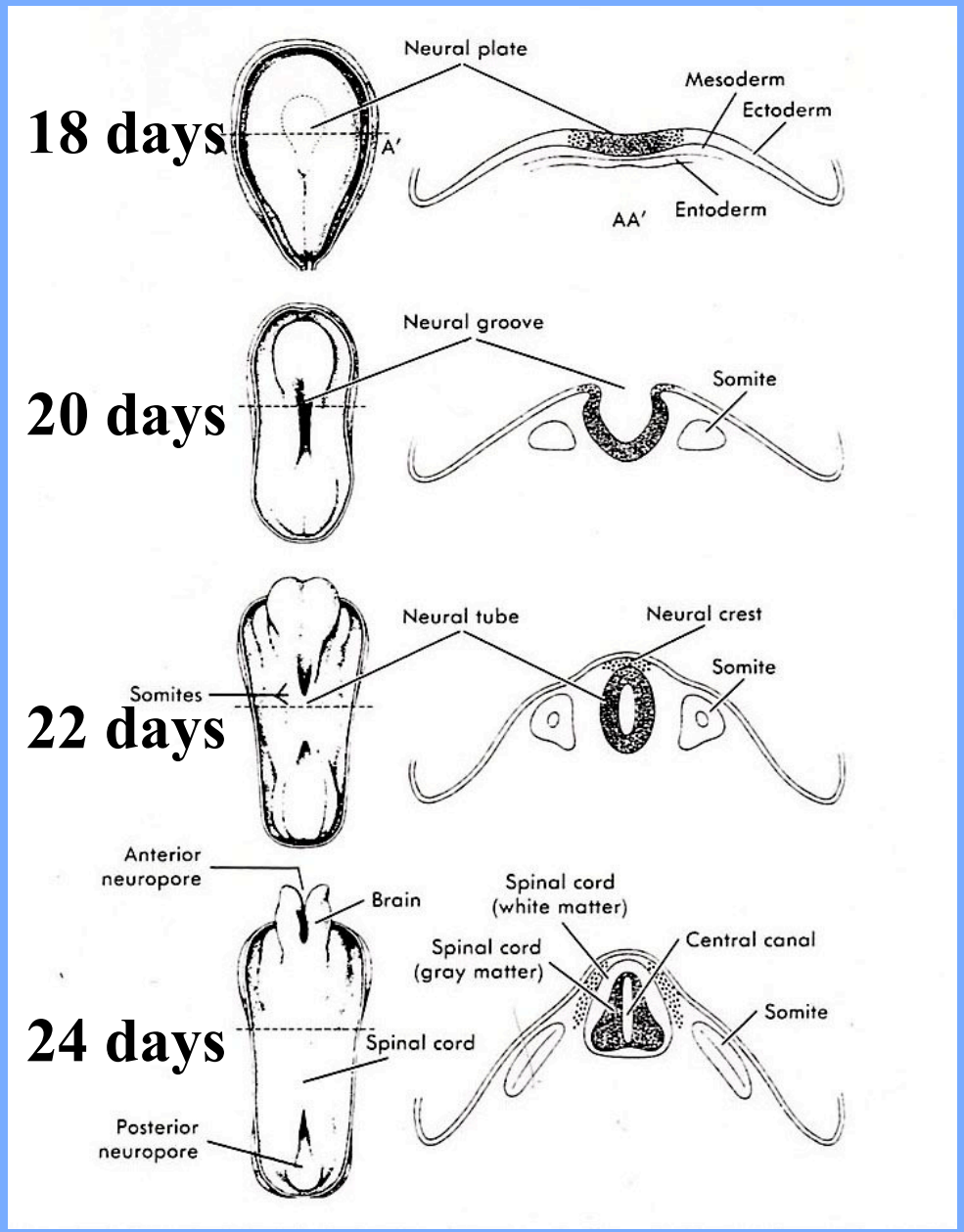
Birth Defects and Pharmaceutical Drugs

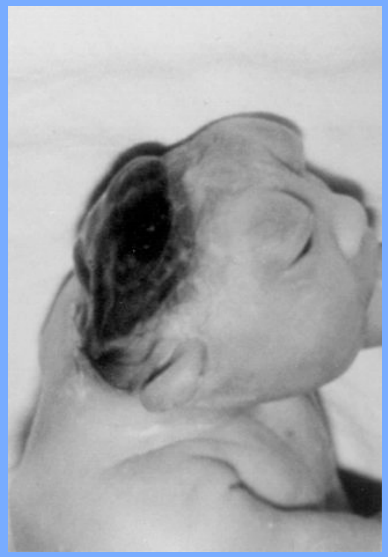
Adverse Outcomes in Pregnancy

1. 57% of pregnancies detected by hCG at 8-9 days after fertilisation do not develop as clinically detectable pregnancies
2. 15-20% of recognisable pregnancies end in spontaneous abortion – 90% in the first trimester
3. 0.4% of pregnancies end in miscarriage >20 weeks.
4. 2-3% of newborn have a major malformation severe enough to require hospitalisation.



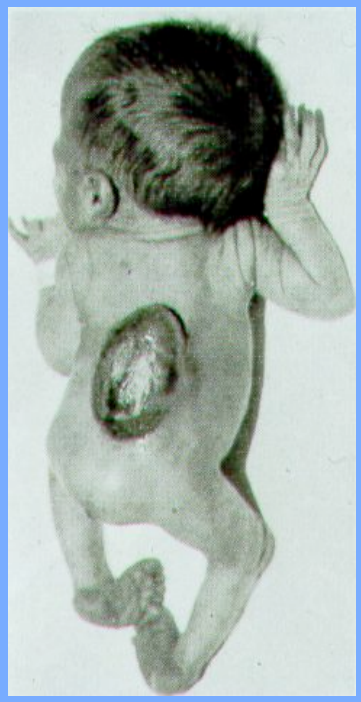
Neurulation

Cowan WM The Development of the Brain Sci Am 1979; 241:112



Anencephaly

www.vh.org/.../FetalYoung CNS/Images/fig03.gif

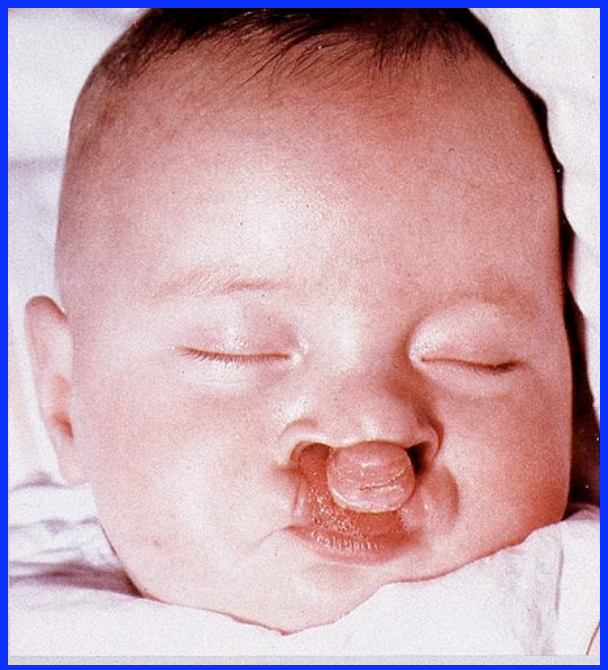


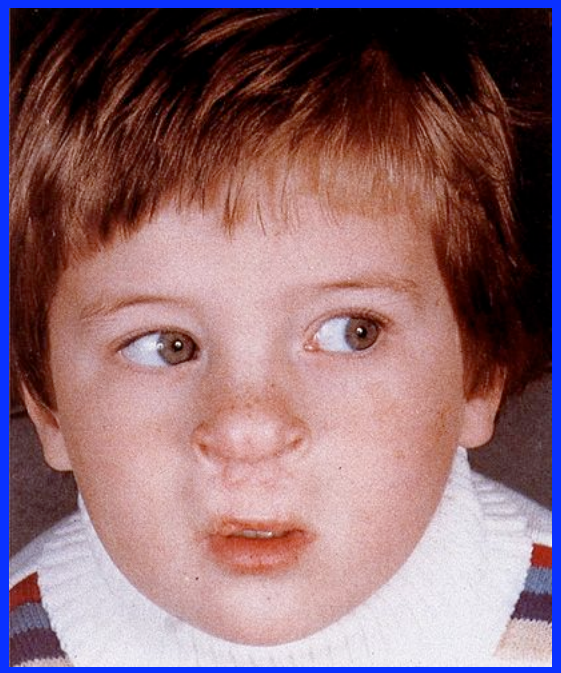
Spina bifida

Picture from Illustrated guide To malformations of the CNS at Birth by N.C. Nevin and J.A.C. Weatherall 1982. Churchill Livingstone.

5-week human embryo

From Conception to Birth Our Most Important Journey by A. H. Lipson
1994 Millennium Press

