Teratology

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Mrs. B

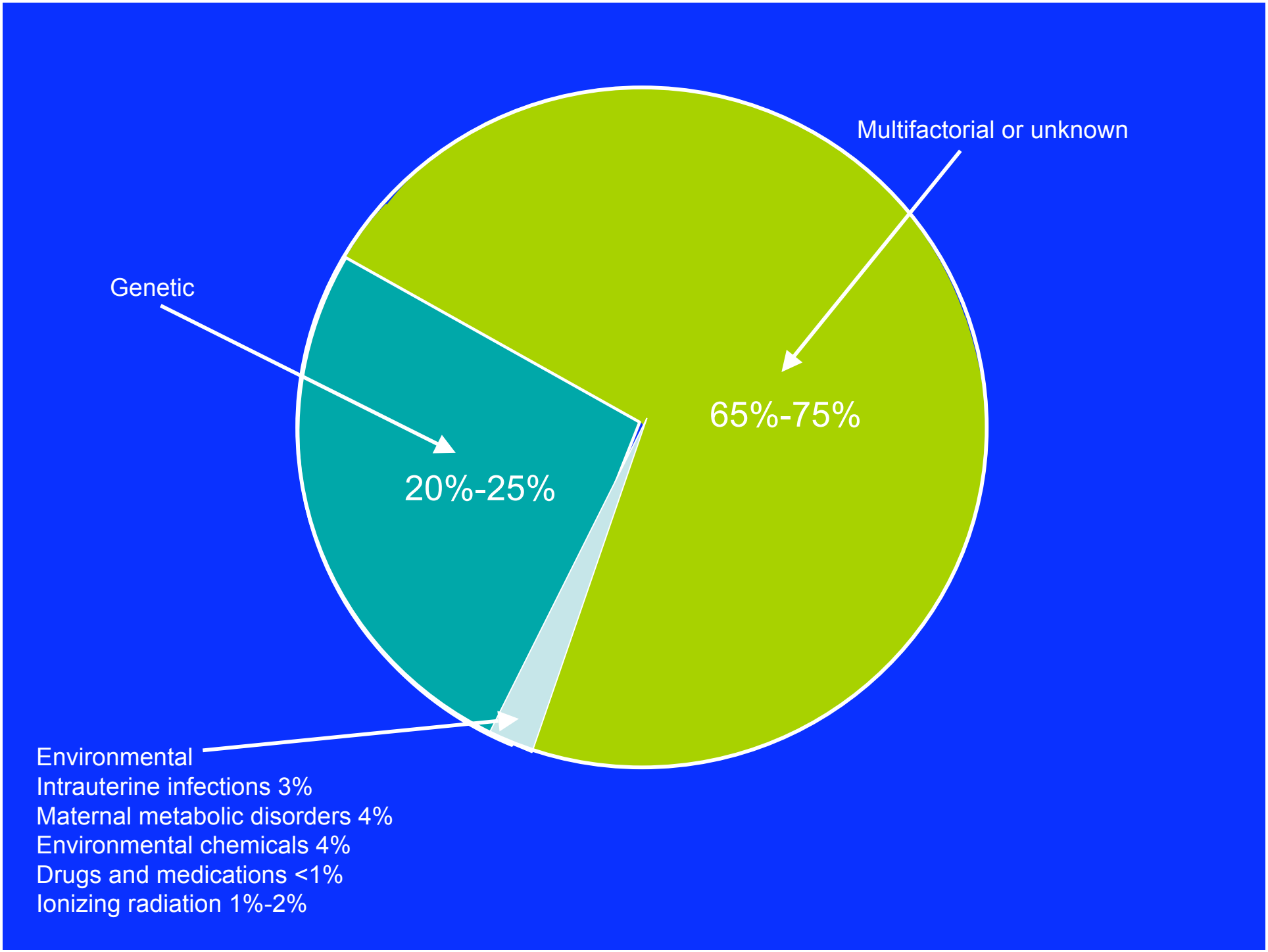
- 30 year old woman comes to you because her 20 week prenatal ultrasound showed a hole in the heart
- Patient and her husband have many questions:
  - What caused this birth defect?
  - Was it caused by the glass of wine she had before she found out she was pregnant?
  - Will there be other problems for this child?
  - If they have other children, what is the risk of recurrence?

Teratology

- The study of abnormal development in embryos and the causes of congenital malformations or birth defects

Birth Defects

- Observed in 3% of newborns
- Observed in another 3% of children later
- May or may not be outwardly visible
- Etiology: genetic and environmental

