Developmental Toxicology
(Teratogenesis)

- Embryogenesis – a complex process involving cell proliferation, differentiation, migration, and organogenesis
- Predictions
  - Sequence & interrelationships easily disrupted
  - Timing of effects
  - Anything that affects biochemical pathways

Stages of Development

- Preimplantation (Predifferentiation)
  - No teratogenesis
  - All or none effect
- Embryonic Stage
  - Germ layer formation & Organogenesis
  - Embryo most susceptible to teratogenesis
- Fetal Stage
  - Growth & functional maturation
  - Functional abnormalities

Stages of Embryogenesis
Periods of Peak Teratogenesis During Gestation

Access to the Embryo and Fetus

- Placenta
  - Binding to proteins
  - MW< 1000
  - Lipophilic
  - Phagocytosis of proteins
- Maternal biotransformation & excretion
- Fetal metabolism

Dose Response Relationships
### Teratogenic Agents

- Radiation
- Infections – Viral & Microbial
  - Alcoholism
  - Diabetes
  - Folic acid deficiency
  - Hyperthermia
  - Phenylketonuria
- Maternal metabolic imbalances
  - Alcoholism
  - Diabetes
  - Folic acid deficiency
  - Hyperthermia
  - Phenylketonuria
- Drugs and Chemicals
  - Thalidomide, Cocaine, Retinoids

### Mechanisms

#### Cytotoxicity – alkylating agents; MNNG
- Limb or organ bud damage
- Embryo lethality

#### Receptor mediated teratogenicity
- Thalidomide
- Glucocorticoid hormones

### Mechanisms

#### Dna Damage & Mutation
- Somatic vs. germ cells
- Cell cycle perturbation - cyclophosphamide
- Chromosomal aberrations
- Mitotic interference - Inhibition of spindle formation or DNA synthesis may result in incorrect separation of chromosomes
  - Cytosine arabinoside, vincristine, colchicine
- Homeobox Genes
Mechanisms

- Interference with nucleic acid metabolism
  - Cytosine arabinoside, mytomycin C, 6-mercaptopurine
- Substrate deficiency
- Energy deficiency
- Enzyme inhibition
- Maternal and placental homeostasis

Maternal & Developmental Toxicity

Cell Cycle Perturbation