The Role of Plausibility in Biomedical Causation

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Medical Schemes of Causation

- (Henle, 1840)
- Koch, 1882, 1890
- Rivers, 1937
- Hammond, 1955
- Huebner, 1957
- Yerushalmy and Palmer, 1957
- Surgeon General, 1964
- Hill, 1965
- Cassel, 1976
- Rothman, 1976
- Evans, 1976
- Elwood, 1988

Causation in medicine

- 3 strands:
  - Medical schemes of causation
  - Causal arguments in medical literature
  - Philosophical literature on causation

How does plausibility come into this?

- Explicitly present in some medical schemes of causation
  - Also implicitly present
- Frequently occurs in the medical literature when discussing causation
- Problematic when used in theory construction

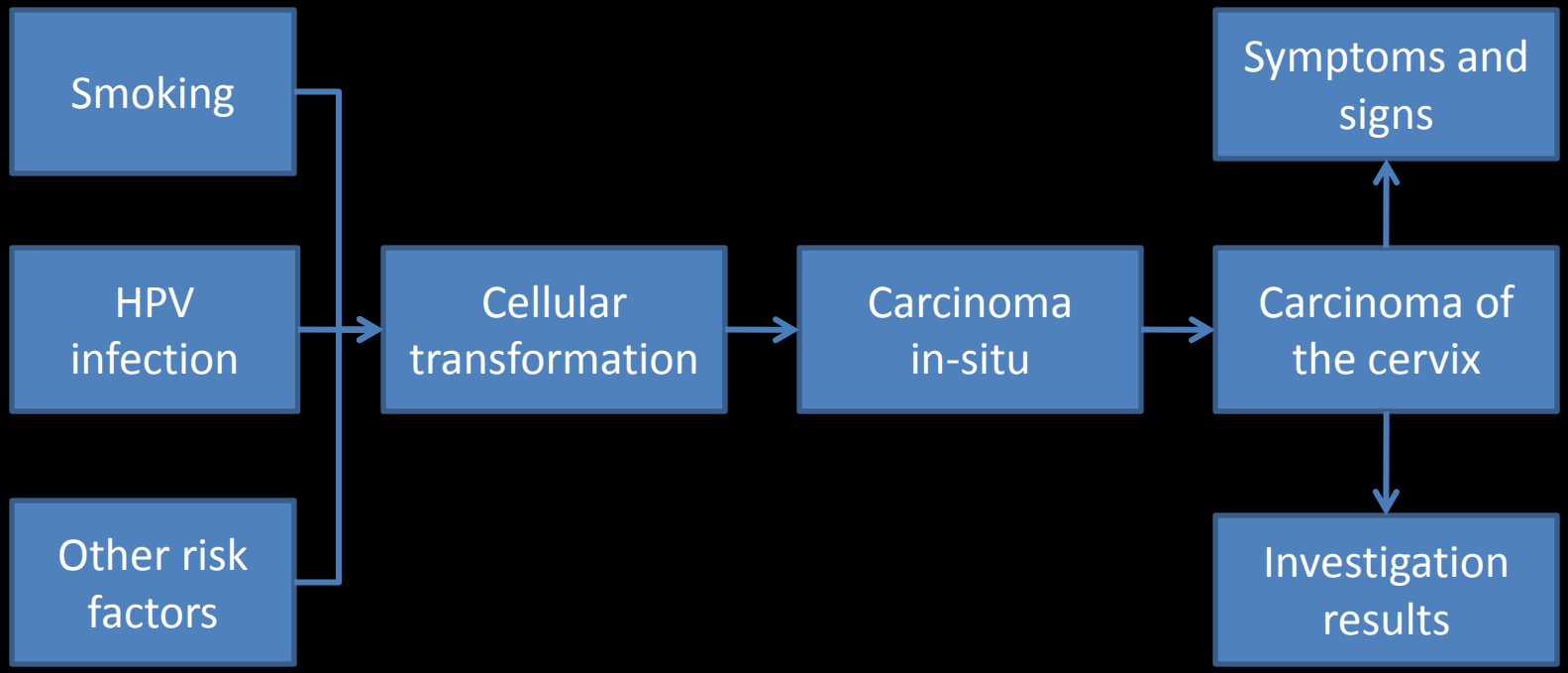
Plausibility in Schemes of Causation

- Surgeon General, 1964
  - Requirement for determining the *"Coherence of the association"* in determining causation
- Hill, 1965
  - "*Coherence:...the cause-and effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease*"
- Evans, 1976
  - *"The whole thing should make biologic and epidemiologic sense"*
- Elwood, 1988
  - *"Are the results plausible, in terms of a biological mechanism?"*

Cervical cancer and herpes simplex virus

- We now think of cancer as being caused by human papilloma virus (HPV)
- However, it was though for many years that herpes simplex virus type 2 (HSV-2) was the cause

Causal Mechanism for cervical cancer



Why herpes simplex?

- Statistically strongly associated with cervical cancer
  - Further, patients appeared to display an immune response to HSV-2 before developing cervical cancer
- Plausible causal mechanism
  - HSV-2 recovered from many cervical tumours
  - HSV known to be capable of causing malignant transformation *in vitro*
  - Many other human and animal tumours causally related to herpesviridae

Herpesviridae and malignant disease

Name	Disease
Epstein-Barr virus (HHV-4)	Burkitt's lymphoma
	Nasopharyngeal carcinoma
	Various leukaemias and lymphomas
Kaposi's sarcoma virus (HHV-8)	Kaposi's sarcoma
	Abdominal cavity B-cell lymphoma / Primary effusion lymphoma
	Multicentric Castleman's disease
Gallid herpesvirus 2 (GaHV-2)	Marek's disease (chickens)
Saimiriine herpesvirus type 2 (HVS-2)	Transmissible tumours in new world monkeys
Herpesvirus ateles type 1 (HVA-1)	T-cell lymphomas in new world monkeys
Ranid herpesvirus 1 (RaHV-1)	Lucké renal adenocarcinoma (Northern leopard frog)

HHV – human herpes virus

HSV-2 as plausible cause of cervical cancer

- So HSV-2 appeared to be a highly plausible cause for cervical cancer
- But actually not. Why wasn't HPV considered causal?
  - Technological difficulties of testing for, and working with HPV
  - HSV seemed a sufficiently good cause at the time (problem of partial success)
  - Accident

Where now?

