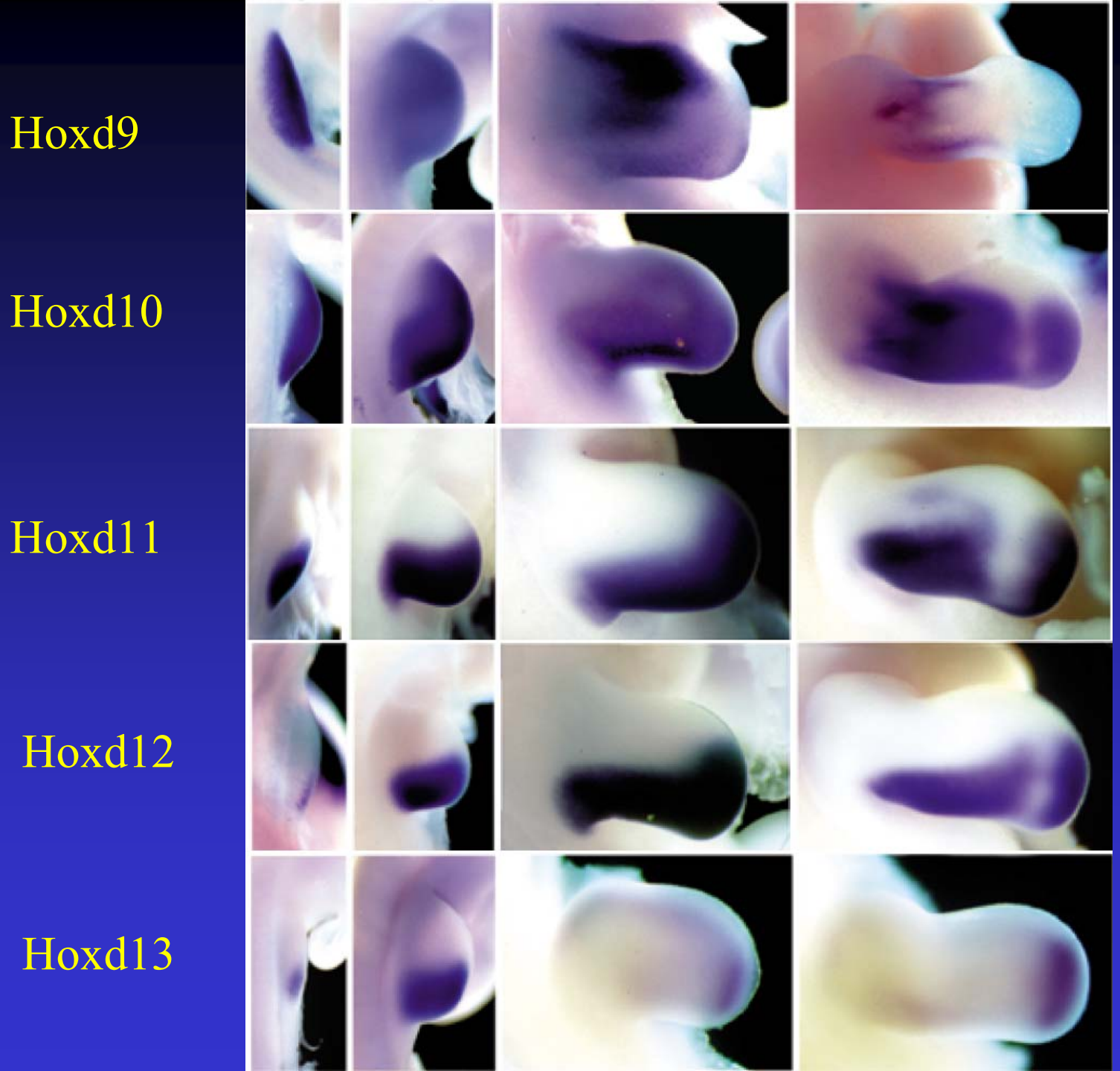




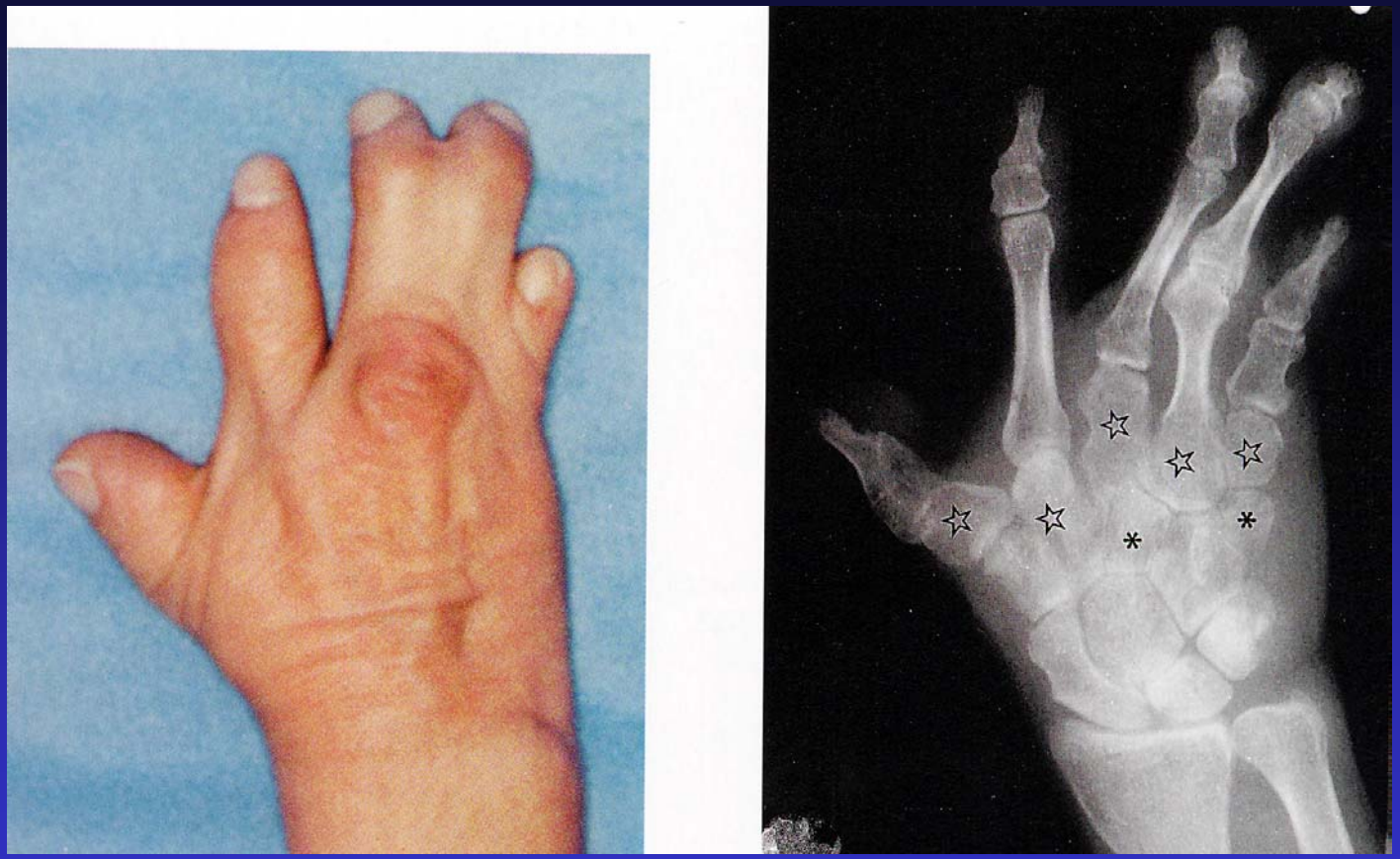





Direction of transcription of ANT-C and BX-C genes
Chromosome
3'
5'
Drosophila
lab
pb
Dfd
Scr
Antp
Ubx
Abd-A
Abd-B
3
Anterior
ANT-C
BX-C
Posterior (tissue expression)
Paralogous group
1 2 3 4 5 6 7 8 9 10 11 12 13
Hoxa (Hox-1)
A1 A2 A3 A4 A5 A6 A7 A9 A10 A11 A13
Human 1F 1K 1E 1D 1C 1B 1A 1G 1H 1I 1J 7
Mouse 1.6 1.11 1.5 1.4 1.3 1.2 1.1 1.7 1.8 1.9 1.10 6
Hoxb (Hox-2)
B1 B2 B3 B4 B5 B6 B7 B8 B9
Human 2I 2H 2G 2F 2A 2B 2C 2D 2E 17
Mouse 2.9 2.8 2.7 2.6 2.1 2.2 2.3 2.4 2.5 11
Hoxc (Hox-3)
C4 C5 C6 C8 C9 C10 C11 C12 C13
Human 3E 3D 3C 3A 3B 3I 3H 3F 3G 12
Mouse 3.4 3.3 3.1 3.2 3.6 3.7 15
Hoxd (Hox-4)
D1 D3 D4 D8 D9 D10 D11 D12 D13
Human 4G 4A 4B 4E 4C 4D 4F 4H 4I 2
Mouse 4.9 4.1 4.2 4.3 4.4 4.5 4.6 4.7 4.8 2
3'
5'
Direction of transcription of Hox genes


