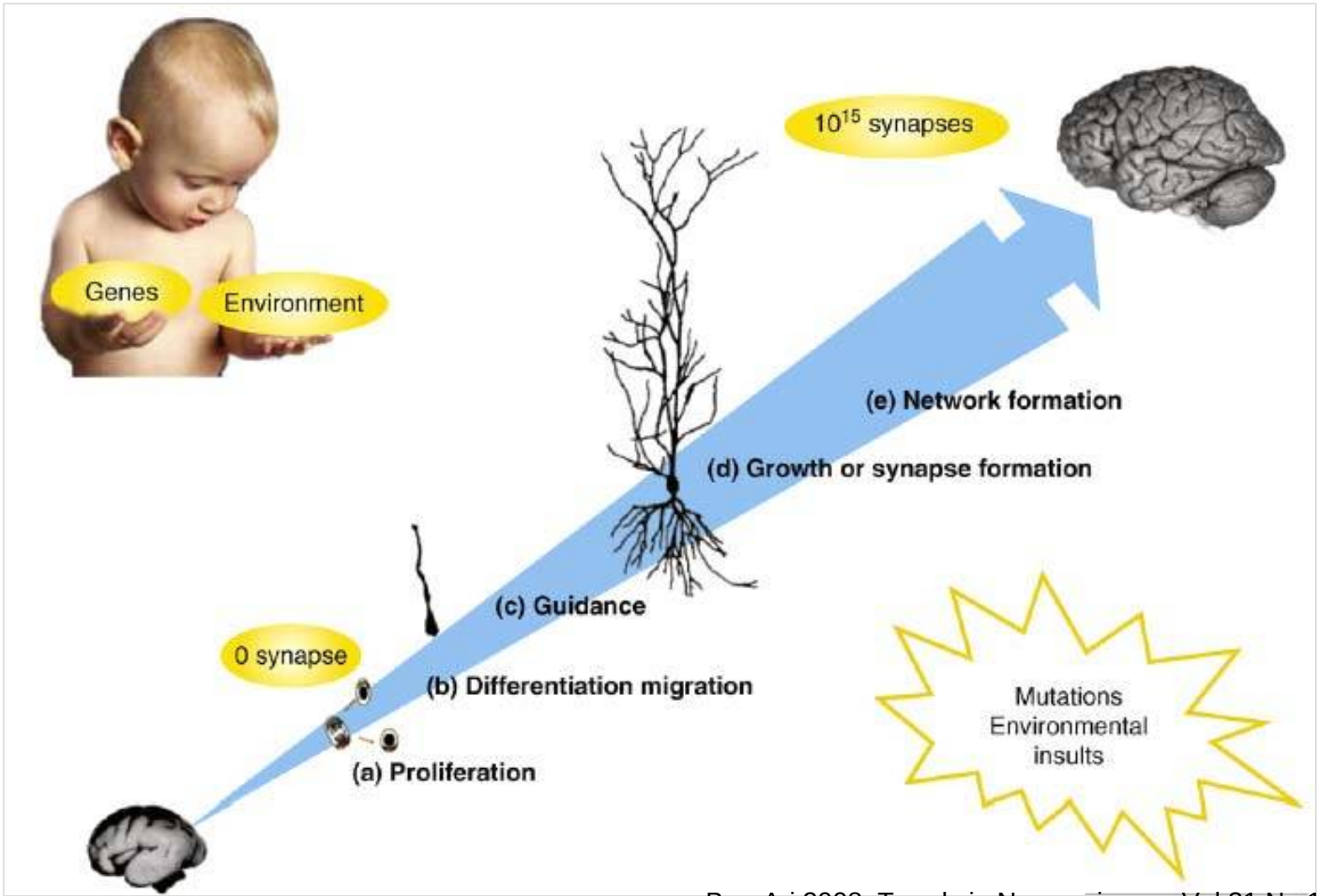
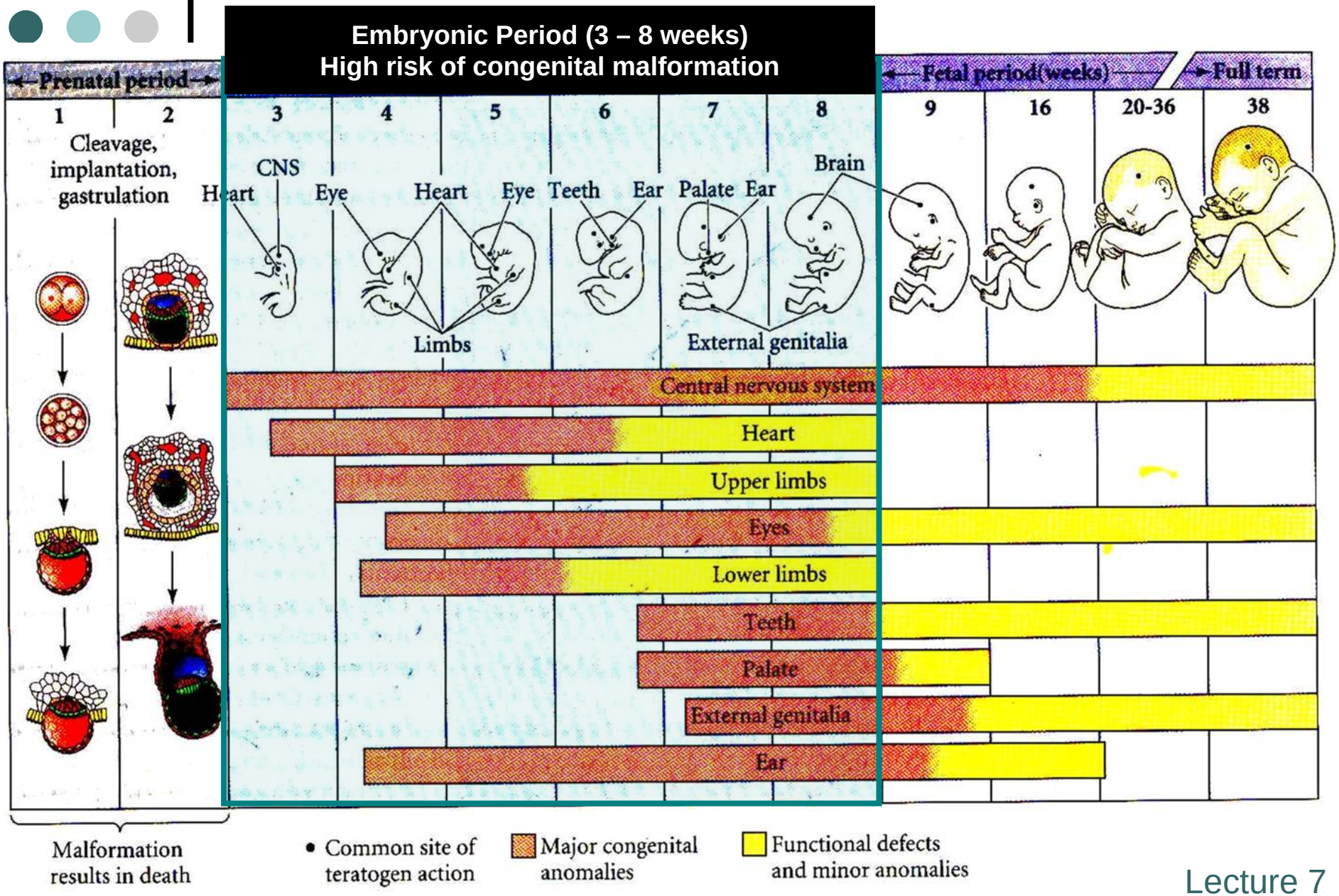
ENVIRONMENTAL FACTORS

