Mechanism of Teratogenesis: Environmental Asssaults on Human Development

- In addition to genetic mutation several environmental factors can disrupt development. The summer of 1962 brought two portentious discoveries.

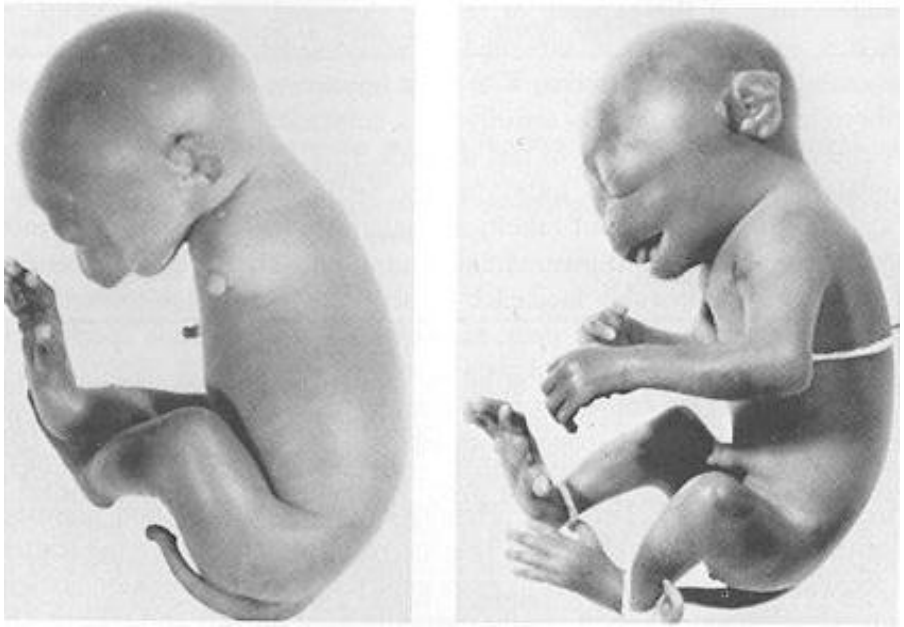
1. The first was disclosure by Rachel Carson (1962) that the pesticide DDT was destroying bird eggs and was preventing reproduction in several species.

2. The second was the discovery that thalidomide, a sedative drug used to manage pregnancies, could cause limb and ear abnormalities in the fetus.

Therapeutic agents can be teratogens

THALIDOMIDE

Absence of arms 38-42 days (absence of legs 39-45 days) *Gilbert (2006)*



Abnormalities in forelimb, lower jaw, ear and tail in 100 day Rhesus monkey foetus following treatment of pregnant mother with 30 mg/kg thalidomide on day 26 of pregnancy. Normal foetus on right *Wilson (1973)*

These two discoveries showed that the embryo was vulnerable to environmental agents. This was underscored in 1964, when an epidemic of rubella (German measles) spread across America. Adult showed mild symptoms when infected by this virus, but over 20,000 fetuses infected by rubella became either blind, deaf or both.

Disruptions

Abnormalities caused by exogenous agents called disruptions.