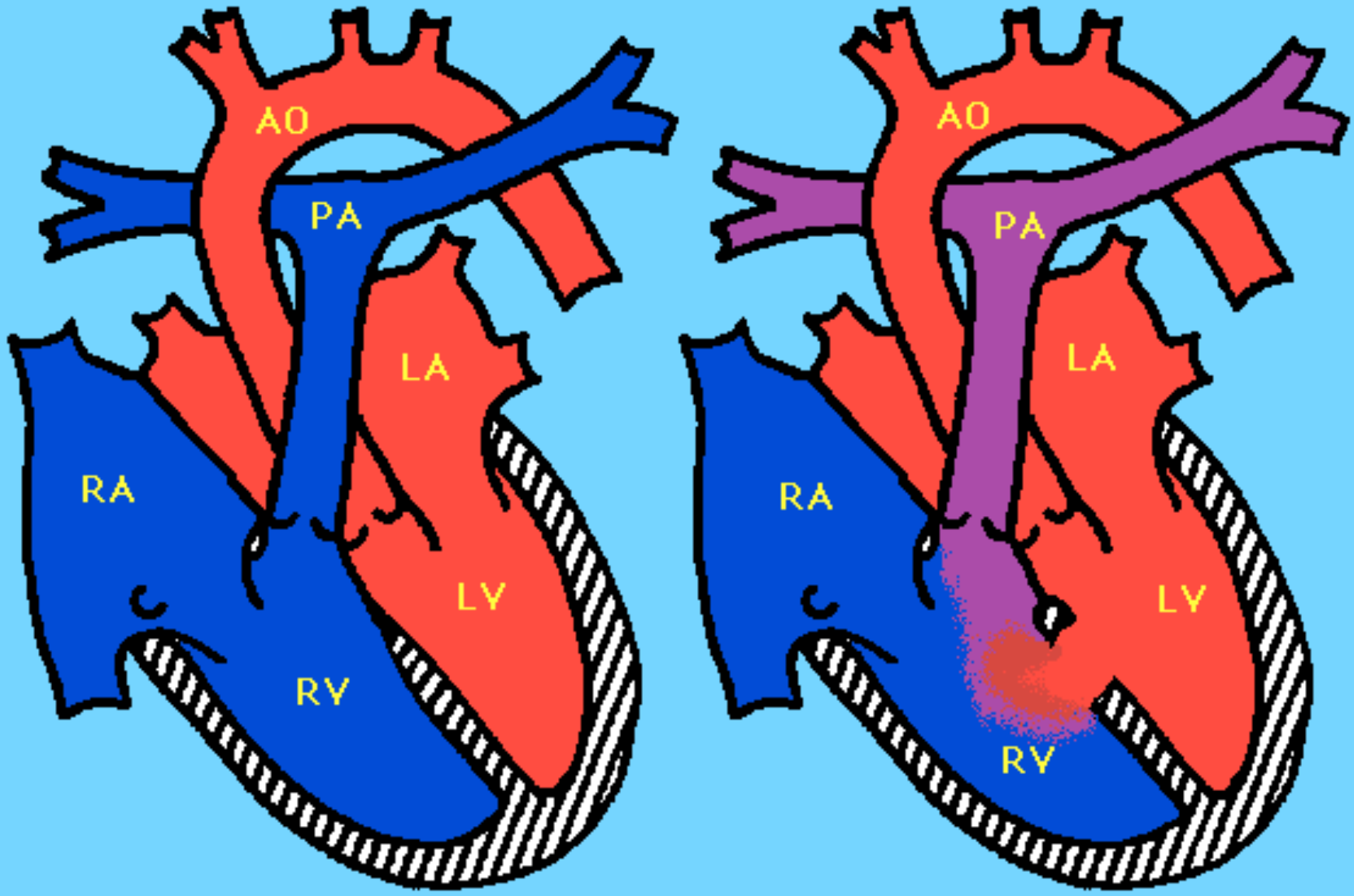




Bilateral cleft lip

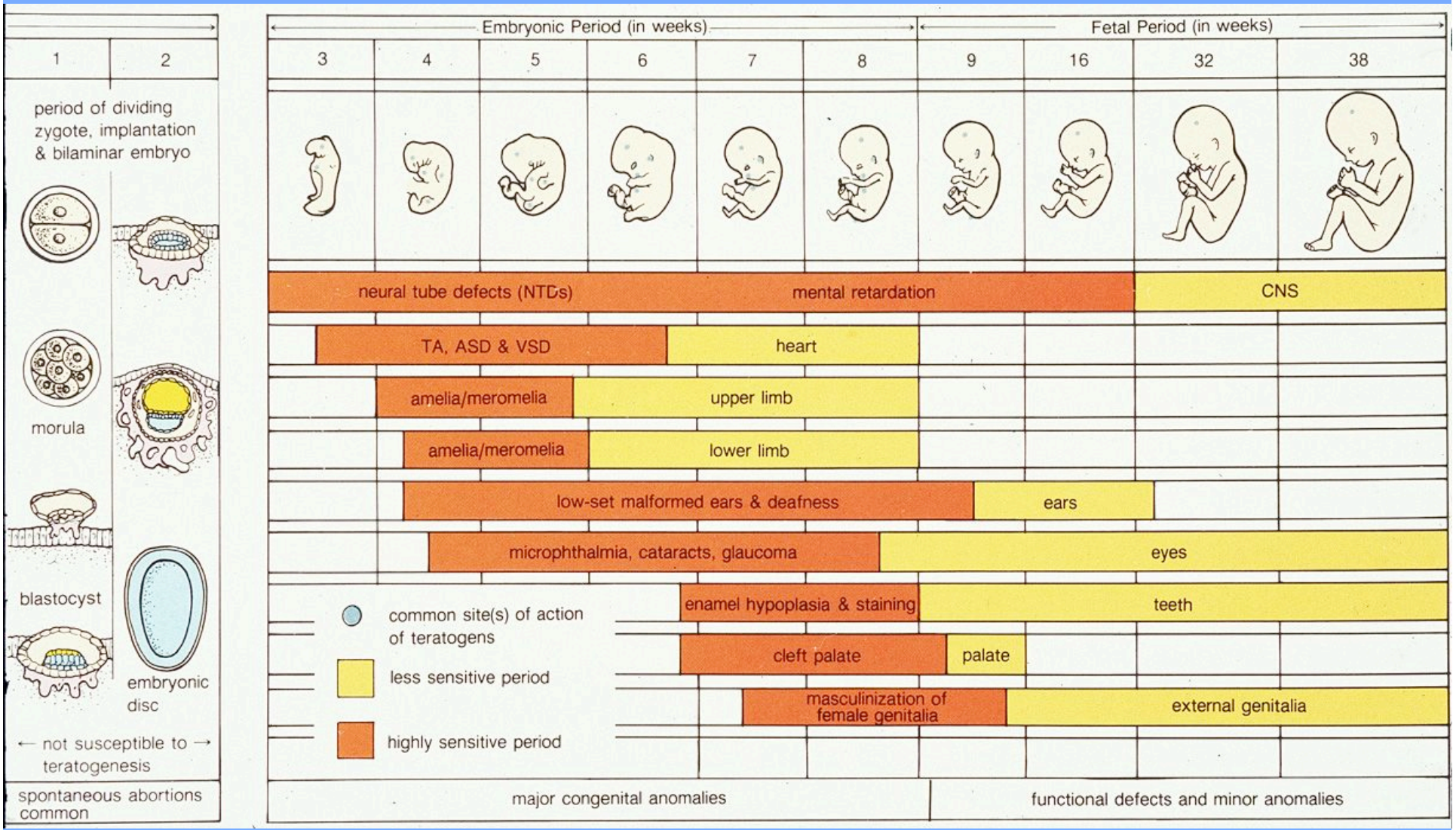
Cleft Lip and Palate A Parents Guide by The Cleft Palate Clinic, Children's Hospital, Camperdown. 1993

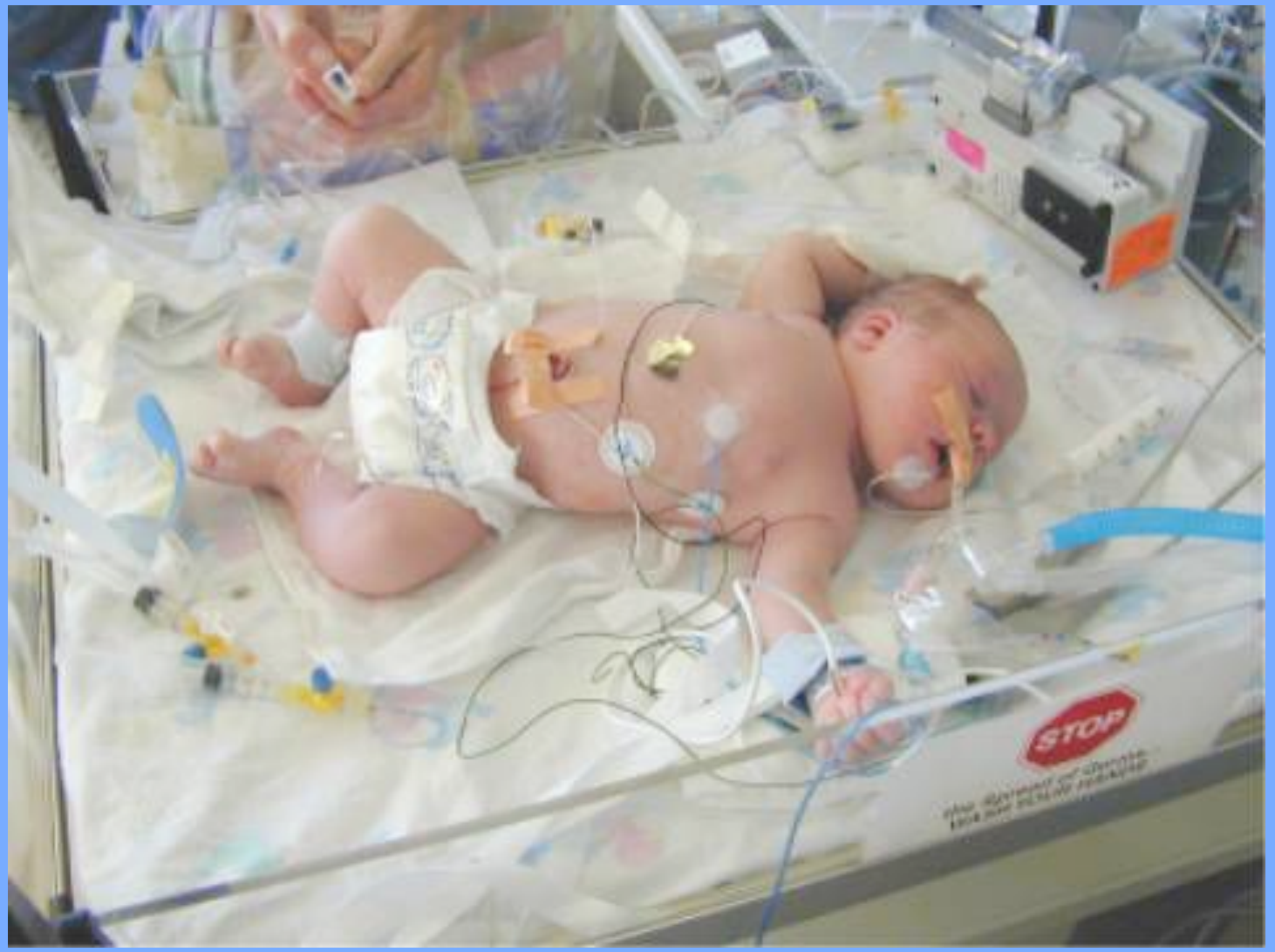
Ventricular Septal Defect



Normal

Ventricular Septal Defect


Embryonic Period (in weeks)
Fetal Period (in weeks)
1
2
3
4
5
6
7
8
9
16
32
38
period of dividing zygote, implantation & bilaminar embryo
morula
blastocyst
embryonic disc
← not susceptible to teratogenesis
spontaneous abortions common
neural tube defects (NTDs)
mental retardation
CNS
TA, ASD & VSD
heart
amelia/meromelia
upper limb
amelia/meromelia
lower limb
low-set malformed ears & deafness
ears
microphthalmia, cataracts, glaucoma
eyes
enamel hypoplasia & staining
teeth
cleft palate
palate
masculinization of female genitalia
external genitalia
common site(s) of action of teratogens
less sensitive period
highly sensitive period
major congenital anomalies
functional defects and minor anomalies



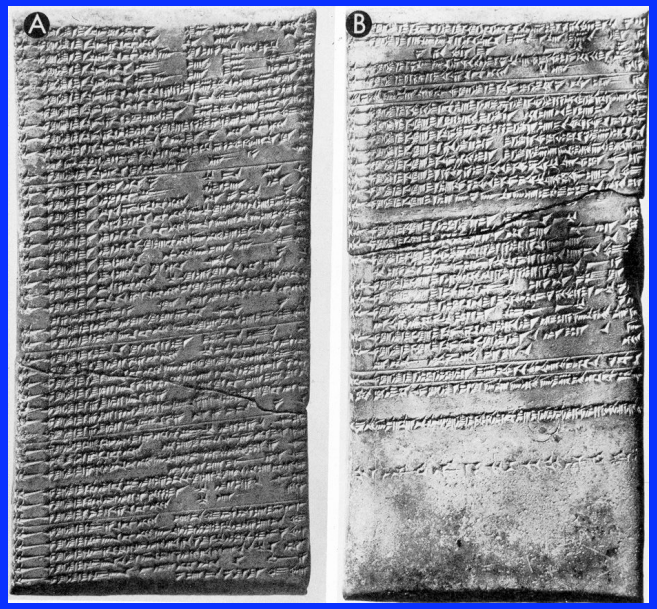
Birth Defects – Every Parent's Nightmare

Causes of Birth Defects?

