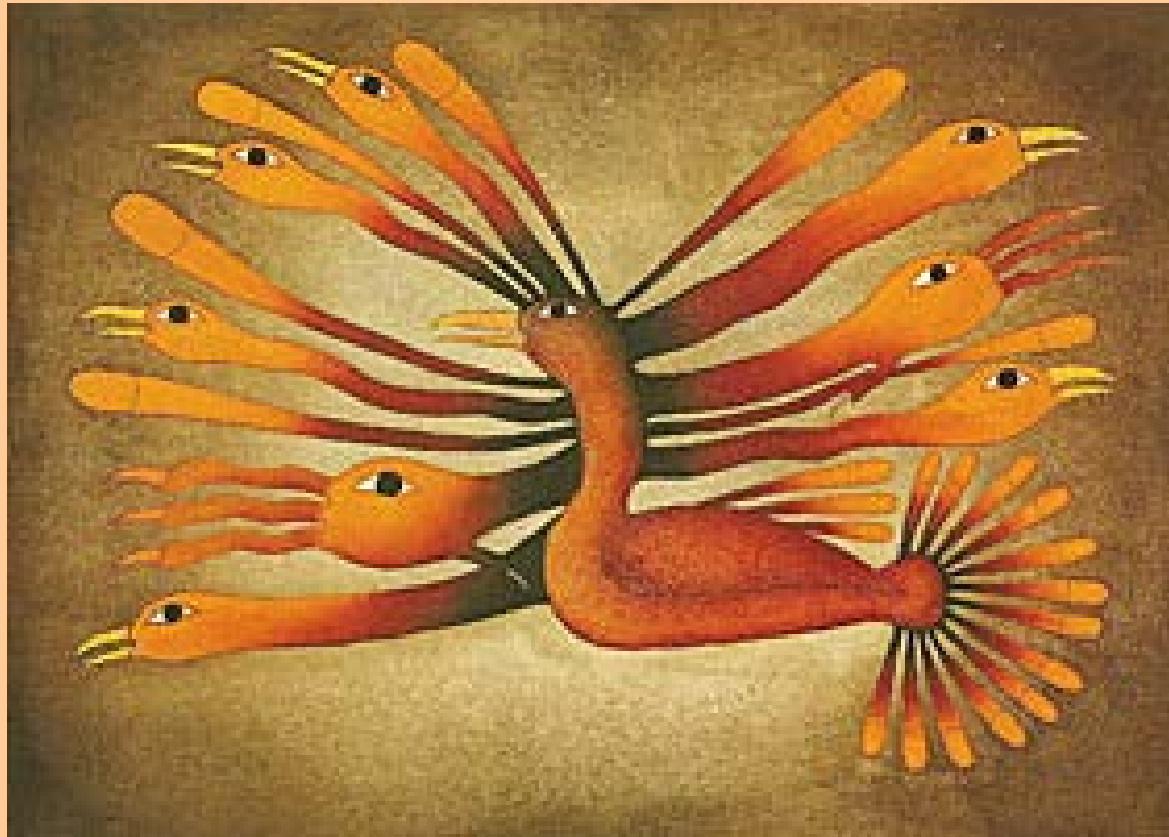


# CANCER AS DEVELOPMENT GONE AWRY

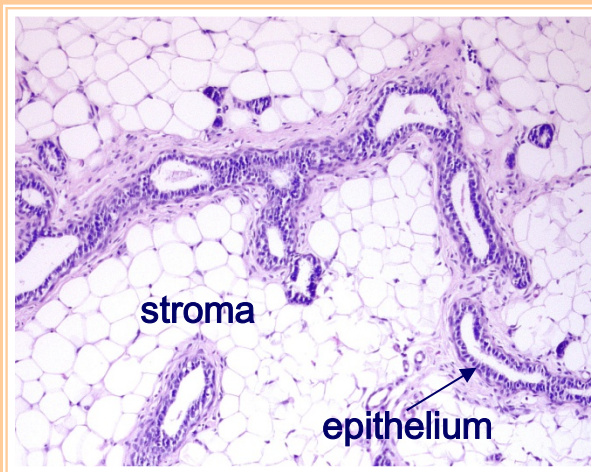


Ana M. Soto & Carlos Sonnenschein

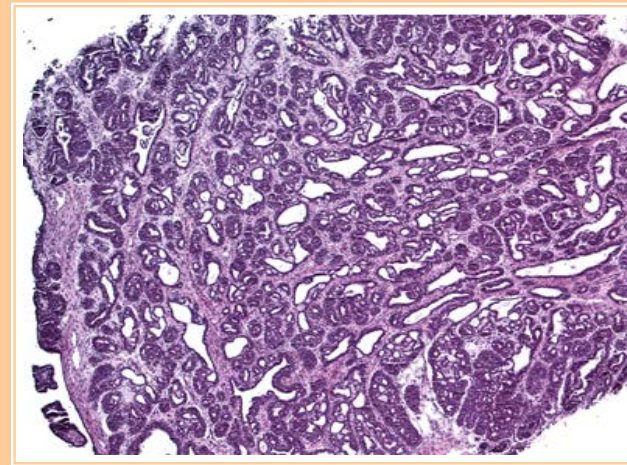
# What is a cancer?

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- The hallmark of neoplasms (cancers) is altered tissue organization.
- Tumors are more complex and less organized than normal tissues.
- Neoplasms are diagnosed by pathologists, and *only by pathologists*, by using light microscopes.



Normal



Neoplasm

# Since when has cancer been studied?

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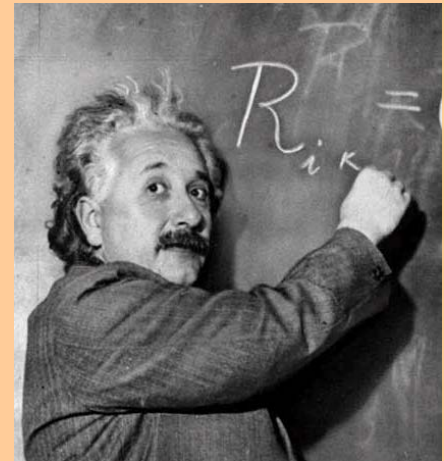
- **1850s to 1900s.** Cancer as a *tissue-based* disease (Ribbert and others, precursor of the Tissue Organization Field Theory).
- **1914-present.** Cancer as a *cell-based* disease (Boveri's theory, considered a precursor of the Somatic Mutation Theory).
- **1908-1925.** Development of cell culture techniques.
- **1935-1950s.** Cancer as a developmental disease (Waddington, Needham, Orr, precursors of the TOFT).
- **1953-present.** Molecular biology revolution ("greedy" reductionism).
- **1960s-present.** SMT became the dominant paradigm in cancer (*cell-based* disease; oncogenes, suppressor genes).
- **1999.** The Society of Cells. TOFT (*tissue-based* disease).

# Why is it necessary to adopt a theory to explain cancer?

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- Scientific theories provide organizing principles and construct objectivity by framing observations and experiments.
- “It is the theory which decides what can be observed.”

(Einstein, oral remark)



# What are the differences between CANCER CAUSES AND EXPLANATIONS?

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## CAUSES

- Viruses (hepatitis, HPV, herpes, etc)
- Radiation (X,  $\alpha$ ,  $\gamma$ -rays)
- Environment (tobacco, DDT, BPA, BP, asbestos, hormones, etc)
- Inflammations (Leishmania, Schistosomes, *H. pylori*, EBV, etc)
- Germ line mutations (retinoblastoma, BRCA)

## EXPLANATIONS

- Somatic Mutation Theory (SMT)
- Tissue Organization Field Theory (TOFT)

# What are the differences between CANCER CAUSES AND EXPLANATIONS?

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## CAUSES

Thoughtful preventive (avoid exposure, vaccines) and “therapeutic” (antibiotics) measures have effectively dealt with a few *proximate causes of some cancers*. However, these measures are neither cancer “cures” nor help in explaining cancer.