Hoxd9
Hoxd10
Hoxd11
Hoxd12
Hoxd13

Synpolydactyly / HOXD13



Digit fusions

Supernumerary carpals

Transformation of metacarpal to carpals

Developmental Disorders

General Principles

Causes:

Genetic

Environmental (Maternal, Physical, Chemical)

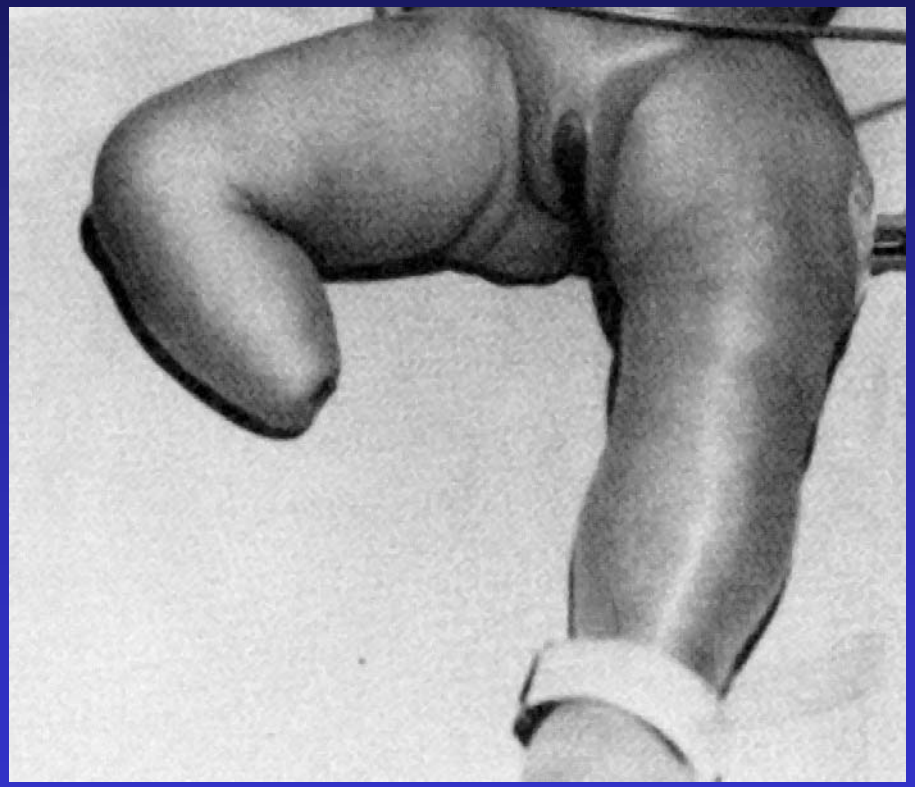
Mechanisms (Retinoic Acid)

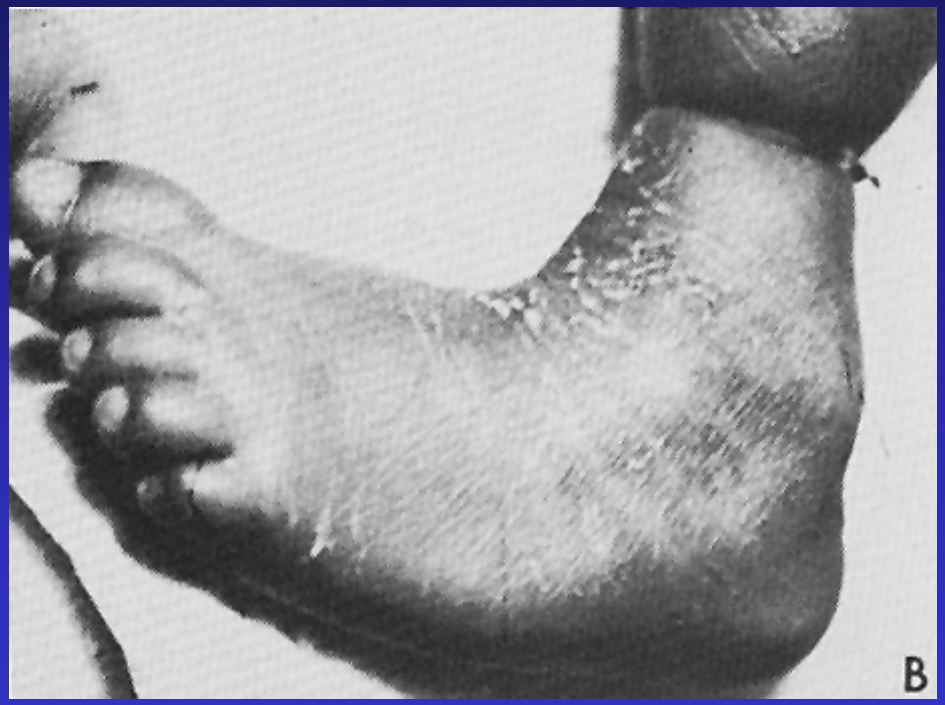
Environmental Causes

Maternal Infections

Infectious agent	Disease	Congenital defects
VIRUSES		
Rubella virus	German measles	Cataracts, deafness, cardiovascular defects, fetal growth retardation
Cytomegalovirus	Cytomegalic inclusion disease	Microcephaly, microphthalmia, cerebral calcification, intrauterine growth retardation
SPIROCHETES		
Treponema pallidum (syphilis)	Syphilis	Dental anomalies, deafness, mental retardation, skin and bone lesions, meningitis
PROTOZOA		
Toxoplasma gondii	Toxoplasmosis	Microcephaly, hydrocephaly, cerebral calcification, microphthalmia, mental retardation, prematurity

Physical Causes (ABS)