1. Message from the Gods?
2. Hybrids between man and animals or man and demons?
3. Maternal impressions?
4. Genetics
5. Spontaneous and unavoidable?
6. Drugs taken during pregnancy or exposure to pollution?

1. Message From the Gods

Many, if not all civilisations have believed that gods ruled their lives and they were always looking for signs of the gods pleasure or displeasure.

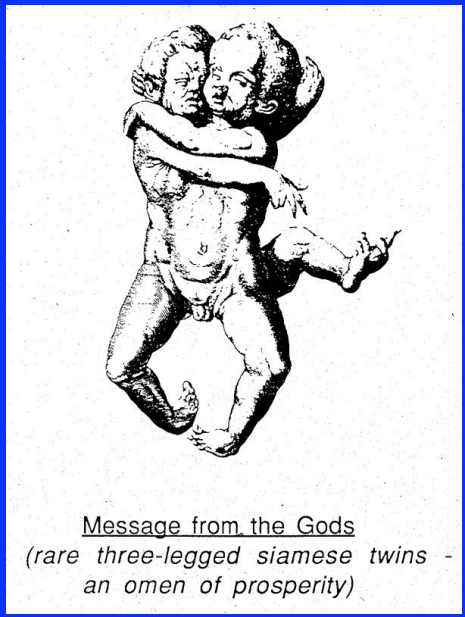


When a woman gives birth to an infant that:

has no mouth, the mistress of the house will die

whose upper lip overrides the lower, the peoples of the world will rejoice

that has no right hand, the country will be convulsed by an earthquake



Message from the Gods
(rare three-legged siamese twins - an omen of prosperity)

Babylonian clay tablets discovered in the Middle East about 100 years ago. Part of the Royal Library of Ninevah dating back to 2000 BC. They listed 62 birth defects – each had an interpretation.

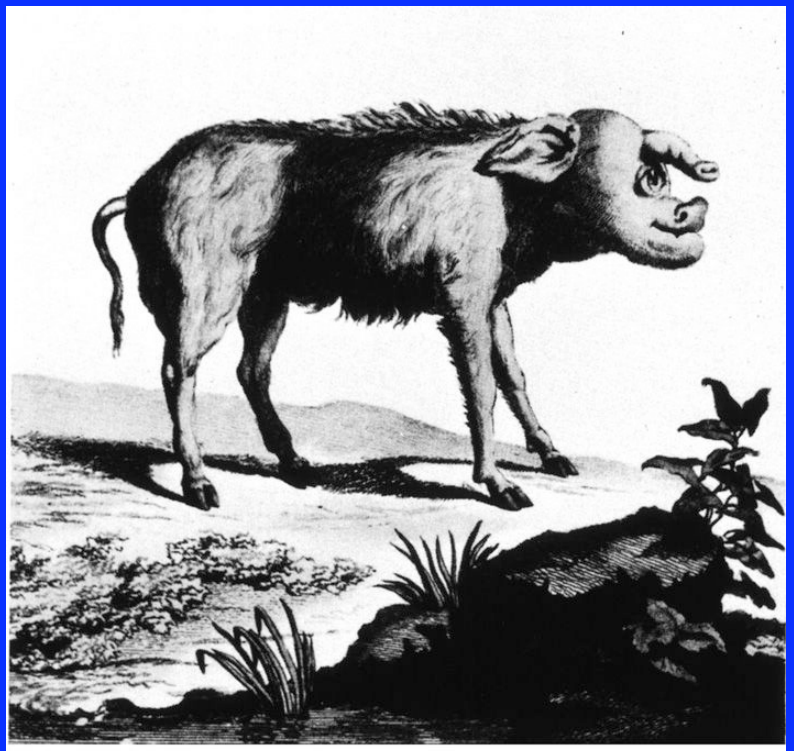
Report in the Sydney Morning Herald

Sydney Observatory got a number of calls yesterday from pregnant women (and a few from men, too) who were worried that the total solar eclipse yesterday visible in northern Thailand and Burma would adversely affect unborn babies. As you would expect the answer was no.

2. Hybridity

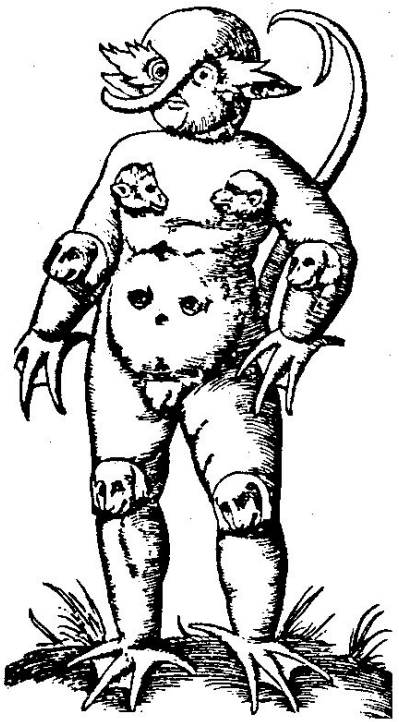
It was believed that malformations with fanciful similarity to animal offspring could result from intercourse between animals and humans

Other features were thought to result from human intercourse with demons.



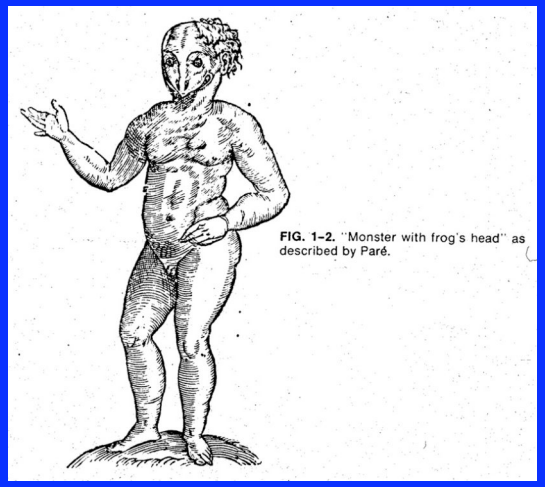
A cyclopic pig with proboscis.
Engraved by N. F. Regnault in Moreau de la Sarthe, Paris, 1808.

Fig. 2-7. – Satan's birth of Kraków (1543). (From E. Holländer.[20]) Illustration from *Wunder, Wundergeburt und Wundergestalt* used with permission of Ferdinand Enke Verlag, Stuttgart, Germany.

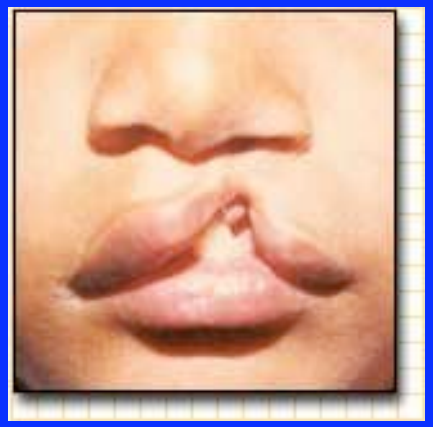


3. Maternal Impressions

The idea that objects seen by a pregnant women and causing a strong emotional response could subsequently affect the development of the fetus.



A “monster” with a “frogs head” drawn in 1517 and thought to be due to the shock caused by a living frog being placed in the hand of a pregnant women.



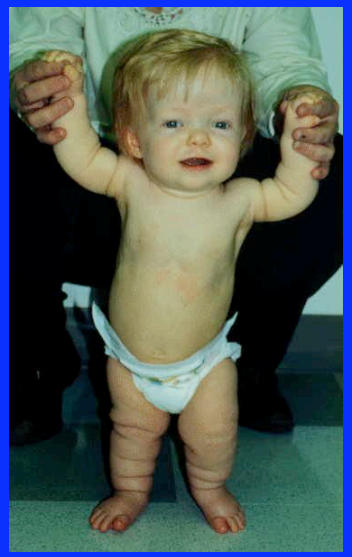
Cleft or "hare" lip

4. Genetics

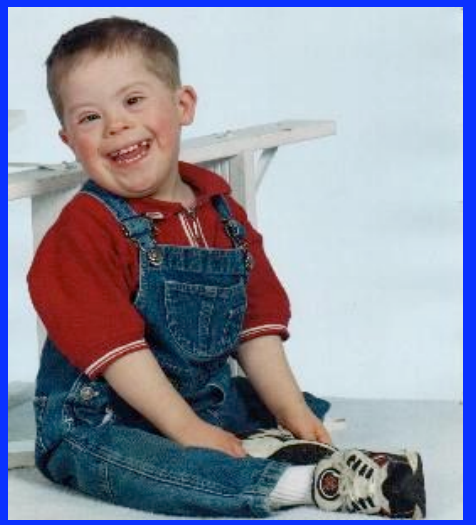
Genetics developed as a science at the beginning of the 20th century. It was believed for many years that all birth defects were due to "faulty germ plasm" and were inherited.

It is now estimated that genetic defects are responsible for about 25% of congenital malformations.