- So, given that plausibility seems unreliable when used in theory construction, can we dispense with it?

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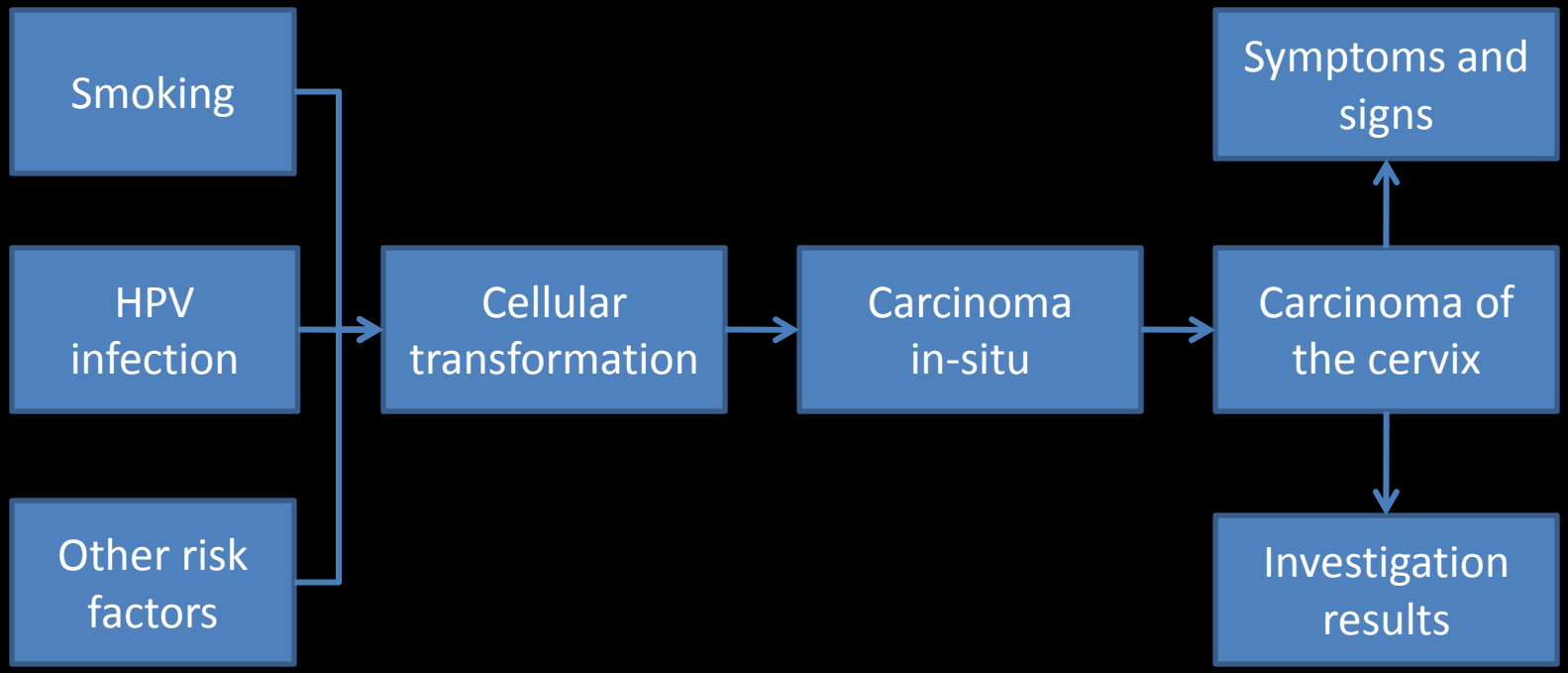
- Required for mechanistic accounts of causation