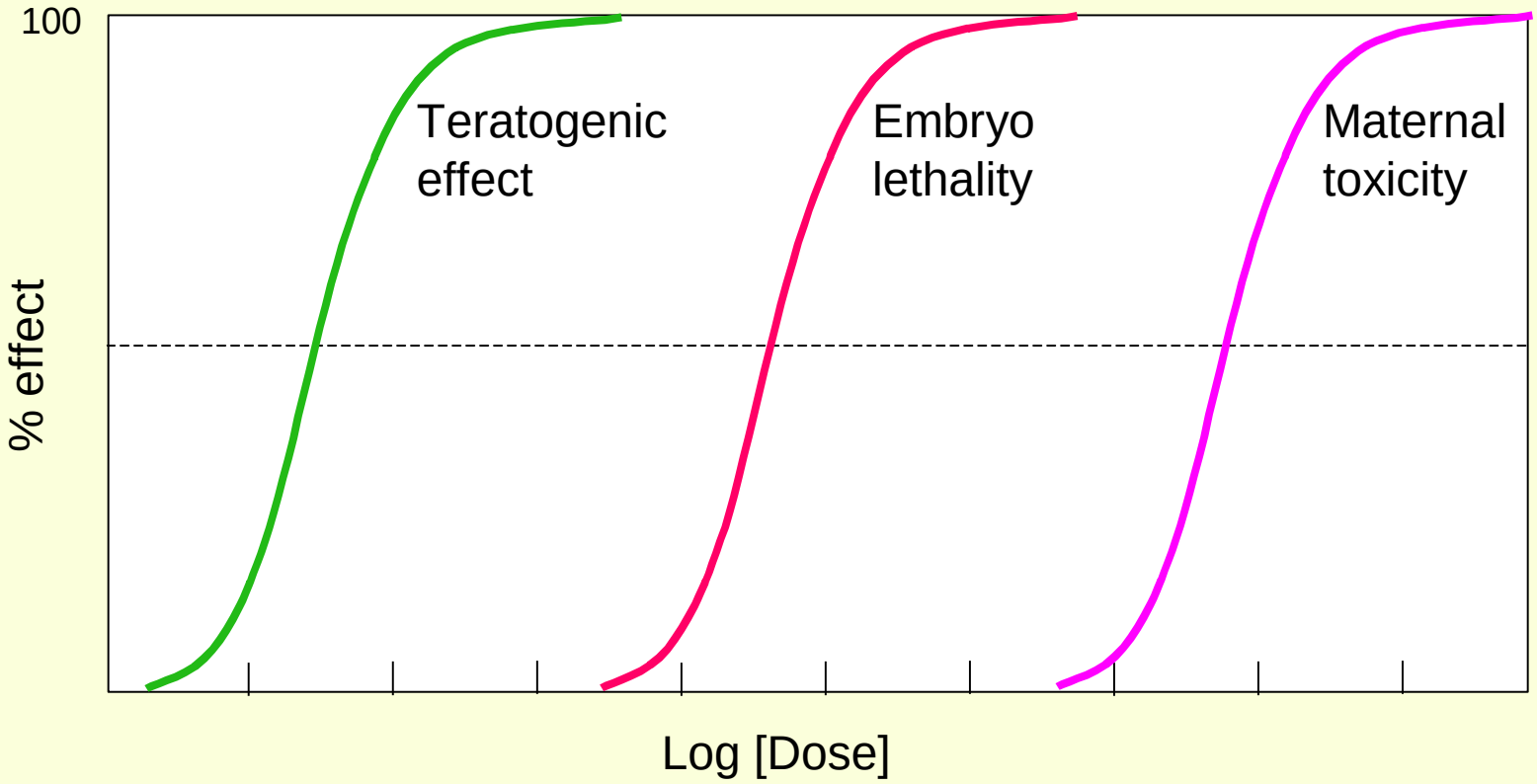
Teratogens

The agents responsible for these disruptions are called **teratogens**. Most teratogens produce their effects only during certain critical period of development.
Human development is divided into two periods:

- The embryonic period (to the end of week 8)
- The fetal period (the remaining time in uterus)

In embryonic period most of the organ systems form; the fetal period is generally one of growth and modeling.

Embryos can be vulnerable to low concentrations of teratogen



Footnotes:

1. Teratogens usually have a general toxicity
2. But: distinguish between general toxicity and specific formation of defects
3. Maternal toxicity can be much lower. In some cases (eg thalidomide in humans), there is no maternal toxicity
4. Teratogenicity can be very variable in different mammals

