- TERATOGENS
- ENDOCRINE DISRUPTORS

Teratogens

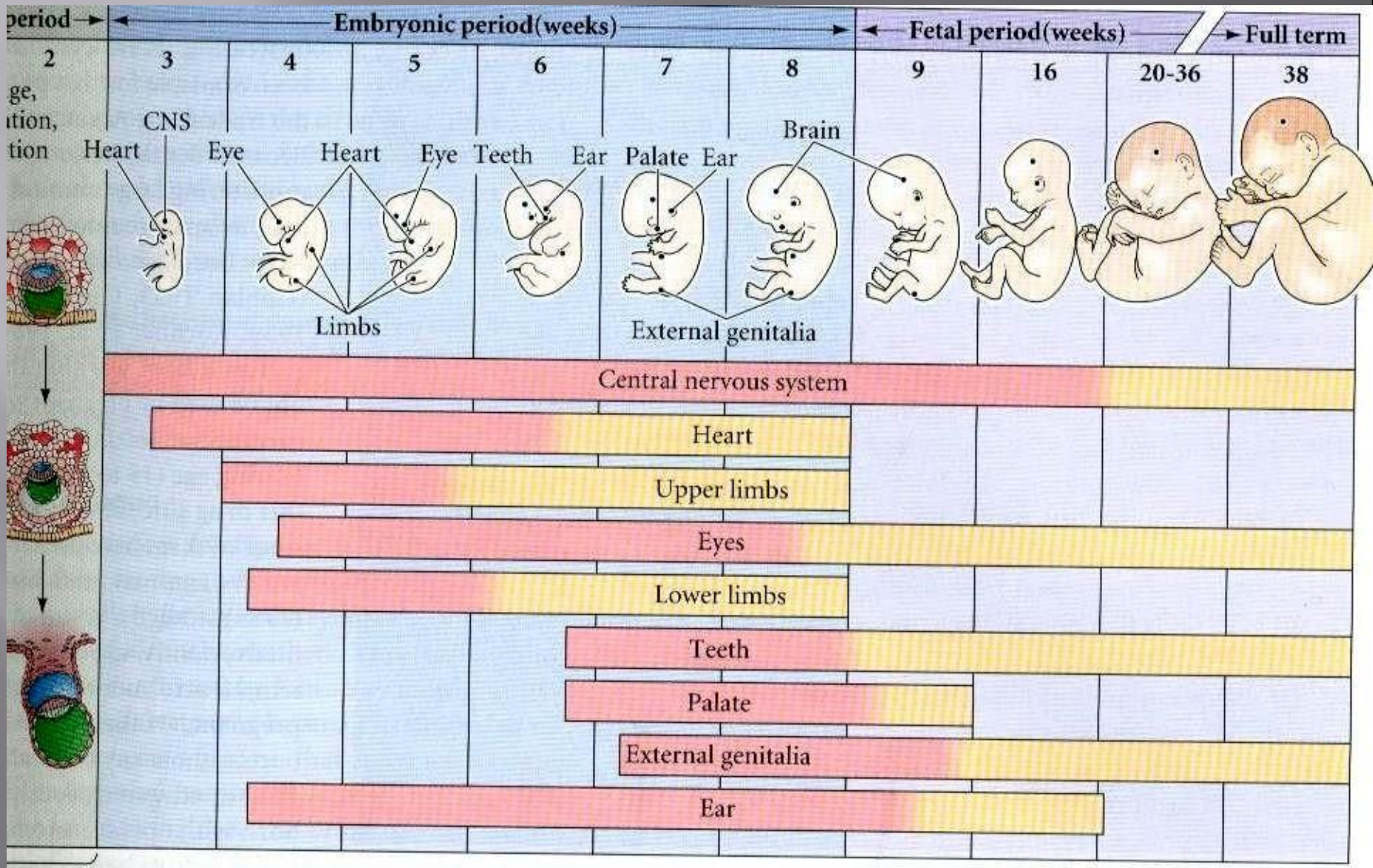
In addition to genetic mutations that can affect development, numerous environmental factors can disrupt development

Abnormalities caused by exogenous agents are called '**disruptions**'

Agents responsible for these disruptions are called '**teratogens**'.

- Rachel Carlson-1962-DDT- Destroying birds egg
- Lenz-1962- Thalidomide- a sedative drug used to manage pregnancy- limb and ear abnormalities in fetus
- Rubella infection– 20,000 fetuses- blind deaf or mentally retarded.

Human development is usually divided into two periods: 1) embryonic, 2) fetal



A **teratogen** is an agent that can produce a permanent alteration of structure or function in an organism exposed during embyronic or fetal life.

Many agents can produce a teratogenic effect under some circumstances.

Factors That Influence Teratogenicity

- Nature of the agent
  Dose
  Route
  Frequency of exposure
  Duration of exposure

Factors That Influence Teratogenicity

- Gestational timing
  Concurrent exposures
  Concurrent illness
  Genetic susceptibility
  - Mother
  - Fetus

Principal Mechanisms of Teratogenesis

Cell growth or proliferation
Cell death
Cell migration
Cell and tissue interactions
Disruptions

Mutagenesis

Principal mechanisms

- Gene mutation
- Chromosomal abnormalies

Before or after conception

Males and females both affected

Birth Defects Caused By Teratogenic Exposures Are Preventable.