Genetic causes of birth defects

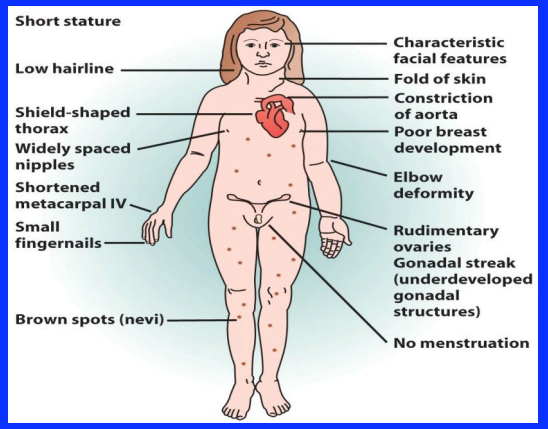


Achondroplasia – dominant autosomal mutation



Down syndrome –trisomy 21

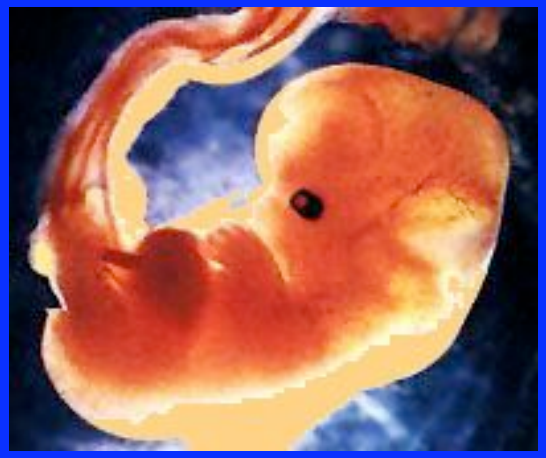
Cystic fibrosis – recessive mutation



Turner's syndrome – female missing one X chromosome

5. Spontaneous and unavoidable?

When the Columbia space shuttle crashed in 2003 there was discussion about the complexity of the shuttle and the statistical risk associated with complexity.



Human embryological development – self assembly of a human

6. Drugs taken during pregnancy, maternal infections or exposure to pollution?

The idea that birth defects were primarily due to genetic damage was changed by two major discoveries:

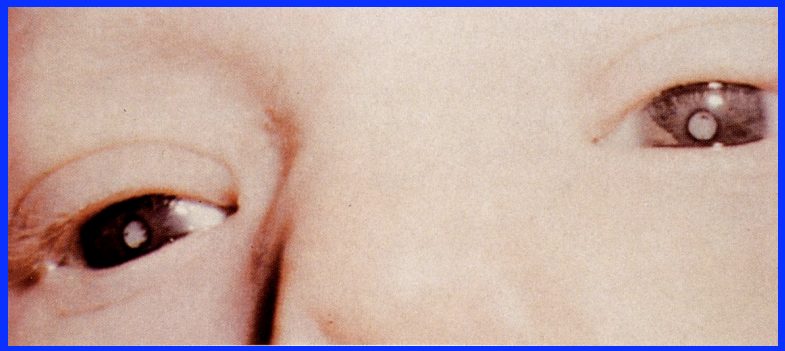
Maternal rubella causes birth defects (1941)
Thalidomide causes birth defects (1960)

It is now known that about 20 drugs or groups of drugs can cause human birth defects. They are responsible for about 1% of all human birth defects.

By far the most important of these drugs are the anticonvulsants (Phenytoin, Carbamazepine and Valproic acid) used to treat epilepsy.

MATERNAL RUBELLA AND BIRTH DEFECTS

1. Eye defects - central cataracts

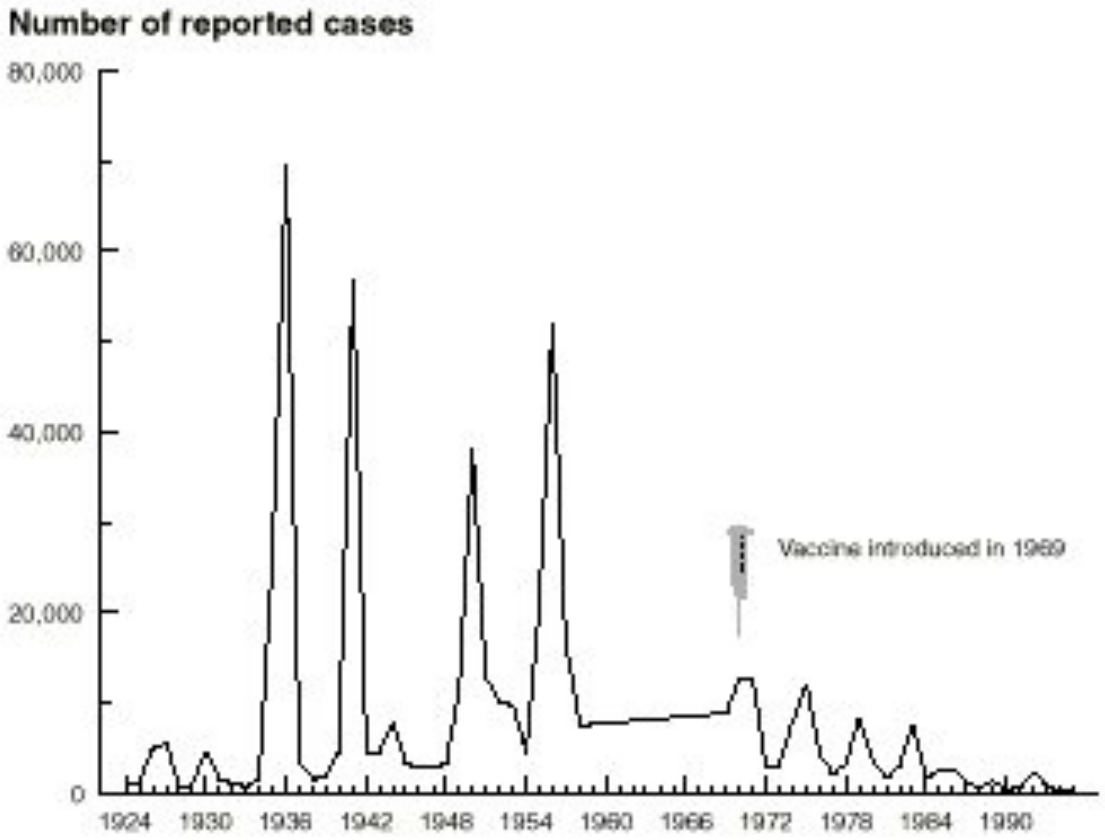


2. Heart defects – patent ductus arteriosus, stenosis of the pulmonary artery
3. Deafness – sensorineural
4. Brain damage – ischemic damage and variable microcephaly, mental retardation
5. Fetal growth retardation

Defects induced by rubella result almost exclusively from infection in the first 16 weeks of gestation.

In 1963 there was a rubella epidemic in Europe followed in 1964-5 by an epidemic in the USA. It was estimated that 1.8 million people were infected and 30,000 children were born with rubella associated defects.

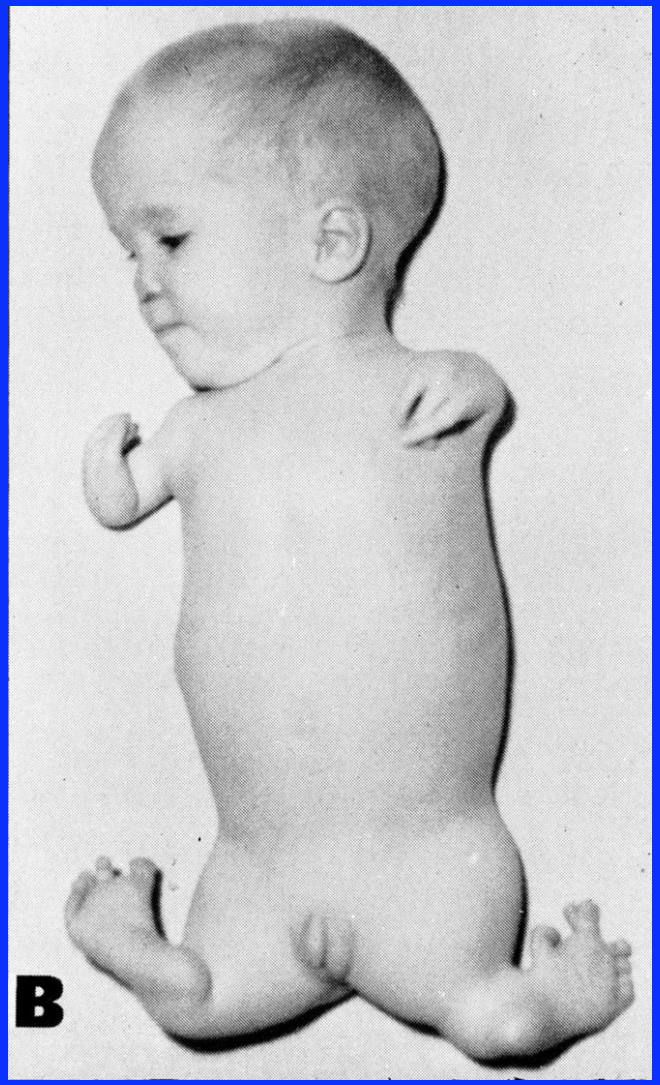
Figure 10
Reported Cases of Rubella, Canada, 1924-1995*



* Not reported nationally from 1959 to 1968

Thalidomide

- Marketed 1957-1961 initially as a sedative and sleeping tablet and subsequently used to treat nausea and vomiting in pregnancy.
- The drug was so "non-toxic" that the LD50 dose in animals could not be determined.
- Used in Australia, Germany, Japan, Britain, Brazil, Sweden and Italy.
- Exposure to the drug in early pregnancy resulted in severe malformations in nearly 10,000 children.



