Introduction to teratology

Teratology is the study of birth defects, and a **teratogen** is something that either induces or amplifies abnormal embryonic or fetal development and causes birth defects.

"Achondroplasia Gladiator"—
Bibliotheque Nationale, Paris

How to recognize a teratogen?

TERATOLOGY

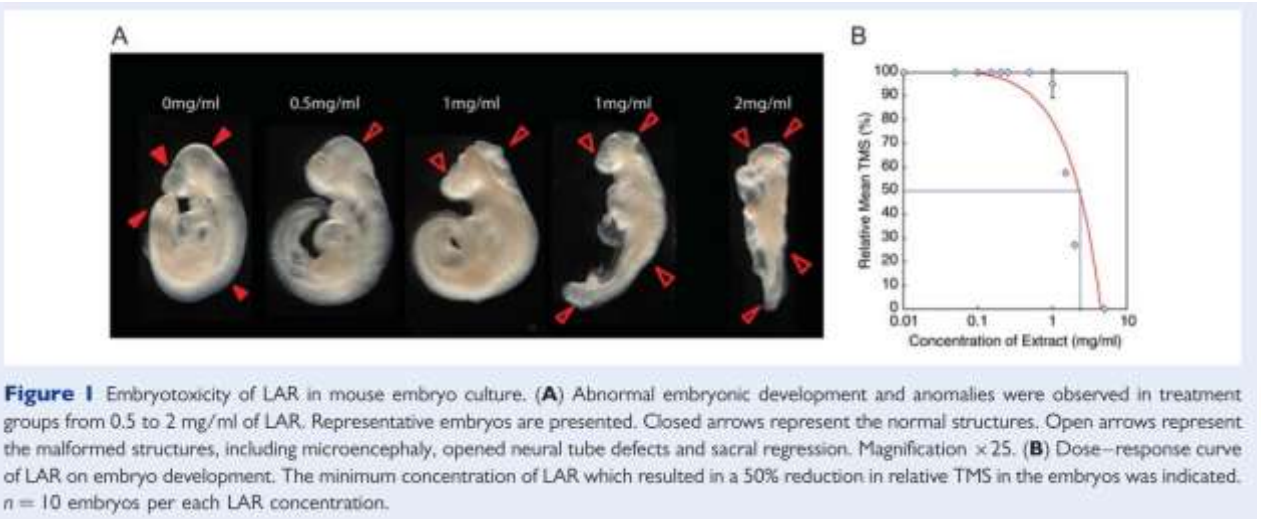

Figure 1 Embryotoxicity of LAR in mouse embryo culture. (**A**) Abnormal embryonic development and anomalies were observed in treatment groups from 0.5 to 2 mg/ml of LAR. Representative embryos are presented. Closed arrows represent the normal structures. Open arrows represent the malformed structures, including microencephaly, opened neural tube defects and sacral regression. Magnification ×25. (**B**) Dose–response curve of LAR on embryo development. The minimum concentration of LAR which resulted in a 50% reduction in relative TMS in the embryos was indicated. $n = 10$ embryos per each LAR concentration.

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MHR ORIGINAL RESEARCH

Molecular studies of the congenital malformation induced by *Largehead Atractylodes Rhizome*, the most commonly used Chinese medicine for threatened miscarriage

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How to confirm a teratogen?

Wilson's **Six Principles of Teratology** as Presented in the Wilson and Fraser Handbook of Teratology (Wilson, 1977)

1. Susceptibility to teratogenesis depends on the **genotype** of the conceptus and the manner in which
this interacts with environmental factors.