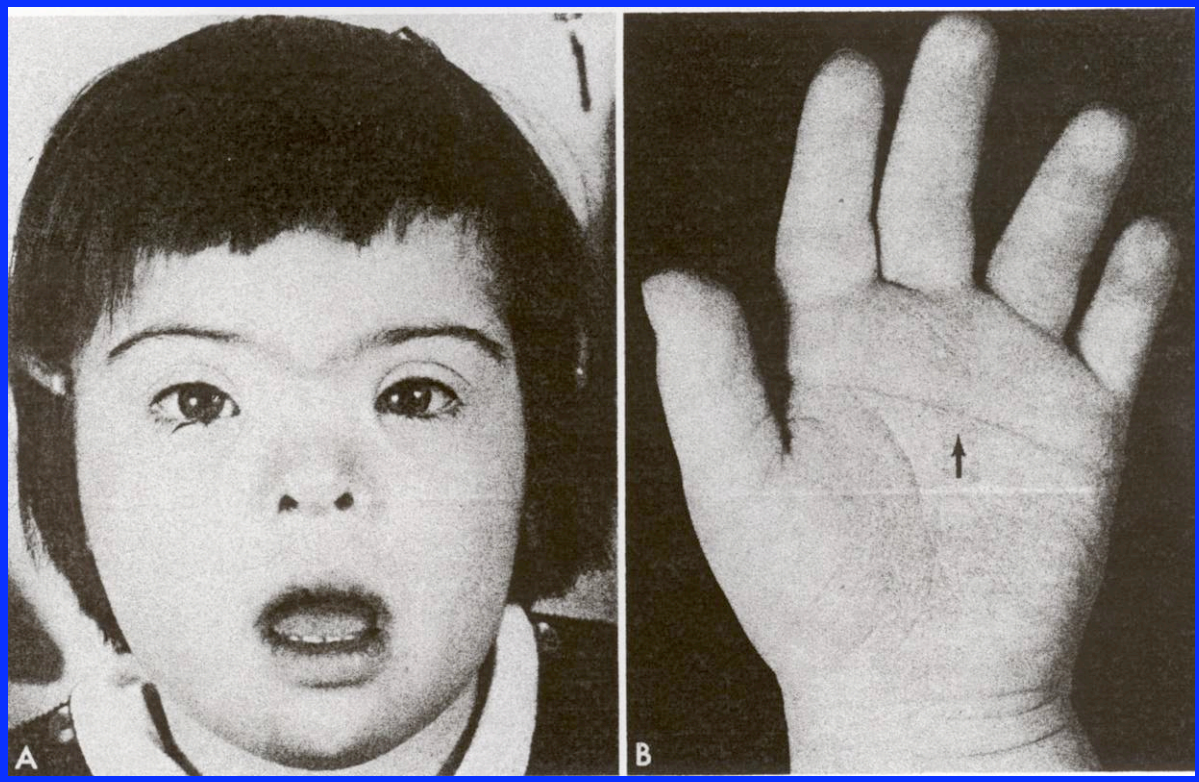

Multifactorial or unknown
Genetic
65%-75%
20%-25%
Environmental
Intrauterine infections 3%
Maternal metabolic disorders 4%
Environmental chemicals 4%
Drugs and medications <1%
Ionizing radiation 1%-2%

Major and Minor Anomalies

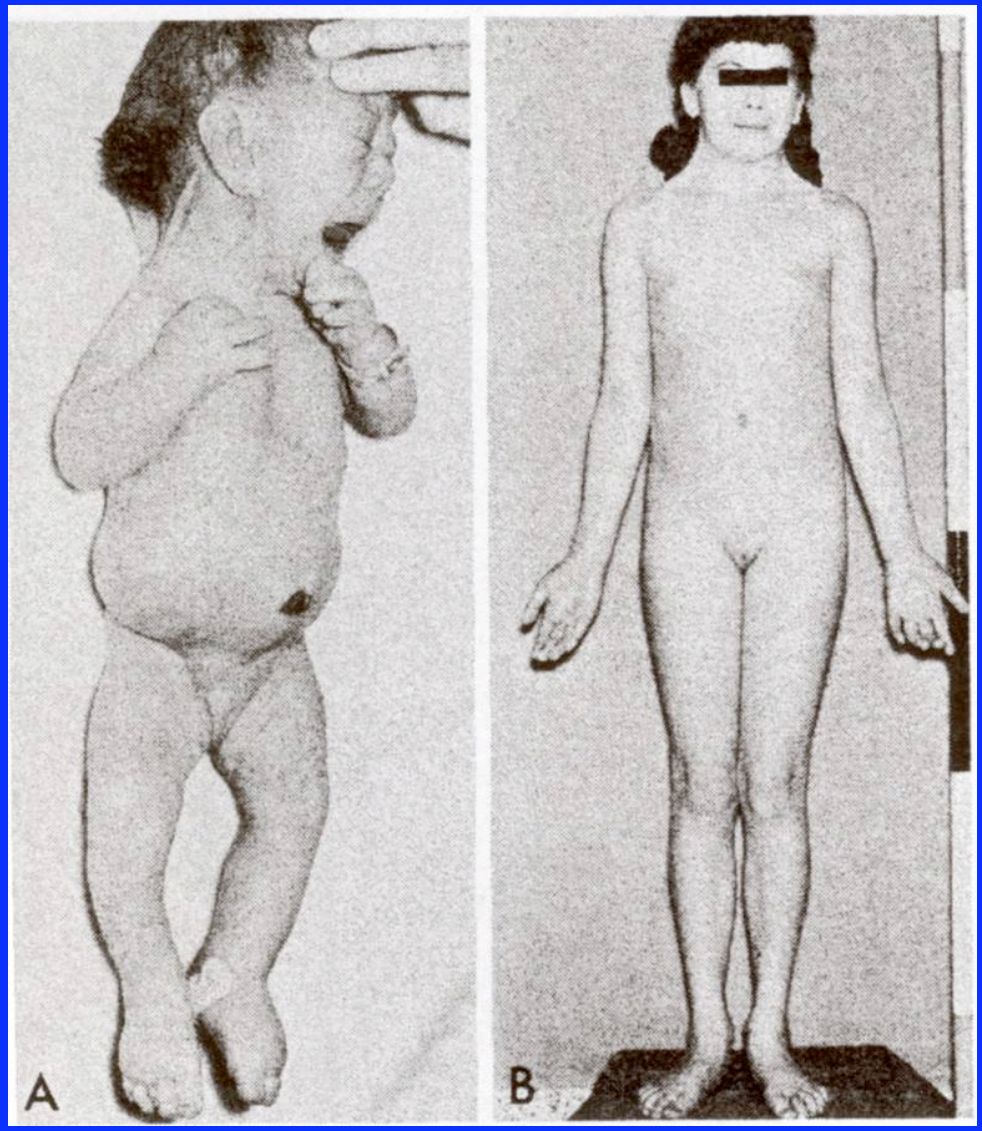
- Major anomalies: life/health threatening
- Minor anomalies: cosmetic