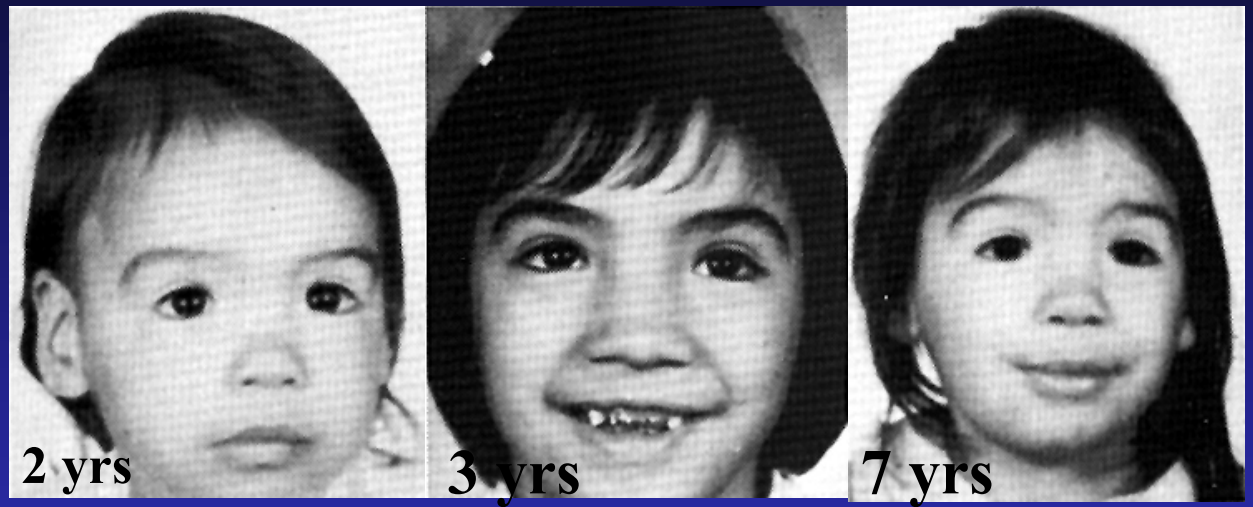




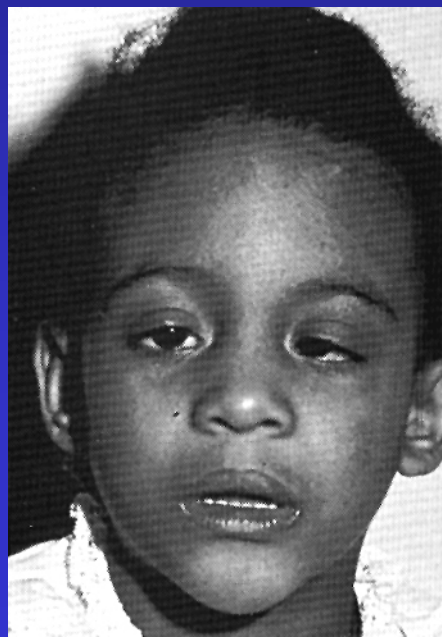
Chemical Causes

Agent	Effects
Alcohol	Growth and mental retardation, microcephaly, various malformations of face and trunk
Androgens	Masculinization of females, accelerated genital development in males
Anticoagulants (warfarin, dicumarol)	Skeletal abnormalities; broad hands with short fingers; nasal hypoplasia; anomalies of eye, neck, central nervous system
Antithyroid drugs (e.g., propyl-thiouracil, iodide)	Fetal goiter, hypothyroidism
Chemotherapeutic agents (metho-trexate, aminopterin)	Variety of major anomalies throughout body
Diethylstilbestrol	Cervical and uterine abnormalities
Lithium	Heart anomalies
Organic mercury	Mental retardation, cerebral atrophy, spasticity, blindness
Phenytoin (Dilantin)	Mental retardation, poor growth, microcephaly, dysmorphic face, hypoplasia of digits and nails
Isotretinoin (Accutane)	Craniofacial defects, cleft palate, ear and eye deformities, nervous system defects
Streptomycin	Hearing loss, auditory nerve damage
Tetracycline	Hypoplasia and staining of tooth enamel, staining of bones
Thalidomide	Limb defects, ear defects, cardiovascular anormalies
Trimethadione and paramethadione	Cleft lip and palate, microcephaly, eye defects, cardiac defects, mental retardation
Valproic acid	Neural tube defects

Fetal Alcohol Syndrome



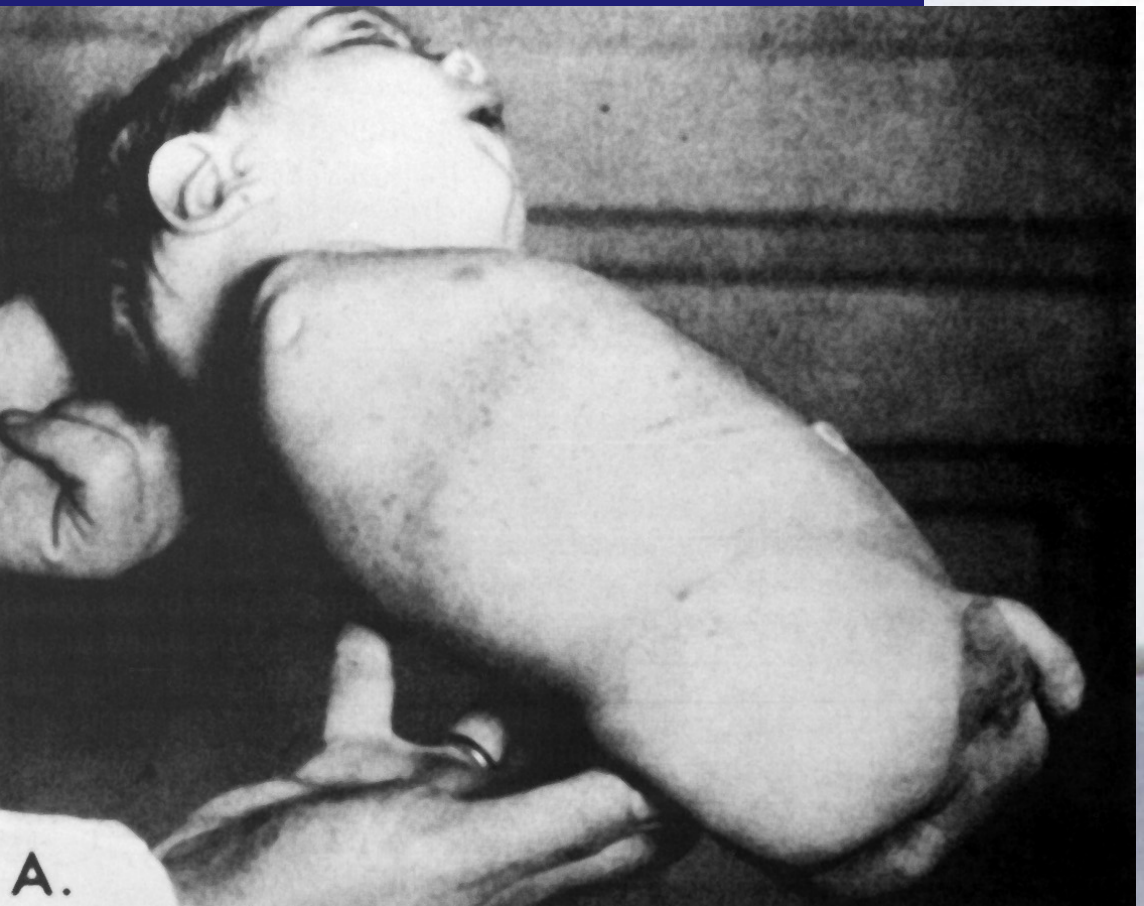
- Growth deficiency
- Low IQ (average = 63)
- Mild to moderate microcephaly
- Short nose, smooth philtrum, thin upper lip
- Heart murmur
- Small distal phalanges

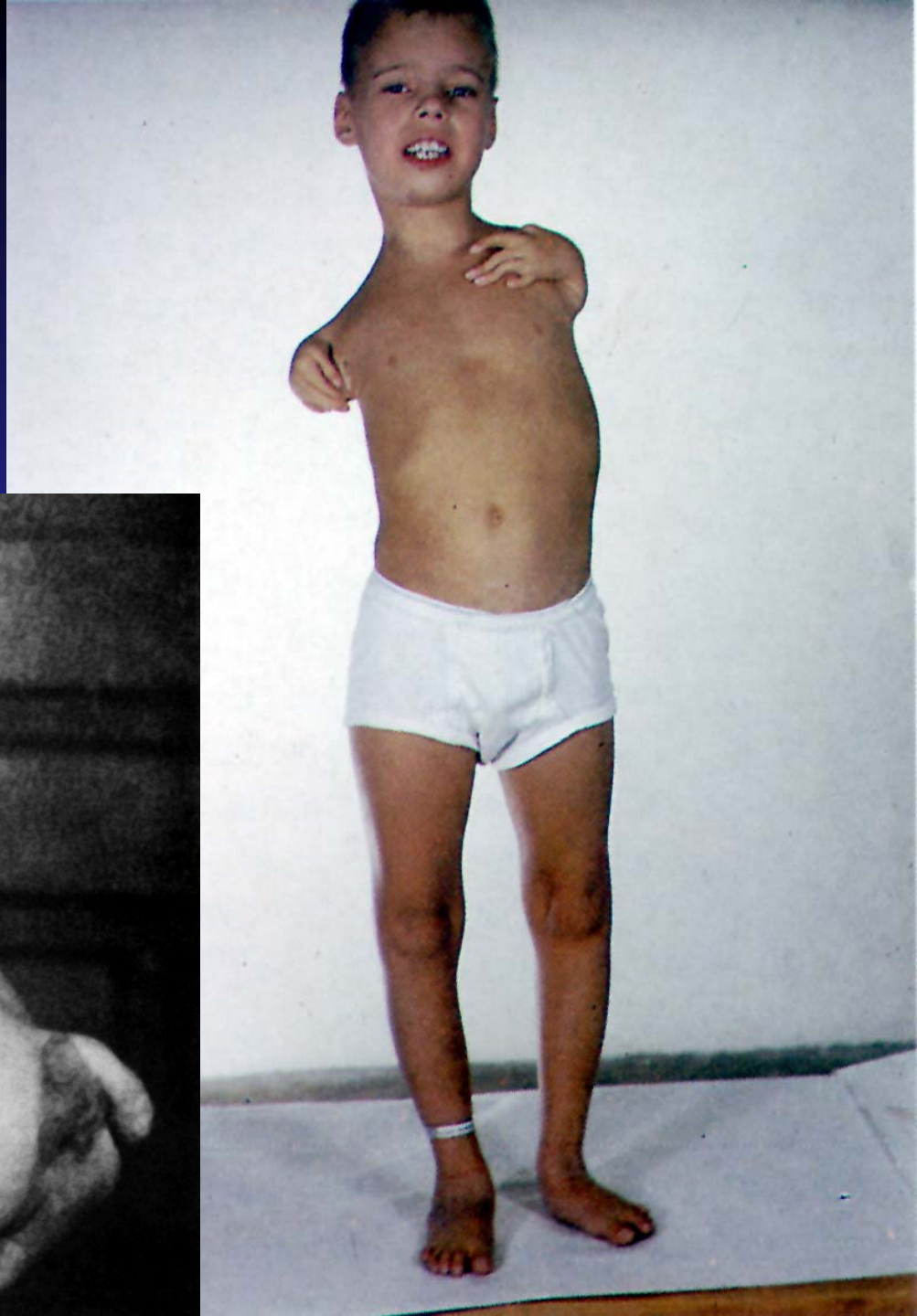


Thalidomide

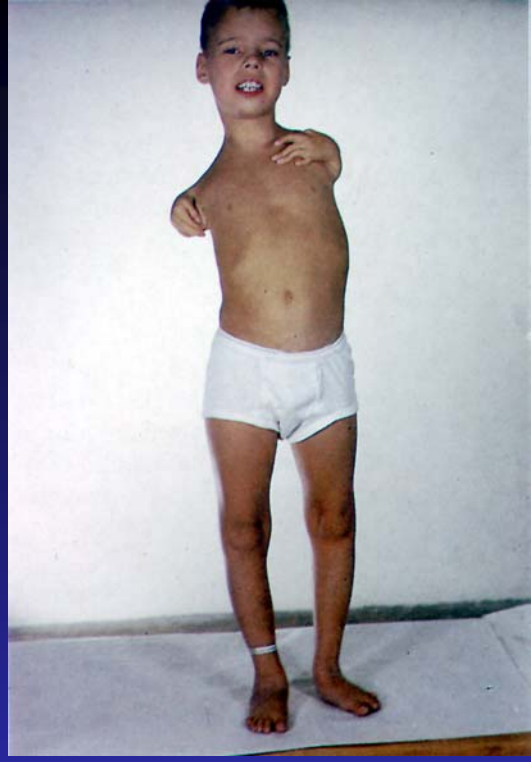
Phocomelia (short limbs)