2. Susceptibility to teratogenic agents varies with the **developmental stage** at the time of exposure.

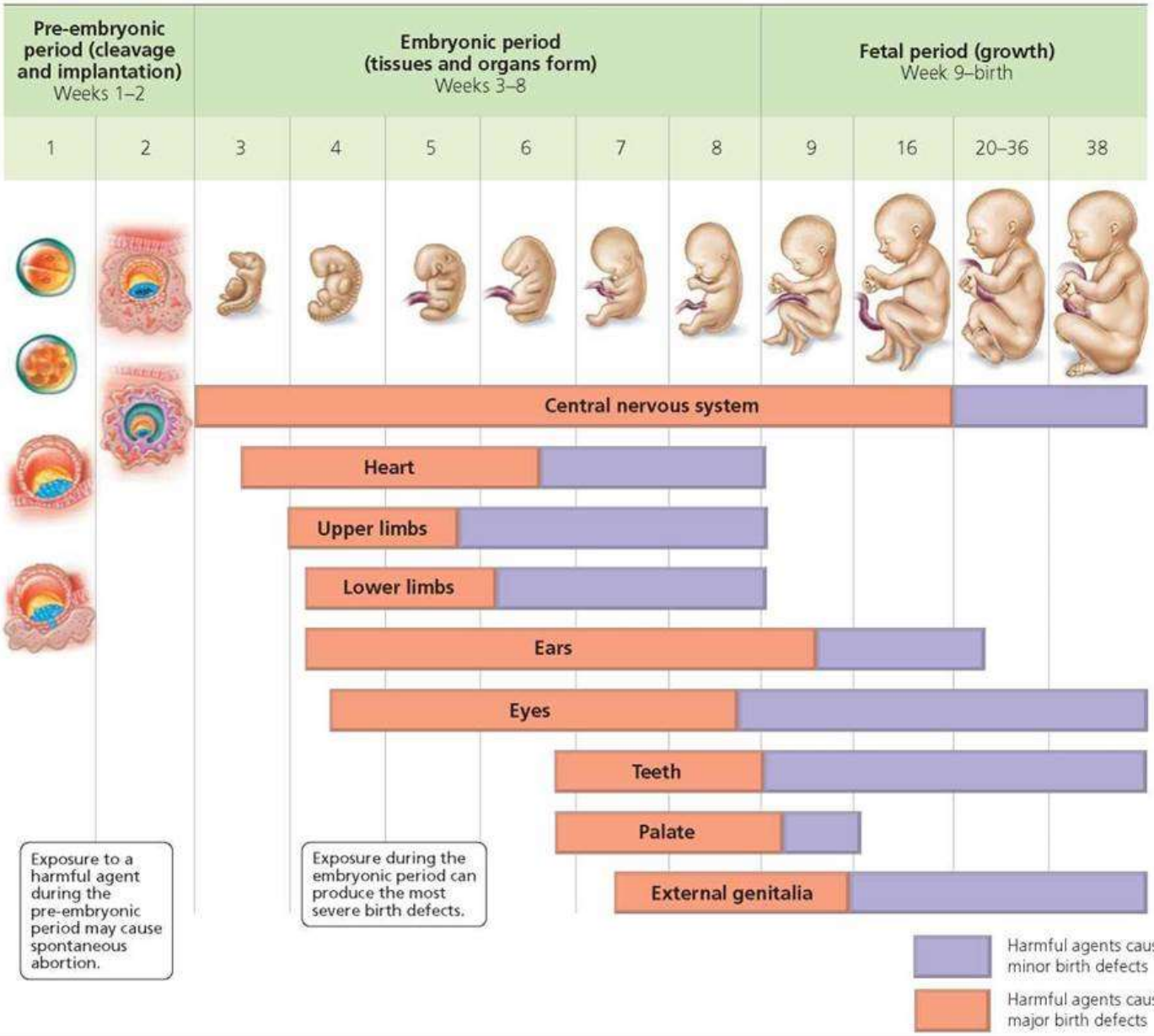
3. Teratogenic agents act in **specific ways** (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).

4. The **final manifestations** of abnormal development are death, malformation, growth retardation, and functional disorder.

5. The access of adverse environmental influences to developing tissues depends on the **nature of the influences** (agent).

6. Manifestations of deviant development increase in degree as **dosage** increases from the no-effect to the totally lethal level.

TERATOLOGY


Pre-embryonic period (cleavage and implantation)
Weeks 1–2
Embryonic period (tissues and organs form)
Weeks 3–8
Fetal period (growth)
Week 9–birth
1
2
3
4
5
6
7
8
9
16
20–36
38
Central nervous system
Heart
Upper limbs
Lower limbs
Ears
Eyes
Teeth
Palate
External genitalia
Exposure to a harmful agent during the pre-embryonic period may cause spontaneous abortion.
Exposure during the embryonic period can produce the most severe birth defects.
Harmful agents cause minor birth defects
Harmful agents cause major birth defects

Teratogens around us

physical ionizing irradiation (UV, RTG, α, β, γ), temperature, mechanical factors (amnion bands, pes equinus, ...)

chemical pharmacological drugs (antibiotics, antiepileptics, anticoagulans, cytostatics) solvents, alcohol, heavy metals, ...

biological patogens (virus), disease of mother (diabetes, myasthenia gravis, PKU)

