Causes and mechanisms of birth defects

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Teratology

- **Teratology** investigates abnormalities of physiological development. It is often thought of as the study of birth defects.

- The term stems from the Greek τέρας (téras, genitive τέρατος- tératos), meaning _monster_, or _marvel_ (miracle).

- **Birth defects (congenital malformations)** result from a negative influence of extrinsic or genetic factors on individual prenatal development.
Heraldry documents many examples of serious monstrosities (often used as national or town emblems)
Birth defect

Inborn deviation of a structure, function or metabolism. It originates prenatally and its manifestation exceeds a threshold of normal variability in a species.

- **Major malformation** - a serious structural disturbance, monstrosity

- **Minor malformation** – a mild structural defect manifesting as a disturbance of function.

- **Metabolic defect** – enzymopathy – affection of enzymes – most often it is a decrease of their catabolic activity
Major malformations
Spina bifida and myelo-meningocele

Figure 4-11. Three newborns with myelomeningoceles. A, B. The myelomeningoceles extend from the thoracic to lumbosacral level. Note the location of the split vertebral elements to the left of the lesion in B. C. The myelomeningocele is localized to the lumbosacral level. In B and C, the infant’s diapers (bottom of each illustration) are shown for orientation.
Partially fused eyes (uncomplete cyclopia) and proboscis
Sirenomelia. Severe reduction of caudal structures has resulted in fusion of the lower limb buds.
Polydactylia
Cephalo-thoraco-pagus
Thoracopagus
Major malformations originate during embryonic period of prenatal development.
# Human stages of life cycle

## Prenatal period

- **Embryo**: 1 - 8 weeks
- **Fetus**: 9 weeks – birth

## Postnatal period

- **Newborn**: birth - 4 weeks
- **Suckling, toddler**: 5 weeks - 2 years
- **Child**: 2 years - puberty (11 - 14 years)
- **Teenage**: puberty - adult age (20 years)
- **Young age**: 20 - 40 years
- **Middle age**: 40 - 65 years
- **Old age**: 65 - death
Determination of the beginning pregnancy
Figure 2-5. Schematic representation of the events taking place during the first week of human development. (1) Oocyte immediately after ovulation. (2) Fertilization approximately 12 to 24 hours after ovulation. (3) Stage of the male and female pronuclei. (4) Spindle of the first mitotic division. (5) Two-cell stage (approximately 30 hours of age). (6) Morula containing 12 to 16 blastomeres (approximately 3 days of age). (7) Advanced morula stage reaching the uterine lumen (approximately 4 days of age). (8) Early blastocyst stage (approximately 4½ days of age). The zona pellucida has now disappeared. (9) Early phase of implantation (blastocyst approximately 6 days of age). The ovary shows the stages of the transformation between a primary follicle and a Graafian follicle as well as a corpus luteum. The uterine endometrium is depicted in the progestational stage.
Determination of pregnancy

• Positive determination of HCG (human chorionic gonadotropin) from urine (9 – 12 day after fertilization)

• Verification of HCG from blood

• Ultrasound investigation - determination of the place of embryo implantation
Pregnancy length

- **280 days, 40 weeks** – calculated from the first day of the last menstruation.

- **266 days, 38 weeks** – calculated from the day of fertilization. A child usually borns at about 38 weeks after conception.
<table>
<thead>
<tr>
<th>AGE (weeks)</th>
<th>Stage 1</th>
<th>Stage 2 begins</th>
<th>Stage 3 begins</th>
<th>Stage 4 Implantation begins</th>
<th>Stage 5 begins</th>
<th>Stage 6 begins</th>
<th>Stage 7 begins</th>
<th>Stage 8</th>
<th>Stage 9</th>
<th>Stage 10</th>
<th>Stage 11</th>
<th>Stage 12</th>
<th>Stage 13</th>
<th>Stage 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>fertilization</td>
<td>zygote divides</td>
<td>morula</td>
<td>early blastocyst</td>
<td>late blastocyst</td>
<td>inner cell mass</td>
<td>coelom</td>
<td>amniotic cavity</td>
<td>Lacunae appear in syncytiotrophoblast</td>
<td>Blastocyst completely implanted</td>
<td>Primitive placental circulation established</td>
<td>extraembryonic mesoderm</td>
<td>primary villi</td>
<td>dorsal aspect of embryo prochordal plate</td>
</tr>
<tr>
<td>2</td>
<td>bilaminar disc</td>
<td>primary yolk sac</td>
<td>epithelium growing over surface defect</td>
<td>coelom</td>
<td>embryonic disc</td>
<td>embryo</td>
<td>coelom</td>
<td>amniotic cavity</td>
<td>Lacunae appear in syncytiotrophoblast</td>
<td>Blastocyst completely implanted</td>
<td>Primitive placental circulation established</td>
<td>extraembryonic mesoderm</td>
<td>primary villi</td>
<td>dorsal aspect of embryo prochordal plate</td>
</tr>
</tbody>
</table>
TIMETABLE OF HUMAN PRENATAL DEVELOPMENT
7 to 38 weeks

7 weeks
- C.R.: 16.0 mm
- Eyelids beginning
- Tip of nose distinct.
- Digital rays appear in foot plates.