- The greater the number of minor anomalies, the greater the likelihood of a major anomaly
- Certain minor anomalies suggest specific major anomalies

Down Syndrome



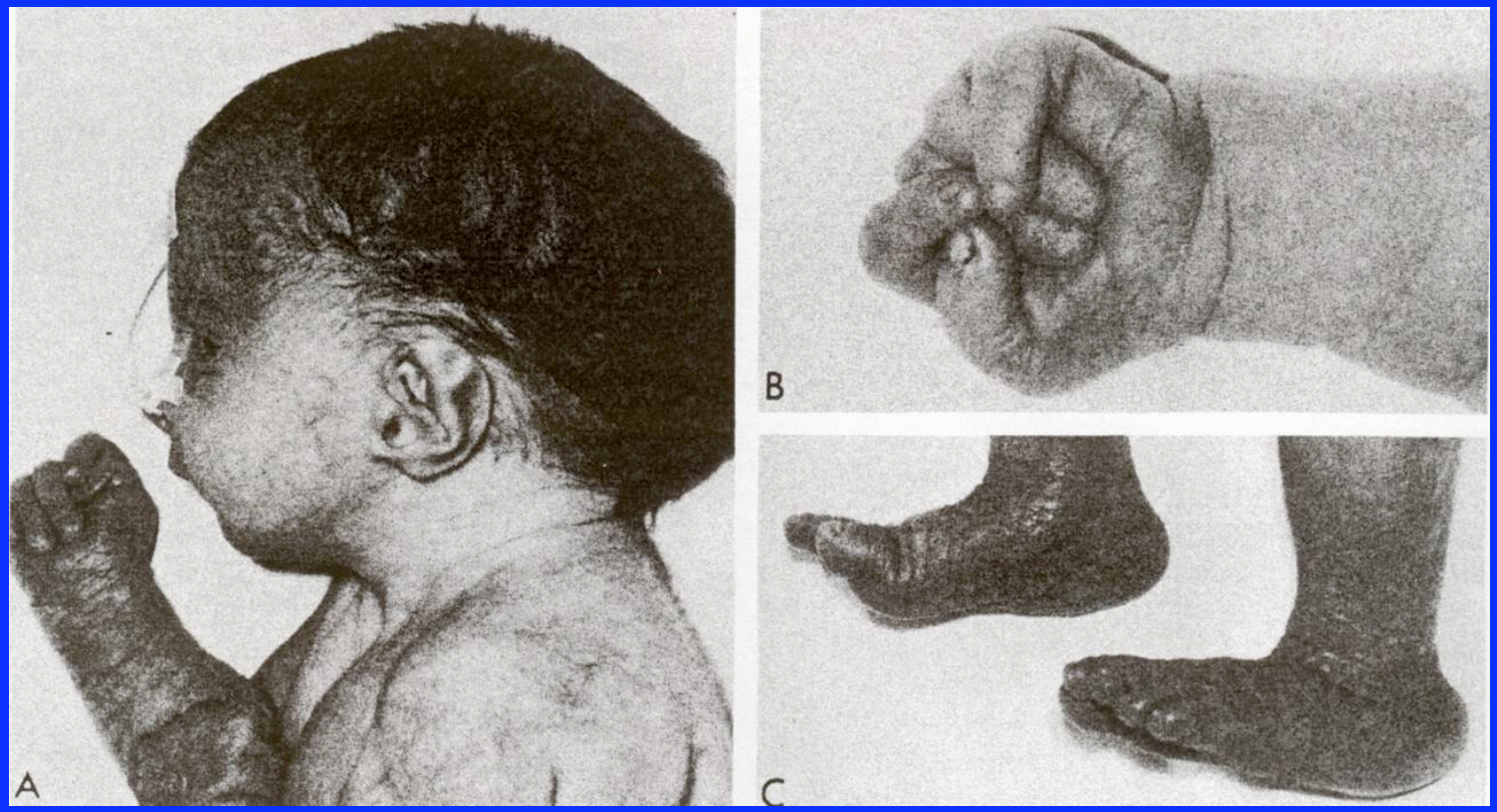
Turner Syndrome



Trisomy 13

- Midline defects (cleft lip and cleft palate)
- Central nervous system malformations
- Micro-ophthalmia
- Congenital heart disease
- Poor growth

Trisomy 18



Mrs. B

- Extensive ultrasound examination does not identify other major anomalies
- Can minor anomalies be excluded?

- An amniocentesis is performed and is normal
- Are genetic etiologies excluded?

