

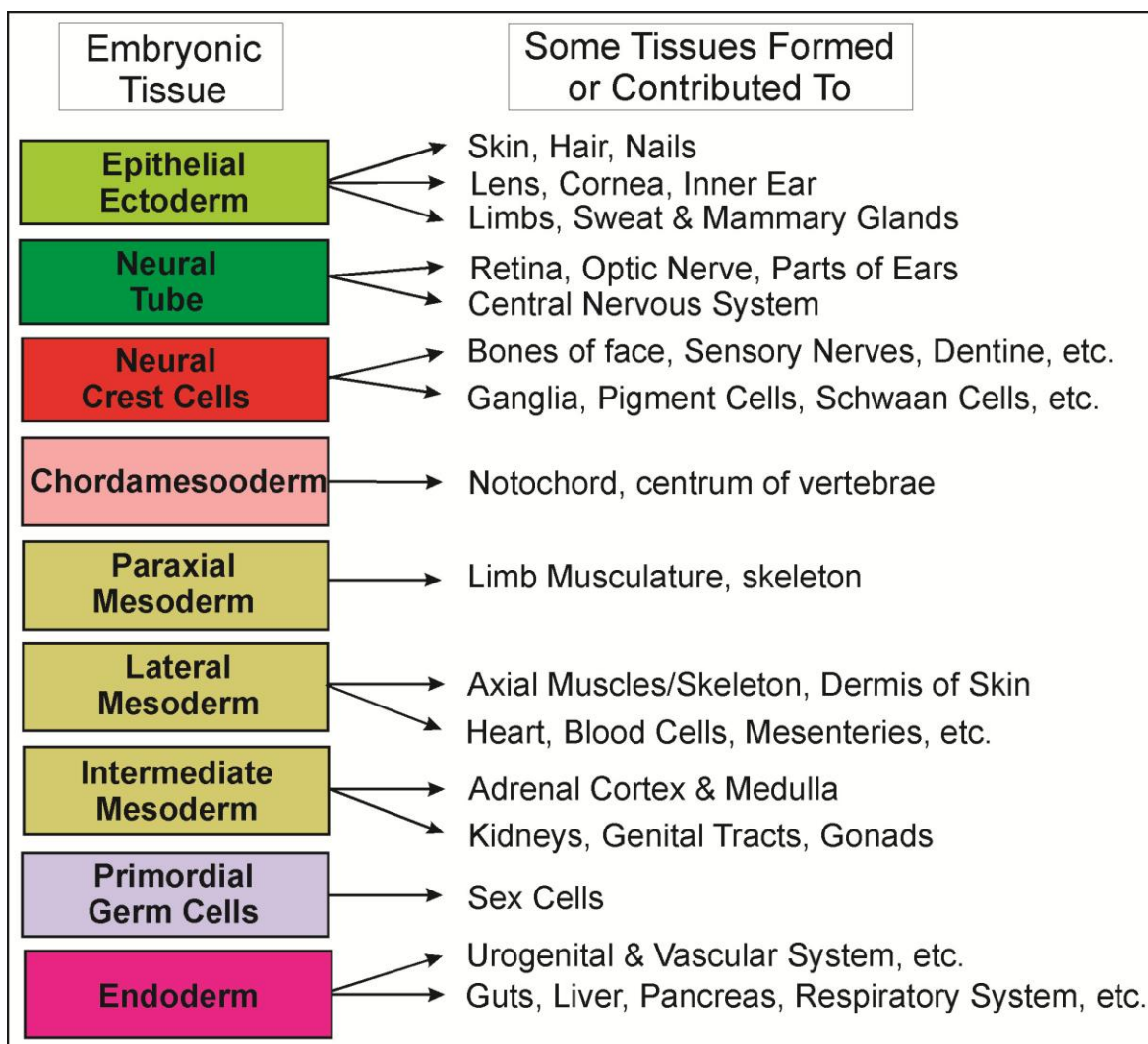


Critical Periods in Development

Neurulation & Other Events

In the previous lecture we examined the events of neurulation. As we mentioned earlier, development is a dynamic process with many events occurring simultaneously. Thus, when we are talking about one process many other things may be going on at the same time. Let's look at a few of the changes that are going on in the neurula and post-neurula embryo. Since we can't cover all of the events we'll just examine a few. In later lectures we'll focus on the development of a select group of organs and tissues.