The impact of the environment and genetic mutations on all developmental stages



Ben-Ari 2008, Trends in Neurosciences Vol.31 No.12

Critical Periods in Human Development



Stages of Prenatal Growth

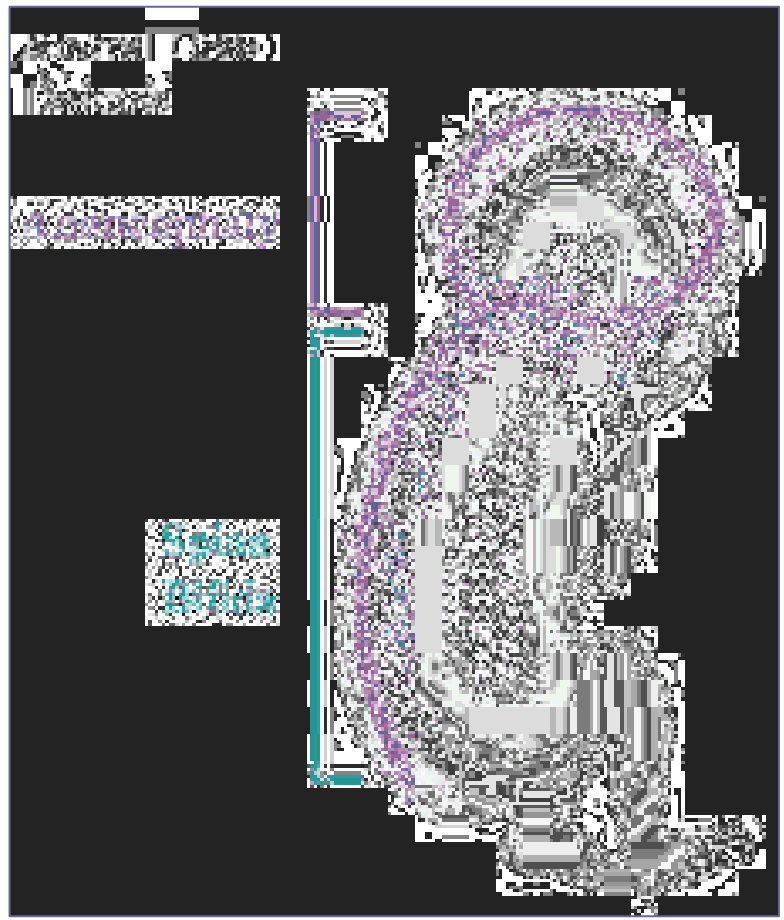
- **Germinal Period**
  - Conception - 2 weeks
- **Embryonic Period**
  - 3 – 8 weeks
- **Fetal Period**
  - **Early** - 3 to 6 months
  - **Later** – 7 to 9 months

Congenital brain defects

- Interruption of proper **formation**, **growth**, and **migration** of billions of neurons, and glial cells **early in development** which can cause **structural defects** in the brain lead to **brain malformation**
- Congenital brain defects may be caused by
  - **inherited genetic** defects,
  - **spontaneous mutations** within the genes of the embryo, or
  - effects on the embryo due to the **mother's infection, trauma, or drug use**.