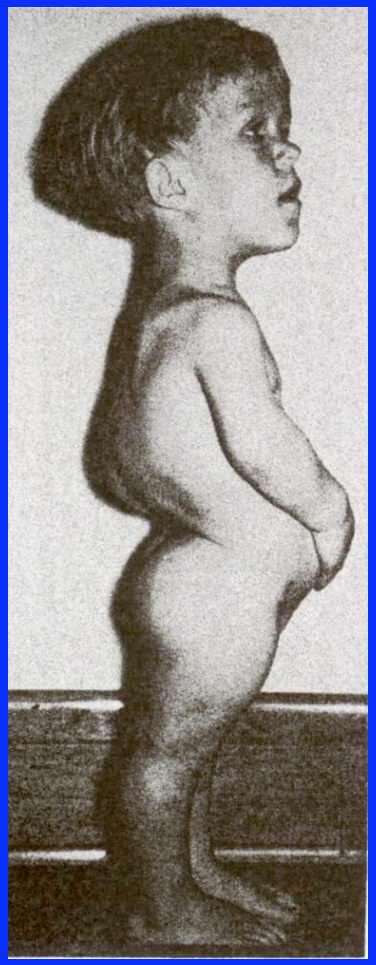
Inborn Errors of Metabolism Causing Birth Defects

- Smith Lemli Opitz
- Congenital disorders of glycosylation
- Fatty acid oxidation disorders

Single genes cause developmental disorders

- PAX6: aniridia
- NEUROD1: pancreatic agenesis
- TTF1: thyroid agenesis
- NKX2.5: congenital heart disease
- ZIC3: holoprosencephaly
- Doublecortin: lissencephaly

Achondroplasia



Teratogens

- A chemical, infectious agent, physical condition, or deficiency that, on fetal exposure, can alter fetal morphology or subsequent function
- Teratogenicity depends upon the ability of the agent to cross the placenta
- The embryo is most susceptible to teratogenic agents during periods of rapid differentiation

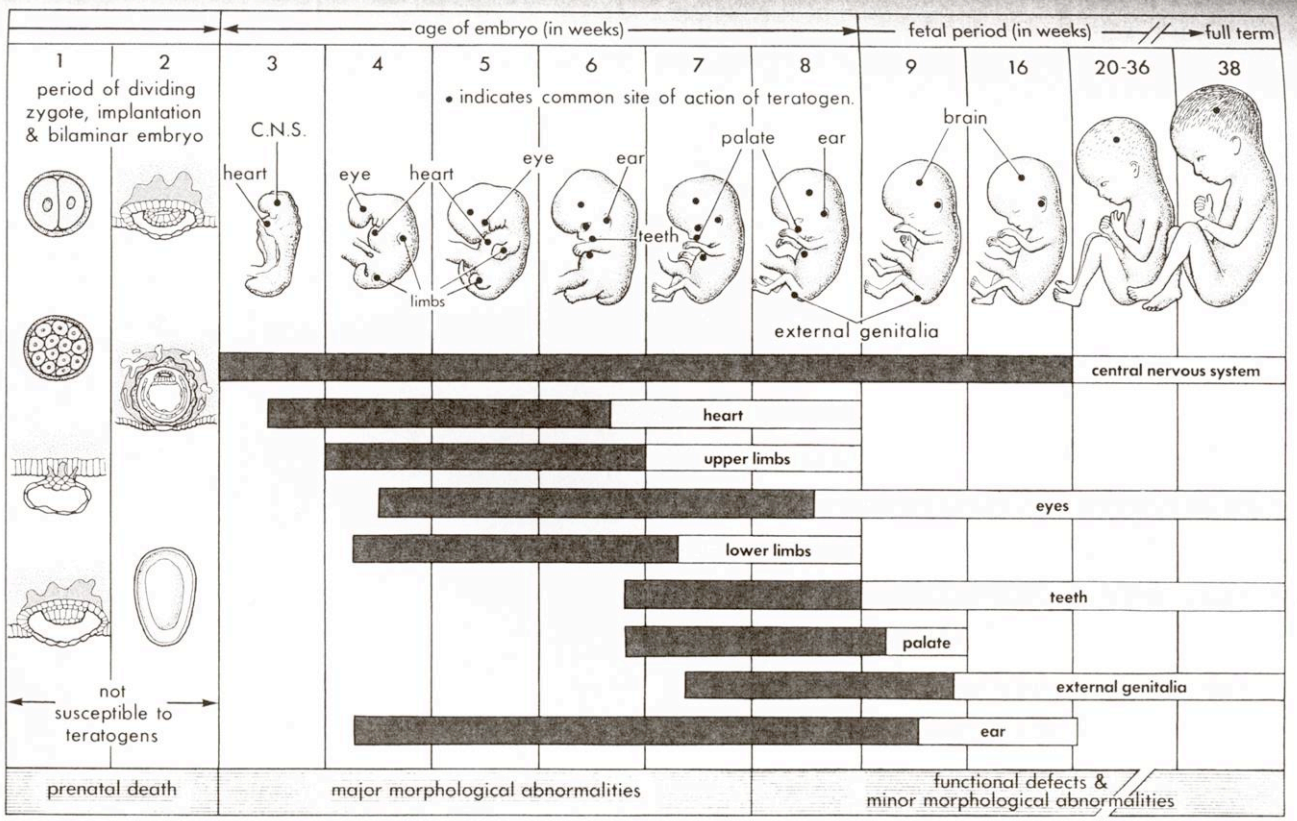


Figure 8–14. Schematic illustration of the critical periods in human development. During the first two weeks of development, the embryo is usually not susceptible to teratogens. During these predifferentiation stages, a substance either damages all or most of the cells of the embryo, resulting in its death, or damages only a few cells, allowing the embryo to recover without developing defects. Red denotes highly sensitive periods; yellow indicates stages that are less sensitive to teratogens. Severe mental retardation may result from the exposure of the embryo/fetus to certain teratogenic agents, e.g., high levels of radiation during the 8- to 16-week period.