Understanding some of the changes that are going on in the neurula and post-neurula stages will help you understand more about the critical periods of development (many of which are centered around this important phase of development). The following figure outlines some of the tissues we've learned about and their basic developmental fates.



Critical Periods in Development

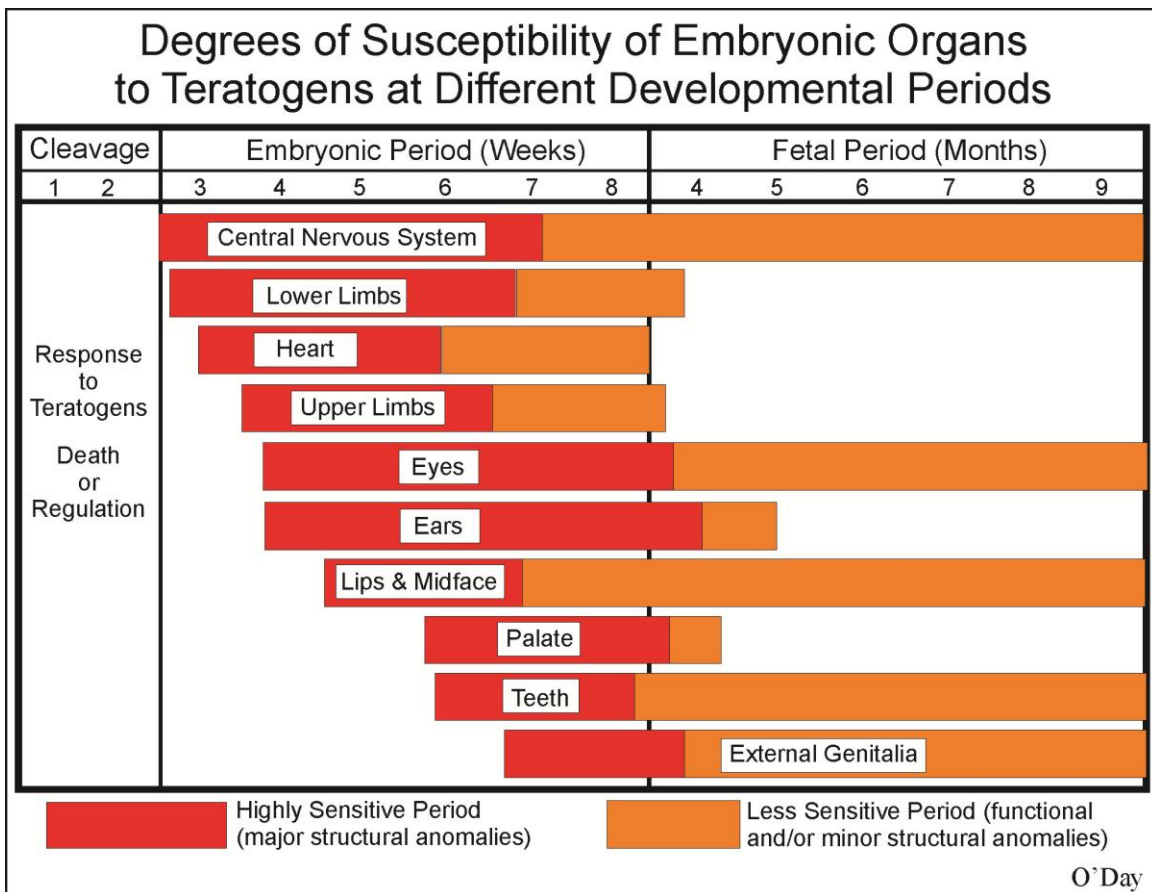
The Formation of Tissues

The final differentiated state of a cell is defined by the events it has experienced throughout development. In some organisms such as *Caenorhabditis elegans* the fate of some cells is determined at the start of cleavage while the rest of the cells are determined by cellular interactions that occur throughout development. In this organism it is possible to determine exactly which embryonic cell will become what differentiated cell came in the adult. The lineage of each cell is clearly defined.