8 weeks
- Upper limbs longer & bent at elbows.
- Anal membrane perforated.
- Urogenital membrane degenerating.
- Fingers distinct.
- Testes and ovaries distinguishable.

9 weeks
- Beginning of fetal period.

10 weeks
- Face has human profile.
- Note growth of chin compared to day 44.
- Face has human appearance.

21 days
- Stage 21 begins
- External genitalia still in sexless state but have begun to differentiate.

22 days
- Stage 22 begins
- Genitalia show some female characteristics but still easily confused with male.

23 days
- Stage 23 begins
- Phallus urogenital fold labioscrotal fold perineum
- Genitalia show fusion of urethral folds.
- Urethral groove extends into phallus.

24 days
- Stage 24 begins
- Clitoris
- Labium minus
- Labium major
- Genitalia have female or male characteristics but still not fully formed.

25 days
- Stage 25 begins
- Glans penis
- Urethral groove
- Scrotum
- Genitalia have female or male characteristics but still not fully formed.
Prenatal and postnatal losses
Death during prenatal and postnatal ontogenesis

- Prenatal age in months
- Postnatal age in years

- Men
- Women

Birth
16% unfertilized

42% lost before the end of implantation

11% aborted

31% living

number of oocytes

major

minor malformations

prenatal week
Spontaneous abortions

• Czech Republic 1965 – 1999

• A – official statistics record no abortions during the first month of pregnancy

• B – situation after mathematical extrapolation of data A using an exponential curve
CRITICAL
PERIOD
### Critical Periods in Human Development

<table>
<thead>
<tr>
<th>Period</th>
<th>Age of Embryo (in weeks)</th>
<th>Fetal Period (in weeks)</th>
<th>Full Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>period of dividing zygote, implantation &amp; bilaminar embryo</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>C.N.S.</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>heart</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>eye heart limbs</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>palate ear external genitalia</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>teeth</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>external genitalia</td>
<td>16</td>
<td>20-36</td>
</tr>
<tr>
<td>8</td>
<td>not susceptible to teratogens</td>
<td>38</td>
<td>38</td>
</tr>
</tbody>
</table>

*Red indicates highly sensitive periods when teratogens may induce major anomalies.*
Threshold in TERATOGENESIS
Developmental defect (malformation, death, growth retardation)
DOSES and EMBRYOTOXICITY
Three components of embryotoxicity

- Developmental defect - teratogenicity
- Death of embryo/fetus - lethality
- Growth retardation
Head deformation and protrusion of eyes
Skin defects
Reduction deformity of limbs
CAUSES of BIRTH DEFECTS
Figure 5-1. Mutations in the SONIC HEDGEHOG (SHH) gene have multiple manifestations. A, Infant with bilateral cleft lip and facial findings associated with holoprosencephaly. B, Foot of an infant with preaxial polydactyly.
HUMAN TERATOGENES
A factor present in environment in such a concentration, which, in exposed population, significantly increases incidence of birth defects above their spontaneous frequency in un-exposed population.
Teratogene

- A qualitative definition:

Environmental factor of chemical, physical or biological nature.

It can induce a structural birth defect in exposed offspring, which is not hereditary.
Mutagene

- A qualitative definition:

Environmental factor of chemical or physical nature.

It can induce DNA damage in exposed offspring. In case it also affects germ cells, the birth defect becomes hereditary.
1832  / GEOFFROY ST. HILAIRE

1930  
- X-rays  / GOLDSTEIN, MURPHY
- vit. A - free  / HALE
diet

1940  
- riboflavin - free  / WARKANY, SCHRAFFENBERGER
diet

1950  
- anoxia  / INGALLS, cortisone  / BAXTER, FRASER
- aminopterin  / THIERSCH

1960  
- thalidomide  / LENZ et al.

1900  
- Homo

Aves, Amphibia

Mammalia
<table>
<thead>
<tr>
<th></th>
<th>Thalidomide</th>
<th>Aminopterin</th>
<th>Methotrexate</th>
<th>Methylmercury</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamster</td>
<td>-</td>
<td>-</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mouse</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rat</td>
<td>-</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rabbit</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cat</td>
<td>+</td>
<td>-</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dog</td>
<td>+</td>
<td></td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Swine</td>
<td>+</td>
<td></td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Monkey</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Humans</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Number of newborns with malformation of the limbs (black) and quarterly thalidomide sales (white).
FIGURE 8-2. Phocomelia in all four limbs. This fetus had not been exposed to thalidomide. (Courtesy M. Barr, Ann Arbor, Mich.)
Frances Kathleen Oldham Kelsey
(she has prevented the thalidomide catastrophe in USA)
Therapy of leprosy by thalidomide + interdict of abortion (Brazil, 2002)
VITAMINS

A

E

K₁

PP

derapeutic. p.

embryotoxické p.