TERATOLOGY

Teratogen	Vrozená vada
Infekce	
rubeola virus	katarakta, glaukom, srdeční vady, hluchota, abnormality zubů
cytomegalovirus	microcephalia, slepota, mentální retardace, odumření fetu
virus Herpes simplex	microphthalmia, microcephalia, retinální dysplasie
virus varicelly	hypoplasie končetin, mentální retardace, svalové atrofie
HIV	microcephalia, růstová retardace
Toxoplasma gondii	hydrocephalia, mozkové kalcifikace, microphthalmia
Treponema pallidum	mentální retardace, hluchota
Fysikální činitelé	
rtg záření	microcephalia, spina bifida, rozštěp patra, defekty končetin
hypertermie	anencephalia, spina bifida, mentální retardace, defekty obličeje, srdeční malformace, omphalokéla, defekty končetin
Chemické látky	
thalidomid	defekty končetin, srdeční vady, hluchota, slepota, malformace dalších vnitřních orgánů
aminopterin	anencephalia, hydrocephalia, rozštěp rtu a patra
fenytoin	fetální hydantoinový syndrom, defekty obličeje, mentální retardace
kyselina valproová	defekty nervové trubice, kraniofaciální, srdeční a končetinové vady
trimethadion	rozštěp patra, srdeční, urogenitální a kosterní vady
lithium	srdeční malformace
amfetaminy	rozštěp rtu a patra, srdeční malformace
warfarin	chondrodysplasie, microcephalia
ACE inhibitory*	růstová retardace, odumření fetu
kokain	růstová retardace, microcephalia, abnormality chování, gastroschisis
ethanol	fetální alkoholový syndrom, krátké oční štěrbiny, hypoplasie maxily, srdeční malformace, mentální retardace
isotretinoin (analog vitaminu A)	embryopatie vyvolaná vitaminem A: malé abnormálně tvarované uši, mandibulární hypoplasie, rozštěp patra, srdeční vady, končetinové vady
průmyslová rozpouštědla	nízká porodní hmotnost, kraniofaciální defekty, defekty nervové trubice
organické sloučeniny rtuti	neurologické poruchy připomínající mozkovou obrnu
olovo	růstová retardace, neurologické poruchy

Teratogen	Vrozená vada
Hormony	
androgeny (ethisteron, norethisteron)	maskulinisace ženského zevního genitálu: splynulá labia, hypertrofický klitoris
diethylstilbestrol	hypoplasie varlat, malformace děložky, vejcovodů a horní části vaginy, v dospělosti karcinom pochvy
diabetes mellitus	řada malformací, hlavně srdečních, defekty nervové trubice, syndrom kaudální regrese spojený s hypoplasií dolních končetin
obesita	srdeční vady, omfalokéla

* ACE – angiotensin-konvertující enzym

- **Growth retardation**
- **Failure of histogenesis, organogenesis**
- **Embryonic/fetal death**

Mechanisms of action?

Classification criteria?

FDA classification

Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Category B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