This is not the case in human cells. Their fate is not predetermined to any significant degree. The fate of cells is progressive being determined almost entirely by cellular contacts and by molecules secreted by other cells. However by gastrulation, certain groups of cells have been formed, each of which will give rise in the normal course of events to specific cells, tissues and organs. By neurulation, even more tissue fates have been specified. The following figure shows the major tissues that exist in the fetus just after neurulation and what they will differentiate into.

Critical Periods in Development

- Cells are changing and following specified developmental programs
- Interference with one stage usually stops the subsequent event preventing the complete sequence of events
- There is a limited time frame in which sets of cells can complete their tasks
- During this time cells can be very sensitive to disruptive agents
- This is the "critical period" for organ or tissue; e.g. disruption of neural tube closure leads to spina bifida, incomplete palate formation leads to cleft palate, etc.



Critical Periods in Development

Agents Affecting the Critical Periods

Teratogen: any agent that disrupts a developing embryo such as the following:

- Mutated Genes: interfere with developmental program
- Physical Agents: X-Rays, Heat
- Chemical Agents: Steroids, Alcohol, Drugs
- Viruses: herpes, Rubella (German Measles) viruses
- Other: lack of a specific, essential component can lead to abnormal development (e.g., folic acid & Spina Bifida)

Some Genetic Mutations Lead to Abnormal Development

	Condition	Symptoms
Autosomal dominant	Neurofibromatosis	Multiple neural crest derived tumors on skin, abnormal pigment areas on skin
	Polycystic Kidney Disease: Adult onset Type III	Numerous Cysts in Kidneys
	Achondroplasia	Dwarfism, mainly due to shortening of limbs
Autosomal Recessive	Congenital Phocomelia syndrome	Limb Deformities
	Polycystic Kidney Disease: Perinatal Type I	Numerous Cysts in Kidneys
	Albinism	Absence of Pigment
X-linked Recessive	Hydrocephalus	Enlargement of Cranium
	Testicular Feminization Syndrome	Inability to Respond to Testosterone Results in Female Phenotype
	Hemophilia	Defective Blood Clotting

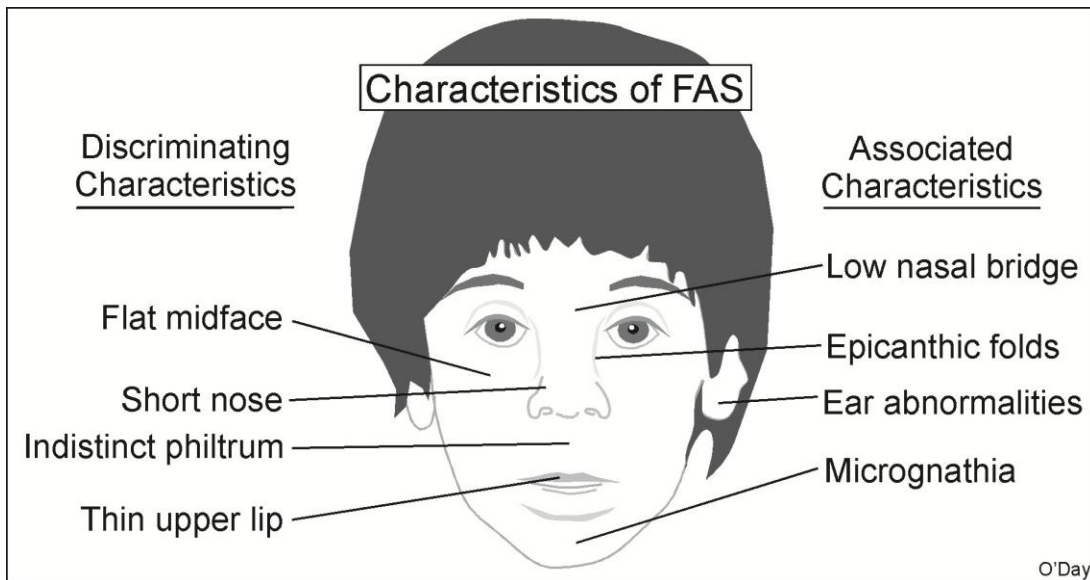
Chemical Teratogens Cause Birth Defects in Humans