Causal Mechanism for Cervical Cancer - Generalist



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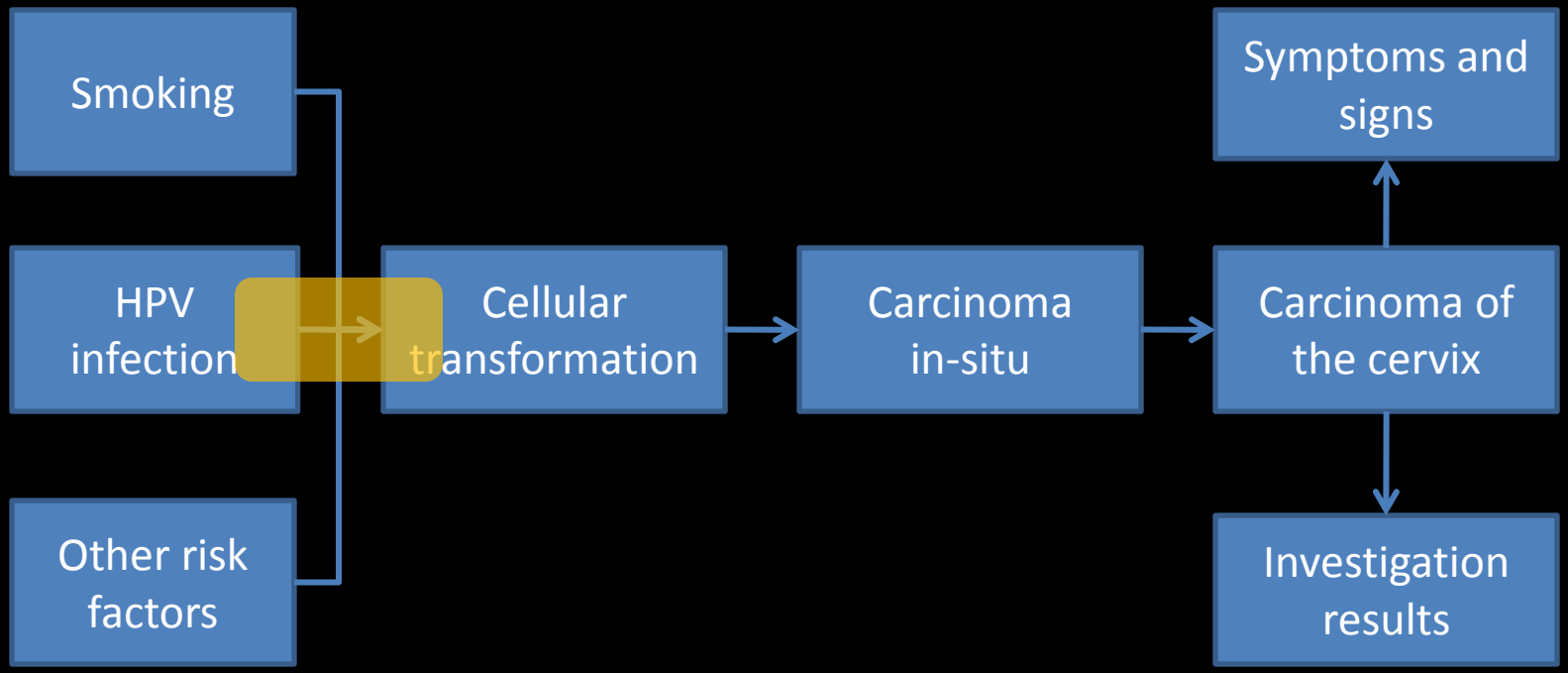
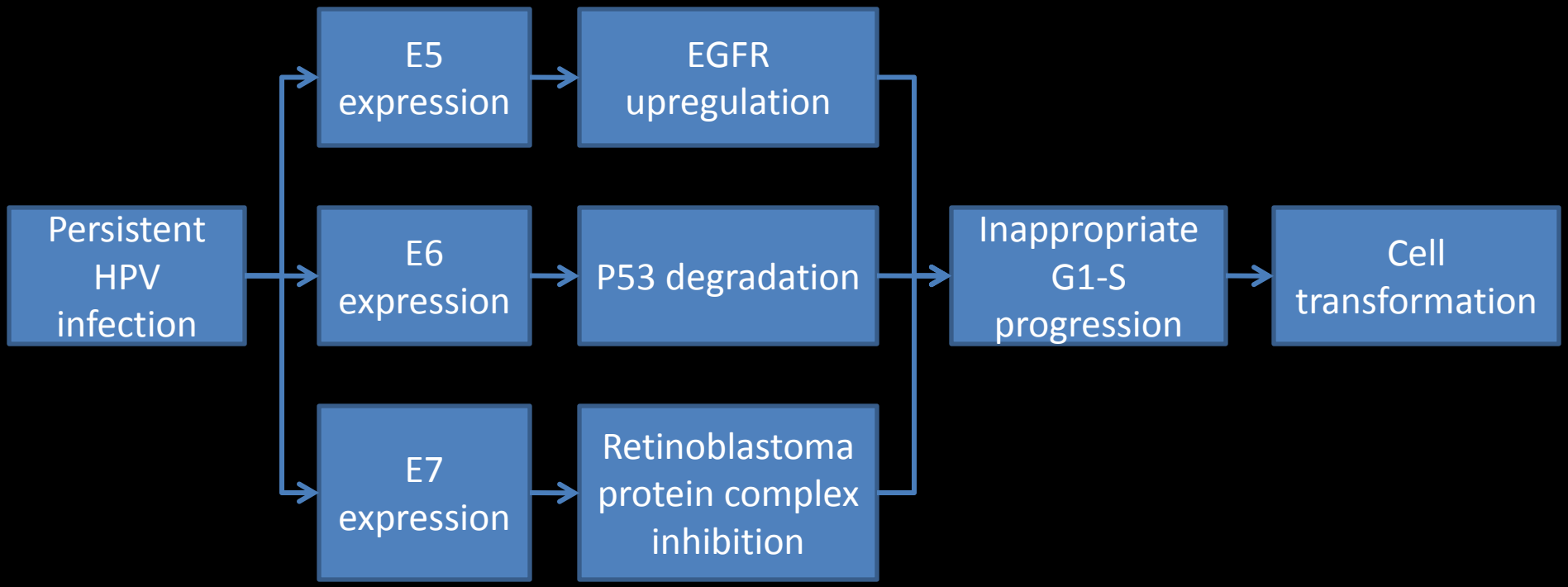