Amelia (no limbs)





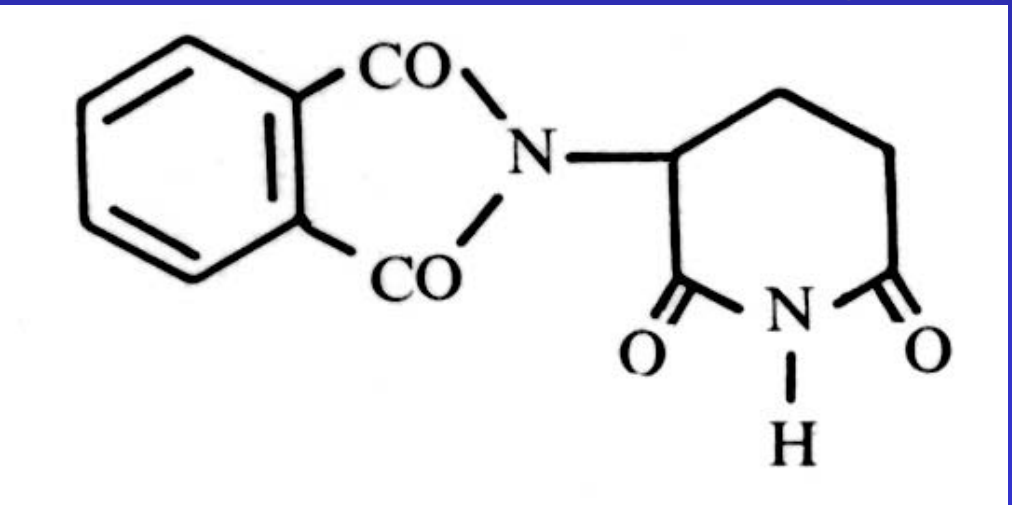
Thalidomide History



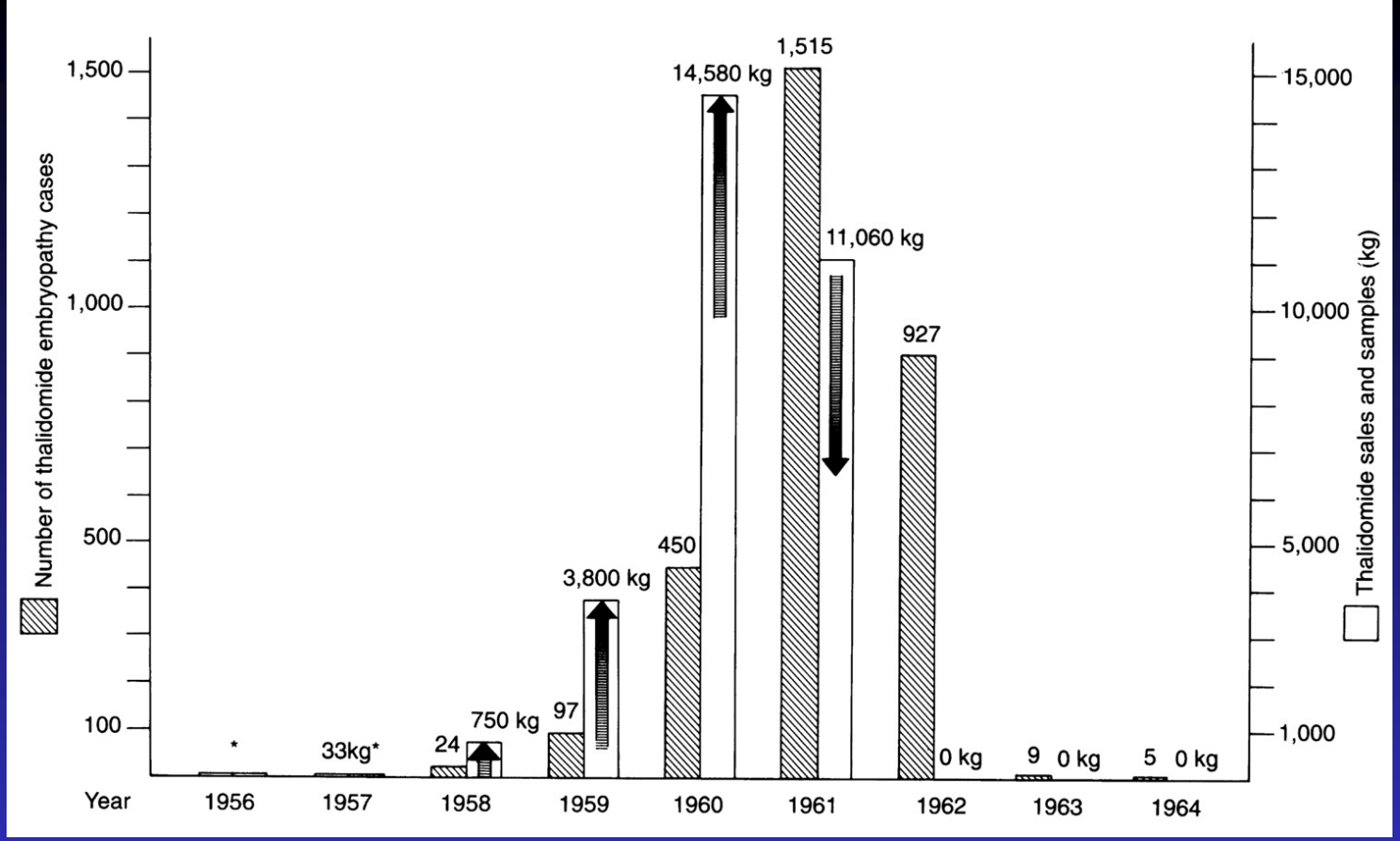
1954 – Chemists synthesize thalidomide – trying to produce a new anti-histomine – instead they discover that it is an effective sedative

1956 – Free samples to workers at the manufacturing plant – a baby without ears

1957 –Marketed by Chemie Grunenthal in Germany – as a wonder drug – no side effects. It was prescribed to women to combat morning sickness associated with pregnancy



Thalidomide has no effect on rodent embryos (standard testing).

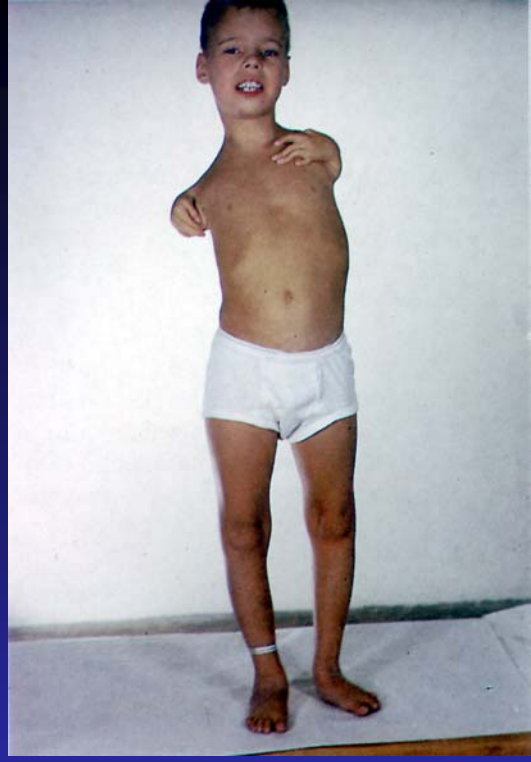


Thalidomide was sold over the counter in some countries, it was immediately popular and taken like aspirin

Babies born with severe limb defects began to increase.

