Late lessons from early warnings vol. 2 what does BPA teach us about the status of regulatory policy

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Outline

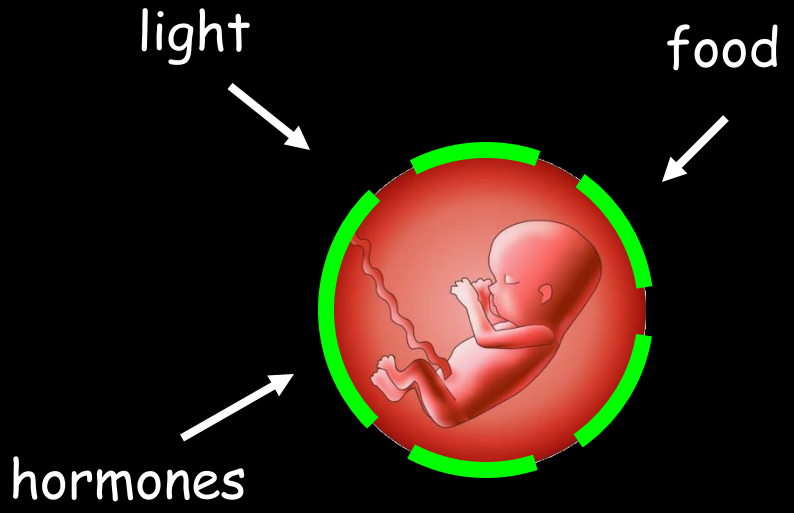
- Science and its changing paradigms
- Criteria for evaluating scientific evidence
- BPA: science and regulatory science
- Recommendations

Theoretical background

- Embryonic development: a program or an open system?
- Cancer: a cell-centered or a tissue-centered disease?

Development is a genetic program

Development is an open system (developmental plasticity)