Causal Mechanism for Cervical Cancer - Specialist



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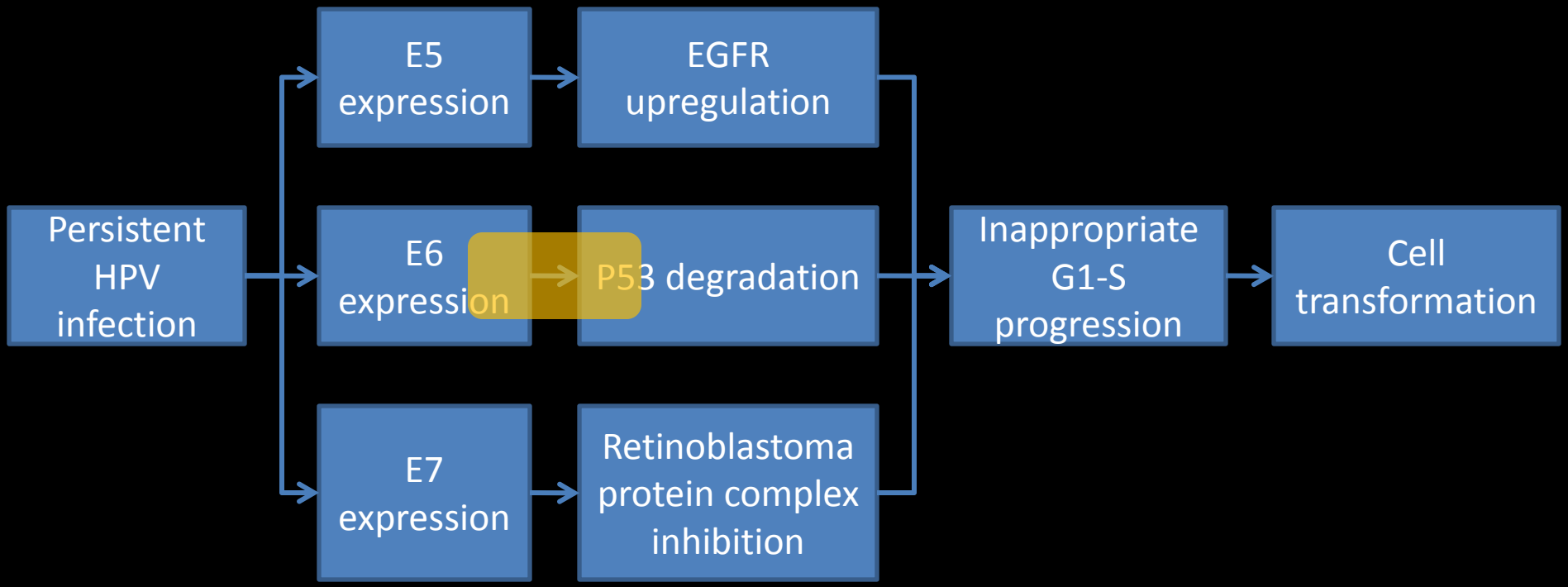
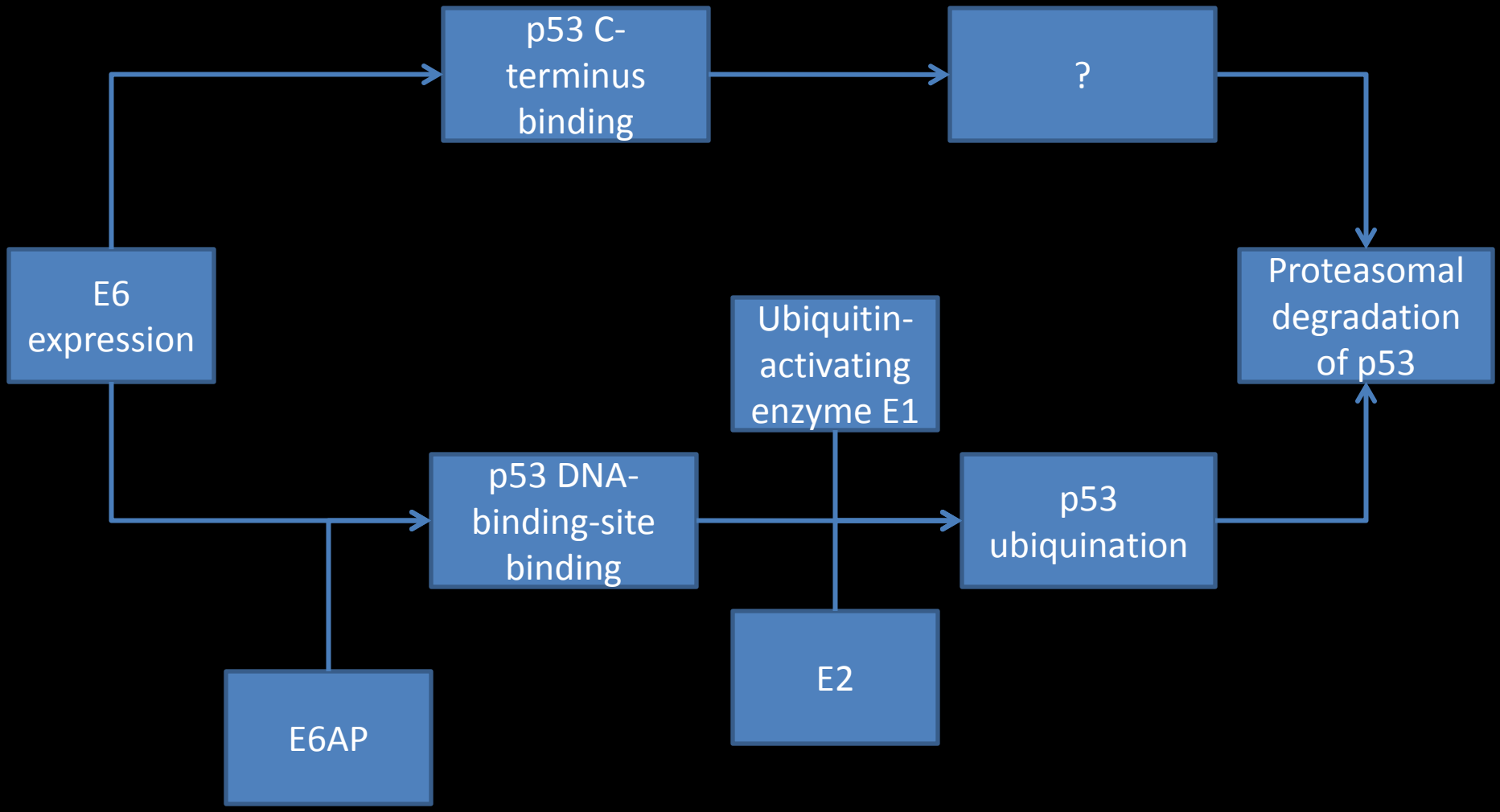