Tissue	Malformation	Defect	Timing of Cause	Additional Information
Central nervous system	Holoprosencephaly	Prechordal mesoderm	23 days	Associated facial defects
	Anencephaly	Closure of anterior neural tube	26 days	Subsequent degeneration of forebrain
	Meningomyelocele	Closure in portion of posterior neural tube	28 days	80% lumbosacral
Face	Cleft lip	Closure of lip	36 days	42% associated with cleft palate
	Branchial sinus or cyst	Resolution of branchial cleft	8 weeks	Preauricular and along line anterior to sternocleidomastoid
	Robin sequence	Early mandibular hypoplasia	9 weeks	U-shaped posterior cleft palate
	Cleft maxillary palate	Fusion of maxillary palatal shelves	10 weeks	
Neck	Esophageal atresia and tracheoesophageal fistula	Lateral septation of foregut into trachea and foregut	30 days	
	Posterior nuchal cystic hygroma	Lymphaticovenous communication	40 days	Common in XO Turner's syndrome
Abdomen	Rectal atresia with fistula	Lateral septation of cloaca into rectum and urogenital sinus	6 weeks	
	Diaphragmatic hernia	Closure of pleuroperitoneal canal	6 weeks	
	Duodenal atresia	Recanalization of duodenum	7–8 weeks	
	Malrotation of gut	Rotation of intestinal loop so that cecum lies to right	10 weeks	Associated incomplete or aberrant mesenteric attachments
	Omphalocele	Return of midgut from yolk sac to abdomen	10 weeks	
	Meckel diverticulum	Obliteration of vitelline duct	10 weeks	May contain gastric or pancreatic tissue
Genitourinary system	Extroversion of bladder	Migration of infraumbilical mesenchyme	30 days	Associated müllerian and wolffian duct defects
	Urethral obstruction sequence	Usually prostatic urethra valves	9 weeks	More common in males
	Bicornuate uterus	Fusion of lower portion of müllerian ducts	10 weeks	
	Hypospadias	Fusion of urethral folds (labia minora)	12 weeks	
	Cryptorchidism	Descent of testicle into scrotum	7–9 months	
Heart	D-transposition of great vessels	Directional development of bulbus cordis septum	34 days	
	Ventricular septal defect	Closure of ventricular septum	6 weeks	
	Patent ductus arteriosus	Closure of ductus arteriosus	9–10 months	
Limb	Aplasia of radius	Genesis of radial bone	38 days	Often accompanied by other defects of radial side of distal limb
	Severe syndactyly	Separation of digital rays	6 weeks	

How are agents determined to be teratogenic ?

- Anecdotal data in humans
- Data from animal studies

Effect of Exposure Depends on Timing

- All or none effect early
- Effect of organogenesis during embryonic development
- Effect on size and function during fetal development

Teratogens	Congenital Malformations
Androgenic Agents	
Ethisterone Norethisterone Testosterone	Varying degrees of masculinization of female fetuses: ambiguous external genitalia caused by labial fusion and clitoral hypertrophy.
Drugs and Chemicals	
Alcohol	*Fetal alcohol syndrome:* intrauterine growth retardation (IUGR); mental retardation; microcephaly; ocular anomalies; joint abnormalities; short palpebral fissures.
Aminopterin	Wide range of skeletal defects; IUGR; malformations of the central nervous system, notably meroanencephaly (a large part of the brain is absent).
Busulfan	Stunted growth; skeletal abnormalities; corneal opacities; cleft palate; hypoplasia of various organs.
Phenytoin (Dilantin)	*Fetal hydantoin syndrome:* IUGR; microcephaly; mental retardation; ridged metopic suture; inner epicanthal folds; eyelid ptosis; broad depressed nasal bridge; phalangeal hypoplasia.
Lithium carbonate	Various malformations, usually involving the heart and great vessels.
Methotrexate	Multiple malformations, especially skeletal, involving the face, skull, limbs, and vertebral column.
Large doses of retinoic acid (vitamin A).	Facial abnormalities; neural tube defects, such as spina bifida cystica (see Fig. 18–14).
Tetracycline	Stained teeth; hypoplasia of enamel.
Trimethadione	Developmental delay; V-shaped eyebrows; low-set ears; cleft lip and/or palate.
Infectious Agents	
Cytomegalovirus	Microcephaly; hydrocephaly; microphthalmia; microgyria; mental retardation; cerebral calcifications.
Herpes simplex virus	Microcephaly; microphthalmia; retinal dysplasia.
Rubella virus	Cataracts; glaucoma; chorioretinitis; deafness; microphthalmia; congenital heart defects.
Varicella	Skin scarring; muscle atrophy; mental retardation.
Venezuelan equine encephalitis	Cataracts; brain destruction.
Toxoplasma gondii	Microcephaly; mental retardation microphthalmia; hydrocephaly; chorioretinitis; cerebral calcifications.
Treponema pallidum	Hydrocephalus; congenital deafness; mental retardation; abnormal teeth and bones.
High levels of ionizing radiation	Microcephaly; mental retardation; skeletal malformations.

