Teratogenesis

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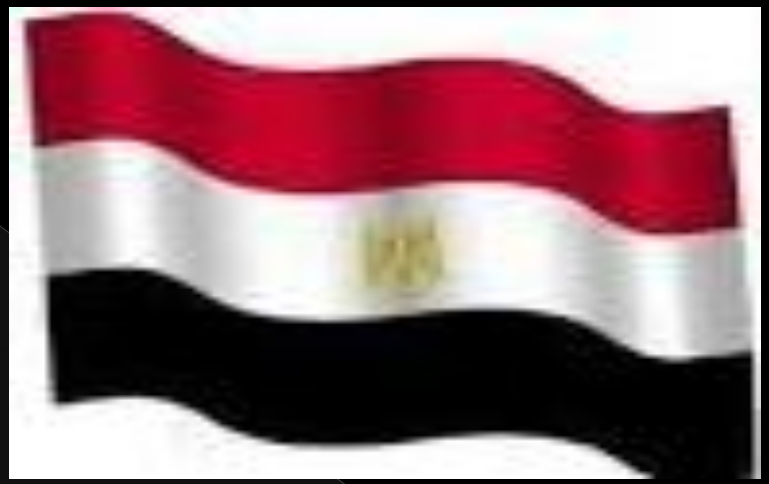


تحيا مصر

◉1941:

- Rubella epidemic "German measles"→ several deaths, blindness and deafness of fetuses born to exposed women
- 1st recognition of the potential of exogenous agents to produce developmental defects of fetus.

- **1950's:**
- Thalidomide crisis → birth of approximately 10,000 malformed infants born to exposed women
- 2nd recognition of the potential of xenobiotics (chemicals) to produce fetal developmental error.

- **Congenital defect:**
  - All morphological, biochemical and functional abnormalities produced before or at birth.
- **Congenital malformation:** "Anomalies"
  - Refers merely to structural aberrations.
- **Teratogens:**
  - Substances that cause defects or abnormalities in fetal development
  - Defects may occur in one organ or more

- Teratogens may be:
  - Drugs
  - Occupational conditions: chemicals, solvents, radiation
  - Environmental contaminants
- Exposure to teratogens may occur to pregnant women or women at child-bearing age (genetic)

- **Embryogenesis:**

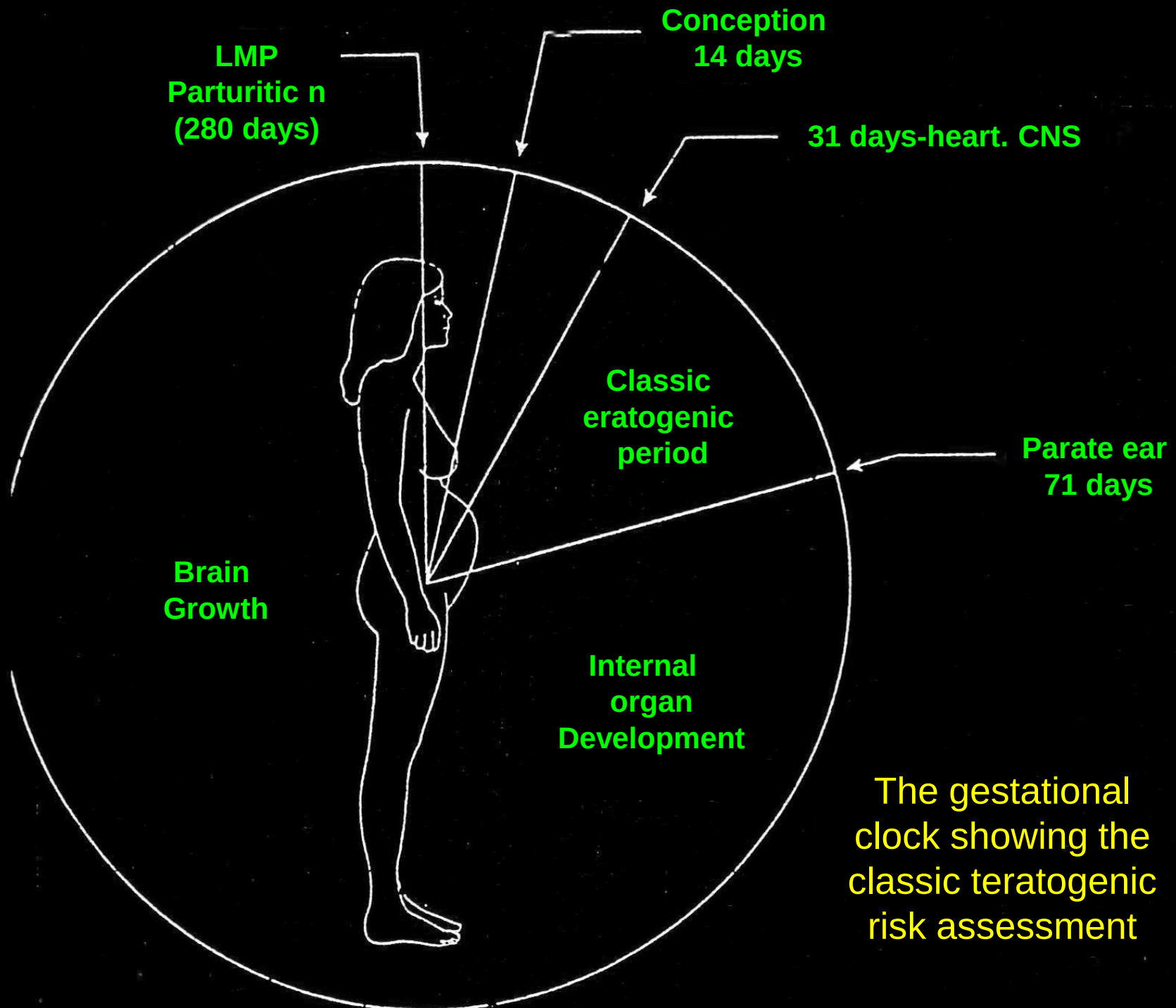
- It is complete precisely programmed sequence of cell proliferation, differentiation, migration, and finally organogenesis
- It involves complete cellular interaction in both time and space
- The critical period of human embryogenesis is divided into two periods:

1. Embryonic period
2. Fetal development period

- N.B.: most organogenesis is completed during the first trimester (12 weeks)

I. 1st two weeks of gestation:

- Fast cellular proliferation period
- Cells are "Totipotential"
- No Teratogenesis may occur
- Not susceptible to teratogens
- But cell death may occur
- ↑ cell death → embryo death
- ↓ cell death → embryo save → "Totipotential cells"
- Ex.: ionizing radiation, ↑ doses of teratogens → cell death

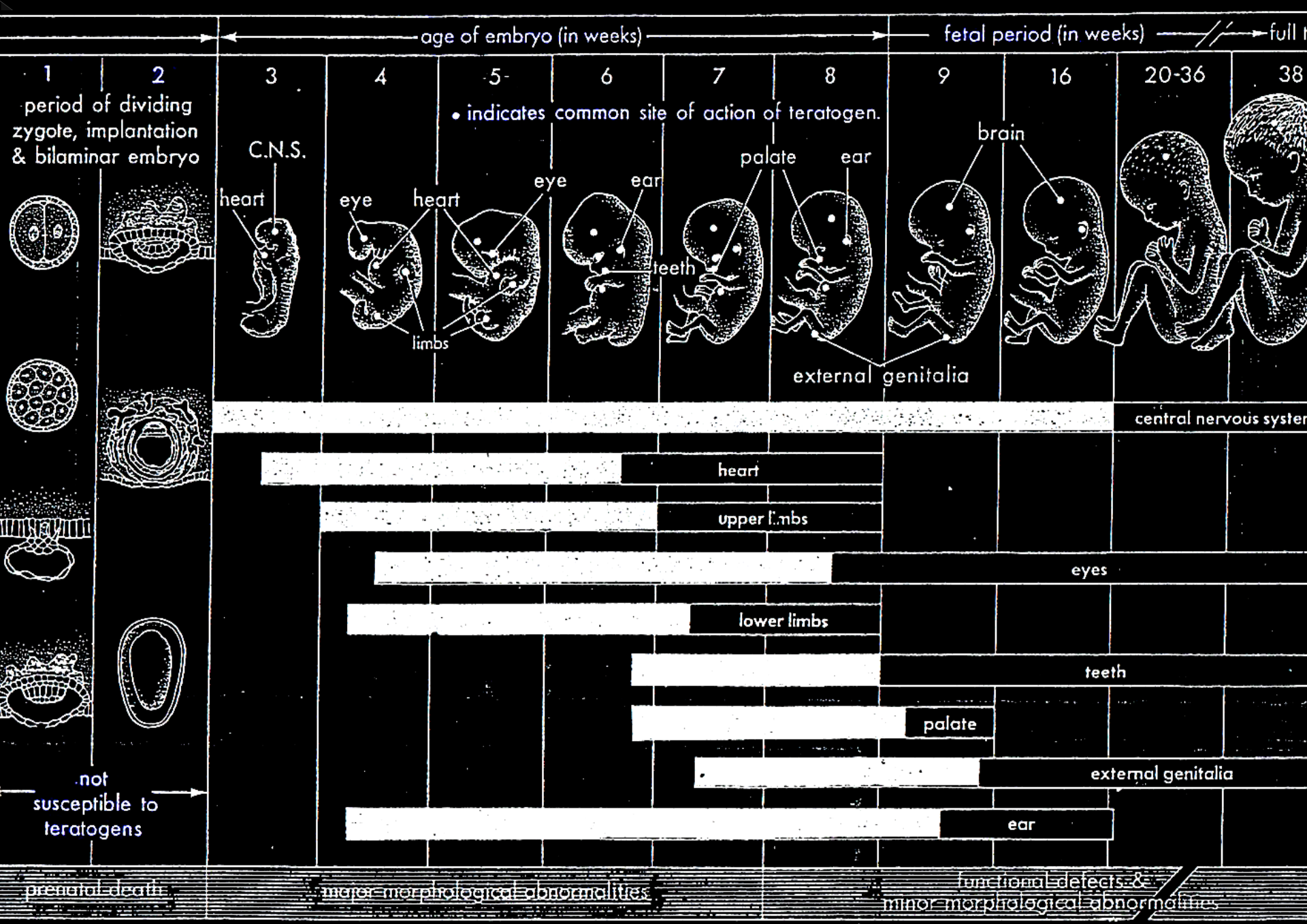


The gestational clock showing the classic teratogenic risk assessment

. COMPARISON OF GESTATION IN SEVERAL SPECIES

	Number of Days After Conception		
	Implantation	*Embryonic Period*[a]	*Fetal Period*
Human	6-7	20--56	56-280
Rabbif	6-8	8-16	17-34
Rat	6-8	9-17	18-22
Mouse	5-7	7-16	17-20

anogenesis and greatest teratogenic risk.