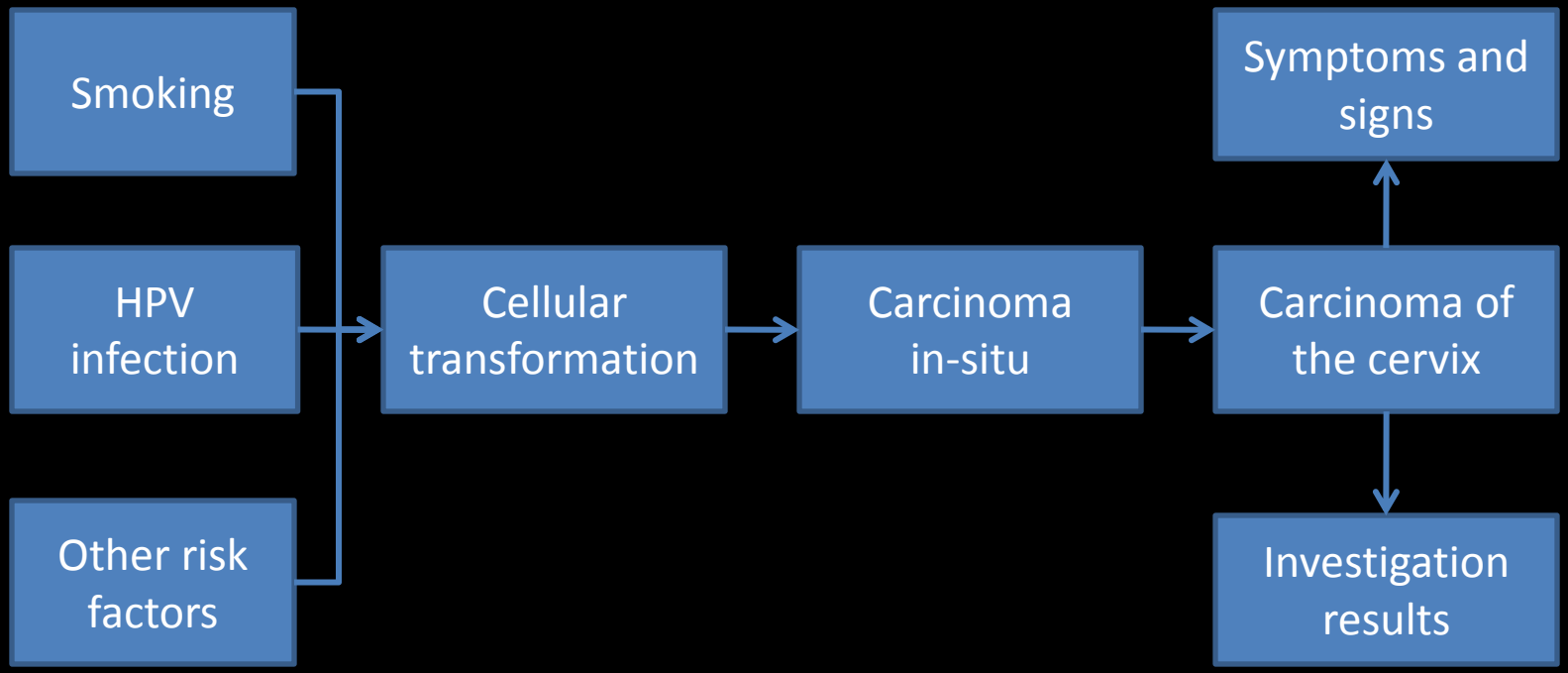
Causal Mechanism for Cervical Cancer - Research