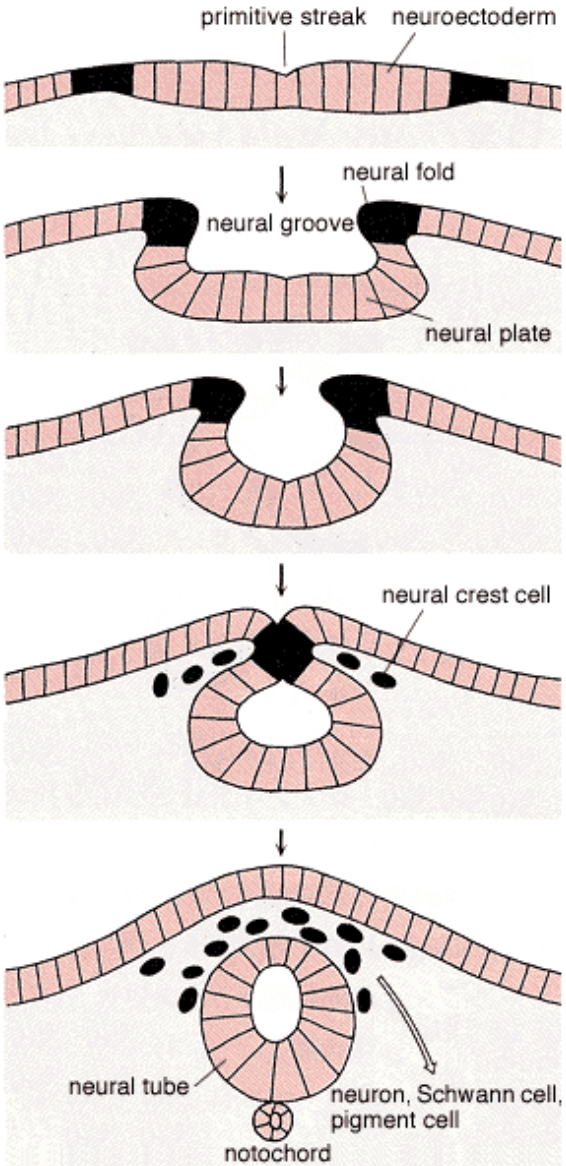
Neural Tube Defects (NTD)

- Defect of the CNS (brain and spinal cord)
- Anencephaly
  - Much of the brain, head and possibly the spinal cord do not develop
- Spina Bifida
  - Latin term meaning “open spine”
  - Medically refers to the birth defect where the spine does not form completely



Folic acid deficiency !

Neural Tube Defects



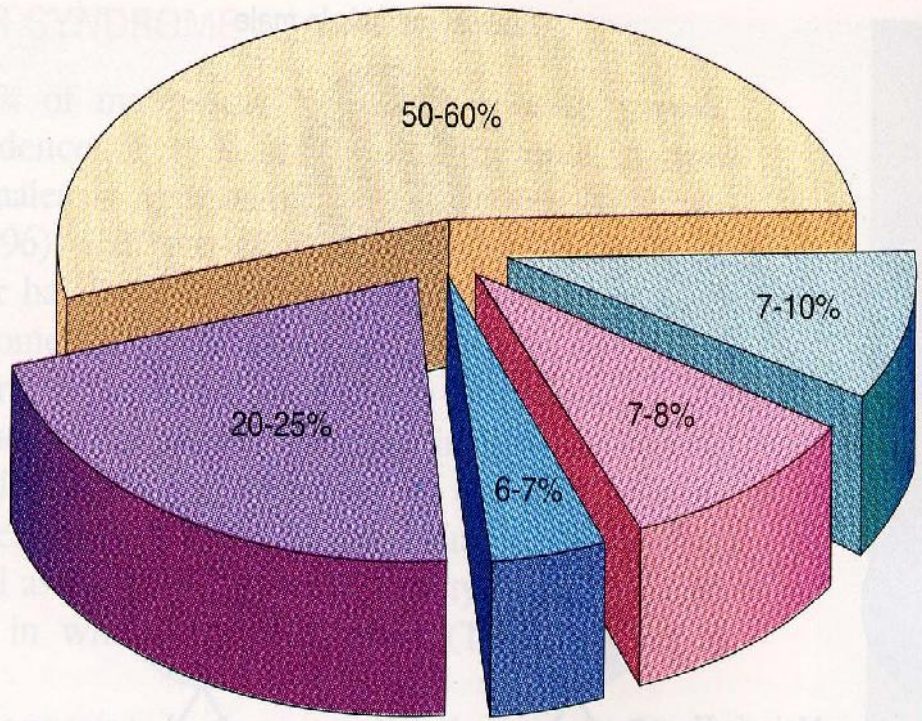
Normal embryological development

- **Neural plate** development -18th day
- **Cranial closure** 24th day (upper spine)
- **Caudal closure** 26th day (lower spine)

Teratology

- **Teratology** is the study of developmental anomalies and their causes, whether they are genetic or environmental in origin
- Teratology studies the causes, mechanisms, and patterns of abnormal development
- Developmental disorders present at birth are called **congenital anomalies**, birth defect or congenital malformation.
- Congenital anomalies are of four clinically significant types:
  - malformation,
  - disruption,
  - deformation and
  - Dysplasia (an abnormality of development)

Causes of congenital anomalies



Unknown etiology

Multifactorial inheritance

Chromosomal abnormalities

Mutant genes

Environmental agents

Figure 9–1. Graphic illustration of the causes of human congenital anomalies. Note that the causes of most anomalies are unknown and that 20 to 25% of them are caused by a combination of genetic and environmental factors (multifactorial inheritance).