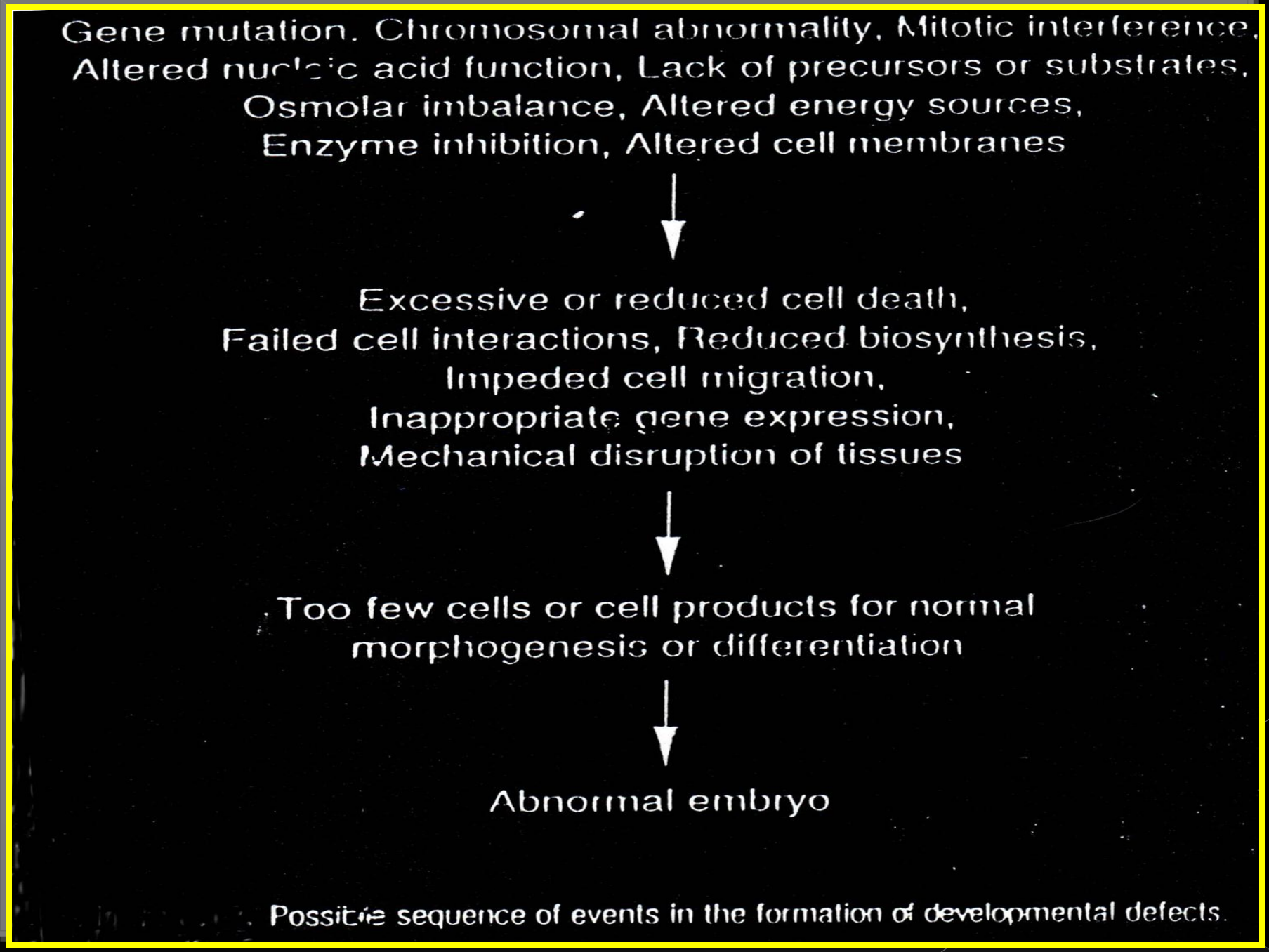


Comparison of developmental time frames and major organogenesis events in the human embryo

- ◉ **Placental barrier:**
- **Protects fetus and its environment**
- **It is not an absolute protection**
- **It acts like a sieve**
- **Substances pass placenta barrier according to their molecular size, and residual changes (+,-)**
- ✓ **Size → table**
- ✓ **Charge → ex: neuromuscular blockers**
- ◉ **Most pharmacological agents, occupational and environmental chemicals have the potential of crossing placenta and produce fetal harm.**

Effect of Molecular Weight on Placental Transfer of Drugs

Molecular Weight	Drug Example	Rafe of Placental Transfer
<500 g/mole	acetaminophen, caffeine, cocaine, labetalol, morphine, penicillins, theophylline	Readily crosses the placenta
600-1000 g/mole	digoxin	Crosses placenta at a slower rate
>1000 g/mole	heparin, insulins	Transfer across placenta severely impeded



Possible sequence of events in the formation of developmental defects.

Categorization of substances in relation to teratogenicity

Category A: Not teratogen in humans or animals .

Category B: Not teratogen in humans but teratogen in animal models i.e. potential exist.

Category C: - Incidence of human teratogenesis .

- Cross placenta.
- Risk and benefit analysis is a must before use.

Category D: - Higher Incidence of human teratogenesis .

- Used only in life threatening situation.

Category X: - Proven teratogen in human, should not be used during pregnancy.

FDA Pregnancy Categories

Category	Interpretation
A	Controlled studies show no risk: Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	No evidence of risk in humans: Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.
C	Risk cannot be ruled out: Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify potential risk.
D	Positive evidence of risk: Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh risks.
X	Contraindicated in pregnancy: Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.