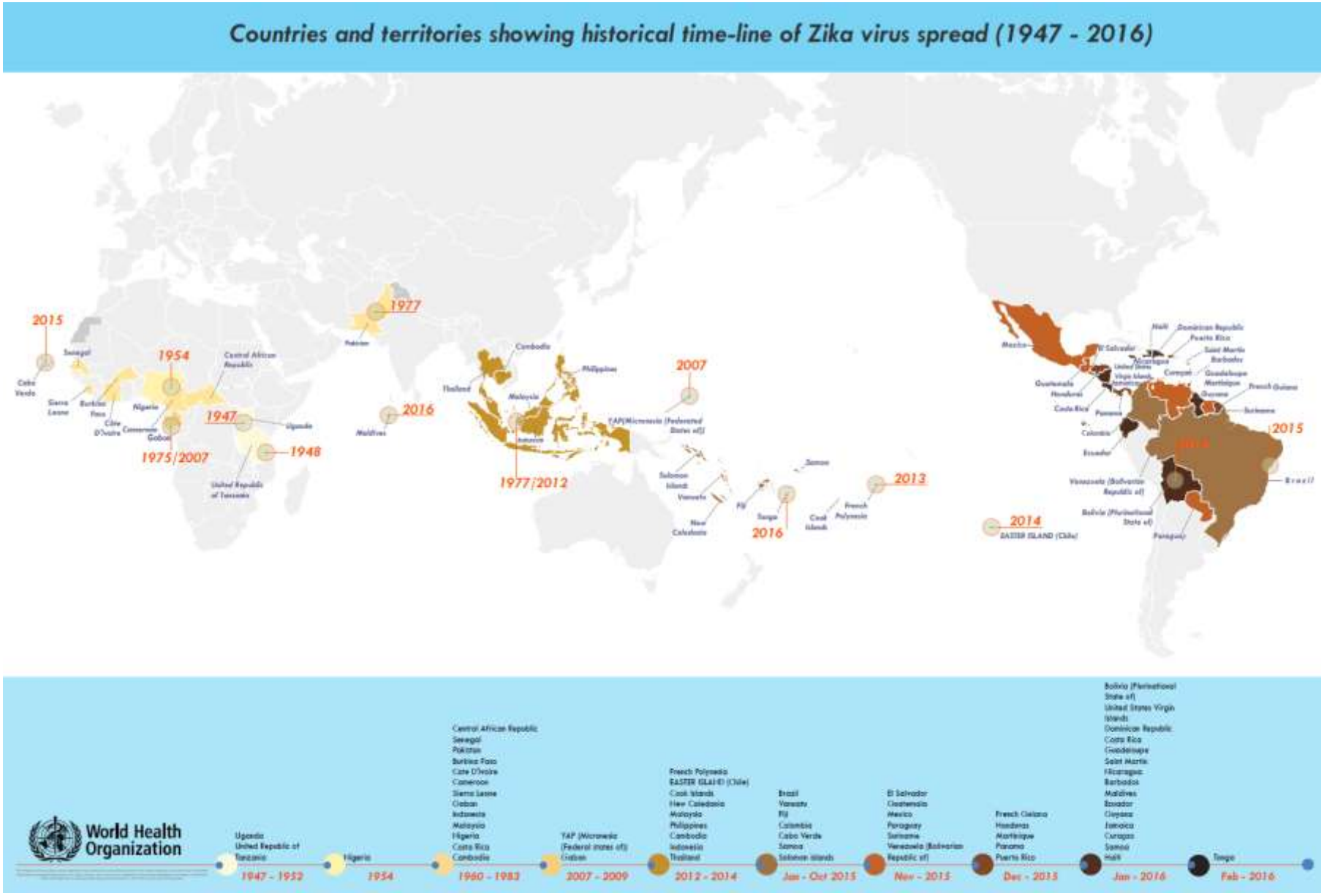
Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X: Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

https://www.govinfo.gov/content/pkg/FR-2008-05-29/pdf/E8-11806.pdf

TERATOLOGY


ZIIKA FOREST.
PROPERTY
OF
UGANDA VIRUS RESEARCH
INSTITUTE (UVRI)
P.O. BOX 49 ENTEBBE


Countries and territories showing historical time-line of Zika virus spread (1947 - 2016)
2015
1954
1947
1975/2007
1948
1977
2016
2007
1977/2012
2013
2016
2014
2015
World Health Organization
Uganda
United Republic of Tanzania
1947 - 1952
Nigeria
1954
Central African Republic
Senegal
Pakistan
Burkina Faso
Cote D'Ivoire
Cameroon
Sierra Leone
Gabon
Indonesia
Malaysia
Nigeria
Costa Rica
Cambodia
1960 - 1983
YAP (Micronesia (Federal states of))
Gabon
2007 - 2009
French Polynesia
EASTER ISLAND (Chile)
Cook Islands
New Caledonia
Malaysia
Philippines
Cambodia
Indonesia
Thailand
2012 - 2014
Brazil
Vanuatu
Fiji
Colombia
Cabo Verde
Samoa
Solomon Islands
Jan - Oct 2015
El Salvador
Guatemala
Mexico
Paraguay
Suriname
Venezuela (Bolivarian Republic of)
Nov - 2015
French Guiana
Honduras
Martinique
Panama
Puerto Rico
Dec - 2015
Bolivia (Plurinational State of)
United States Virgin Islands
Dominican Republic
Costa Rica
Guadeloupe
Saint Martin
Nicaragua
Barbados
Maldives
Ecuador
Guyana
Jamaica
Curaçao
Samoa
Haiti
Jan - 2016
Tonga
Feb - 2016

Evidence for ZIKV induced microcephaly?

Bradford Hill criteria

Strength (effect size): A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.

Consistency (reproducibility): Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.

Specificity: Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.[1]

Temporality: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).