Anomalies caused by genetic factors

- **Chromosomal aberrations** are common and are present in 6 to 7% of zygotes – (result =abort)
- **Numerical chromosomal abnormalities** – usually non-disjunction- error in cell division
  - Down syndrom (21)
  - Edwards (18)
  - Turner (X0)
  - Klinenfelter (XXY)
- **Structural chromosomal abnormalities** – chromosome breaks = translocation, deletion (cri du chat syndrome), duplication, inversion
- **Mutant genes** – fragile-X syndrome

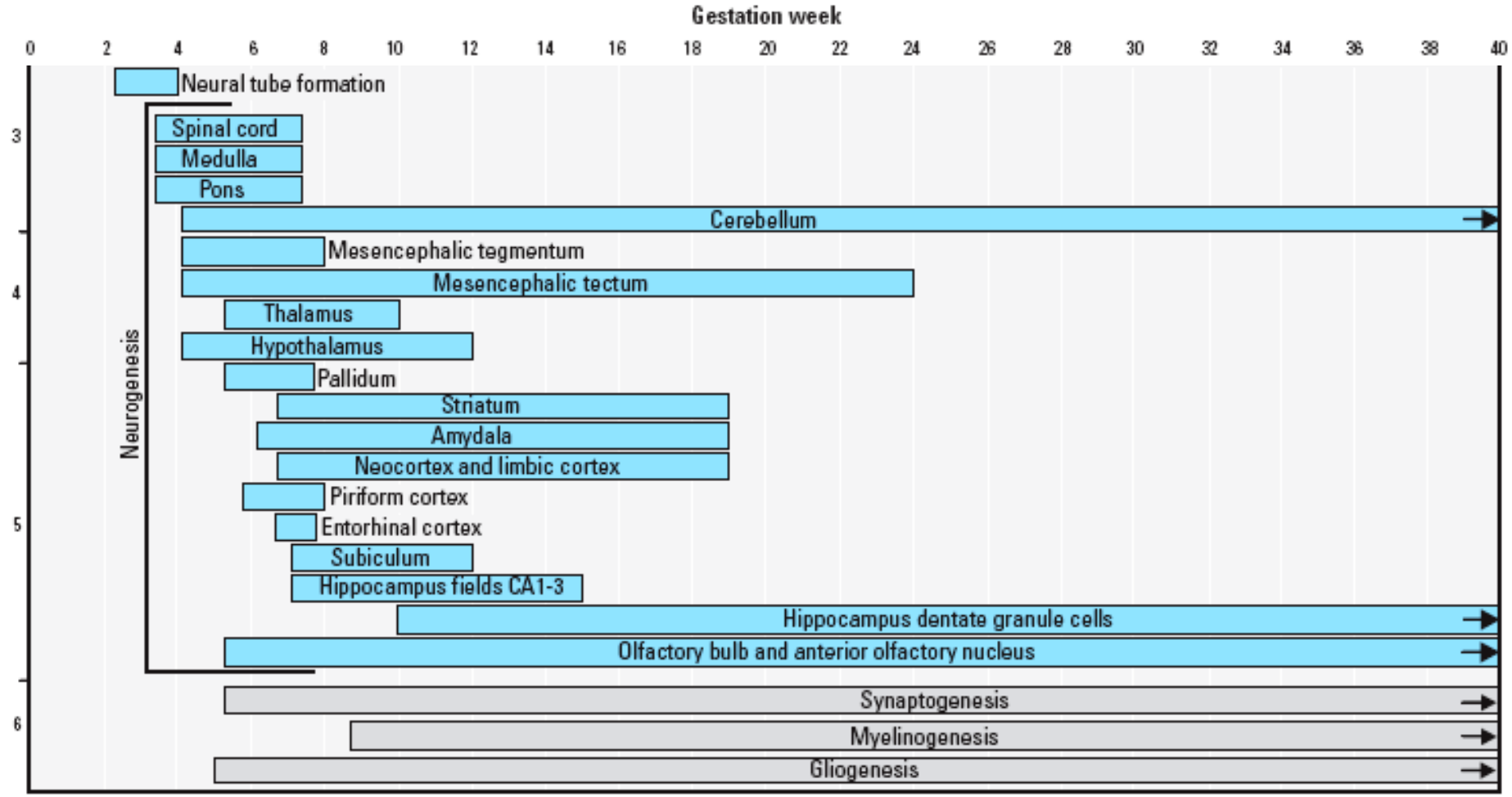
Anomalies caused by environmental factors

- **Teratogens** are exogeneous agents that may cause developmental defects:
  - ***Drugs*** (warfarin, valproic acid, phenytoin, vitamin A, thalidomide)
  - ***Chemicals*** (PCBs, methylmercury, alcohols)
  - ***Infections*** (rubella, cytomegalovirus, herpes, toxoplasma, syphilis)
  - ***Ionizing radiation*** (RTG)
  - ***Maternal factors*** (diabetes mellitus, hyperthermia, phenylketonuria)

Basic principles in teratogenesis

- **Critical periods** of development
- **Dosage** of the drug or chemical
- **Genotype** (genetic constitution) of the embryo and mother