Spatial correlation of defects – spreading from Germany to regions of high use

Thalidomide History



1961 (December) – First published correlation between Thalidomide and birth defects – based on 3 babies

1962 (Summer) – Thalidomide taken off the market

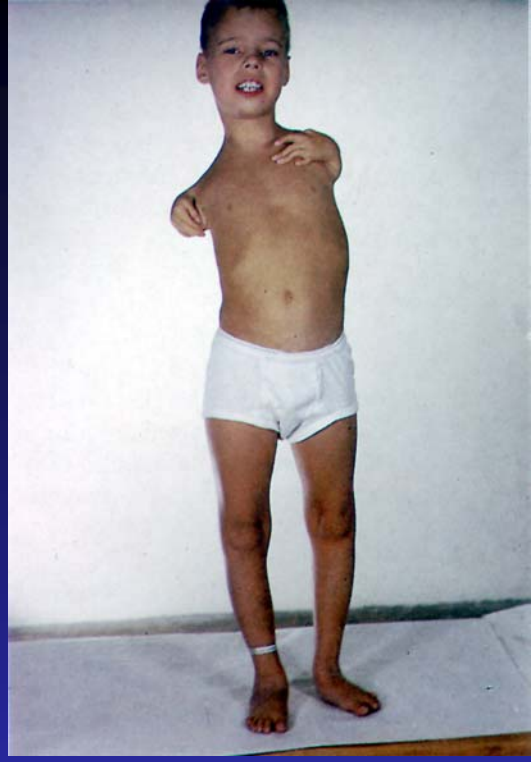
12,000 Thalidomide babies born / 8,000 Thalidomide babies survived

Many are alive today – they are in their late 30's and early 40's

Spectrum of malformations (besides limbs): Absence of ears, deafness, Defects of eye and facial muscles, Malformations of heart, bowel, uterus, gallbladder

2-Week sensitive period - 35 days to 49 days

Thalidomide History



1965 – Thalidomide is found to be a significant treatment for Leprosy patients that develop severe skin lesions assoicated with an inflammatory reaction (erythema nodosum leprosum, ENL) – Thalidomide is the treatment of choice

Brazil begins manufacturing Thalidomide for use with leprosy treatment.

Brazil now has a new generation of Thalidomide children.

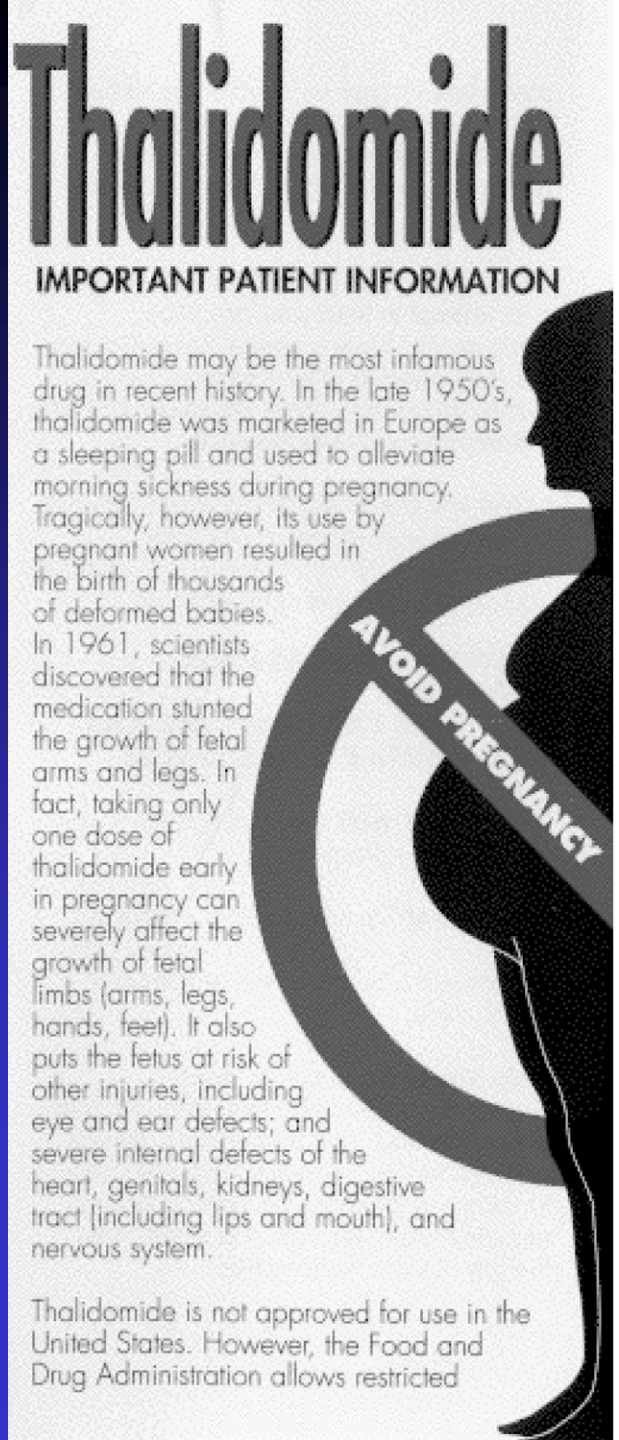
Thalidomide History

1980's – Thalidomide is shown to be a effective in treating other diseases involving ulceration or lesions, including HIV-related symptoms.

1990's – A black market for Thalidomide emerges in the US

Thalidomide is in clinical trials as an anti-angiogenesis agent for the treatment of Cancer

1998 – FDA approves Thalidomide for treatment of ENL



Today – Thalidomide's mechanism of action in embryopathy or in clinical treatment is unknown

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Environmental (Maternal, Physical, Chemical)

Mechanisms (Retinoic Acid)

Mechanisms – Retinoic Acid

Vitamin A – Retinol and its derivatives are called Retinoids

They are essential for the embryo and the adult

Too little – abortions

Too much - malformations

Retinoic Acid is a Teratogen and also a Morphogen for the vertebrate embryo

Retinoic Acid is used widely for treatment of skin disorders, and some Cancers.

Tradename: Accutane

Vitamin A and Human Teratology

Recommended Daily Intake (RDI) – 5,000 IU

Morphological Defects are reported at >10,000 IU (controversial) and 25,000 IU (generally accepted)

Defects: Cranial neural crest cell migration, axial patterning.

Accutane (isotretinoin) = 13-cis-RA; used to treat severe cystic acne

Therapeutic doses – 0.5-1.5 mg/kg.

Defects during 1st trimester: spontaneous abortion and severe malformations

Etretinate (synthetic retinoid) – used to treat psoriasis,

Defects: spontaneous abortion, severe malformations

One case of an infant conceived 1 yr after termination of treatment – stored in maternal adipose tissue

Accutane

13-cis-retinoic acid

Licensed in 1982; Recognized as human teratogen in 1983

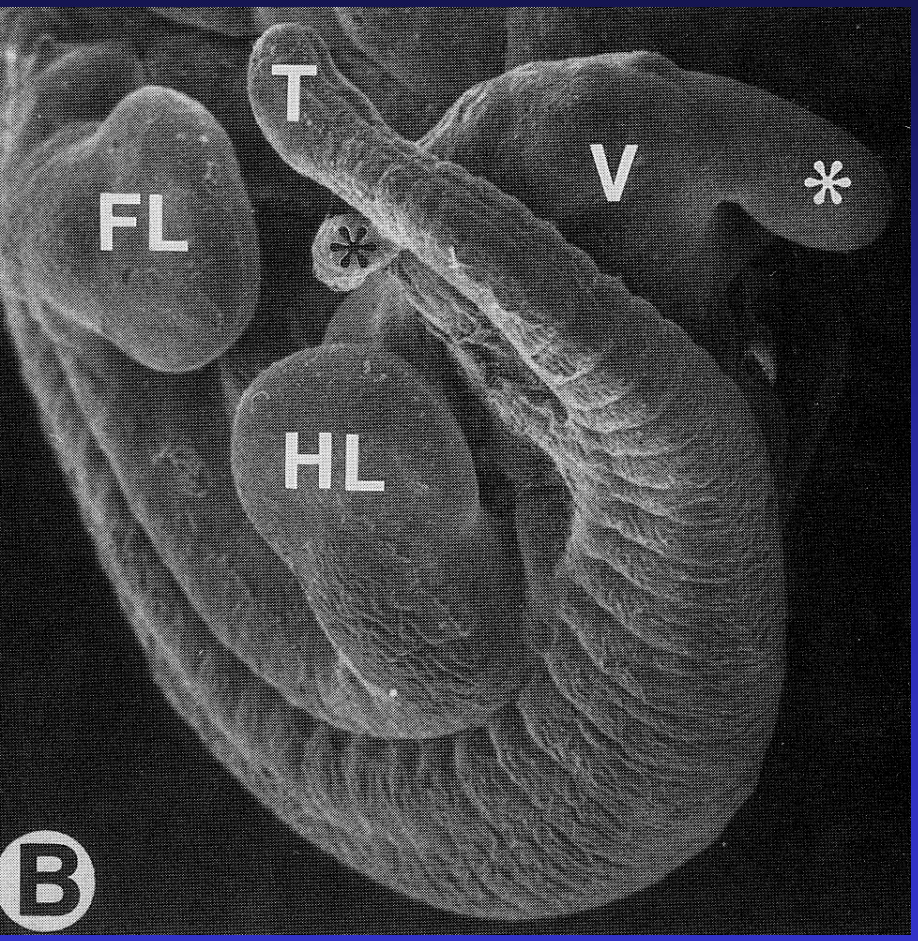
Hydrocephalus – problems with cortical and cerebellar cell migration (IQ ~70)