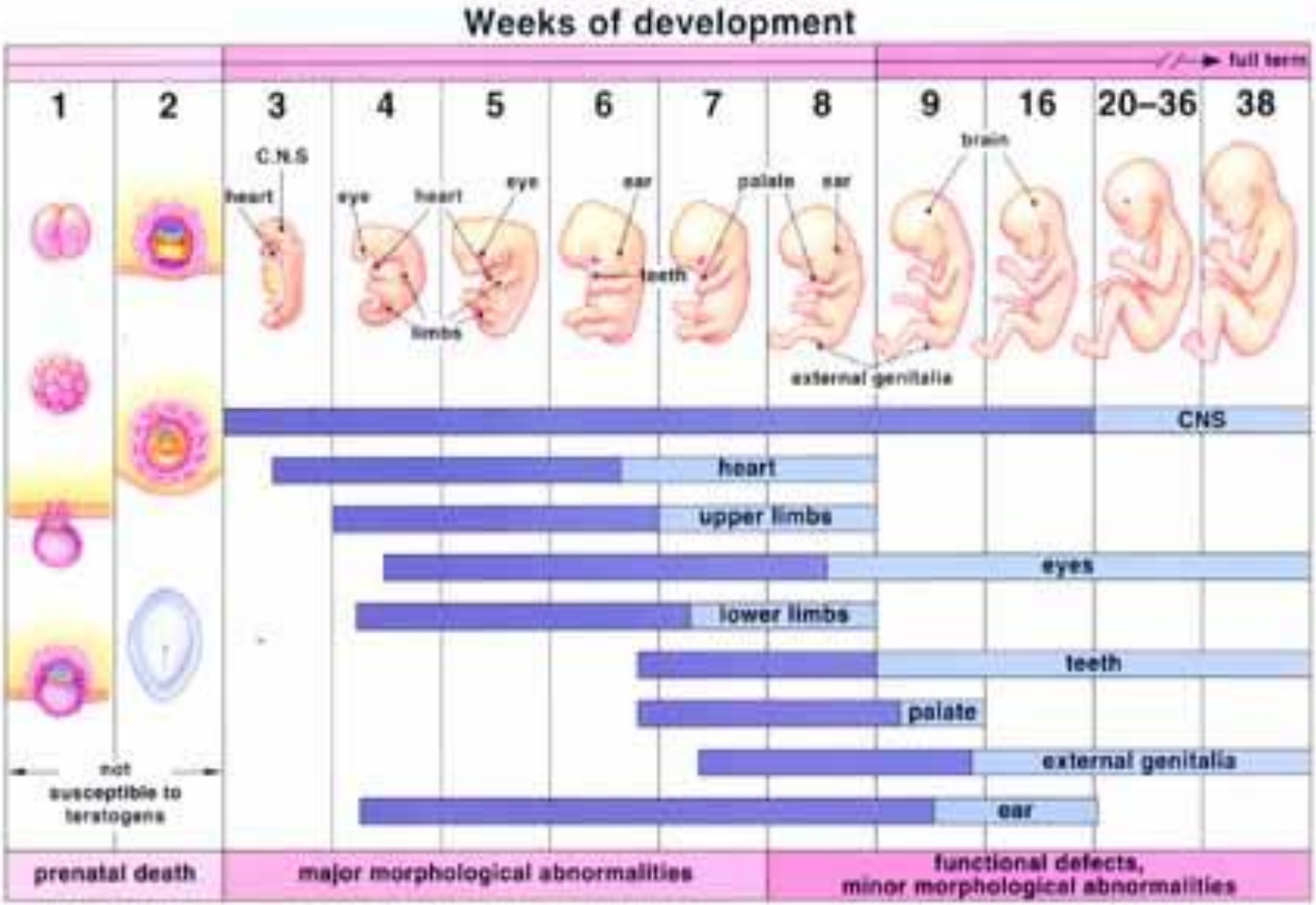