TABLE 21.2 Some agents thought to cause disruptions in human fetal development[a]

DRUGS AND CHEMICALS	IONIZING RADIATION (X-RAYS)
Alcohol	HYPERTHERMIA
Aminoglycosides (Gentamycin)	INFECTIOUS MICROORGANISMS
Aminopterin	Coxsackie virus
Antithyroid agents (PTU)	Cytomegalovirus
Bromine	Herpes simplex
Cortisone	Parvovirus
Diethylstilbesterol (DES)	Rubella (German measles)
Diphenylhydantoin	*Toxoplasma gondii* (toxoplasmosis)
Heroin	*Treponema pallidum* (syphilis)
Lead	METABOLIC CONDITIONS IN THE MOTHER
Methylmercury	Autoimmune disease (including Rh incompatibility)
Penicillamine	Diabetes
Retinoic acid (Isotretinoin, Accutane)	Dietary deficiencies, malnutrition
Streptomycin	Phenylketonuria
Tetracycline	
Thalidomide	
Trimethadione	
Valproic acid	
Warfarin	

Source: Adapted from Opitz 1991.

Endocrine Disruptors

What is an Endocrine Distruptor?

Any chemical agent in the environment that can alter normal endocrine system actions leading to deleterious effects on an organism or its progeny.

Disruptors may act directly or indirectly.

Direct acting disruptors are usually hormone agonists or antagonists that interfere with hormone actions on target cells.

Indirect acting disruptors alter hormone dynamics in circulation, change hormone metabolism, or interfere with hormone regulation.

Timeline for Endocrine Disruptors

1874	DDT synthesized
1881	PCB synthesized
1930-77	Widespread PCB use in transformers & as cutting oils
1938	DES synthesized
1942-72	Widespread DDT application in malaria control & agriculture
1941-54	FDA & USDA: DES approved for use in humans & animals
1959	DES produces cancer in experimental animals
1962	Publication of *Silent Spring* by Rachel Carson
1972	EPA bans DDT, FDA warnings on DES in pregnant women
1977	EPA bans PCBs
1979-95	Meetings & publications on estrogens in the environment
1995	EPA endocrine disruptor workshop; NAS/NRC panel meets
1996	*Our Stolen Future*, Colborn, Dumanoski & Myers, published; FQPA passed & Safe Drinking Water Act amended
1998	International Conference on Endocrine Disruptors, Kyoto
1999	NRC report, *Hormonally Active Agents in the Environment*

Known Classes of Endocrine Disruptors

Estrogens	DES, o,p'-DDT, DEHP, bisphenol A
Anti-estrogens	hexachloro-4-biphenylol, luteolin
Anti-androgens	p,p'-DDE, vinclozolin
Progestogens	norethindrone, norgestrel
Adrenal toxins	o,p'-DDD, glycyrrhizic acid
Thyrotoxic agents	PCBs, goitrin
Aryl hydrocarbons	[often anti-estrogens] TCDD, PAH
Pancreatic toxins	azoxyglycosides, streptozotocin
Metals	cadmium, nickel, aluminum
Retinoids	vitamin A analogs

Endocrine Disruptors Include

Pesticides (herbicides, insecticides, …)

Plasticizers

Natural plant metabolites

Pharmaceuticals (contraceptives, drugs,…)

Detergents

Chemicals from cooking & burning

Antibiotics

Metals

Results of Disruptions

Inability to maintain homeostasis

Altered growth & development

Altered responses to external stimuli

Altered behavior

Suppressed gametogenesis

Elevated gestational losses

Induced neoplasiEmbryonic malformation

a or carcinogenesis

Diethylstilbestrol

*SAX TOXICITY EVALUATION: THR: Poison by intraperitoneal and subcutaneous routes. Moderately toxic by ingestion and other routes. A human carcinogen and teratogen by many routes. It causes skin, liver and lung tumors in exposed humans as well as uterine and other reproductive system tumors in the female offspring of exposed women. An experimental carcinogen, neoplastigen, tumorigen and teratogen by various routes. A transplacental carcinogen. Glandular system effects by skin contact. Human reproductive effects by ingestion. Implicated in male impotence and enlargement of male breasts. Other experimental reproductive effects. Mutagenic data.

Bis (2-ethylhexyl) phthalate

New Jersey Department of Health and Senior Services
Cancer Hazard
*Bis (2-Ethylhexyl) Phthalate may be a CARCINOGEN in humans. It has been shown to cause liver cancer in animals…
Reproductive Hazard
*Bis (2-Ethylhexyl) Phthalate may be a TERATOGEN in humans since it has been shown to be a teratogen in animals.
* Bis (2-Ethylhexyl) Phthalate may damage the testes…

Conclusions

Endocrine disruptors or hormonally active agents have been with us for millennia as elements of plants and cooking. The new abundance of synthetic compounds has unleashed a wave of new challenges to our physiology, including the endocrine system. The impacts are as pleiotropic as endocrine actions are. Not surprisingly they involve altered reproductive success, growth, and cancer risks because of endocrine controls or inputs in these processes. Due care will help minimize impacts, but some increased risks are here permanently.