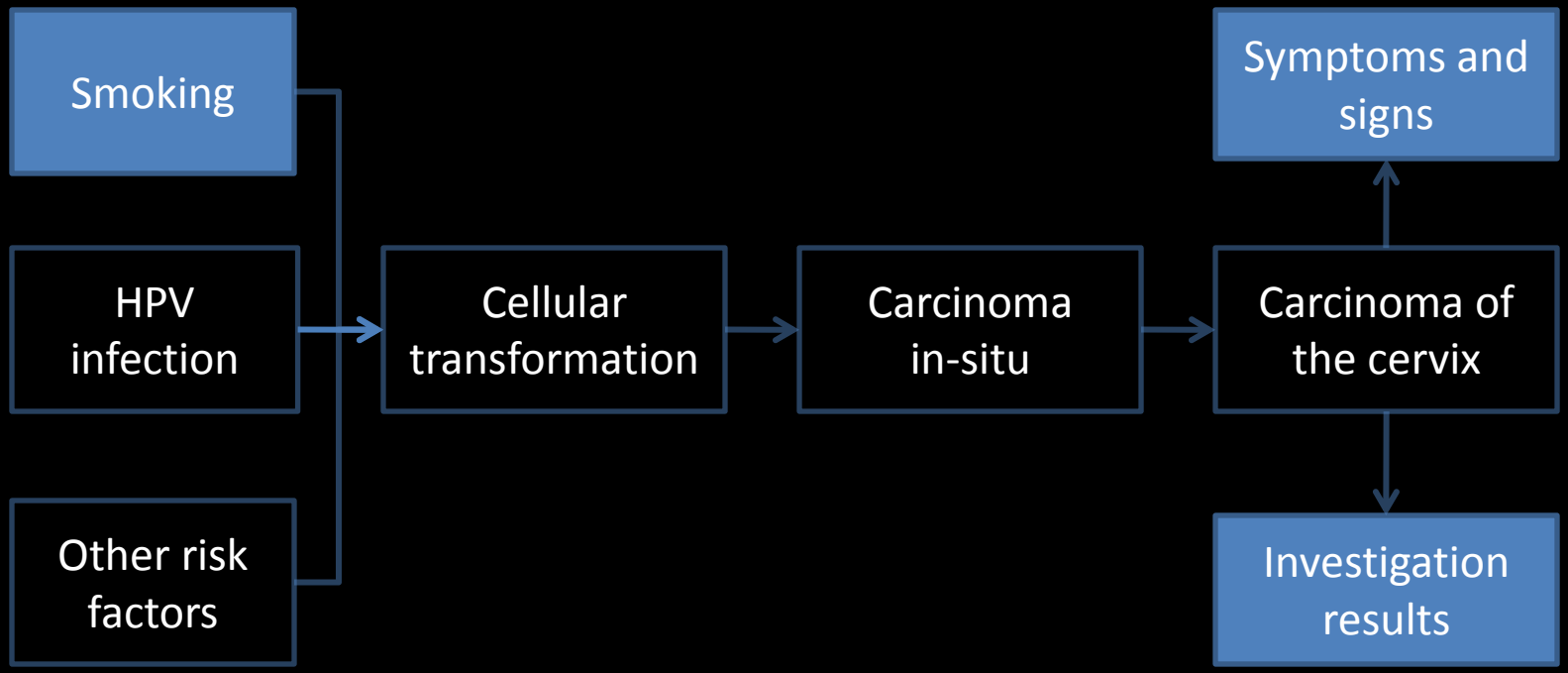
The problem of ellipticism

- Causal mechanisms, as used, are gappy
  - Some of this is elective
    - Degree of ellipticism depends on the intended purpose of the causal mechanism
  - Some of this is innate

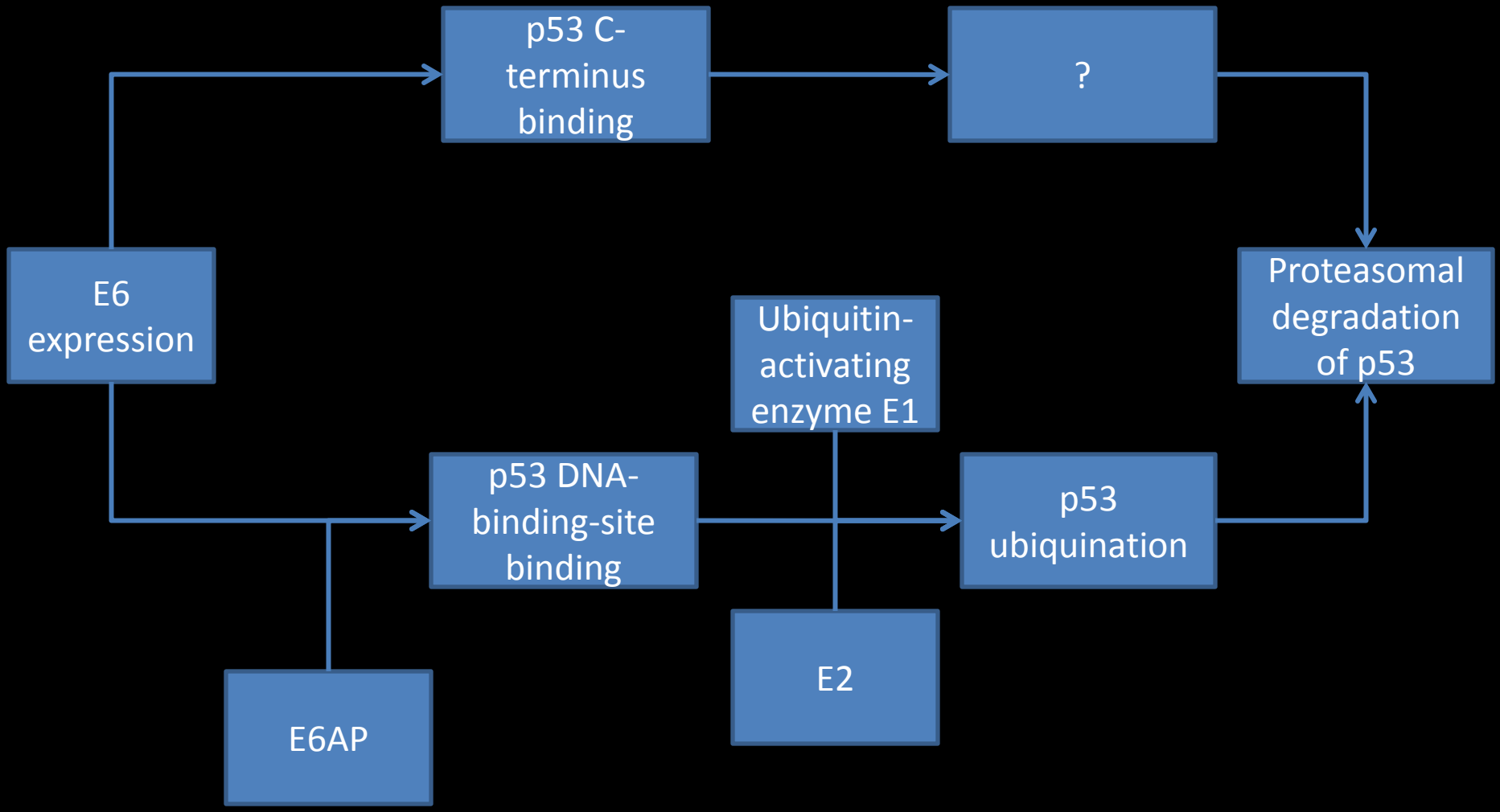
Causal Mechanism for Cervical Cancer - Generalist