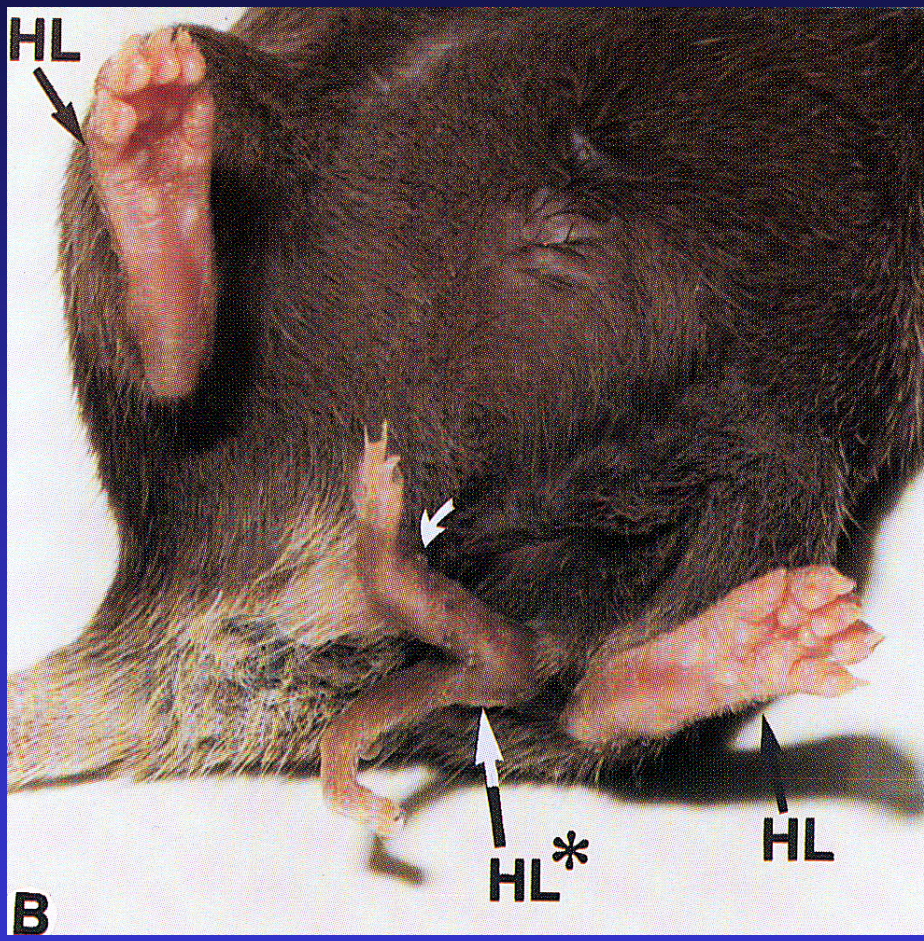
Craniofacial – facial assymetry, ear defects

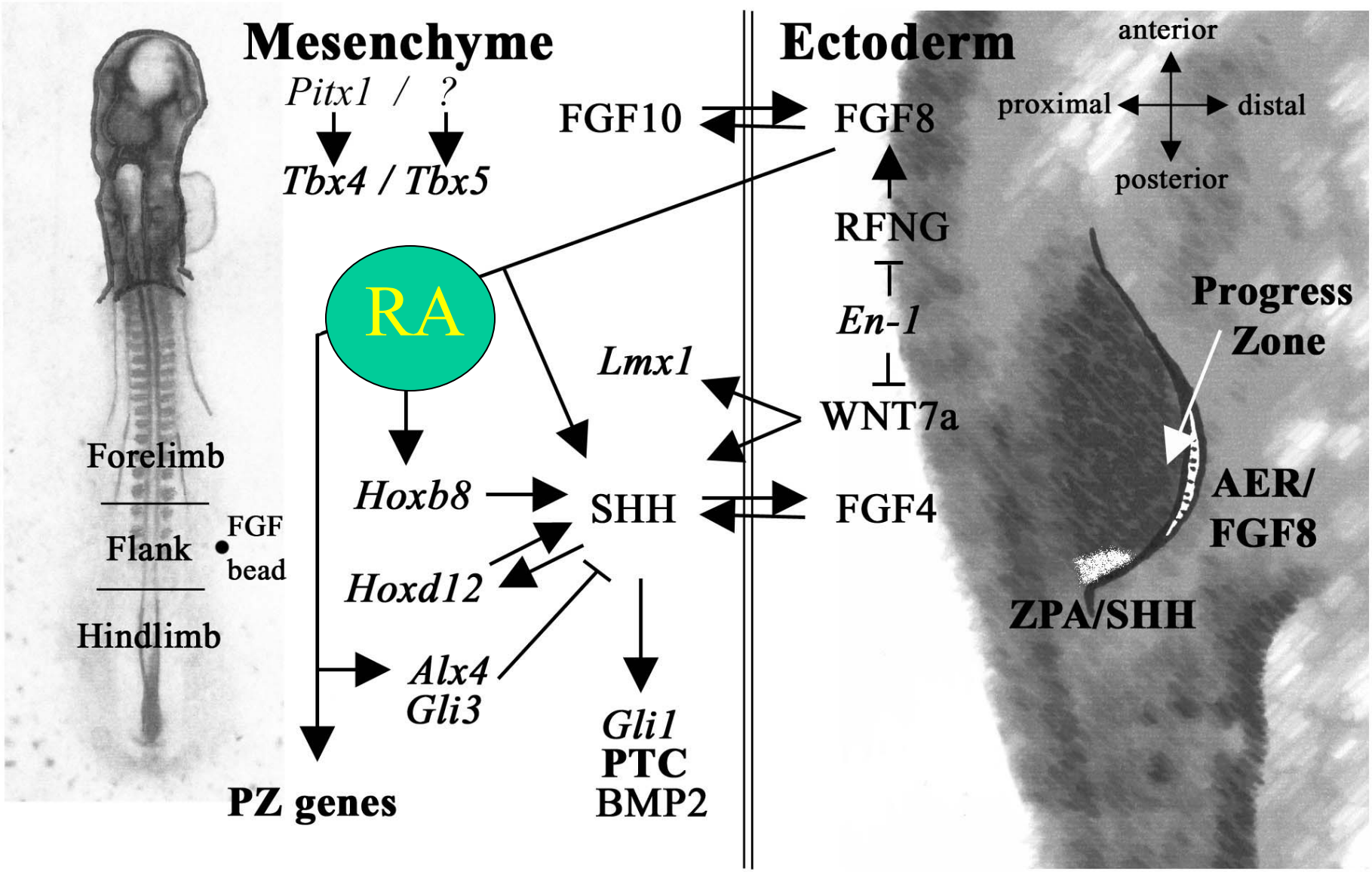
Heart defects

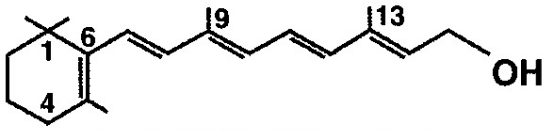
RA and Limb Development

RA Induces Extra Limbs

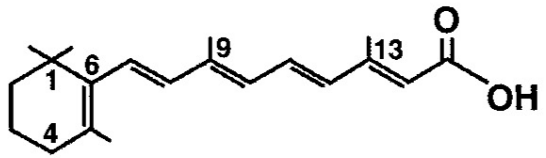




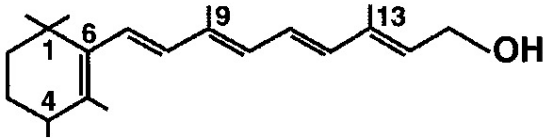

Mesenchyme
Ectoderm
Pitx1 / ?
Tbx4 / Tbx5
FGF10
FGF8
anterior
proximal
distal
posterior
RFNG
RA
En-1
Lmx1
WNT7a
Progress Zone
Forelimb
Flank
FGF bead
Hindlimb
Hoxb8
SHH
FGF4
AER/ FGF8
Hoxd12
ZPA/SHH
Alx4
Gli3
Gli1
PTC
BMP2
PZ genes



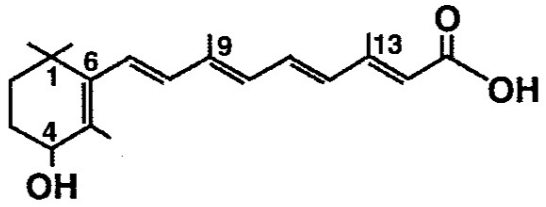
RETINOL (Vitamin A)