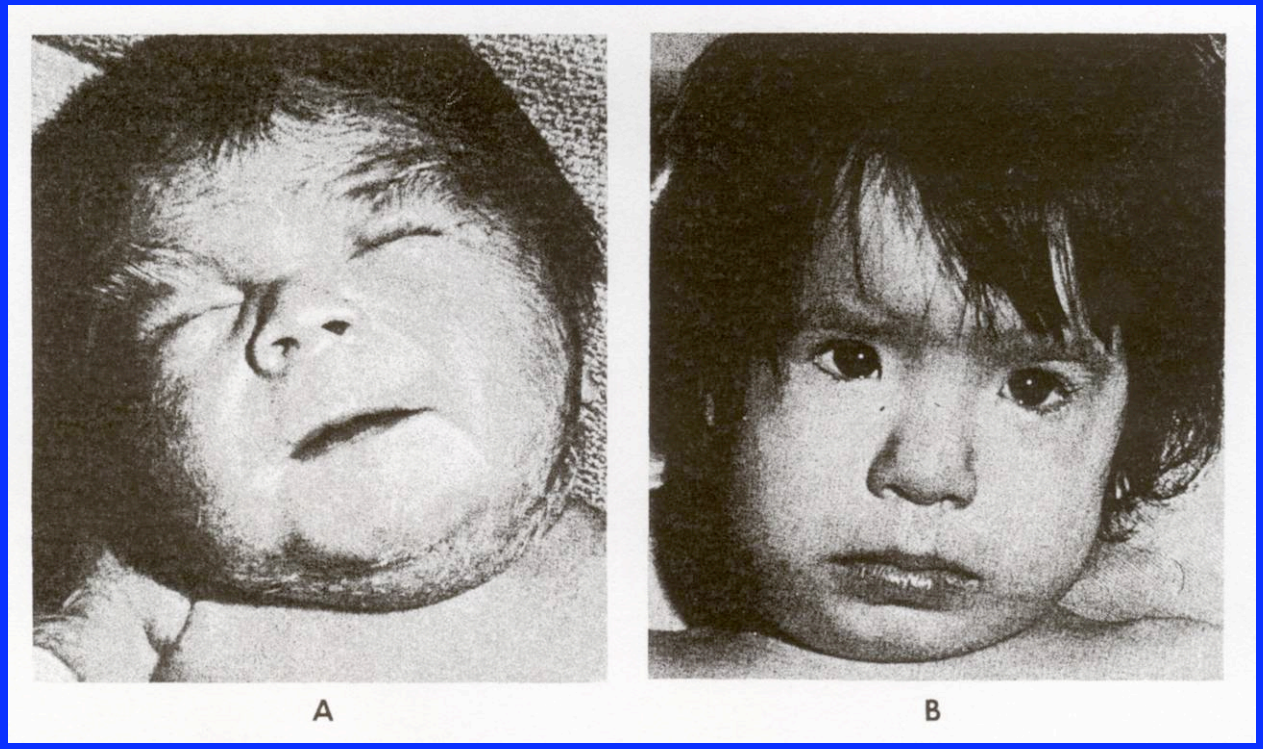
Nicotine

- IUGR
- Premature delivery
- Neurocognitive development

Fetal Alcohol Syndrome

- Characteristic facial features
- Congenital heart disease
- Growth deficiency
- Behavioral/neurocognitive deficits

Fetal Alcohol Syndrome



Mrs. B

- Do you believe her fetus' congenital heart disease was caused by the glass of wine she drank two weeks after conception?

Tetraclycine

- Yellow/brown teeth
- Decreased bone growth

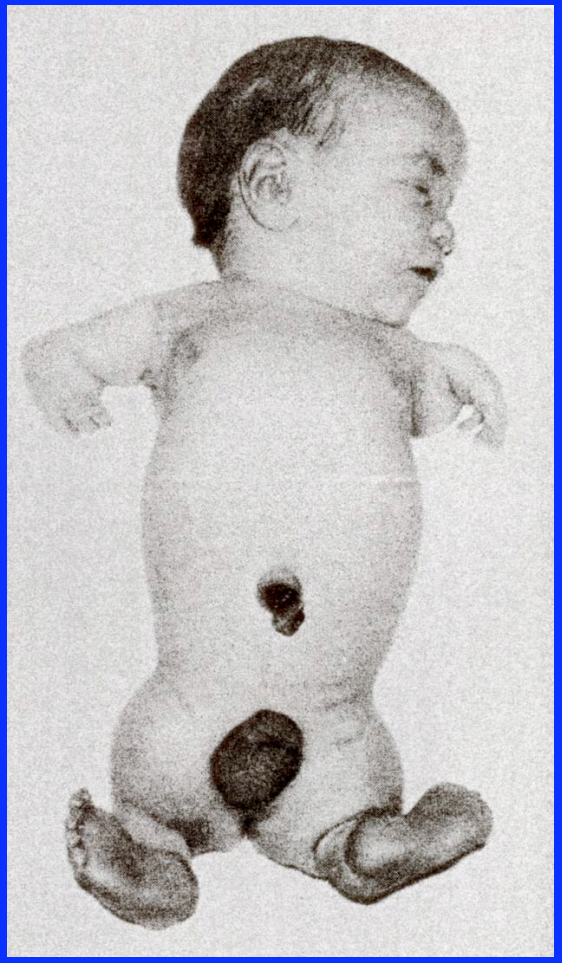
Fetal Hydantoin Syndrome

- Intrauterine growth retardation
- Microcephaly, mental retardation
- Distal phalangeal hypoplasia
- Specific facial features