Biological gradient: Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.

Plausibility: A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).

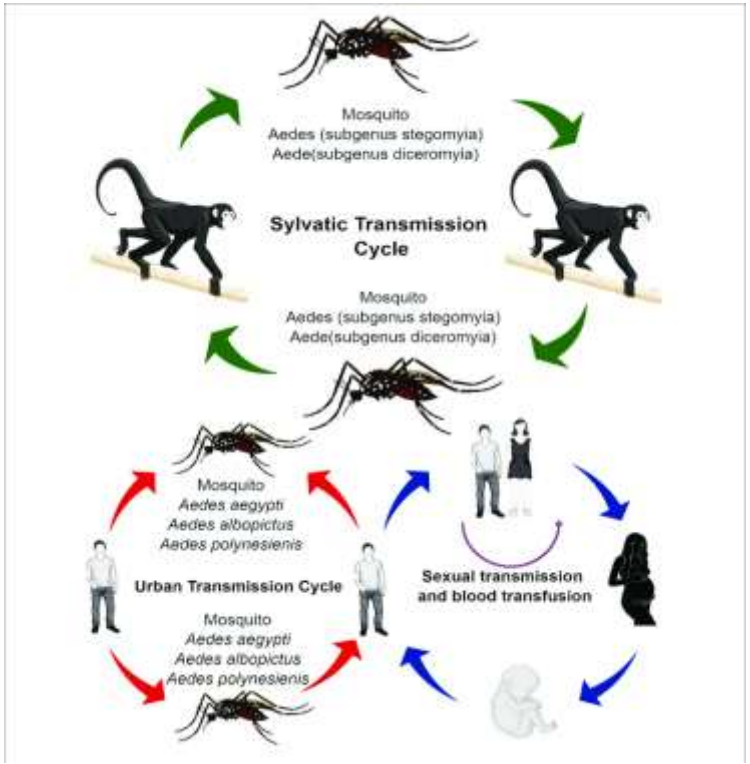
Coherence: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".

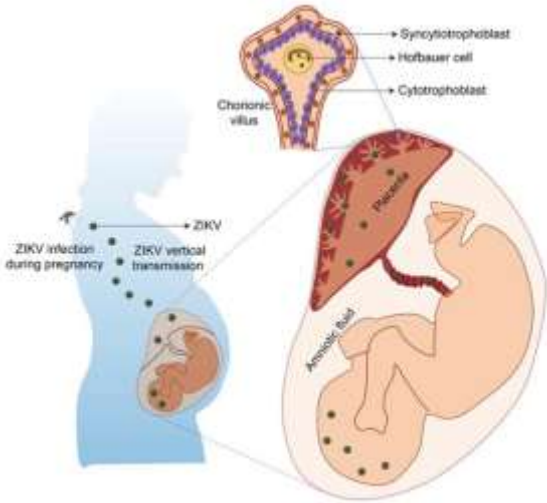
Experiment: "Occasionally it is possible to appeal to experimental evidence".

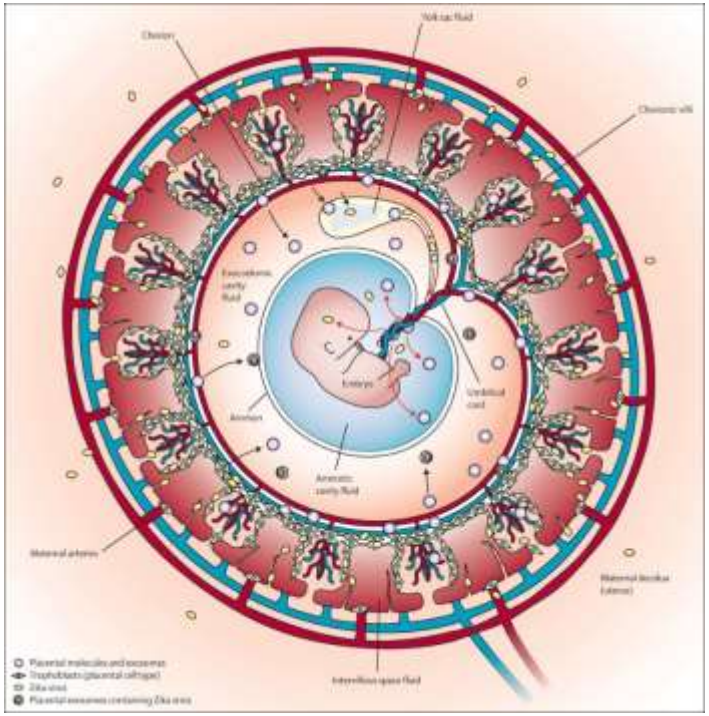
Analogy: The use of analogies or similarities between the observed association and any other associations.