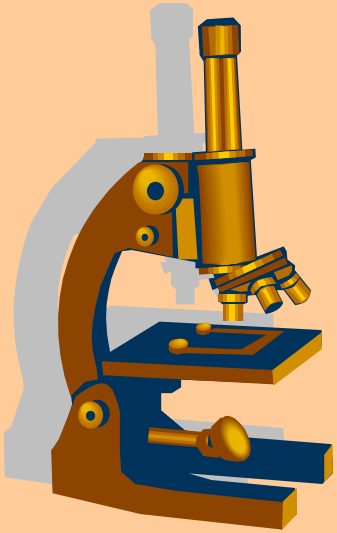
Mother is the fetal incubator

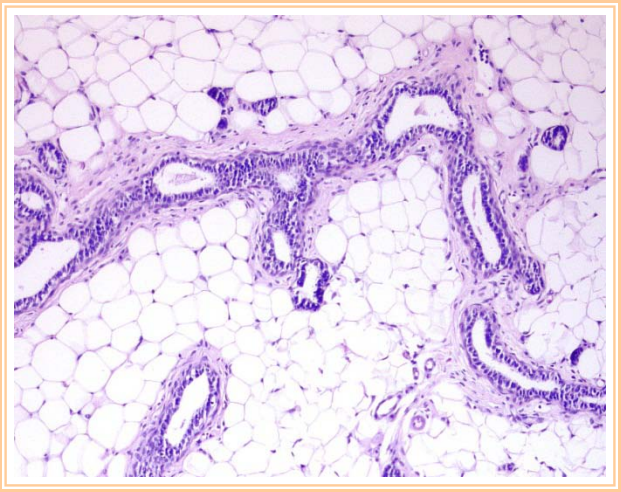
Mother is the fetal environment

Eco-Evo-Devo

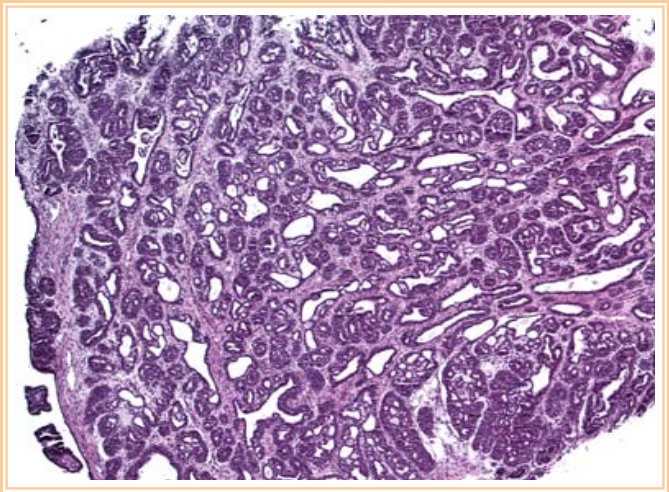
- There is no program or “central control.”
- Genes do not hold a privileged causal role.
- The environment plays a main role on the determination of phenotype.
- During development decisions are made at the local level by “ad-hoc” committees.
- Morphogenesis-the genesis of shape-involves physical forces.

What is a neoplasm?





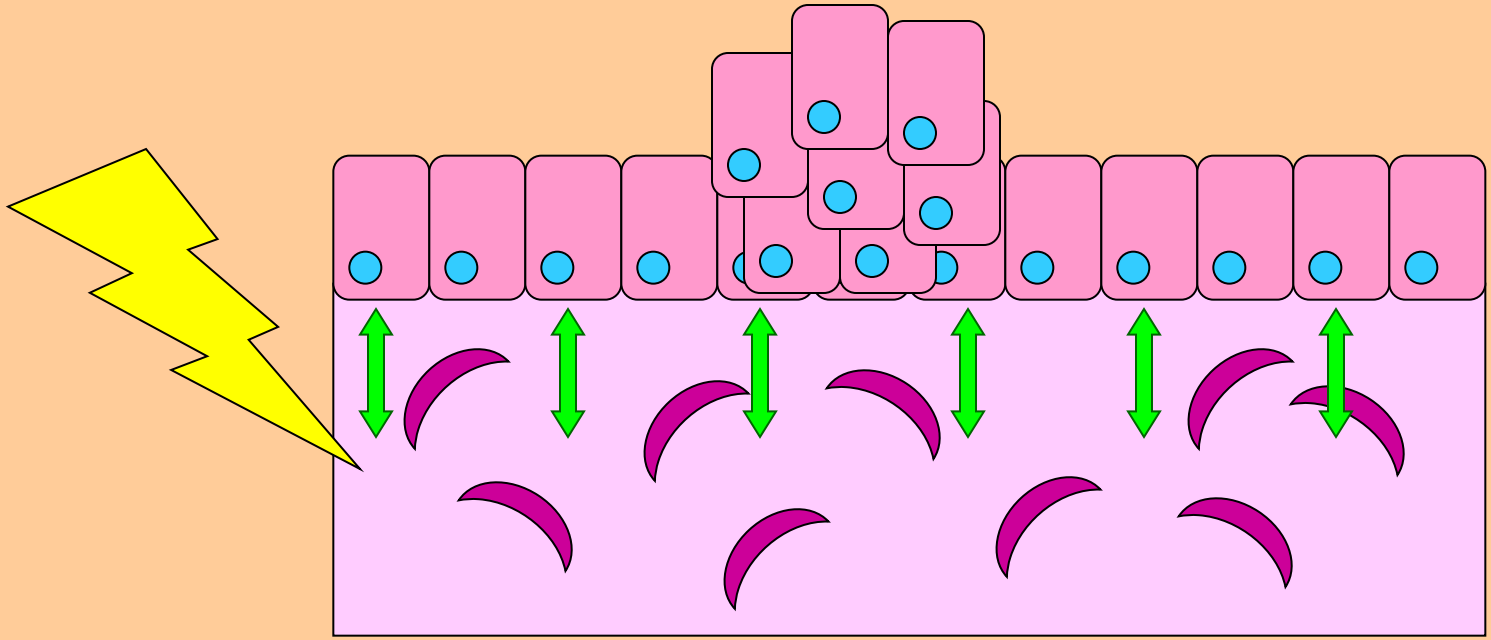
normal



tumor

The hallmark of neoplasms is altered tissue organization and excessive accumulation of cells. Neoplasms are diagnosed by pathologists using light microscopes.