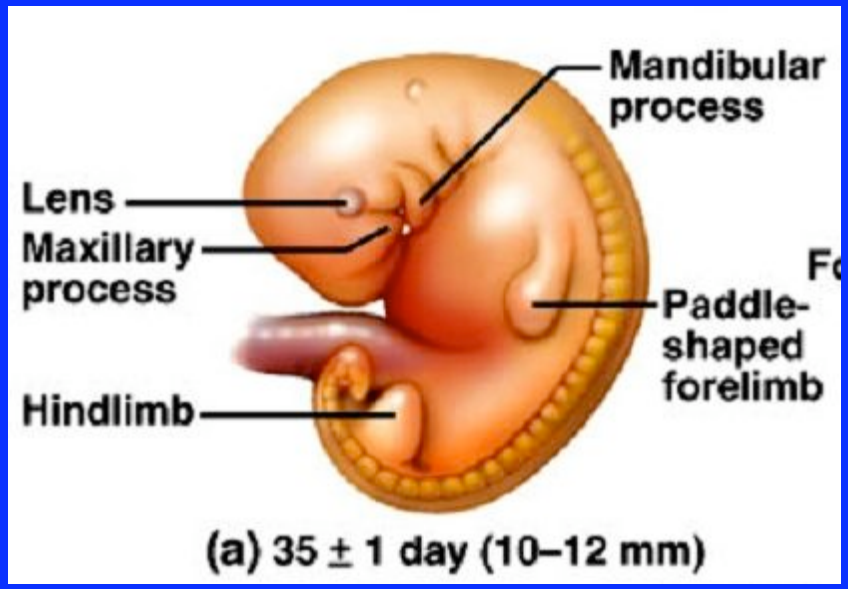
London 1960

Brazil 2001

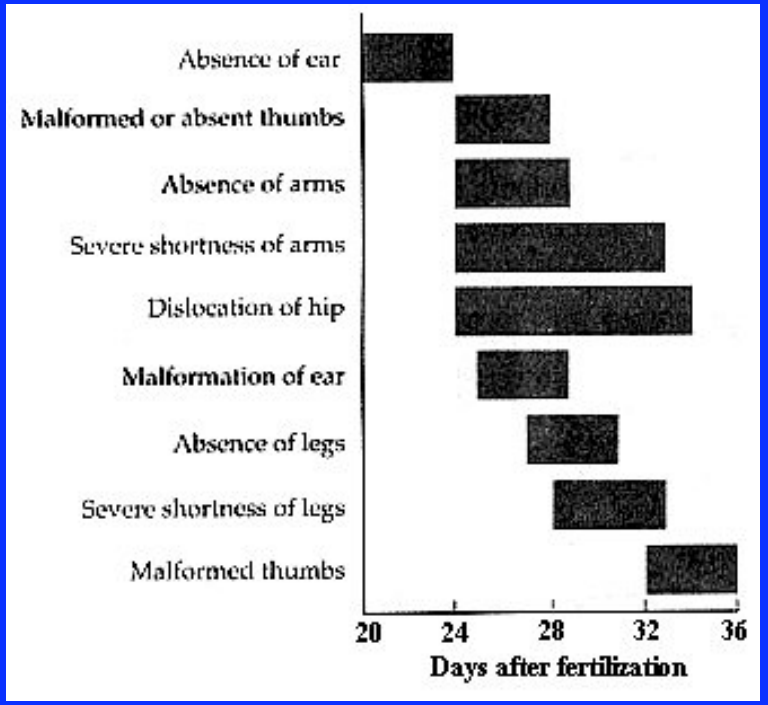
Courtesy Dr. M Edgerton, Dept Plastic Surgery University of Virginia

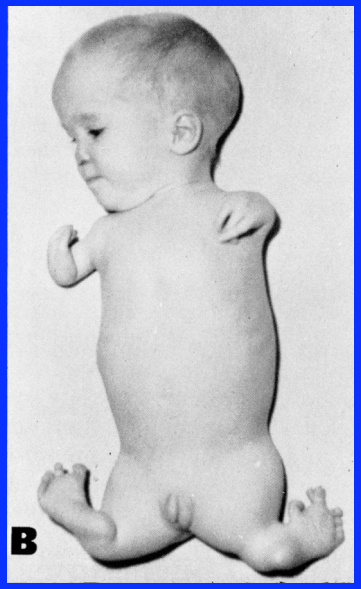
In: Langman's Medical Embryology T.W. Sadler, 1985

www.thalidomideuk.com



www.clt.astate.edu/mgilmore/A&P%202/Pregnancy,%20Growth%20and%20Development.ppt

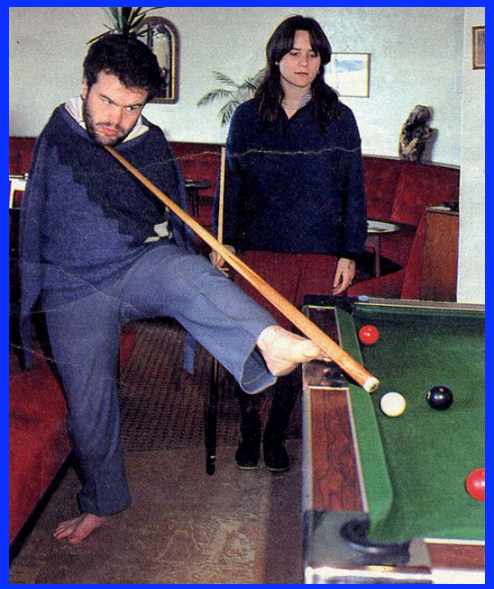




Courtesy Dr. M Edgerton, Dept Plastic Surgery University of Virginia
In: Langman's Medical Embryology T.W. Sadler, 1985
Copyright Williams and Wilkins

Sensitive times for induction of thalidomide defects

Legacy of Thalidomide



Sunday Times Colour Magazine 1985

Sunday Times Colour Magazine 1985

The Australian Magazine November 4 1989

Lessons learnt from Thalidomide

- The developing embryo is not protected by the placenta and most, if not all, chemicals or drugs with a molecular weight of less than 1000 reach the embryo.
- Most malformations result from damage to the embryo during the organogenic period - weeks 3 - 8 of human development.
- The embryo may be more sensitive to the toxic properties of a drug than the adult.
- There may be major metabolic or other differences between species such that a particular drug may cause birth defects in one species but not in another.

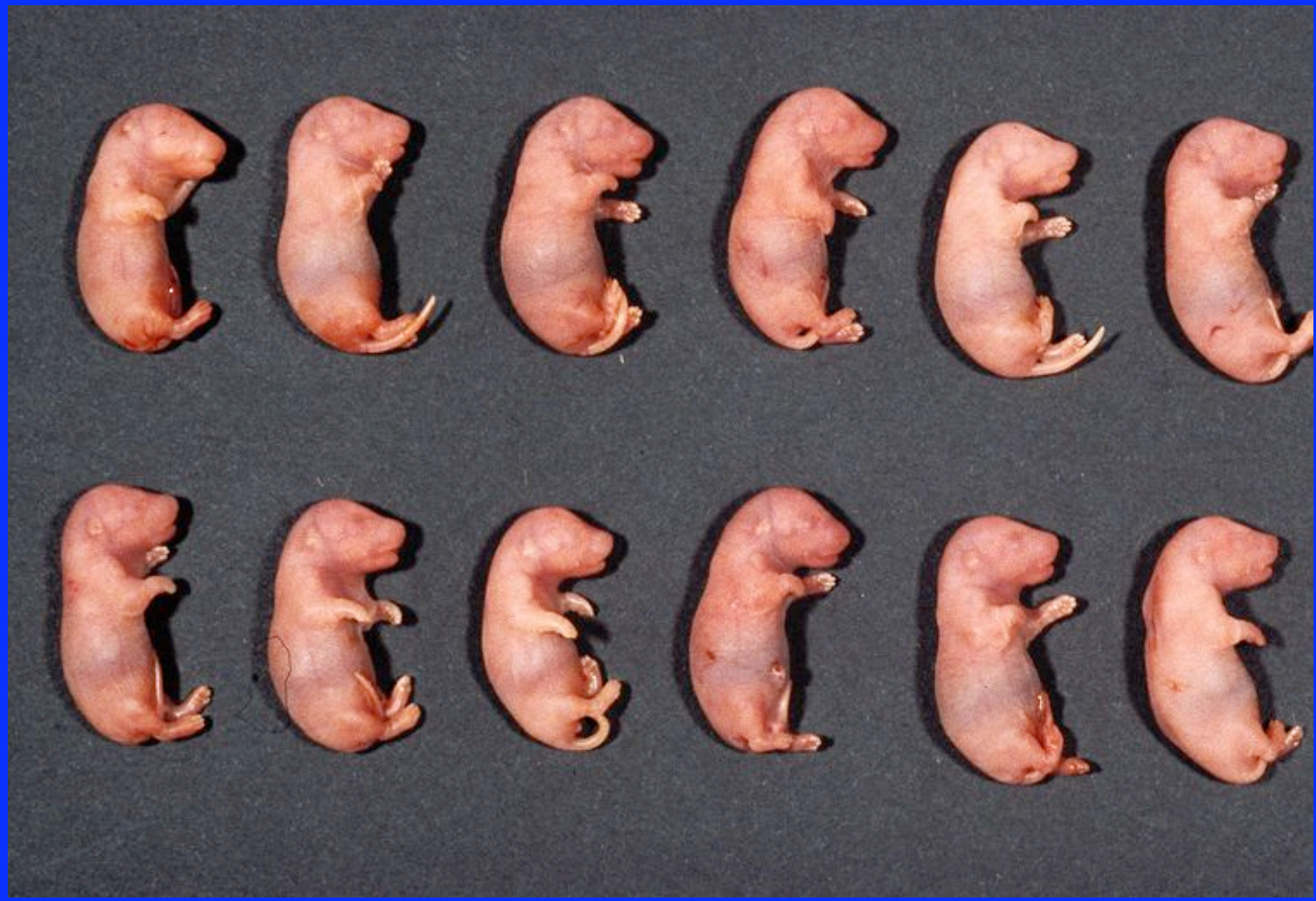
Testing Chemicals for Teratogenicity

1. Legal regulations require that drugs and other chemicals are tested in two species - usually rats and rabbits.

2. Usually chemicals are tested at three doses, the highest dose is required to produce signs of maternal toxicity. This is controversial

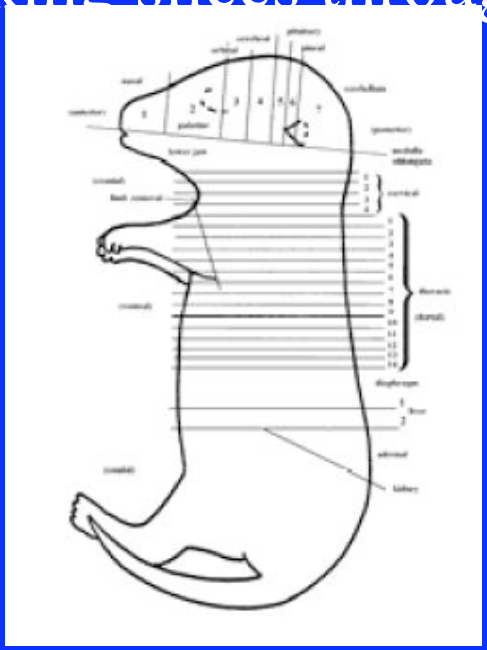
3. The pregnant animals are dosed with the test chemical from the time of implantation to the end of the organogenic period. The pregnant animals are killed before birth and the fetuses examined for malformations.