Reversibility: If the cause is deleted then the effect should disappear as well

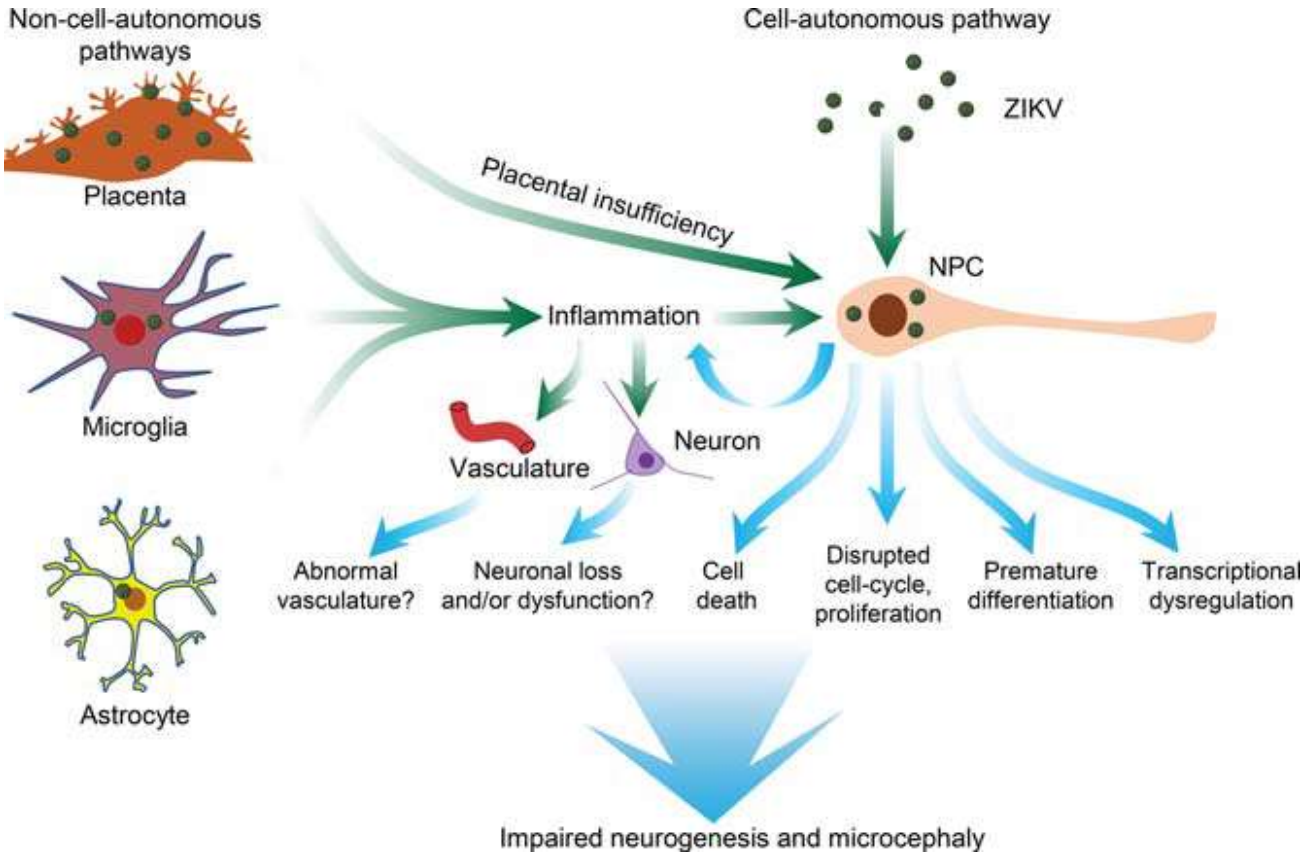
ZKV transmission







ZKV mechanism of action



Take home message

- **Teratology, teratogens → Wilson's principles**
- **Mechanisms of action → any embryology and/or cell biology textbook**
- **Classification & examples → any embryology textbook, FDA (EU) categories**
- **Identification, validation → ZIIKA forest virus story & Bradford Hill criteria**

Thank you for attention