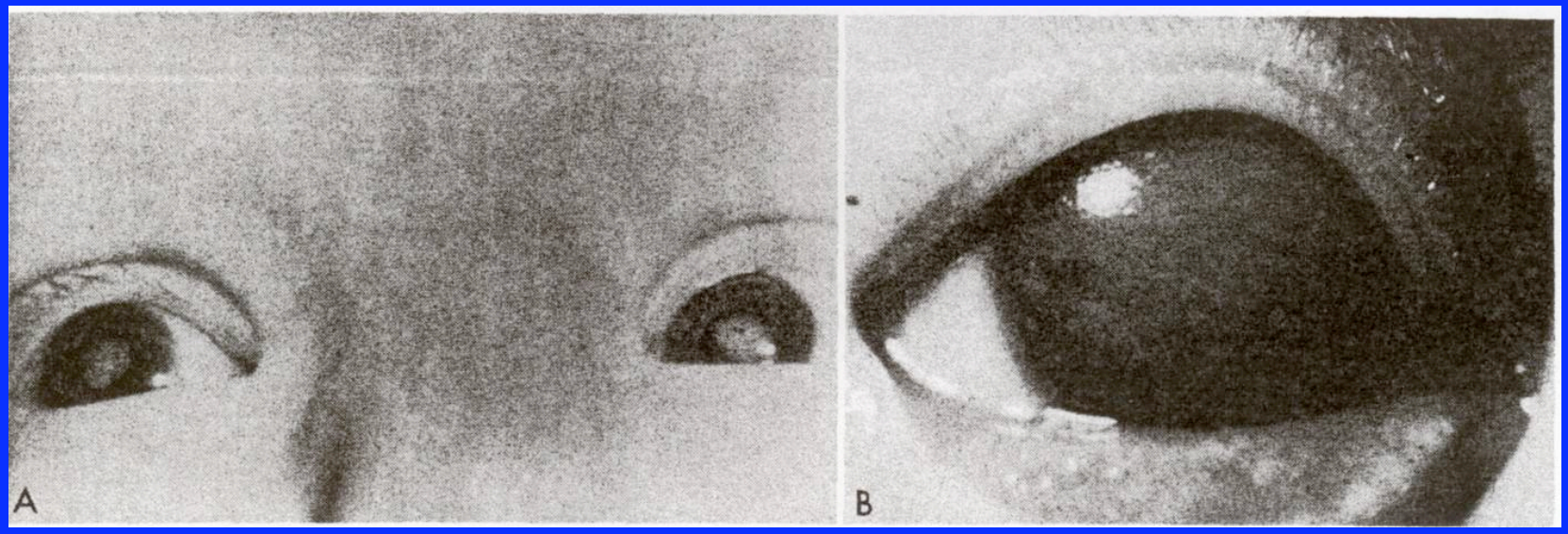
Retinoic acid

- Craniofacial dysmorphisms
- Cleft palate
- Thymic aplasia
- Neural tube defects

Thalidomide Syndrome



Congenital Rubella



Congenital CMV

- Intrauterine growth retardation
- Micromelia
- Chorioretinitis, blindness
- Microcephaly
- Cerebral calcifications, mental retardation
- Hepatosplenomegaly

Ionizing Radiation

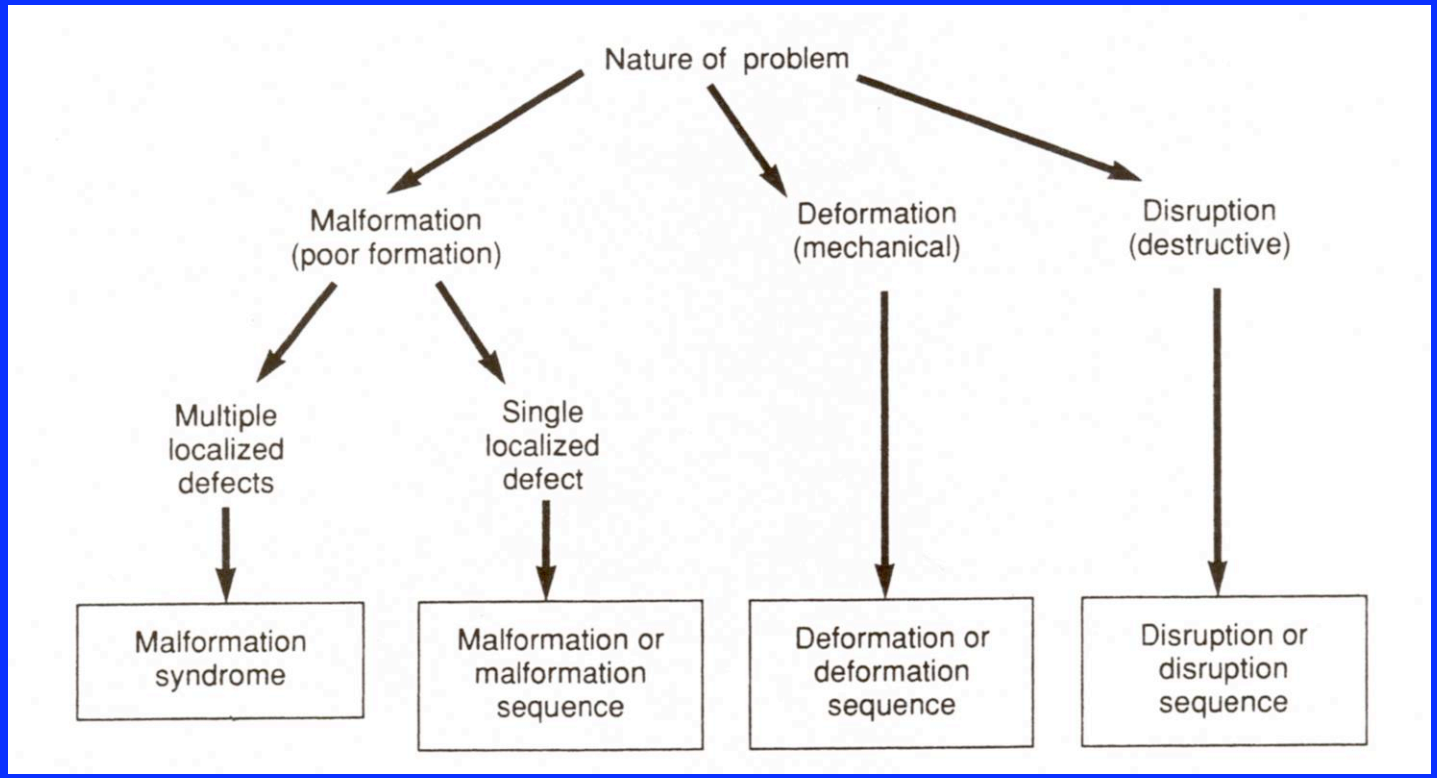
- Affects brain development at 10-18 weeks of gestation a HIGH dose
- No evidence of effect of exposure associated with typical diagnostic studies