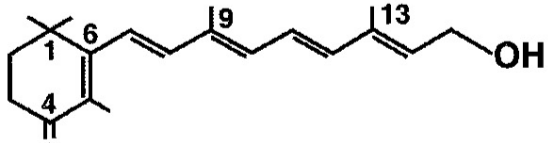
ALL-TRANS-RETINOIC ACID



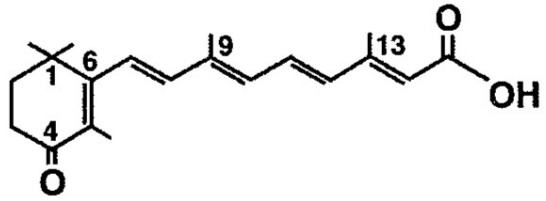
ALL-TRANS-4-HYDROXYRETINOL



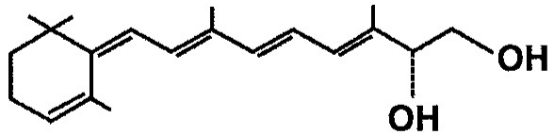
ALL-TRANS-4-HYDROXYRETINOIC ACID



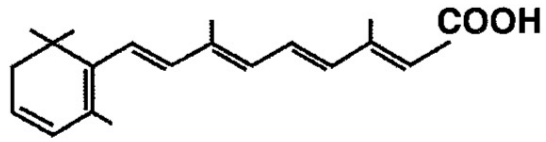
ALL-TRANS-4-OXORETINOL



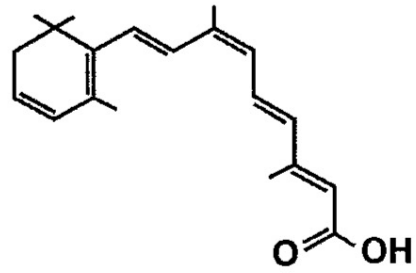
ALL-TRANS-4-OXORETINOIC ACID



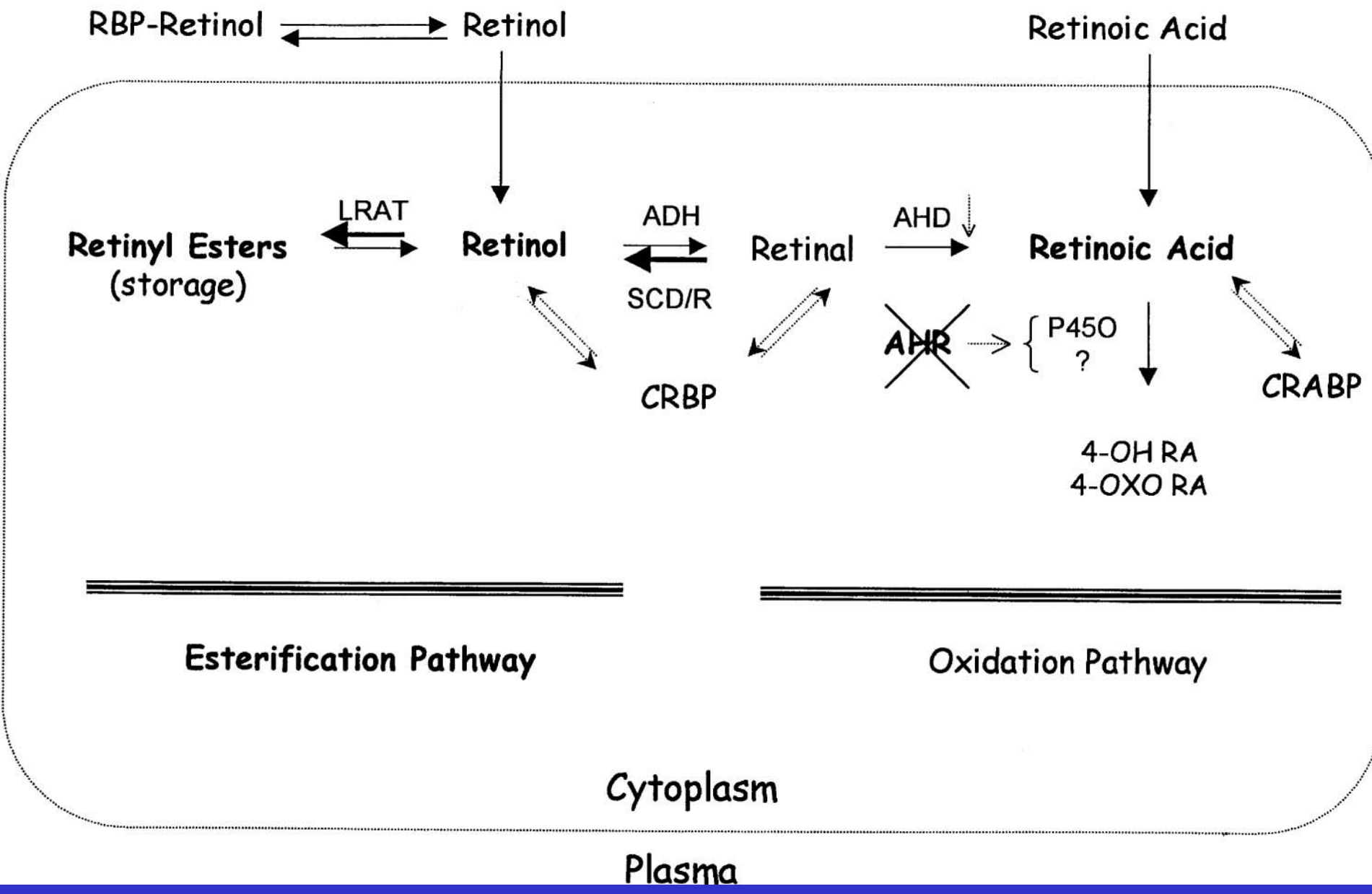
14-HYDROXYL-4, 14-RETRORETINOL



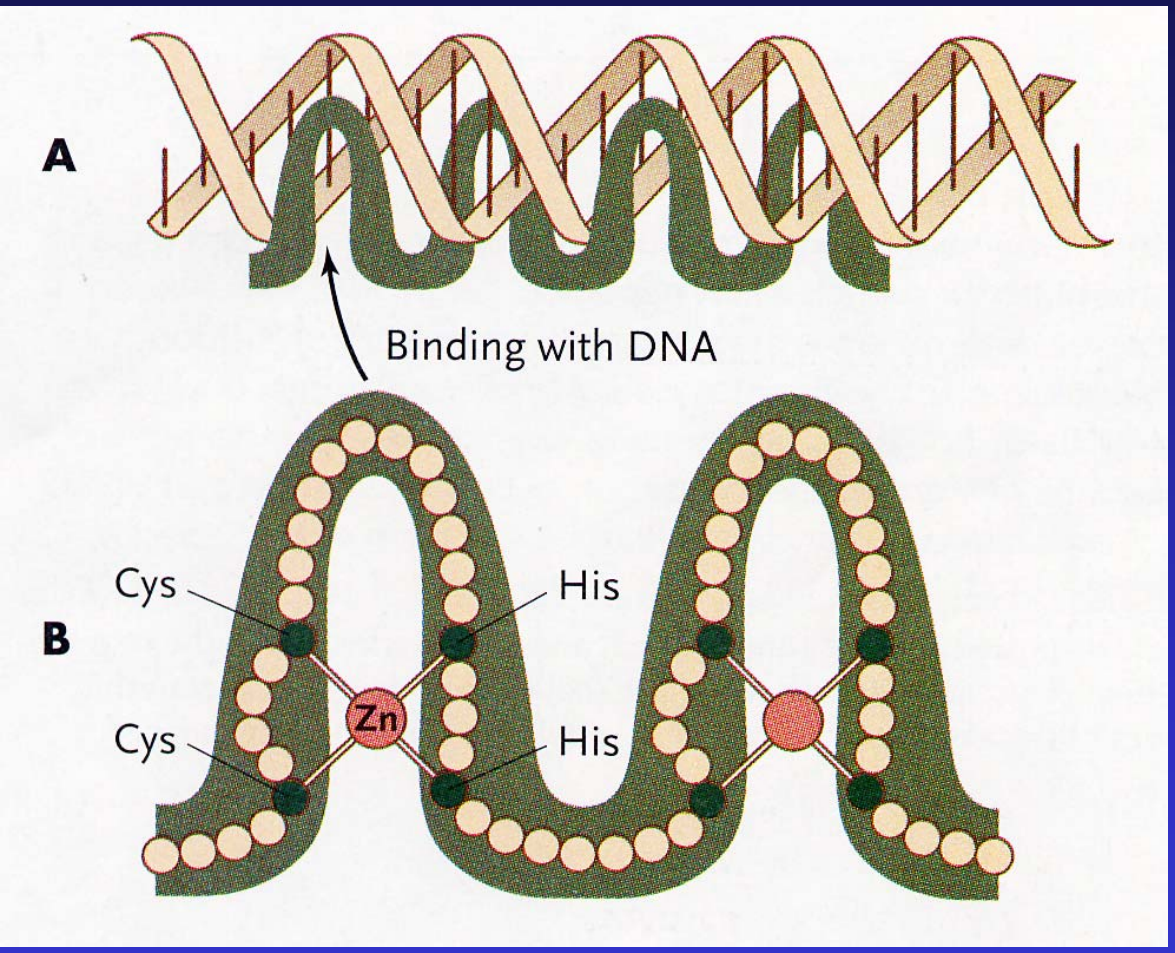
3,4-DIDEHYDRORETINOIC ACID

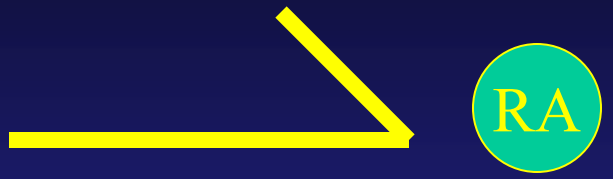