Critical Periods in Human Development



Howdeshell 2002

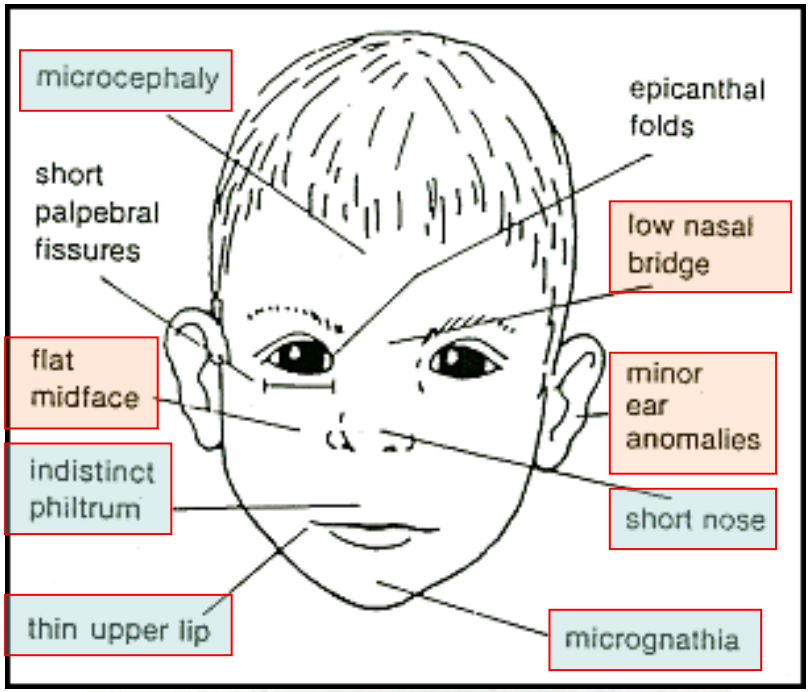
Exposure to teratogens

- About **80%** pregnant women use prescribed or over-the-counter drugs
- The drugs should only be taken when essential thereby avoiding unnecessary and unknown risks
- There is no “safe” dose for social drugs like and medications such as:
  - Alcohol
  - Addictive drugs – Cocaine, heroine, LSD etc.
  - Tobacco
  - Thalidomide

Fetal Alcohol Syndrome (FAS)

- Prevalence (Centre for Disease Control, 2003)
  - 130,000 women in US consume alcohol during pregnancy at levels known to increase birth defects
  - 13% use alcohol during pregnancy
  - 2% binge drink
  - 3% drink frequently

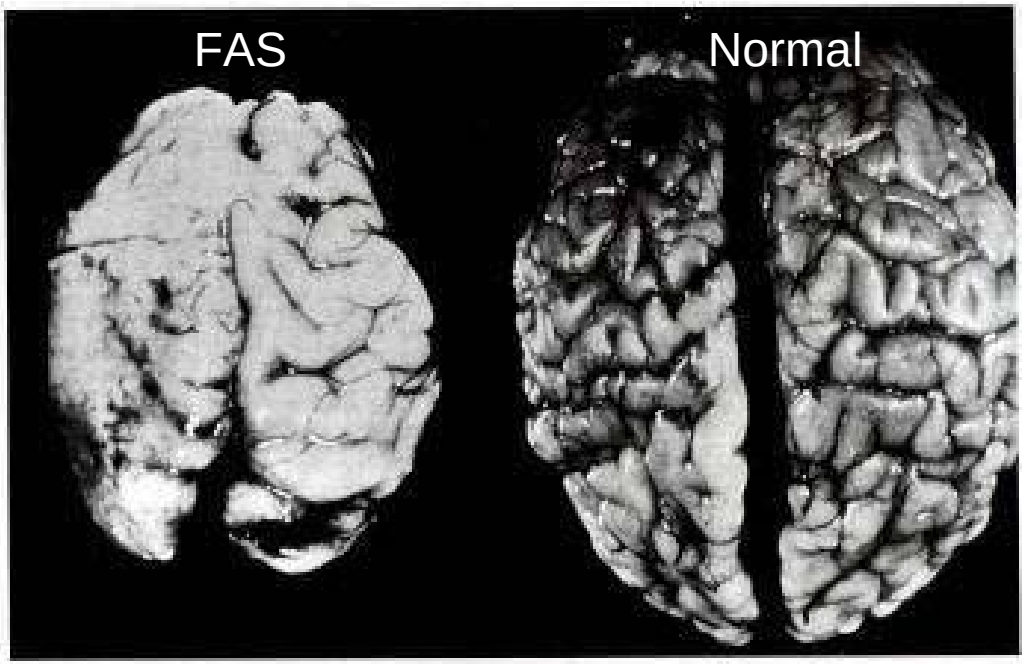
- **Alcohol passes through the placenta**
- There is **no safe dose** of alcohol for pregnant women
- Growth retardation found with **one drink per day**
- Infant symptoms related to maternal alcohol use: **1 in 300 births** (in general population)
- FAS is the third most prevalent type of **mental retardation** (behind fragile X syndrome and Down syndrome)



Fetal Alcohol Syndrome (FAS)

- Growth deficiency
- Mental retardation
- Low IQ (average 63)
- Mild to moderate **microcephaly** (small head size)
- Characteristic facial features
  - Short nose
  - Smooth philtrum
  - Thin upper lip
  - **Micrognathia** (undersized jaw)
- Attention deficit hyperactivity disorder (ADHD)
- Retarded physical growth in stature and weight

Fetal Alcohol Syndrome (FAS)



- Comparison of a brain from an infant with **FAS** (***left***) with a brain from a **normal** infant of the same age (***right***)
- The brain from the infant with FAS is
  - significantly **smaller**
  - the pattern of **convolutions is obscured by glial cells** that have migrated over the top of the brain (due to **defects in neuronal and glial migration**)

Fetal Alcohol Syndrome (FAS)

- **Facial dysmorphia** occurs during embryonic period (**week 4-8**)
- **CNS problems** during the fetal period
  - **Cell migration** (neural crest migration is severely impaired)
  - **Smaller dendrites**
  - **Fewer neurons** in brain regions
  - **Increased apoptosis of neuron**
  - Alcohol directly interferes with the ability of **cell adhesion molecules** to function in holding cells together
- The midline structures fail to form
- Forebrain anomalies are also seen, and the more severely affected fetuses lack a forebrain entirely

Fetal Alcohol Syndrome (FAS)

- **Developmental delay**
  - FAS patients with a mean chronological age of **16.5** years were found to have the functional **vocabulary** of **6.5**-year-olds and to have the **mathematical abilities** of fourth graders
- Most adults and adolescents with FAS cannot handle money or their own lives, and they have difficulty learning from past experiences

Cocaine

- Prevalence & Risk
  - 1 in 10 newborns affected (IN GENERAL POPULATION)
  - Like alcohol, just a single use can cause severe problems