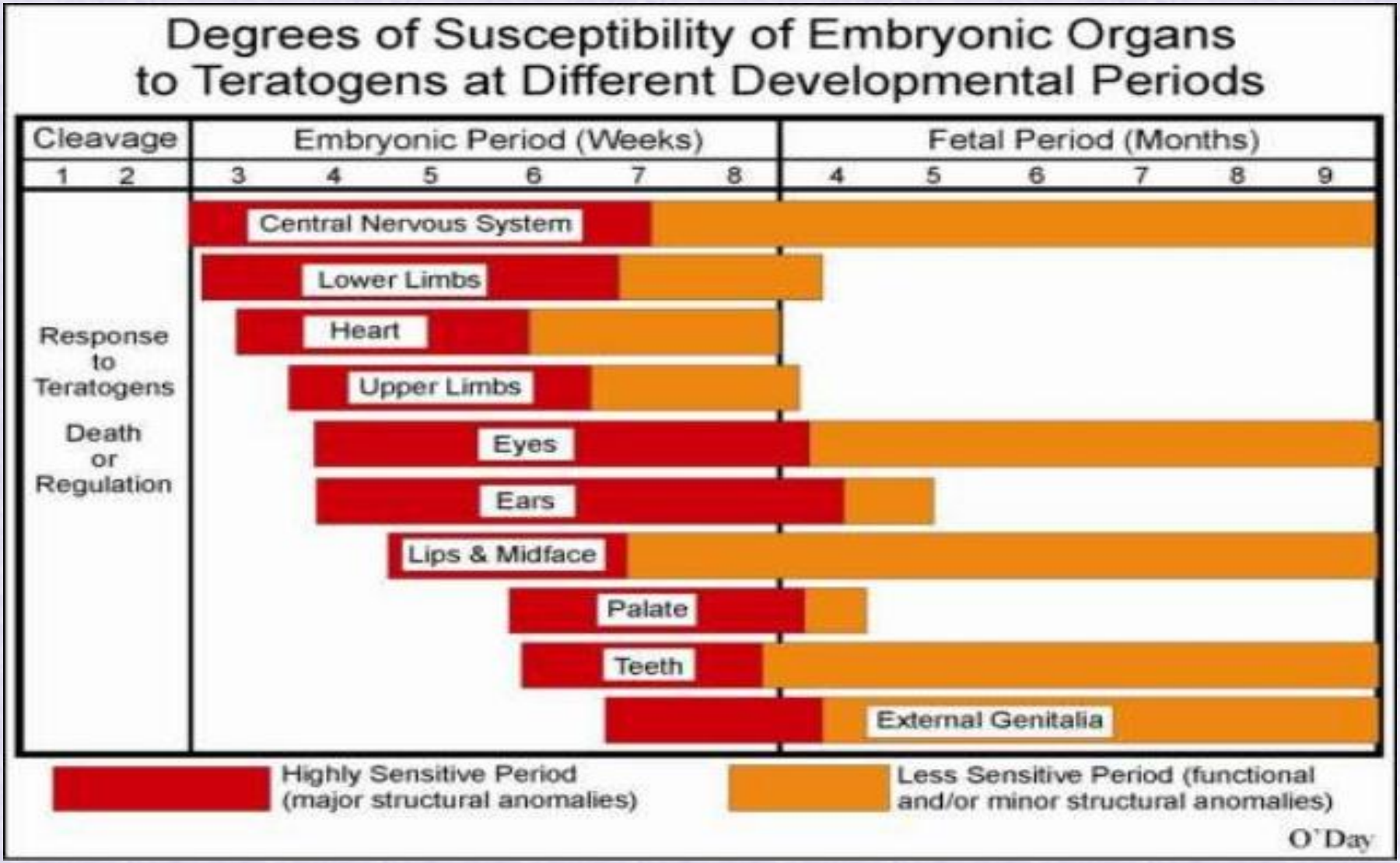