9-CIS RETINOIC ACID


RBP-Retinol
Retinol
Retinoic Acid
LRAT
Retinyl Esters
(storage)
Retinol
ADH
SCD/R
Retinal
AHD
Retinoic Acid
AHR
P450
?
CRBP
CRABP
4-OH RA
4-OXO RA
Esterification Pathway
Oxidation Pathway
Cytoplasm
Plasma

Retinoic Acid Receptor



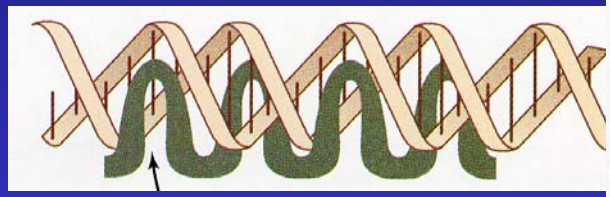


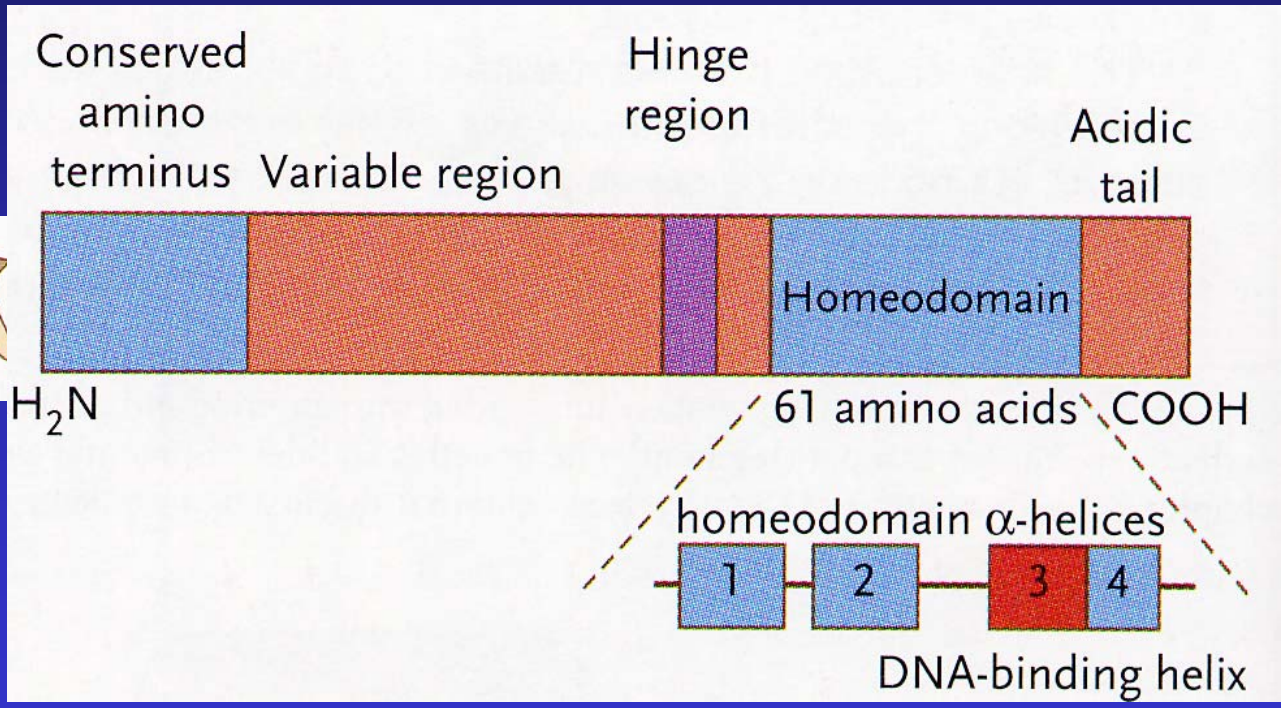
Inactive

Active

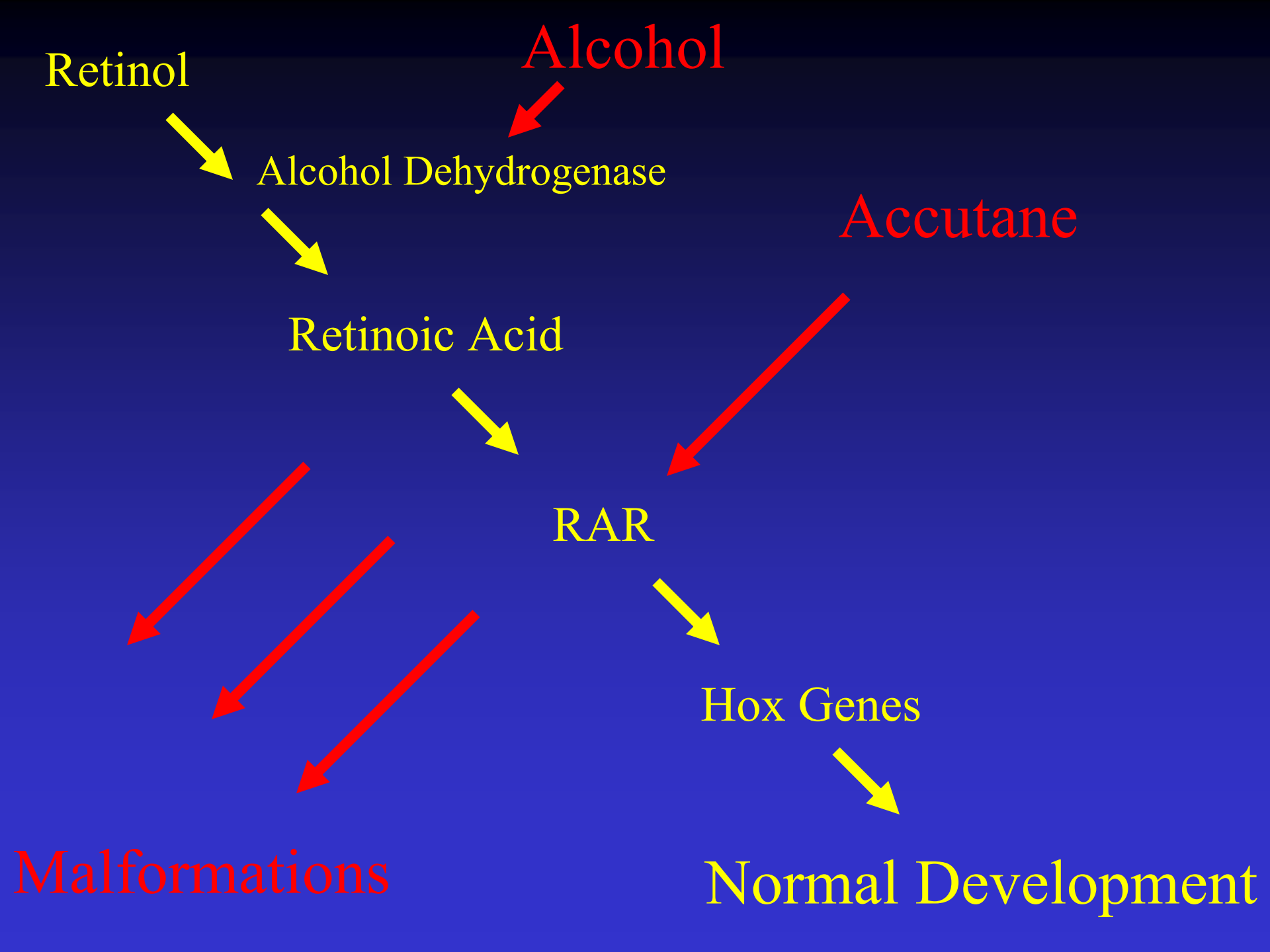
RA Controls Some Hox Genes

RA-RAR





HOX Genes


Retinol
Alcohol
Alcohol Dehydrogenase
Accutane
Retinoic Acid
RAR
Hox Genes
Malformations
Normal Development