

Applied Toxicology

NURS 735

Developmental Toxicology

• Section 2

Michael M. Lipsky, Ph.D.
UM Department of Pathology
mlipsky@umaryland.edu

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Developmental Toxicology

- **Learning Objectives**

- 1. Understand the scope and potential causes of developmental toxicity
- 2. List major agents responsible for human developmental toxicity
- 3. Describe and understand Wilson's general principals of teratology
- 4. Understand the sequence and timing of human developmental events
- 5. List and understand potential mechanisms of teratogenesis
- 6. Understand what maternal conditions affect development and how they act in developmental toxicity

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Developmental Toxicology

- **Scope of the problem**

1. Successful pregnancy outcome in the general population occurs at a surprisingly low frequency
2. Estimated adverse outcomes:
 - a. post-implantation loss 31%
 - b. major birth defects 2 – 3 % at birth, rising to 6 – 7 % at 1 year old
 - c. minor birth defects 14 %
 - d. low birth weight 7 %
 - e. infant mortality 1.4 %
 - f. Abnormal neurological function 16 – 17 %

Thus, less than 50% of all human conceptions result in the birth of a completely Normal, healthy infant.

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Developmental Toxicology

The data on the next slide is used to explain the high level of adverse pregnancy outcomes listed in the first slide. That is to say genetic causes and unexplained etiology covers a large majority of this situation. It is not due to exposures to developmental toxicant chemicals or environmental factors. One could argue that the statistics provided on the success rate of conception leading to full term pregnancy and healthy offspring describe the normal situation. That is, a high percentage of conceptions do not lead to full term pregnancy. As noted in the previous slide about 1/3 of conceptions result in loss pre-implantation or immediately post-implantation.

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Developmental Toxicology

- Numerous authors attribute human birth defects to the following causes
 - 15 -25 % to genetic causes
 - 4% to maternal conditions
 - 3% to maternal infections
 - 1-2 % to deformations
 - less than 1 % to chemicals and environmental influences (about 35-40 known chemical, human developmental toxicants)
 - 65 % unknown etiology

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Developmental Toxicology

- **Human Developmental Toxicity Agents**

1. Radiation

Therapeutic
Radioiodine
Atomic fallout

Obviously the radiation agents are active only in specific situations. In Western society there is little to no effect of therapeutic radiation due to our understanding of the problem and precautions used.

2. Infections

Rubella virus
Cytomegalovirus
Toxoplasmosis
Syphilis

Herpes simplex I & II
Parvovirus B-19
Varicella virus
Venezuelan equine encephalitis virus

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- Maternal Trauma and Metabolic Imbalances

Alcoholism

Amniocentesis (early)

Diabetes

Folic acid deficiency

Hyperthermia

Phenylketonuria

Rheumatic disease and congenital heart block

Virilizing neoplasms

Chorioniv villus sampling (prior to 60days)

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- Drugs/Chemicals (a partial list)

Thalidomide

Anticonvulsants

Angiotensin converting enzyme inhibitors

Ethanol

Chelators

Cigarette smoke

Ethylene oxide

Cocaine

Coumarin anticoagulants

Retinoids

Metals

Tetracyclines

Anticancer drugs (cyclophosphamide)

Androgenic chemicals

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Developmental Toxicology

Wilson's General Principles of Teratology (A)

- I. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with adverse environmental factors
- II. Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to the adverse influence.
 - I. Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate sequences of abnormal developmental events

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Developmental Toxicology

Wilson's General Principles of Teratology (B)

- IV. The access of adverse influences to developing tissues depends on the nature of the influence (agent)
- V. Manifestations of deviant development include death, malformation and growth retardation
- VI. Manifestations of deviant development increase in frequency and degree as dosage increases, from the no effect level to the totally lethal level

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Developmental Toxicology

(The bullets below refer to the next slide)

1. Toxicity during pre-implantation is generally thought to give rise to slight effects on growth or in death. However, some experimental studies suggest exposure during this time can lead to fetal malformations.
2. The period of gastrulation is very susceptible to teratogenesis with fetal malformations occurring after toxicant exposure.
3. Organogenesis starts at the time of formation of the neural plate in the ectoderm. This period from 3 to 8 weeks of gestation is one of heightened susceptibility to malformations. Within organogenesis there are periods of peak susceptibility for each forming structure.
4. The end of organogenesis marks the beginning of the fetal period characterized by tissue differentiation, growth and physiologic maturation. Exposure to developmental toxicants during this period results in effects on growth and functional maturation. Functional anomalies of the CNS and reproductive organs, including behavioral, mental and motor deficits and decreased fertility are possible. These may not be manifested until postnatally and careful observation and testing is required.