- **Prenatal Complications**
  - Constricted blood vessels in uterus
  - Heart rate and blood pressure fluctuations of mother and fetus
  - Fetal brain damage
  - Miscarriage

- **Postnatal Complications**
  - Preterm birth (25% higher incidence among cocaine users)
  - Low responsiveness / Irritability
  - SIDS (Sudden Infant Death Syndrome)
  - Mental retardation (5x greater prevalence)
  - Fine and gross motor deficiencies (even after age 2)

Tobacco

- **Prevalence**
  - 12%-22% of women smoke during pregnancy
- **Concerns**
  - 2200 ingredients in tobacco leaves and smoke
    - Carbon monoxide reduces hemoglobin's oxygen carrying/releasing capacity
    - Nicotine affects placental blood vessels
  - Fetal hypoxia (lack of oxygen to body tissues)

Tobacco

- **Prenatal complications**
  - Growth retardation
  - Premature rupture of membranes (birth)
  - Miscarriage
  - Stillbirth
- **Postnatal complications**
  - Low birth weight
  - Mental alertness
  - Visual alertness
  - **S**udden **I**nfant **D**eath **S**yndrome (SIDS)
  - Growth retardation (weight, stature, head circumference)
  - Respiratory disorders (pneumonia, bronchitis)

Tobacco

- Smoking during breastfeeding → high risk for the baby
- Second hand smoke
  - Children in homes where there is second hand smoke have more respiratory problems (bronchiolitis, pneumonia, asthma)

June 16, 2008
Ontario Passes Ban on Smoking in Cars with Kids

- $250 fine
- Children under 16
- 23 times the toxins when in enclosed space size of car
- In effect in NS and BC

http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/20080429/car_smoking_ban_080429?s_name=&no_ads=

Other causes of congenital brain defects - Maternal Diseases

- **Viral infections**
  - **Cytomegalovirus (CMV)**
  - **Rubella [Congenital Rubella Syndrome (CRS)]**
  - **Herpes simplex virus (HSV)**
  - **Varicella zoster** (causes chicken-pox in children)
  - **HIV**
- Maternal **diabetes mellitus**
- Maternal **phenylketonuria**
- **Fetal trauma**
- **Hematologic diseases**
  - Rh incompatibility
- **Parasitic diseases**
  - Toxoplasmosis

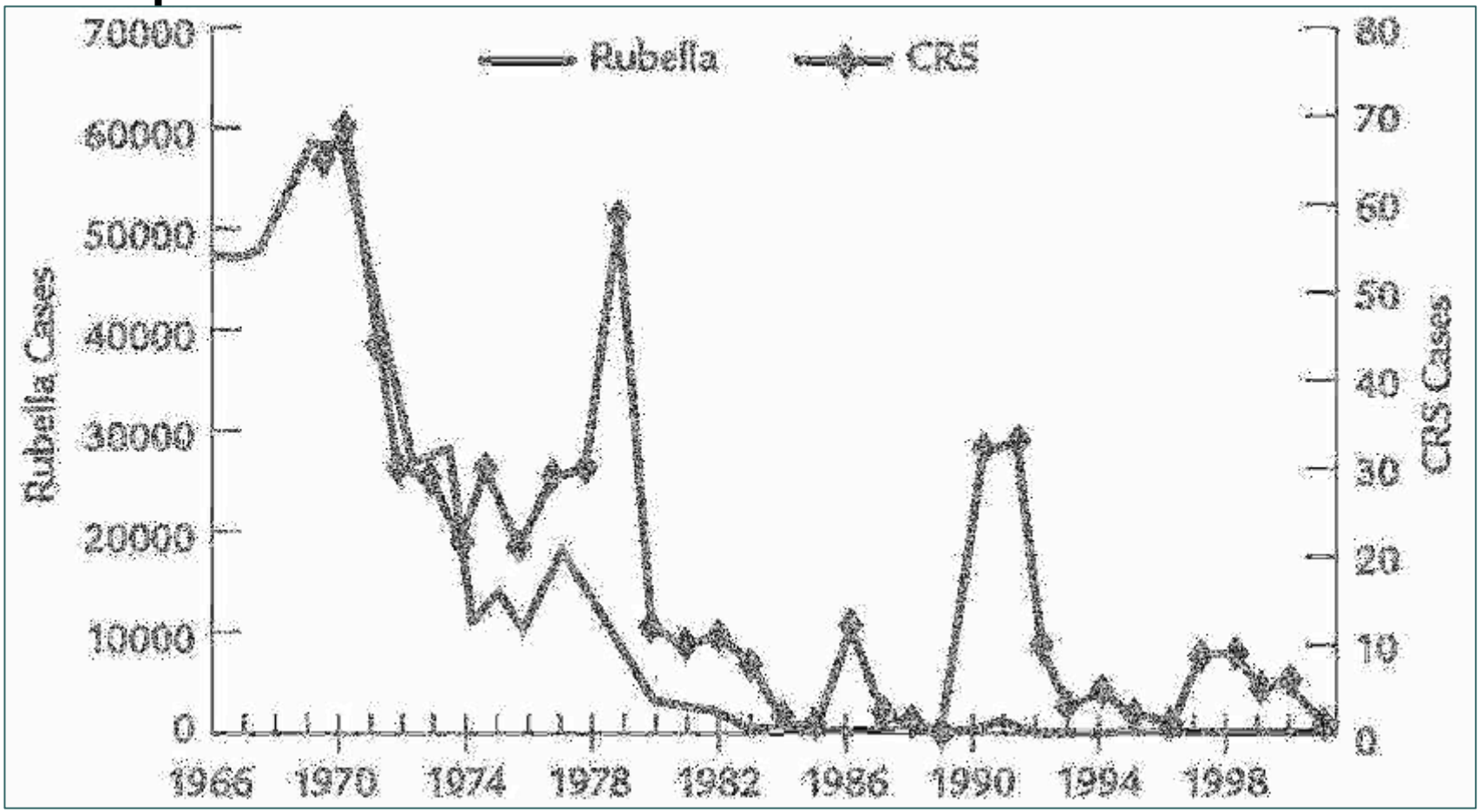
Rubella

- Common Name
  - **German measles**
  - Highly contagious
  - Once epidemic (e.g. 15 million cases in US in 1965)