## EXPLANATIONS

- Somatic Mutation Theory (SMT)
- Tissue Organization Field Theory (TOFT)

# Which are the current theories on carcinogenesis?

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- **Somatic mutation theory (SMT)**, centered at the cellular level of biological organization.
- **Tissue organization field theory (TOFT)**, centered at the tissue level of biological organization.

**WHICH ARE THE PREMISES AND RATIONALE  
OF THE CURRENT CANCER THEORIES?**



# What is a Default State?

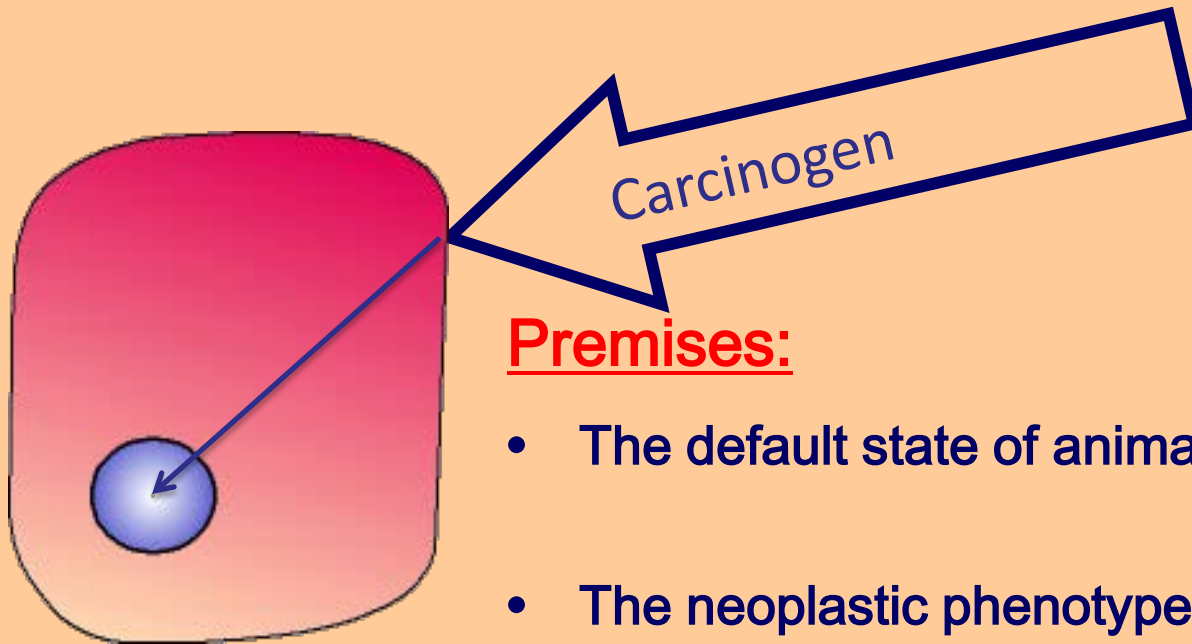
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**A DEFAULT STATE HAPPENS WHEN NOTHING HAPPENS TO PREVENT IT.**

- In physics, the default state is **INERTIA**.
- In biology, the default state is **PROLIFERATION AND MOTILITY**.

# Which are the premises of the Somatic Mutation Theory of Carcinogenesis?

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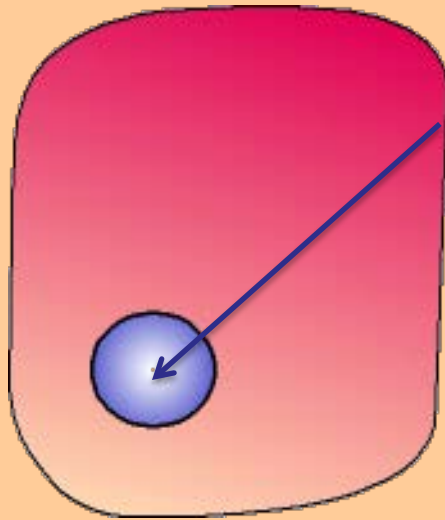


A single  
epithelial  
cell

## Premises:

- The default state of animal cells is *quiescence*.
- The neoplastic phenotype is due to somatic mutations in the DNA of *a single epithelial cell*. Thus, the putative clonality of tumors.