Maternal Hyperglycemia

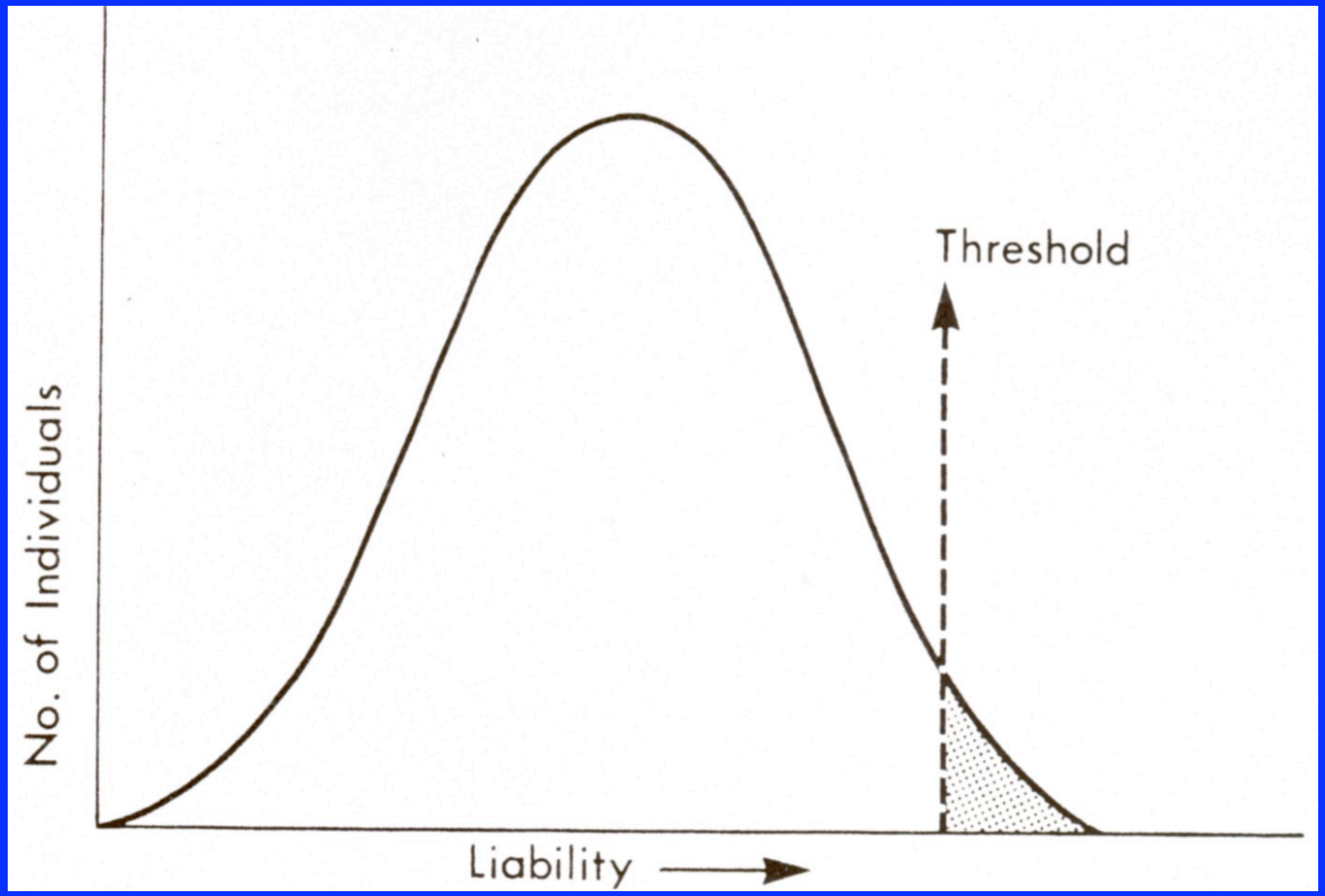
- Congenital heart disease
- Renal, gastrointestinal, and central nervous system malformations such as neural tube defects

Babies of Mother's with PKU

- Mental retardation
- Low birth weight
- Congenital heart diseas


Nature of problem
Malformation (poor formation)
Deformation (mechanical)
Disruption (destructive)
Multiple localized defects
Single localized defect
Malformation syndrome
Malformation or malformation sequence
Deformation or deformation sequence
Disruption or disruption sequence

Threshold Effect-Multifactorial



Mrs. B

- After birth, the newborn examination is unremarkable
- The baby's congenital heart disease is repaired
- At age three, the child is growing well and has met all his milestones

- What caused his congenital heart disease?
- What is the risk of recurrence for a future sibling?