Causal Mechanism for Cervical Cancer - Patient



Causal Mechanism for Cervical Cancer - Research



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    - Unknown sections of mechanism
    - Sections of mechanism that fall outside biomedicine

The problem of ellipticism

- Causal mechanisms, as used, are gappy
  - Some of this is elective
    - Degree of ellipticism depends on the intended purpose of the causal mechanism
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    - Unknown sections of mechanism
    - Sections of mechanism that fall outside biomedicine
- Plausibility bridges these gaps

How does plausibility come into this?

- Explicitly present in some medical schemes of causation
  - Also implicitly present
- Frequently occurs in the medical literature when discussing causation
- Problematic when used in theory construction
- Required for mechanistic accounts of causation

So how might we pin down plausibility?

- Look at failures of plausibility
  - Cervical cancer and Herpes Simplex virus
  - (Peptic ulcers and *H. Pylori)*
- Distinguish different types of plausibility
  - Applying known mechanisms
  - Formulating new mechanisms
- Determine features of plausible relations

Philosophical approaches to plausibility

- These problems of plausibility might be amenable to analysis
  - How can we describe plausibility?
  - How can we rank completing claims in order of plausibility?
- Counterfactual other-worlds
  - Lewis, 1979
- Analogy in theory construction
  - Lindley Darden, 1982

Lewis and counterfactual closeness

- *It is of the first importance to avoid big, widespread, diverse violations of law.*
- *It is of the second importance to maximise the spatiotemporal region throughout which perfect match of particular fact prevails.*
- *It is of the third importance to avoid even small, localized, simple violations of law.*
- *It is of little or no importance to secure approximate similarities of particular fact, even in matters that concern us greatly.*

Lewis, D. 1979. “Counterfactual Dependence and Time's Arrow,” *Noûs.* **13**(4): 472

Darden and Construction by Analogy

- Based on Hesse, 1966 and Oppenheimer, 1956
- 4 methods of theory construction
  - Exploitation of neutral analogy
  - Deconstruct causal links in new theory in terms of connections in similar theories
  - Construct new theory from relevant pieces of old, unconnected theories
  - Recognition of shared abstraction

Darden, L. 1982. "Artificial Intelligence and Philosophy of Science: Reasoning by Analogy in Theory Construction," *PSA: Proceedings of the Biennial Meeting of the Philosophy of Science Association, Vol. 2.* 147-65.

Hesse, M. 1966. *Models and Analogies in Science*. Indiana: University of Notre Dame Press.

Oppenheimer, R. 1956. "Analogies in Science," *American Psychologist*. **11**: 127—35.

But...

- Lewis, 1979
  - Lack of applicability of laws of nature
  - Particular matters of fact are very important in these cases
- Darden, 1982
  - Does analogy help in these cases either?

Case 2: *Helicobacter Pylori* and peptic ulcers

- Pre-1983
  - "Excess-acid theory" of peptic ulcer causation
    - Primarily due to diet and lifestyle factors
      - Smoking
      - Stress
      - Blood group
      - Missed meals / bolting food / spicy food
      - Alcohol
      - Drugs (NSAIDS, laxatives)
      - Neuroendocrine causes ?excess vagal innervation