# Somatic Mutation Theory: corollaries

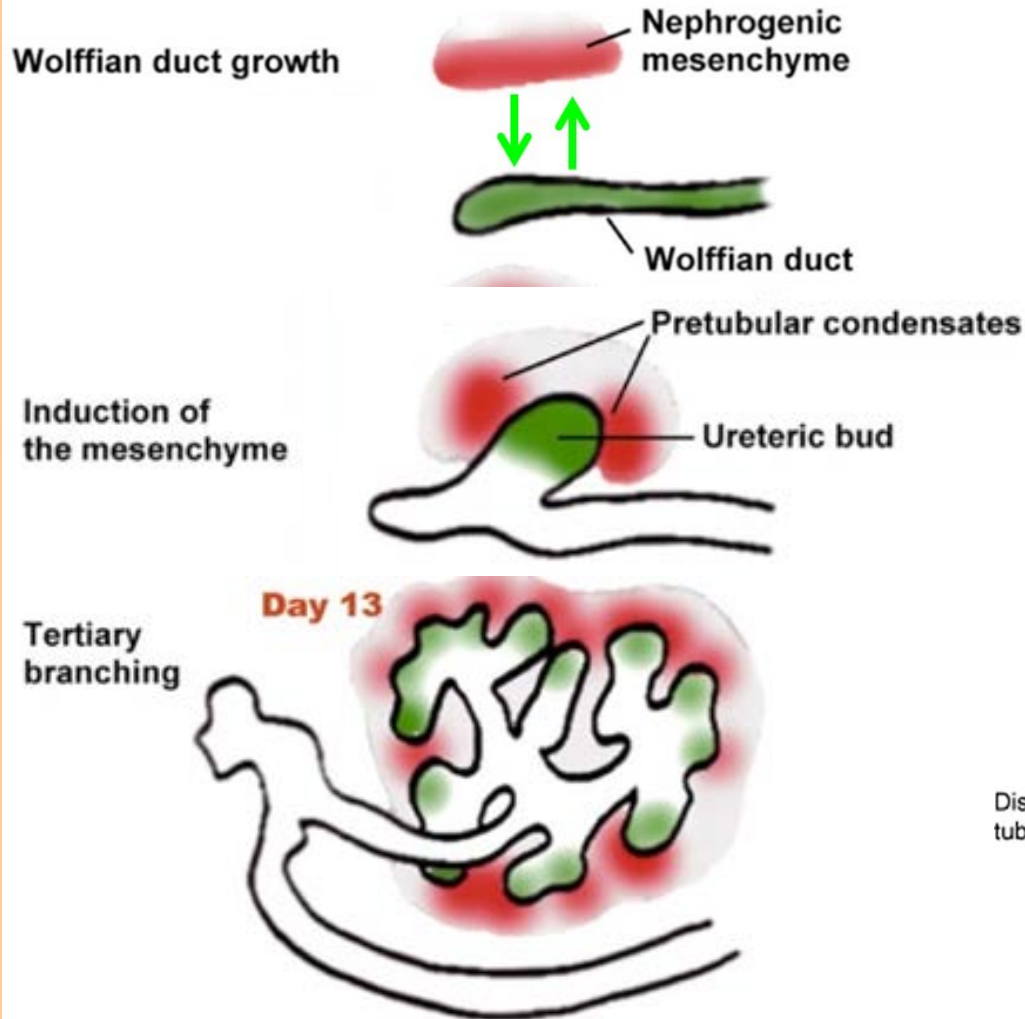


A single epithelial cell

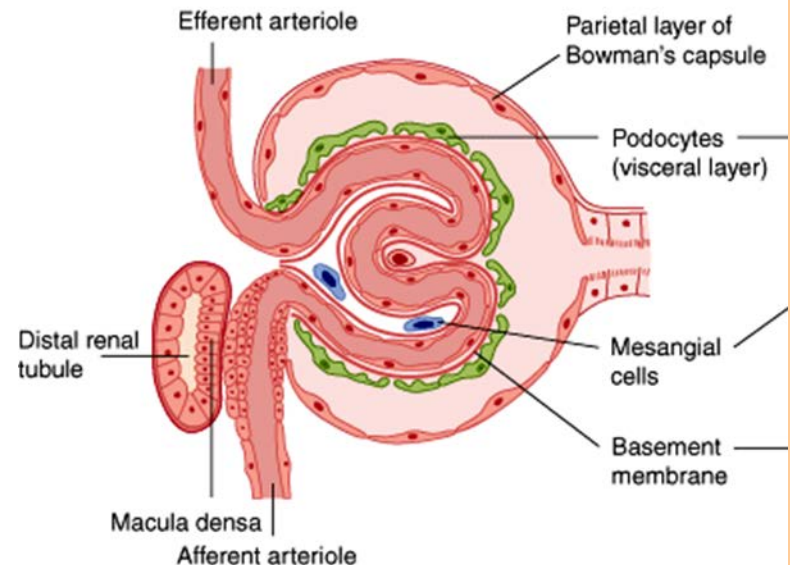
- **Corollary 1:** Carcinogenesis is a problem of control of cell proliferation/differentiation.
- **Corollary 2:** Carcinogenesis may be studied *in vitro* (in 2D cultures); that is, by exposing normal cells of a single cell type to a carcinogen (epithelial cells when studying carcinomas).
- **Corollary 3:** Cancers are clonal; cancer cells proliferate autonomously and cancer is irreversible.

# How are organs formed?

## The kidney as an example



Organs are formed by means of reciprocal interactions among tissues (nephrogenic mesenchyme and Wolffian duct) present in the organization field (kidney field).



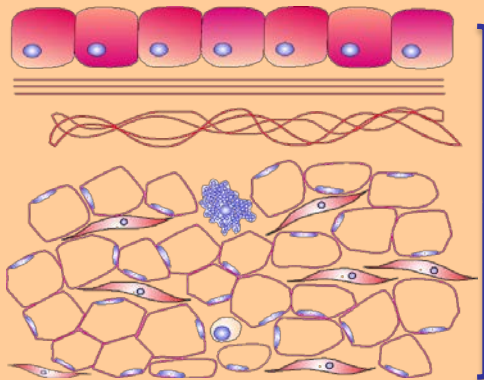
# Which are the premises of the Tissue Organization Field Theory?

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## Explicit premises:

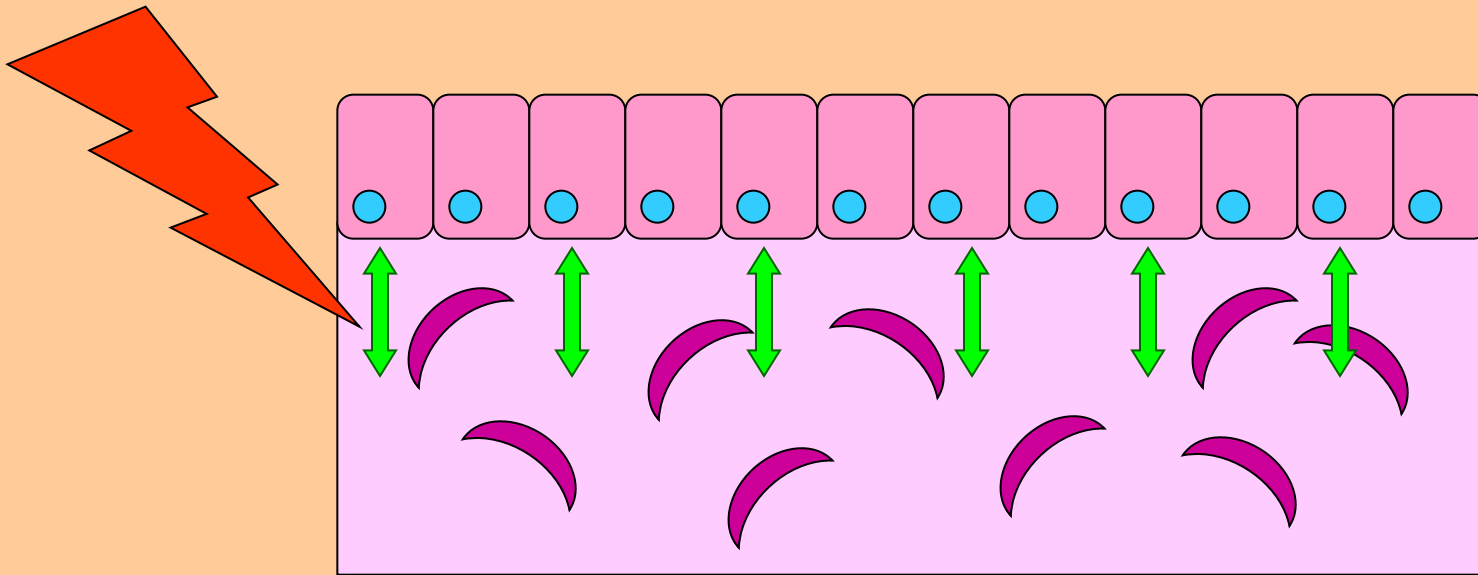
- The default state of cells is ***proliferation with variation and motility*** (consistent with evolutionary theory). And
- The targets of carcinogens are ***tissues***.

## Normal morphogenetic unit (organization field)



# How can the Tissue Organization Field Theory of Carcinogenesis be explained?

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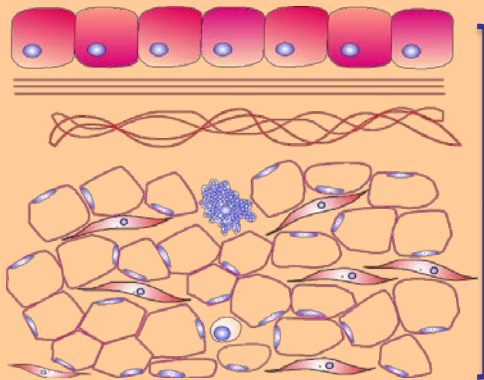
Carcinogens disrupt the reciprocal interactions among cells and tissues

# The Tissue Organization Field Theory: corollaries

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- **Corollary 1:** Cancer is a problem of tissue organization comparable to organogenesis during development, but gone awry.
- **Corollary 2:** Cancer is reversible

## Normal morphogenetic unit (organization field)



**Why should SMT and TOFT not be merged  
into a single theory?**

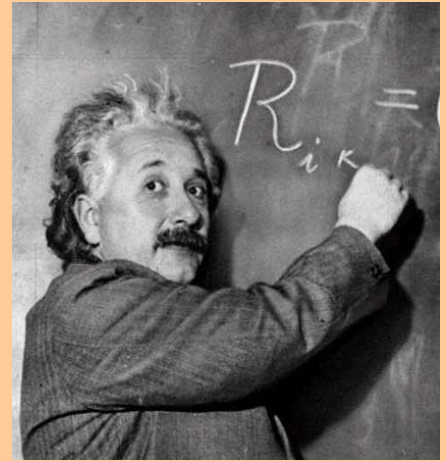
**ANSWER:** Because they are founded in  
opposite and thus, incompatible premises.



# CONCLUSION: Theories do matter!

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- “It is the theory which decides what can be observed” (Einstein)
- The theory determines the type experiments to be done.
  - The SMT focuses on the inside of cells (DNA mutations): cancer is irreversible.
  - The TOFT focuses on the reciprocal relations among cells and tissues: cancer is reversible.



**THANKS TO ALL!**

**QUESTIONS?**