- **Symptoms**
  - Swollen lymph nodes, mild fever, headache, aching joints, pink rash on face, body, arms, and legs
  - 20%-50% of infected may not notice symptoms

Congenital Rubella Syndrome (CRS)

- **Prevalence**
  - 20,000 newborns / year in US
- **Concerns**
  - Maternal infection leads to fetal damage
  - Symptoms more severe in fetus than adult
  - Severity depends on when pregnant woman incurs virus
  - Often masked during infancy – and evident only in later months/years
- **Associated defects**
  - Growth retardation
  - Mental retardation
  - Congenital glaucoma, cataracts
  - Pneumonia
  - Hepatitis
  - Cardiac anomalies
  - Deafness (80%)



Incidence of rubella and congenital rubella syndrome have decreased since introduction of vaccines. (US trends)

Thalidomide

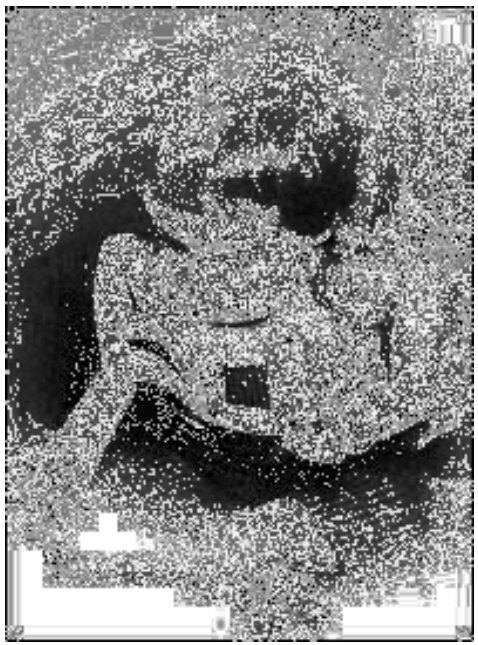
- **1954** – Chemists synthesize thalidomide – trying to produce a new anti-histomine – instead they discover that it is an effective **sedative**
- **1956** – Free samples to workers at the manufacturing plant – a baby without ears
- It was prescribed to women to combat morning sickness associated with pregnancy
- **1961** – First published correlation between Thalidomide and birth defects – based on 3 babies
- **1962** – Thalidomide taken off the market

Thalidomide

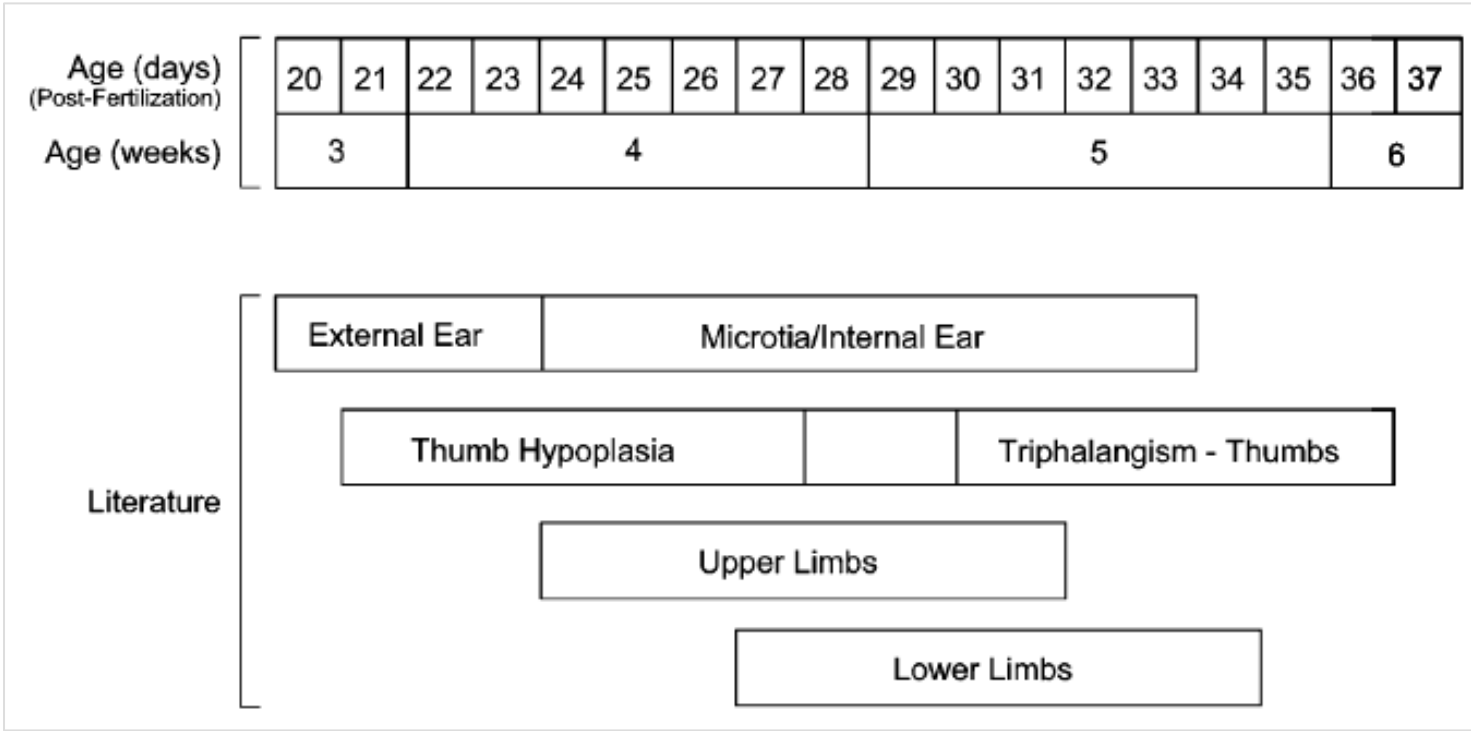
- **1965** – Thalidomide is found to be a significant treatment for **Leprosy** patients that develop severe skin lesions associated with an inflammatory reaction – Thalidomide is the treatment of choice
- **1980's** – Thalidomide is shown to be a effective in treating other diseases involving ulceration or lesions, including **HIV-related symptoms**