The **tissue** organization field theory of carcinogenesis



Tissue level of organization

The targets of carcinogens are ***tissues***.
Cancer is a problem of tissue organization comparable to organogenesis.

The default state of cells is ***proliferation*** and ***motility*** (consistent with evolutionary theory).

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Science and applied science

- **Basic science (science for its own sake):** Living with uncertainty; there is always a new experiment to be done, a ***t*** to cross, an ***i*** to dot…100years from Galileo to Newton…time *is not* of the essence.
- **Medical Practice:** Time *is* of the essence, physicians have to reach conclusions and act ***now*** to prevent/cure/or save a life.
- **Medical epidemiology:** When testing a pharmacological agent the null hypothesis is chosen (no effect expected). Best to err on the side of a false-negative.
- **Public health epidemiology:** When studying exposures to potentially harmful agents choosing the alternative hypothesis (a deleterious effect expected) is a sound practice. Best to err on the side of a false-positive.

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Effects of perinatal low-dose BPA exposure: Fetal xenoestrogen syndrome

- Advanced puberty (Howdeshell et al)
- Altered estrous cycles and early cessation of cyclic activity (Rubin et al), altered plasma LH levels, altered activation of LHRH neurons, altered LH surge (Rubin et al)
- Decreased fertility/fecundity (Cabaton et al)
- Obesity (Rubin et al, Howdeshell et al, Newbold et al), metabolic syndrome, diabetes (Nadal et al)
- altered behaviors (Palanza et al, Rubin et al)
- Autism-like behaviors (Rubin and Soto)
- Increased risk of neoplastic development (Ho et al, Murray et al)

Lessons learned from BPA studies

- BPA is a hormonally-active agent; it should be studied and regulated using **principles of endocrinology**, not classical toxicology. This applies to every endocrine disruptor.
- Hormonal activity implies non-monotonic dose-response curves and various end points that are not included in the so-called regulatory science.
- Low doses may produce different and more harmful effects that high doses.

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- The fetus is, for the most part, a more sensitive target than the adult (organizational vs activational effects).
- Evolution and experimental work show that: mouse=rat=monkey; we should thus assume monkey=human, and accept that what is bad for mice is bad for humans.

Some worrisome facts (same old story)

- When industry started using BPA for making of plastic polymers it was already known that BPA was an estrogen (BPA was considered for therapeutic use before DES was synthesized).
- Regulatory bodies use GLP as if this was a gold standard of science; it is in fact a protocol to make it more difficult for industry to commit fraud without being noticed. GLP should not be an excuse to exclude innovative science and their novel end points.
- Most regulatory bodies (EFSA, FDA) and even the first NTP study excluded mostly all academic science showing low-dose effects. The French ANSES has instead used innovative academic science. The German UB is in favor of precautionary action, AND Canada was the true pioneer in this regard.
- Banning of BPA baby bottles was a legislative initiative triggered by public outrage. THIS SUGGESTS THAT THE EVALUATION SYSTEM IS BROKEN.
- There were several instances of COI. This is a principal problem regarding regulatory science.

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Our recommendations

- We propose that scientists from the industry should not be invited to be members of regulatory organizations. They are already in COI.
- Risk assessment must be transparent and conducted by those scientists authoring the papers with high scientific impact in this field. Stakeholder conferences may serve as a forum making interests and influence of industry and other NGOs transparent.
- The industry may pay for studies once a truly secure firewall is put between them and those that perform the tests.
- Academic and independent scientists should be the core of the regulatory panels. They should be paid well, and released from full-time duties by their employers (universities, government labs).
- Until final decisions are made, precautionary measures should be taken to lower human exposure well below those doses causing adverse effects in rodents and behavioral changes in humans in epidemiological studies.