Here is a short list of the more common teratogens and their effects in humans:

Agent	Effect on Human Development
Alcohol	Growth & Mental Retardation, Microcephaly, Various Malformations of the Face and Trunk
Chemotherapeutic Agents (Methotrexate, Aminopterin)	Variety of Major Anomalies throughout the Body
Diethylstilbestrol (DES)	Cervical & Uterine Abnormalities
Lithium	Heart Anomalies
Mercury	Mental Retardation, Cerebral Atrophy, Spasticity, Blindness
Streptomycin	Hearing Loss, Auditory Nerve Damage
Tetracycline	Hypoplasia & Staining of Tooth Enamel, Staining of Bones
Thalidomide	Limb Defects, Ear Defects, Cardiovascular Anomalies

Fetal Alcohol Syndrome (FAS)

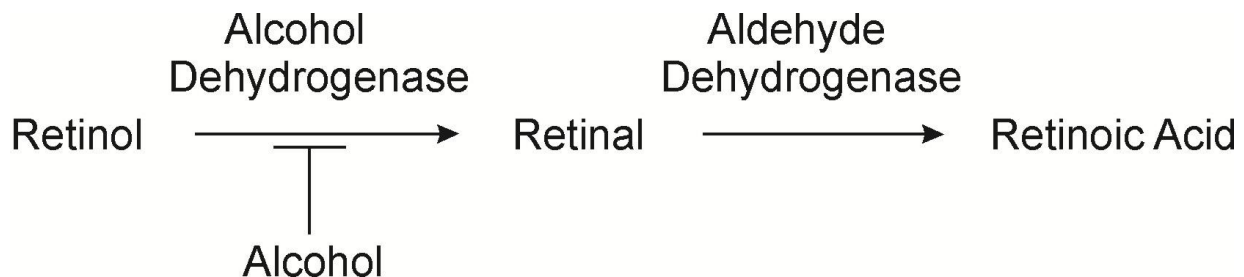
Babies with FAS typically have a small head size, a narrow upper lip, an indistinct philtrum (the pair of ridges that runs between the middle of the upper lip and the nose), and a low nose bridge.



Abnormalities in neuron migration and a smaller brain size reflect the reduced mental ability of FAS children. While fragile-X and Down syndrome lead to the most cases of mental retardation, FAS is third, affecting as many as 1 in 500-750 children in the US. FAS children have a mean IQ of ~68 making them unable to manage their own lives or to learn from past experience. There are likely many reasons for these effects of ethanol. Neural crest migration is hindered in the presence of ethanol leading to premature differentiation of facial cartilage. Ethanol also induces apoptosis (death) of neurons. These are just some of the insights that are being gained as researchers pursue this serious problem that has high costs for society and for the affected individuals.

FAS and Retinoic Acid

Studies in developing animals exposed to alcohol have revealed reductions in neuronal number beyond normal neuronal apoptosis. The teratogenicity of ethanol varies depending on the dose, time and individual, ranging from no detectable effects to embryo death. Retinoic acid, a developmental morphogen, has a possible role underlying the teratogenic effects of ethanol. Retinoic acid, a vitamin A derivative, functions in the specification of spatial patterns during nervous system and limb morphogenesis. It also functions during epithelial cell differentiation. Ethanol inhibits the enzyme alcohol dehydrogenase (ADH) interfering with the production of retinal from retinol (vitamin A), a rate limiting step in the production of retinoic acid.