Normal Rat Litter

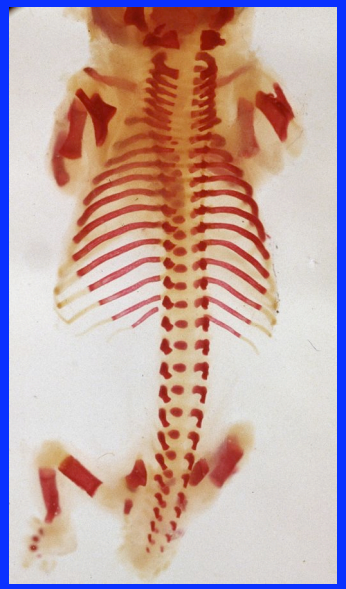


Control fetus and fetuses from a pregnant rat treated with a teratogen

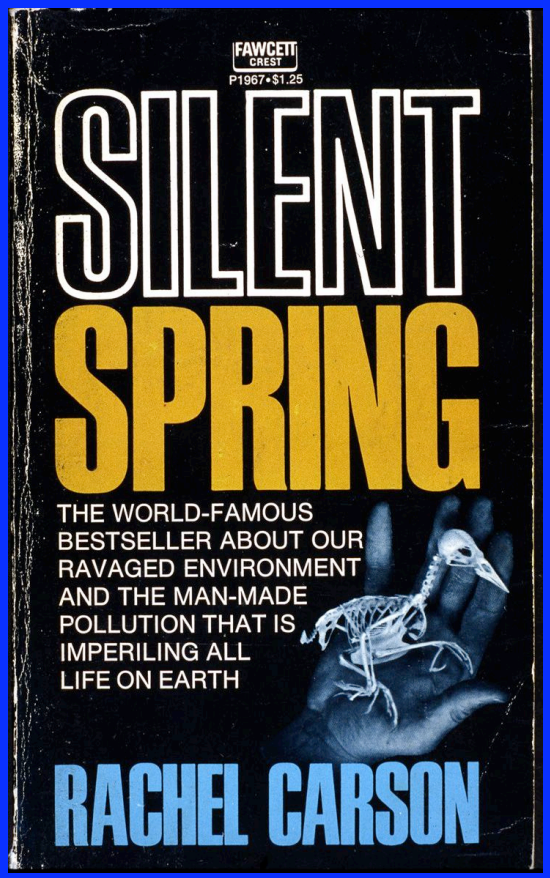
The internal structure of the fetuses is examined by
taking slices through the preserved fetuses



and by examining fetuses
stained to show the skeleton

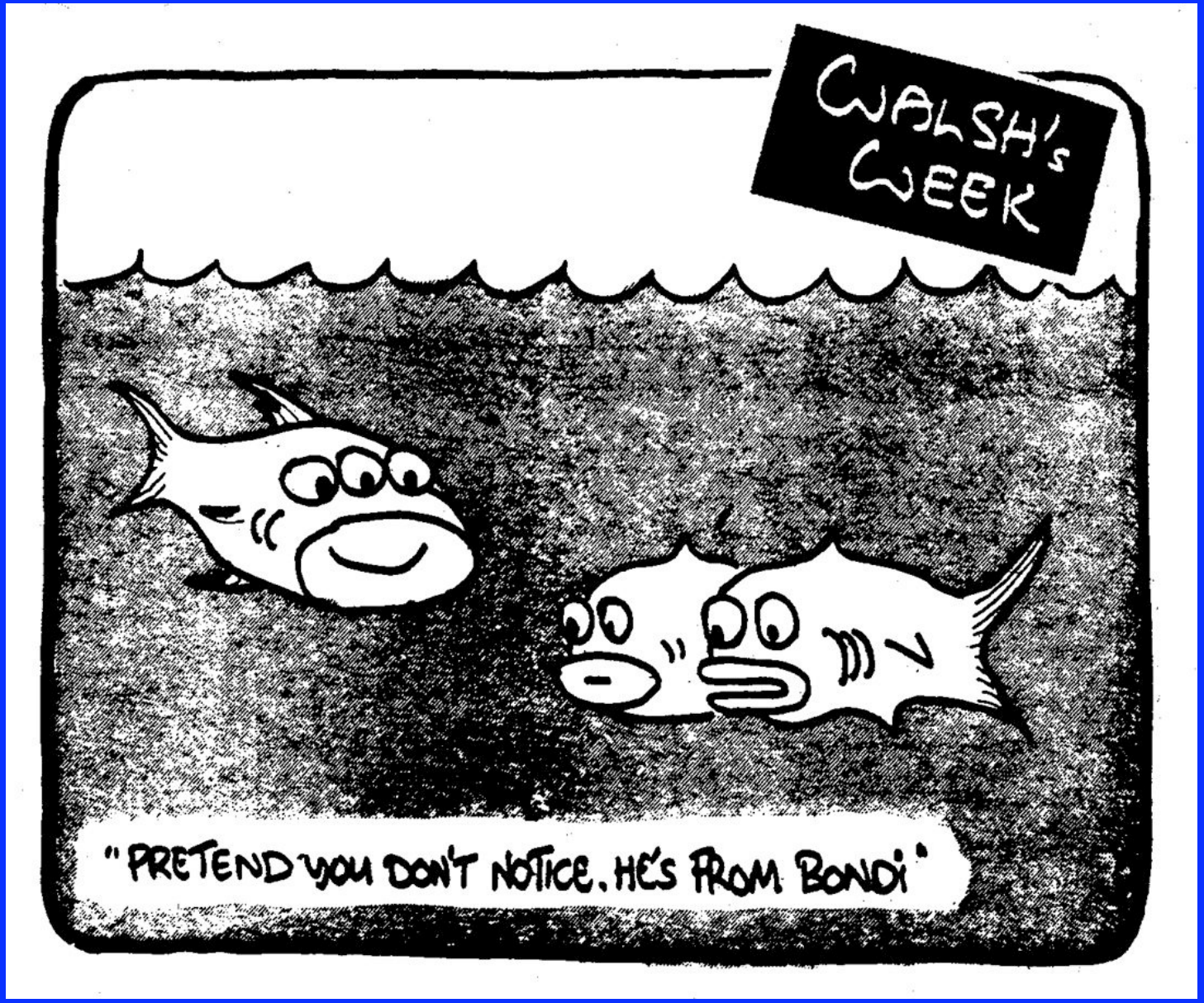


What about pollution?



Carson, R. 1962. Silent Spring. Fawcett Crest.

Bondi beach Australia



Cartoon from Ray Walsh Sunday Telegraph 1989

Pollutants and human "birth defects"

Methyl mercury

Polychlorinated biphenyls (PCBs)

Some of the known and potentially preventable causes of human birth defects.

2-3% of newborn have a severe congenital malformation that may require hospitalisation

What causes these malformations?

1. 20-25% have a clear genetic origin – either a mutated gene or chromosomal abnormality.

2. 10% have an exogenous and potentially preventable cause such as maternal diabetes, maternal infections (rubella, CMV, toxoplasmosis), alcohol abuse, cocaine abuse and therapeutic drugs.

3. 65-70% the cause is basically unknown.

Therapeutic Drugs Teratogenic to Humans

- **Anticonvulsants** *
  phenytoin
  valproic acid
  carbamazepine
- **Anticancer agents**
  Alkylating agents –
  eg cyclophosphamide
  Antimetabolites–
  eg methotrexate
- **Androgenic hormones**
  eg danozol
- **Antithyroid drugs**
  eg propylthiouracil
- **Aminoglycoside antibiotics**
  eg streptomycin
- **Coumarin anticoagulants**
  eg warfarin
- **Retinoic acids** *
  eg isotretinoin
- **ACE inhibitors** *
  eg captopril
- **Tetracyclines**
  eg tetracycline
- **Other drugs**
  diethystilbistrol
  thalidomide
  lithium
  fluconazole

Some causes of birth defects in Sweden

1. There are about 100,000 births in Sweden each year.

2. About 3,000 birth defects (assuming rate is 3%).

3. About 750 of these defects are due to genetic abnormalities

4. About 300 (10%) of these defects have an exogenous cause and are potentially preventable.

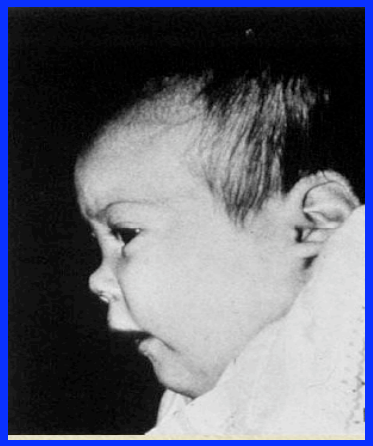
5. About 3% of women have diabetes – their risk of having a child with a birth defect is increased 2x = 180 birth defects.

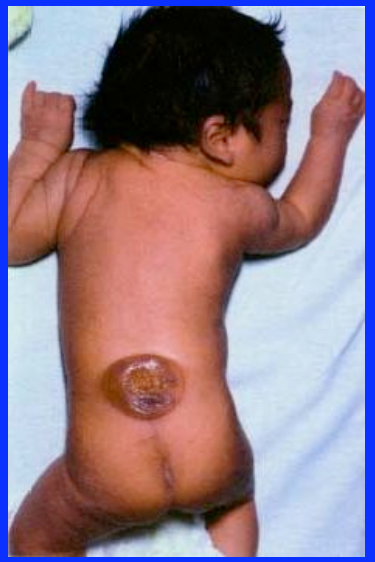
6. 0.2 - 0.5% of women have epilepsy ~ 200-500 women per year – their risk of having a child with a birth defect is increased 2x = 12-30 birth defects.

7. Fetal alcohol syndrome prevalence estimated at 1:1000 this would give 100 cases/year. Estimates of females who drink to dangerous levels ~4-5% .

Anticonvulsants

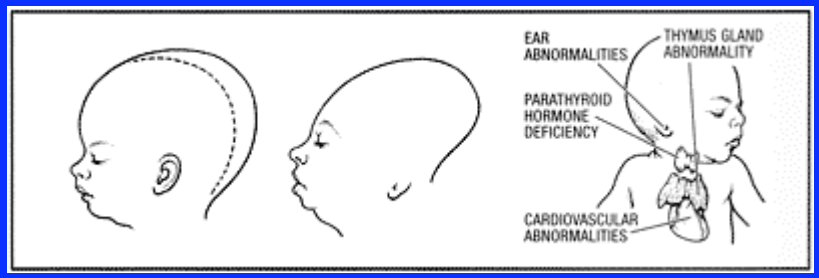
- About 0.2-0.5% of women have epilepsy and most must take anticonvulsant medication during pregnancy.
- **Phenytoin** – appears to double the risk of birth defects particularly cleft lip, cleft palate and heart malformations. Also increased risk of minor defects such as short fingers and flat midface. Growth retardation and mental retardation have also been associated.
- **Carbamazepine** – appears to double the risk of birth defects particularly cleft lip, and heart malformations; 5-10-fold increase in spina bifida, increased risk of growth retardation and microcephaly.
- **Valproic acid** – appears to increase the risk of birth defects 3-4-fold - particularly malformations of the heart and spina bifida (5-10-fold increase). IQ may be reduced by an average of 10 points. Risks particularly great at high doses.
- **Phenobarbital** – increases the risk of birth defects 2-3 fold (heart and facial clefting) also increased risk of microcephaly, growth retardation and mental retardation.
- A large increase in risk associated with polytherapy.
- There is optimism that the newer anticonvulsants such as **lamotrigine**, **gabapentin** and **topiramate** are not teratogenic, but at this stage there is insufficient data. Recent adverse report about lamotrigine.