0.1 1.0 10 100 1000 10000 mg/kg
VITAMINS

$B_1$

$B_2$
terapeut. p.
embryotoxické p.

$B_6$

$B_{12}$

0.1 1.0 10 100 1000 10000 mg/kg
VITAMIN A

27 l of milk = 100 peace of eggs
0.37 kg of carrot
Crash of atomic reactor in Chernobyl 1986

Peterka et al., 2004, 2007
Number of newborn boys and girls in single month.
Mean daily percent of living newborns in each month during 1950 - 99 (Czech Republic)
Newborn sex ratio

= proportion of newborn boys and girls

105 : 100
Percent of newborn boys in single month from 1950 to 1999.
Chernobyl - history


• **28.04.1986** – detection of a radioactive cloud in Sweden (mainly $^{131}$I, $^{132}$Te, $^{103}$Ru, $^{134}$Cs, $^{137}$Cs)

• **30.04.1986** – detection of radioactivity in Czech Republic (mainly $^{131}$I, $^{132}$Te, $^{103}$Ru, $^{134}$Cs, $^{137}$Cs)
Černobyl - historie

- **28.04.1986** – detekce radioaktivního mraku ve Švédsku (hlavně $^{131}$I, $^{132}$Te, $^{103}$Ru, $^{134}$Cs, $^{137}$Cs)
- **01.05.1986** – západní státy zakazují dovoz potravin z ČSSR (přítomnost $^{134}$Cs a $^{137}$Cs)
- **První týden** v květnu 1986 – Rakousko nepřijímá naše kamiony a železniční vagony (kontaminace radioaktivním prachem)
- **05.05.1986** – ČTK oznamuje mírné zvýšení radioaktivity
- **06.05.1986** – hl. hygienik ČSR vyzývá k zachování zásad osobní hygieny a umývání ovoce a zeleniny
A. Three radioactive waves
Prague 1986

B. Mean whole body radioactivity
Prague 1986
Raining during the 1st radioactivity wave

30. 4. - 1. 5.

[mm]
- 0
- <5
- 5-10
- 10-15
- >15
# Radioactivity (Bq/m²²)

<table>
<thead>
<tr>
<th>Raining</th>
<th>No raining</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.5.1986, 7:00 hours</strong></td>
<td><strong>2.5.1986, 7:00 hours</strong></td>
</tr>
<tr>
<td>¹⁰³Ru</td>
<td>4 000,0</td>
</tr>
<tr>
<td>¹³¹I</td>
<td>50 000,0</td>
</tr>
<tr>
<td>¹³²Te</td>
<td>20 300,0</td>
</tr>
<tr>
<td>¹³⁷Cs</td>
<td>3 100,0</td>
</tr>
<tr>
<td>¹³⁴Cs</td>
<td>1 500,0</td>
</tr>
<tr>
<td>¹⁴⁰La</td>
<td>1 470,0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>80 370,0</strong></td>
</tr>
</tbody>
</table>
Radioactive half-time of radionuclides

- $^{140}\text{La}$ - 1.7 days
- $^{132}\text{Te}$ - 3.3 days
- $^{131}\text{I}$ - 8 days
- $^{103}\text{Ru}$ - 1 year
- $^{134}\text{Cs}$ - 2 years
- $^{137}\text{Cs}$ - 30 years
- $^{90}\text{Sr}$ - 30 years
Relative number of newborn boys
Czech Republic

Percent

Year

1980 81 82 83 84 85 86 87 88 89

53
52
51
50
49

86
Number of non newborn boys in November 1986 correlate with meteorological situation (wind and rain)
30.4.

Raining

Wind + radioactive cloud
Wind + radioactive cloud

Raining
Wind + radioactive cloud

Raining

7.5. 7:00 - 8.5. 7:00
Percent of non newborn boys – November 1986
Probable mechanisms of radiation effect on fetuses

• Environmental radiation can cause thyroid disease (Eheman et al., 2003).

• Thyroid disease in pregnant woman can lead to abortion or neonatal death. $^{131}\text{I}$ is absolutely contra-indicated during pregnancy (Bishnoi and Sachmechi, 1996; Ogris, 1997).

• $^{131}\text{I}$ induces hypothyreosis in mothers and increases the risk of premature delivery or spontaneous abortion (Tatham et al., 2002).

• Brain development is sensitive to increased radiation during the 3rd prenatal month (Yamazaki et al., 1990).
Selective accumulation of radioiodine in the thyroid gland was the most probable cause of the death of the male fetuses.