Fig. 34.24 Sensitivity to Teratogens during pregnancy.


Degrees of Susceptibility of Embryonic Organs to Teratogens at Different Developmental Periods
Cleavage
Embryonic Period (Weeks)
Fetal Period (Months)
1 2 3 4 5 6 7 8 4 5 6 7 8 9
Response to Teratogens
Death or Regulation
Central Nervous System
Lower Limbs
Heart
Upper Limbs
Eyes
Ears
Lips & Midface
Palate
Teeth
External Genitalia
Highly Sensitive Period (major structural anomalies)
Less Sensitive Period (functional and/or minor structural anomalies)
O'Day

Teratogenesis

- Genetic, Environmental, Thalidomide episode, DDT & bird egg cases. In 1964 Rubella cases.
- Many teratogens in environment. Embryonic period (8-9 weeks) more susceptible, especially, 3 to 8 weeks.
- **Teratogenic Agents:** Drugs & chemicals. Viruses, radiations, hyperthermia, maternal metabolic defects.

Teratogenesis

- Quinine, Alcohol, Heavy Nicotine and caffeine doses, smoking also reduces the number, quality and motility of sperms.
- Pesticides. Many drugs e.g. valproic acid (anti-convulsant). Even “useful” substances such as retinoic acid------if in excess (13-cis-retinoic acid used for acne), especially thru its binding to neural crest cells)

Teratogenesis

- Alcohol another important teratogen. Fetal Alcohol Syndrome (FAS): small head, mental retardation, low IQ (~68). Brain defects, fusion defects of upper lips.