Retinoic acid - Accutane

- Isotretinoin, a widely-used treatment for acne, causes severe malformations of the face, heart, CNS and thymus if taken during early pregnancy.
- In a prospective study of pregnancies exposed accidentally to isotretinoin during the first trimester 23% developed malformations. The critical period for exposure appears to be weeks 2-5 post conception.
- Follow-up studies of children exposed to isotretinoin during the first trimester indicated that 47% of 5-year olds had intellectual deficits. The safety of retinoids in the second and third trimesters has not been established.
- Dermally applied retinoids are unlikely to be teratogenic as they result in low systemic exposure.



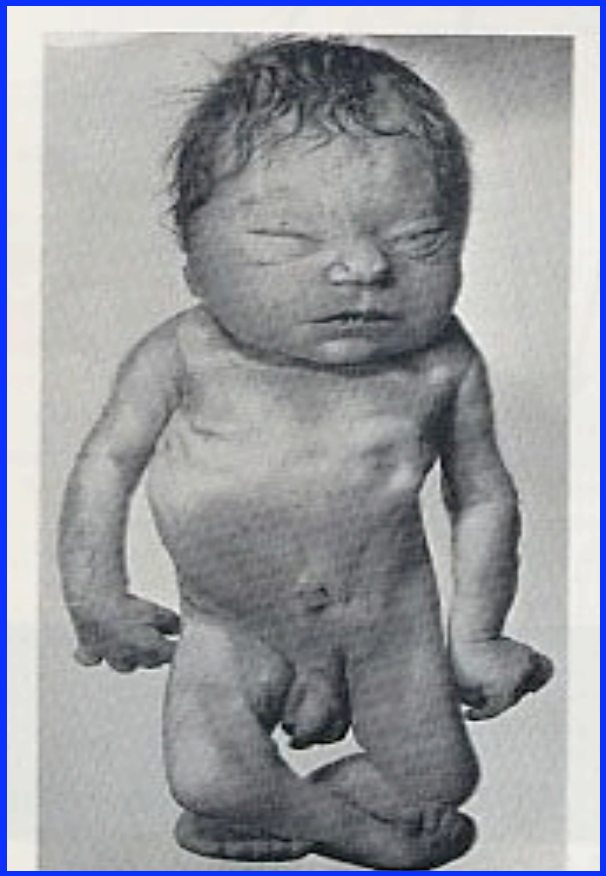
ACE inhibitors

- *ACE inhibitors (and presumably ATII antagonists)* are perhaps the least appropriate antihypertensive drug to use in pregnancy. Their use in the second and third trimester has been associated with reduced amounts of amniotic fluid leading to compression of the fetus and neonatal death from renal failure.

- The presumed mechanism is fetal hypotension causing reduced renal blood flow leading to anuria (no urine) and reduced amniotic fluid production. Normally the fetus swallows amniotic fluid and the kidneys excrete it back into the amnion cavity via the urine.

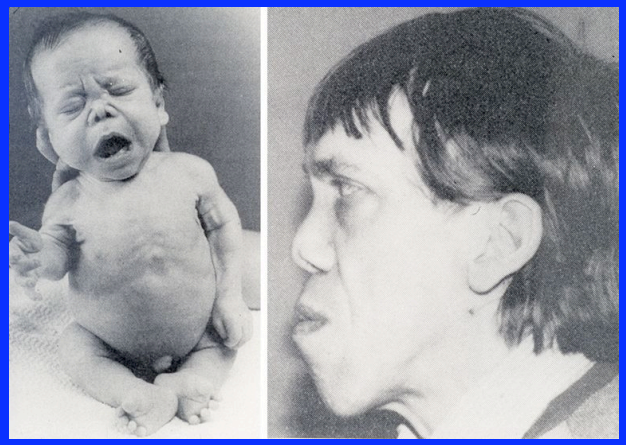
- It was thought that ACE inhibitors were safe in the first trimester which was good since accidental use in pregnancy could be corrected by changing to another anti-hypertensive drug before the start of the second trimester. However……

- Cooper et al., Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors NEJM 354:2443-2451 June 8, 2006



Coumarin anticoagulants - Warfarin

- Anticoagulation in pregnancy may be needed for thromboembolic disorders and in patients with artificial heart valves. Although heparins appear to be safe for the fetus (they are large molecules that do not cross the placenta) it is difficult for outpatients to administer them. Since warfarin is administered orally it the preferred drug for chronic administration.

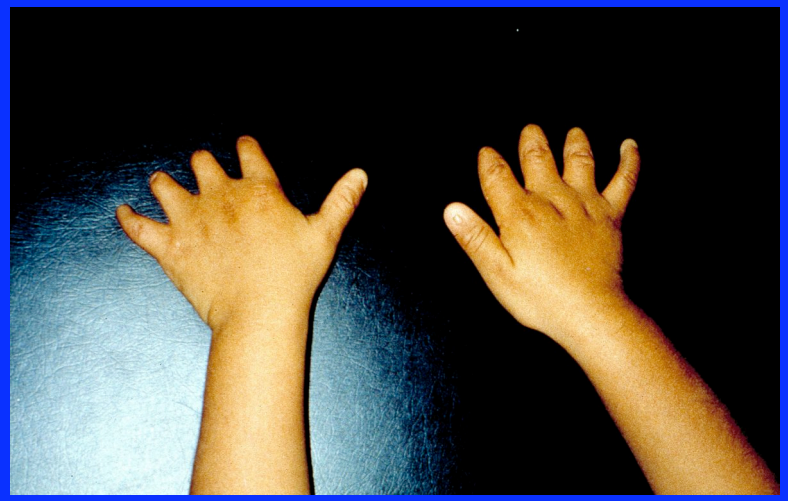


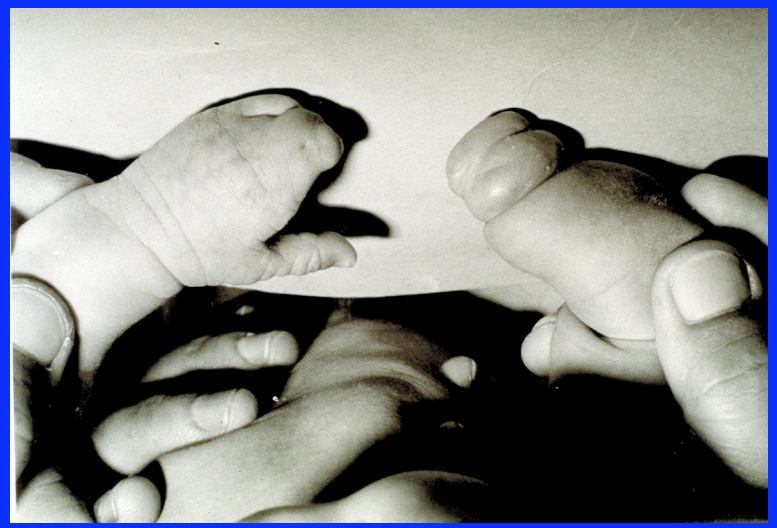
- A recent analysis of 979 pregnancies concluded that warfarin exposure in the first trimester was associated with a 6% prevalence of the warfarin embryopathy. This is characterised by midfacial hypoplasia and abnormal calcification in cartilage and in the cartilaginous parts of growing bones. The embryopathy can be avoided by replacing warfarin with heparin during the 6th to 12th gestational week.

- Bleeding in 3rd trimester

Misoprostol

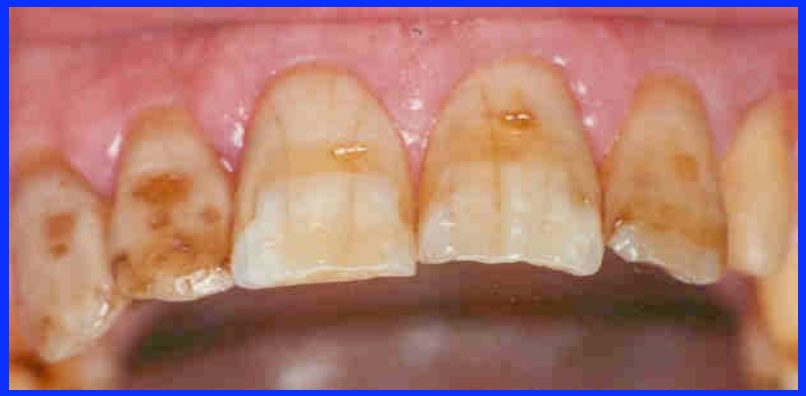
- ***Misoprostol*** - is an analogue of prostaglandin E1. It is used for the treatment of peptic ulcer disease at doses of 200-400 μg.
- In some countries misoprostol has been used at higher doses (600-1800 μg) in an attempt to induce first trimester abortions. If the attempted abortion is unsuccessful there is a considerable risk that the child will be born with birth defects - particularly limb defects and brain abnormalities
- Birth defects have not been associated with use of the drug for the treatment of ulcers.





Tetracyclines

- ***Tetracyclines*** deposit in calcifying teeth and bone. As little as 1 g/day for 3 days at any time after the end of the 4th month of gestation can cause permanent yellow staining of the deciduous teeth. Tetracyclines chelate with calcium and deposit in calcifying teeth and bone. As little as 1 g/day for 3 days at any time after the end of the 4th month of gestation can cause permanent yellow staining of the deciduous teeth. Use near term may stain the crowns of the permanent teeth.