Critical Periods in Development

Since a retinoic acid is needed for normal development of the limbs and central nervous system, disruption of its synthesis organs at critical periods could result in developmental defects. More recently, in addition to retinoic acid, alcohol has been shown to affect the formation of cell adhesion molecules (L1-CAM, L1-cell adhesion molecule) and the enzyme catalase, each of which has roles in neuronal differentiation.

Viruses, Bacteria & Protozoa Can Cause Birth Defects

Here is a short list of the more common infections agents and their effects in humans.

Organism	Disease	Congenital Defect
Rubella Virus	German Measles	Cataracts, Deafness, Cardiovascular Defects, Slow Growth of Fetus
Cytomegalovirus	Cytomegalic Inclusion Disease	Microcephaly, microphthalmia, cerebral calcification, slowing of intrauterine growth
<i>Trepanoma pallidum</i> (Spirochete bacterium)	Syphilis	Dental Abnormalities, Deafness, Mental Retardation, Skin & Bone Lesions, Meningitis
<i>Toxoplasma gondii</i> (Protozoan)	Toxoplasmosis	Microcephaly, Hydrocephaly, Cerebral Calcification, Mental Retardation

Timing of Teratogen Action

- Teratogens can have different effects at different stages
- Rubella affects different tissues depending on time of infection
- Thalidomide at 3 weeks: causes defects in CNS
- Thalidomide at 4 weeks: causes defects in the heart
- Thalidomide at 3-8 weeks: causes defects in limb development

Cleft Lip & Cleft Palate

- Definition: a facial birth defect (congenital abnormality)
- Common; ~ 1/1000 births
- Cleft lip: affects the upper lip, from a notch to a fissure into the nose
- Cleft palate: affects the roof of the mouth; a groove that may extend through the dental arch (hard palate).
- Abnormalities may occur separately or together
- Reason: left & right sides do not contact & fuse

Spina Bifida (SB)

- A neural tube defect
- Caused by the failure of the fetus's neural tube to close properly during the first month of pregnancy
- SB Infants may have an open lesion on their spine with nerve/spinal cord damage
- SB may also cause bowel and bladder complications
- Many children with SB have hydrocephalus (excessive accumulation of cerebrospinal fluid in the brain).
- Spinal opening can be surgically repaired
- Nerve damage can't be fixed, leads to varying degrees of paralysis of lower limbs

Folic Acid and Neural Tube Defects

The importance of folic acid deficiency as a cause of neural tube defects (NTDs; spina bifida and anencephaly) was realized over 30 years ago. Anencephaly is caused by a failure of the cranial neural tube closure. It typically results in the absence of a forebrain often with other brain tissue exposed usually resulting in death. Anencephaly occurs in 1 in 150,000-200,000 births. Clinical trials in Europe and the UK

revealed that folic acid supplementation was the most effective birth defect prevention method ever identified. Supplementing a diet with 0.4mg per day in reproductive females led to an 80% reduction in NTDs. In spite of this, the reason that FA is so effective remains a mystery. Moreover, FA isn't effective in all women. Examining the metabolism of FA it is clear that metabolites of the water soluble molecule plays two critical functions: DNA synthesis and methylation of DNA, RNA and proteins. How these play a role in regulating neural tube closure remains to be determined.

References

Goodlett, C.R., K.H. Horn, and F.C. Zhou, 2005. Alcohol Teratogenesis: Mechanisms of Damage and Strategies for Intervention. *Exp. Biol. Med.* 230: 394 - 406.

FAS Symposium: The June 1, 2005, volume of journal *Experimental Biology and Medicine* (volume 230) presents a number of papers from a symposium on FAS.)

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