Category	Example
A	Folic acid, thyroid hormone
B	Erythromycin, penicillin
C	Labetalol, nifidipine, ACE inhibitors
D	Glyburide, diazepam, aspirin, ACE inhibitors
X	Oral contraceptives, lovaststin, isotretinoin

Some causes of Human developmental defects

- Known genetic transmission
- Chromosomal aberration
- Ionizing radiation
  - Therapeutic
  - Nuclear
  - Radioiodine
- Infections
  - Rubella virus
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Toxoplasmosis
  - Syphilis
- Maternal metabolic imbalances
  - Cretinism
  - Diabetes
  - Phenylketonuria (PKU)
  - Hyperthermia
- Drugs and chemicals
  - Ethanol
  - Androgenic hormones
  - Phenytoin
  - Trimethadione
  - Cyclophosphamide
  - Diethylstilbestrol (DES)
  - Thalidomide
  - Valproic acid
  - Retinoic acids
  - Methotrexate
  - Cocaine
  - Organic mercury
  - Coumarin anticoagulants
  - Tetracyclines
  - Folic acid antagonists (Aminopterin)

Medications Known to be teratogens

- Alcohol
- Androgens
- Anticonvulsants
- Antineoplastics
- Cocaine
- Diethylstilbestrol
- Etretinate
- Lodides (including radioactive iodine)
- Isotretinoin
- Lithium
- Live vaccines
- Methimazole
- Penicillamine
- Tetracyclines
- Warfarin

Medications Suspected to be Teratogens

ACE inhibitors	Estrogens	Progestogens
Benzodiazepines	Oral hypoglycemic agents	Quinolones

Medications with no known teratogenic effects

Acetaminophen	Erythromycin	Phenothiazines
Cephalosporins	Multiple vitamins	Thyroid hormones
Corticosteroids	Narcotic analgesics	Tricyclic antidepressants
Docusate sodium	Penicillins	

Medications with nonteratogenic adverse effects in pregnancy

- Antithyroid drugs
- Aminoglycosides
- Aspirin
- Barbiturates (chronic use)
- Benzodiazepines
- B-Blockers
- Caffeine
- Chloramphenicol
- Cocaine
- Diuretics
- Isoniazid
- Narcotic analgesics (chronic use)
- Nicotine
- Nonsteroidal anti-inflammtory agents
- Oral hypoglycemic agents
- Prophylthiouracil
- Sulfonamides


Thank You!