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Developmental Toxicology

- **Timing of key developmental events in humans.**
- Blastocyst formation - 4 - 6 days
- Implantation - 6-7 days
- Organogenesis - 21 - 56 days
- Primitive streak - 16-18 days
- Neural plate - 18 - 20 days
- First somite - 20 - 21 days
- First brachial arch - 20 days
- First heartbeat - 22 days

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Developmental Toxicology

- **Timing of key developmental events in humans (b)**
- 10 Somites - 25 - 26 days
- Upper limb buds - 29 - 30 days
- Lower limb buds - 31 - 32 days
- Testes differentiation - 43 days
- Heart septation - 46 - 47 days
- Palate closure - 56 - 58 days
- Urethral groove closed in males 90 days

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Developmental Toxicology

The cellular insults listed on the next slide can trigger abnormal development but are not unique to development. They are important in terms of developmental toxicity when they occur in cells in the conceptus and developing embryo.

In the developing embryo many of these cellular insults can trigger unique pathogenic responses such as:

- reduced cell proliferation
- cell death
- altered cell-cell interactions
- reduced biosynthesis
- mechanical disruption of developing structures
- inhibition of morphogenetic movement

There is a delicate balance between cell proliferation, cell differentiation and programmed cell death (apoptosis) in the developing embryo. DNA damage may cause perturbations in cell cycle kinetics and cell death in specific cell populations. For example, maternal exposure to cyclophosphamide (a chemotherapeutic drug) in the rat causes an S-phase cell cycle block leading to widespread cell death in the embryo.

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Developmental Toxicology

Mechanisms of teratogenesis (as defined by Wilson, 1977)

- Mutations
- Chromosomal breaks
- Altered mitosis
- Altered nuclear integrity or function
- Decreased energy supplies
- Diminished supplies of substrates or precursors
- Altered membrane characteristics
- Osmolar imbalance
- Enzyme inhibition

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- Although all developmental toxicity must ultimately result from an insult to the conceptus at the cellular level, the insult may occur through a direct effect on the embryo/fetus, indirectly through toxicity of an agent to the mother and/or placenta, or a combination of direct and indirect effects.

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Developmental Toxicology

Maternal conditions capable of adversely affecting development include:

- decreased uterine blood flow
- maternal anemia
- altered nutritional status
- toxemia
- altered organ function
- autoimmune states
- diabetes
- electrolyte and acid/base disturbances
- decreased milk quantity or quality
- abnormal behavior

Many known human developmental toxicants, including ethanol and cocaine, adversely affect the embryo predominately at maternal toxic levels and part of their developmental toxicity is attributable to secondary effects on maternal physiologic disturbances.

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Developmental Toxicology

- Induction or exacerbation of maternal conditions by toxic agents and the degree to which they manifest in abnormal development are dependent on a variety of maternal factors.
 - Genetic background
 - Age
 - Parity
 - Size
 - Nutrition
 - Disease
 - Stress
 - Other health parameters and exposures

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Developmental Toxicology

The genetic makeup of the pregnant female is well documented as a determinant of developmental outcome.

Numerous diseases are documented to affected development. Uncontrolled maternal diabetes mellitus is a significant cause of prenatal morbidity. Cytomegalovirus is associated with fetal death, microcephaly, mental retardation, blindness and deafness. Hyperthermia is a potent teratogen in lab animal studies. There is evidence associating maternal febrile illness during the first trimester with birth defects in humans, esp. malformations of the CNS.

A wide spectrum of dietary insufficiencies adversely affect pregnancy. Folic acid deficiency is strongly associated with neural tube defects.

Stress has been shown in laboratory animal studies to adversely affect development. Data in humans is scant. However, there are studies in humans that noted an association between stress and adverse developmental effects including low birth weight and congenital malformations

The placenta provides for fetal attachment, nutrition, gas exchange and waste removal. In addition, the placenta produces hormones critical to maintenance of pregnancy. It also may store and metabolize xenobiotic chemicals. Direct toxicity to the placenta by toxicants can compromise placental functions and contribute to developmental problems.