- 12,000 Thalidomide babies born
- 8,000 Thalidomide babies survived
- Many are alive today – they are in their late 30's and early 40's

Thalidomide



- Spectrum of malformations (besides limbs):
- Absence of ears, deafness
- Defects of eye and facial muscles
- Malformations of heart, bowel, uterus, gallbladder
- Many have autism-like symptoms
- **Sensitive period – 20 – 36 days after fertilization**
- Today – mechanism of Thalidomide action in embryopathy or in clinical treatment is unknown



- **Early exposure** (days 20–25) resulted in involvement of
  - the **cranial nerves** (especially 6 and 7)
  - **external ear**
  - abnormal **ocular movement**
  - aberrant **lacrimation** (production of tears), and
  - **thumb** anomalies

- **Later exposure** caused
  - **upper limb** malformations
  - **eye** malformations
  - **systemic anomalies**, and
  - **lower limb** malformations and
  - **thumbs** malformations

Over the Counter (OTC) Medications

Generally Safe	Potentially Dangerous
Acetaminophen (Tylenol)	**Aspirin** **Post-term pregnancy and prolonged labor; bleeding in skull of baby;** **maternal bleeding during delivery**
Ibuprofen **(Advil, Motrin)**	**Cold medications** **Containing alcohol.** **May result in FAS** (Fetal Alcohol Syndrome) **and ARND** (Alcohol-Related Neurodevelopmental Disorder)
Naproxen Sodium (Aleve)	**OTC drugs** **designed to treat a variety of problems**

Long term use of any OTC is not recommended.

Medication	Designed to Treat	Teratogenic Effect
Anticoagulants: Warfarin	**Blood clots**	**CNS defects** **Miscarriage** **Eye defects**
Antidepressants: Lithium	**Bipolar Disorder**	**Congenital heart defects**
Antibiotics: Tetracycline	**Infections**	**Underdevelopment of tooth enamel and tooth yellowing**
Antibiotics: Streptomycin	**Tuberculosis**	**Hearing loss**
Anticonvulsants: Dilantin	**Seizure disorders**	**Mental retardation** **Neural tube defects** **Hand and face defects**
Antithyroid: Propylthiouracil; Iodide; Methimazole	**Overactive thyroid**	**Thyroid gland defects**

OTHER DRUGS used by the mother during critical developmental periods include:

- **retinoic acid**, **alcohol**, **cocaine**

Retinoic acid toxicity

- Form of vitamin A
- Influences the process of **cell differentiation** during embryonic development
- **Important**: **concentration gradient** along the anterior-posterior (head-tail) axis during development
- Each **rhombomere** has a specific pattern of genes being expressed depending on the level of RA
- RA turns on a differential pattern of **Hox genes** (which encode different homeodomain **transcription factors**) which in turn can turn on **cell type specific genes**

Retinoic acid toxicity

Skin products contain retinoids

- RA is widely used product for **skin renewal** by decreasing excessive breakdown of collagen and elastin in the skin
- Anti-aging moisturizers used to reduce wrinkles, darkened spots and improve skin tone (?)
- Over the counter **acne treatment** products. For example, **Acutane**
  Known side effects are:
  - **hydrocephaly** (a buildup of fluid inside the skull – “water in the brain”)
  - **microcephaly**
  - **mental retardation**
  - **ear deformities**, **missing ears**
  - **cleft lip or palate**
  - **defects of the heart**
  - **deformities of the face** and
  - **lowered IQ**

Bisphenol A (BPA)

- It is used to make polycarbonate plastic (i.e. baby bottles)
- Evidence suggests that exposure of fetuses, infants and young children to BPA has toxic effect
- In September 2010, Canada became the first country to declare BPA as a toxic substance !!
- Can mimic the body's own hormones and alter brain functions through multiple pathways

Eureka! Less poison really is more – deadly

For 500 years, science has believed that we can tolerate a little bit of almost kind of any poison. Those days may be gone

http://www.theglobeandmail.com/news/technology/science/eureka-less-poison-really-is-more-deadly/article1499340/

Bisphenol A (BPA) is toxic – evidence from animal studies

- **2007** - Low doses of BPA during development have effects on brain structure, function and behavior in rats and mice
- **2008** - Low-dose BPA maternal exposure causes long-term neurobehavioral development in mice
- **2008** - Low-dose neonatal exposure to BPA alters long-term potentiation (LTP) in the hippocampus and effects memory processes
- **2009** - BPA effect on antero-ventral periventricular nucleus (AVPV, controls sex-typical physiology and behaviors)