2.ENVIRONMENT

The main environmental factors are teratogens-

1. ALCOHOL

Birth defects occur in the children of alcoholic mothers

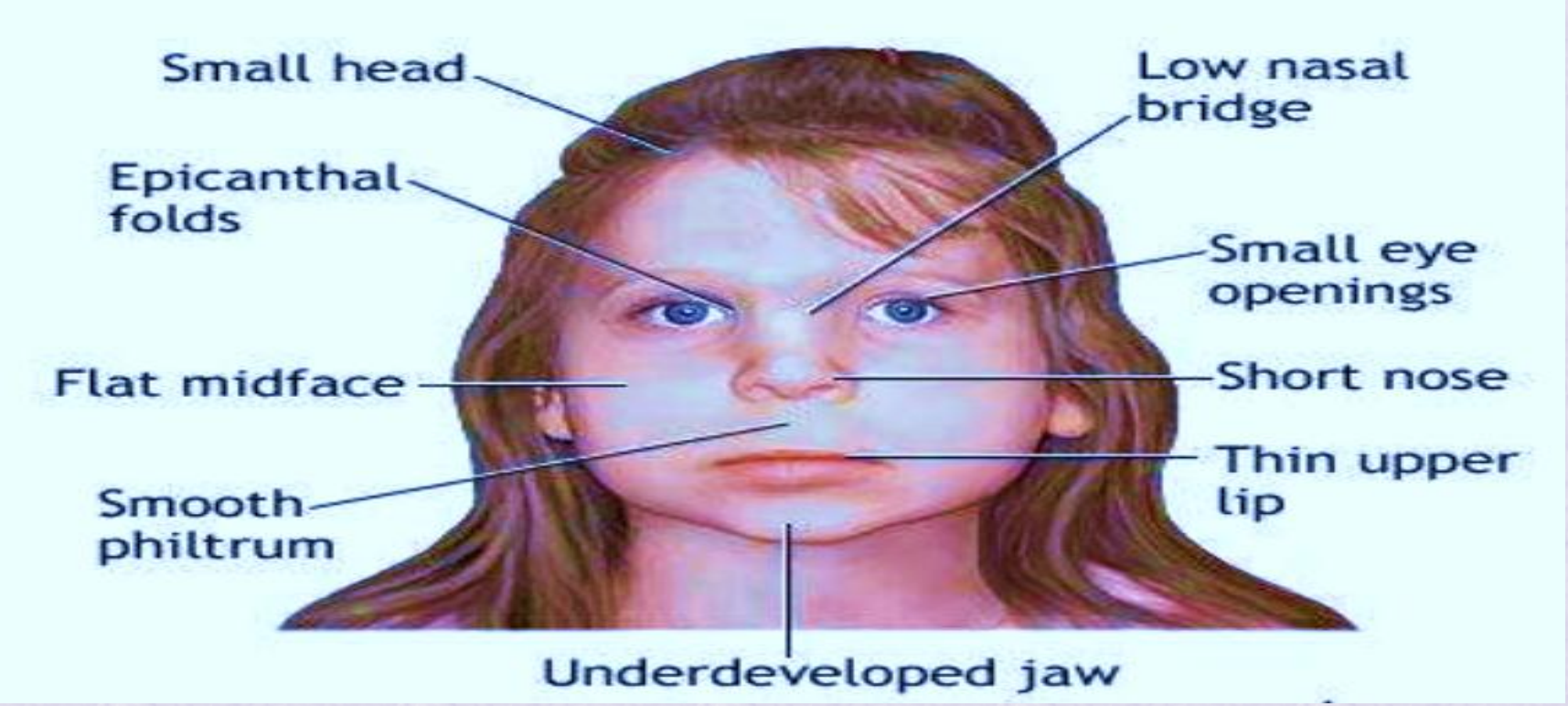
FAS- Fatal Alcohol Syndrome

2. DRUGS AND CHEMICALS

a) Ethanol
b) Retinoic acid
c) Tetracycline }
d) Thalidomide }ANTIBIOTICS
e) Streptomycin }
f) Cigarette smoking
g) Heroin

Fetal alcohol syndrome (FAS)

In 1968, Lemoine and colleagues noticed a syndrome of birth defects in the children of alcoholic mothers. This FAS was confirmed by Jones and Smith (1973).



Retinoic acid as teratogen

Retinoic acid (RA) is important in forming the anterior-posterior axis of the mammalian embryo as well as in forming the jaws. In normal development it is secreted from discrete cells and works in small area.

13-cis-retinoi acid has been useful in treating severe cystic acne and has been available for this purpose since 1982. The dug carries a label warning that it should not be used by pregnant women.

Lammer and his co-worker (1985) studied a group of women who inadvertently exposed themselves to retinoic acid and who elected to remain pregnant. Of their 59 fetuses, 26 were born without any noticeable anomalies, 12 aborted spontaneously, and 21 were born with obvious anomalies.

The infected infants had characteristic pattern of anomalies:

- Absent or defective ears
- Absent or small jaws
- Cleft palate
- Thymic deficiencies
- Aortic arch abnormalities
- Abnormalities of central nervous system.

Radioactively labeled retinoic acid binds to the cranial neural crest cells and arrests both their proliferation and their migration.

Teratogenesis

- **Examples:** diethylstilbestrol, given (in 50's and 60's) to prevent miscarriage → abnormal reproductive system in fetus.
- **HEAVY METALS:** e.g. Zinc, Lead, Mercury etc used in industry, pollute soil, water, air….CNS defects.

Teratogenesis

- **Pesticides**: chlorinated hydrocarbons (DDT), Organophosphates, pyrethroids, Carbamates etc.
- **Endocrine Disruptors:** interfere with hormones, by binding with receptors or blocking synthesis of normal hormones.
- **Other:** over 50,000 artificial chemicals now used. Very little information available.

Some agents thought to cause disruptions in human fetal development

DRUGS AND CHEMICALS
Alcohol
Aminoglycosides (Gentamycin)
Aminopterin
Antithyroid agents (PTU)
Bromine
Cigarette smoke
Cocaine
Cortisone
Diethylstilbesterol (DES)
Diphenylhydantoin
Heroin
Lead
Methylmercury
Penicillamine
Retinoic acid (Isotretinoin, Accutane)
Streptomycin
Tetracycline
Thalidomide
Trimethadione
Valproic acid
Warfarin

IONIZING RADIATION (X-RAYS)
HYPERTHERMIA
INFECTION MICROORGANISMS
Coxsackie virus
Cytomegalovirus
Herps simplex
Parvovirus
Rubella (German measles)
Toxoplasma gondii (toxoplasmosis)
Treponema Pallidum (syphilis)
METABOLIC CONDITIONS IN THE MOTHER
Autoimmune disease (including Rh incompatibility)
Diabetes
Dietary deficiencies, malnutrition
Phenylketonuria

Source: Adapted from Opitz 1991.
[a] This list includes known and possible teratogenic agents and is not exhaustive.