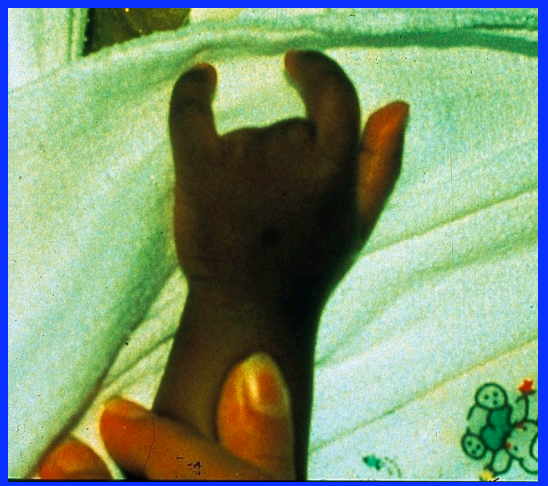


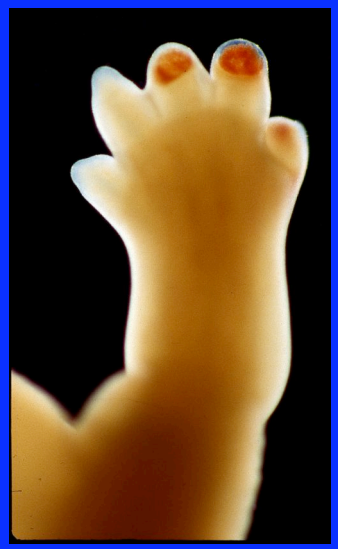
Other Human Teratogens

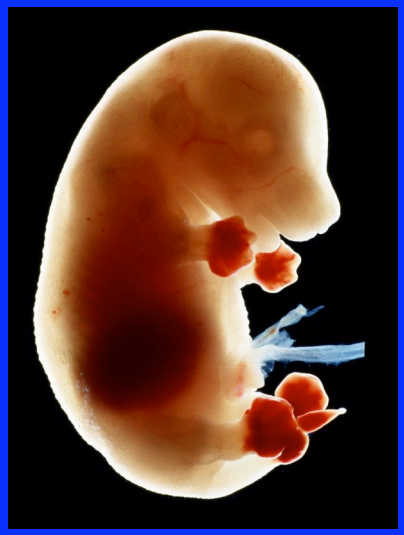
Alcohol
Cocaine
Hyperthermia
Diabetes
Iodine Deficiency
Cigarette smoking?

Cocaine

- General population estimates of cocaine use by pregnant women range from around 3% to 15% in the USA.
- Cocaine causes vasoconstriction of the uterine vessels and reduces blood flow to the embryo.
- Cocaine use increases the probability of intrauterine growth retardation, preterm labor, premature rupture of membranes, pregnancy induced hypertension, precipitous delivery and for certain birth defects (brain, limbs, heart, genitals, urinary tract, intestines).





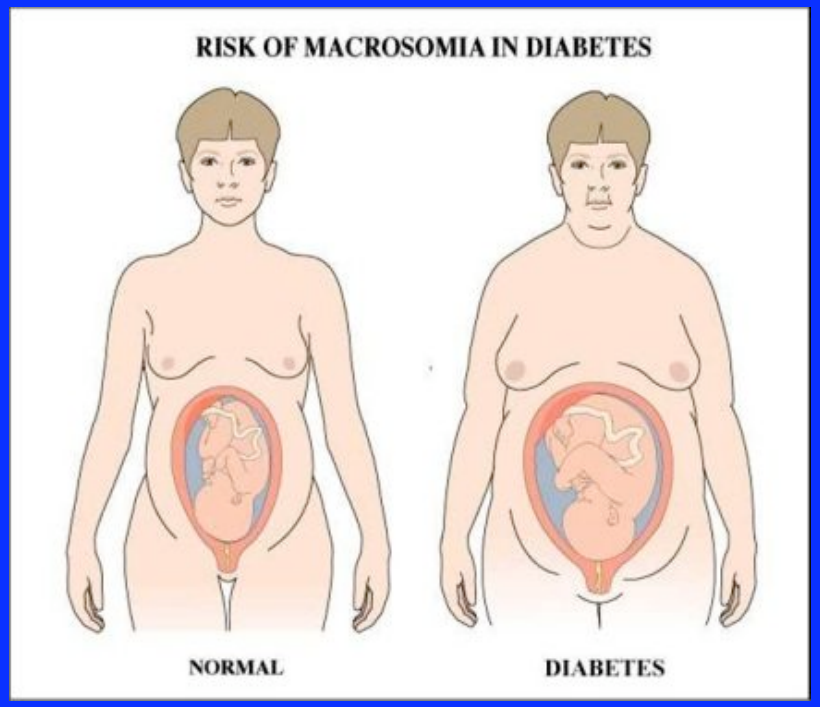


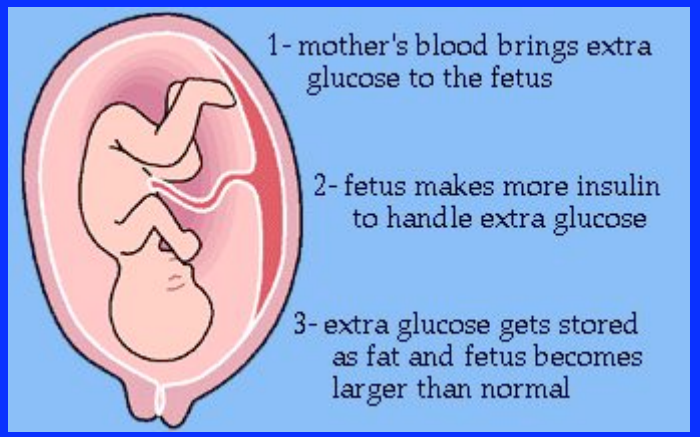
Diabetes

- About 1% of women of childbearing age have diabetes before pregnancy (preexisting diabetes) and another 2 to 5 percent develop diabetes during pregnancy (gestational diabetes). Poorly controlled diabetes in the first trimester is associated with an increased incidence of birth defects (may be increased 2 - 4 x) including neural tube defects (2% risk of neural tube defects = 10x risk for non-diabetic women).

- In the second and third trimester the extra transfer of glucose to the fetus can result in increased fat storage in the fetus (macrosomia) and neonatal problems.

- When drug therapy is required insulin is the drug of choice as it does not cross the placenta.





Cigarette smoking

- Smoking in pregnancy doubles the risk of having a **low birth weight baby** and increases the risk of **preterm delivery**. Premature and low-birthweight babies face an increased risk of serious health problems during the newborn period, chronic lifelong disabilities (such as cerebral palsy, mental retardation and learning problems) and even death.
- Smoking cigarettes appears to double a woman's risk of developing **placental problems**. These include placenta previa (low-lying placenta that covers part or all of the opening of the uterus) and placental abruption (in which the placenta peels away, partially or almost completely, from the uterine wall before delivery).
- Cigarette smoking in pregnancy seems to be associated with a small increase in the risk of **cleft lip**.

Points to consider

Women of Childbearing Age- Are You Pregnant?

- About 50% of pregnancies are unplanned (Hanshaw 1997).
- Less than 50% of women knew they are pregnant by the 4th week of pregnancy and about 15% had still not recognized their own pregnancy by 8 weeks and 5% did not know that they are pregnant by the end of the first trimester (Floyd et al 1999).

Conditions That May Require Medication During Pregnancy

(Percentage = estimated proportion of pregnant women affected)

- Nausea and vomiting ~70%
- Urinary tract infections ~ 8-10%
- Pre-existing hypertension ~ 1-5%
- Gestational hypertension ~ 10%
- Gestational diabetes ~ 2-5%
- Pre-existing diabetes ~ 1-5%
- Pre-eclampsia ~ 4%
- Asthma ~ 5%
- Anxiety ~ 2%
- Schizophrenia ~ 0.5%
- Depression ~ 3%
- Epilepsy ~ 0.2-0.5%
- Hyperthyroidism ~ 0.1%
- Headaches
- Colds

Is there a danger of under-medication?

Since there are only about 20 drugs or groups of drugs that are known to be human teratogens - does that mean that the other several thousand drugs are safe?

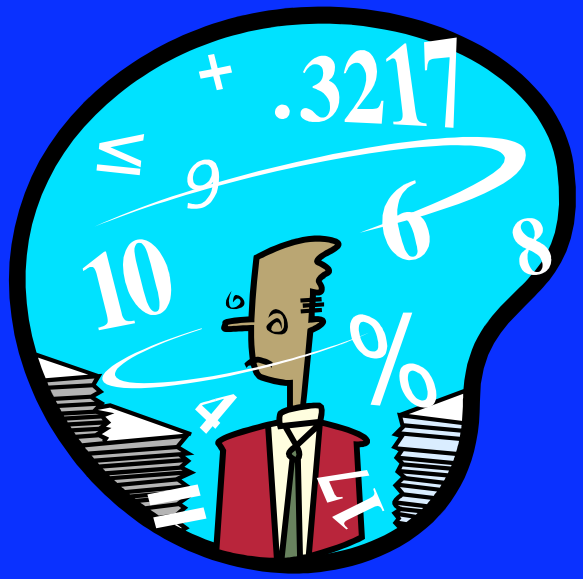
Consider an epidemiology study to investigate the safety of drug x in pregnancy

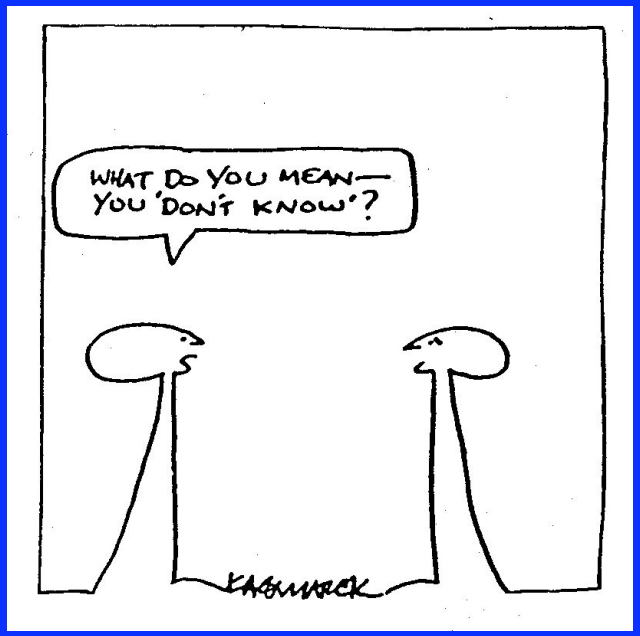
- A good study may have 100 exposed pregnancies and 100 controls.
- Was drug exposure at the critical time of pregnancy - first trimester? Day 24?
- Was the dose that was used the same for all cases?
- Were the offspring examined appropriately so that all defects were identified?
- **If there is no increase in birth defects what can we say about the drug?**

Is the drug safe?

- If we assume all the criteria were met we would only know that the drug did not cause a 4-fold increase in the incidence of birth defects (3%) with 95% significance and power of 80%.

- Only 2 drugs thalidomide and isotretinoin are known to have caused a higher rate of birth defects.





FINISH!