Case 2: *Helicobacter Pylori* and peptic ulcers

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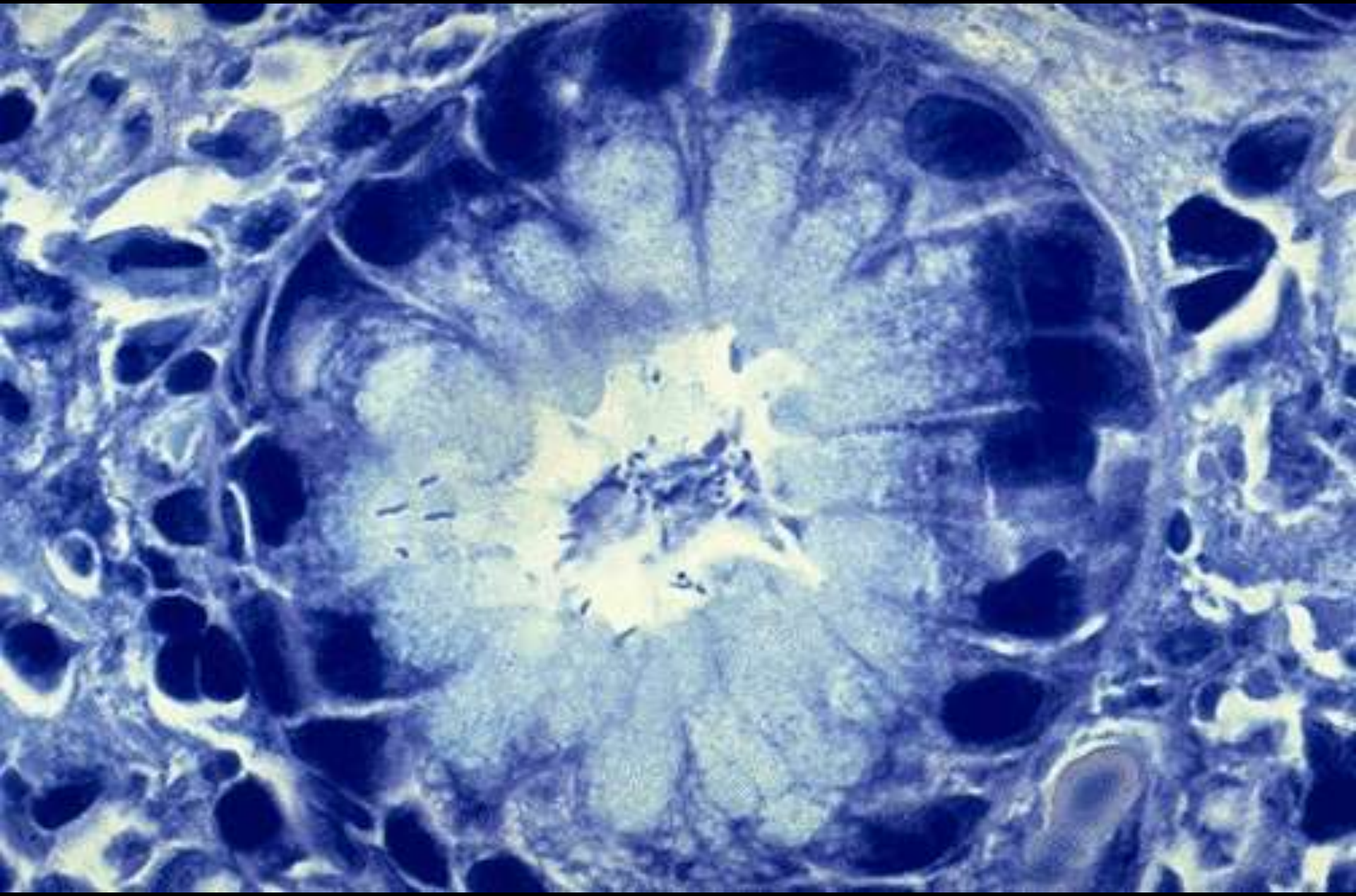
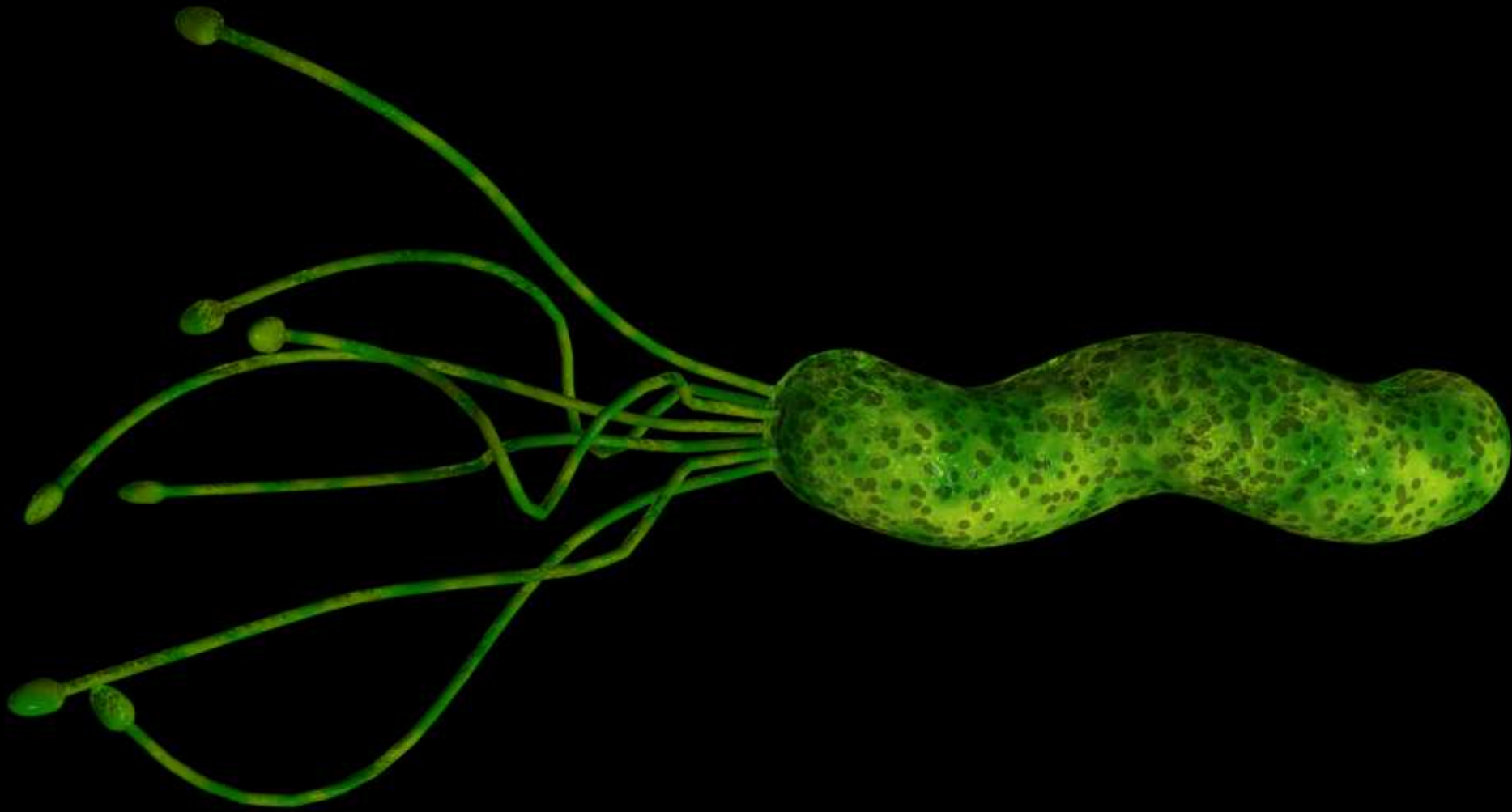
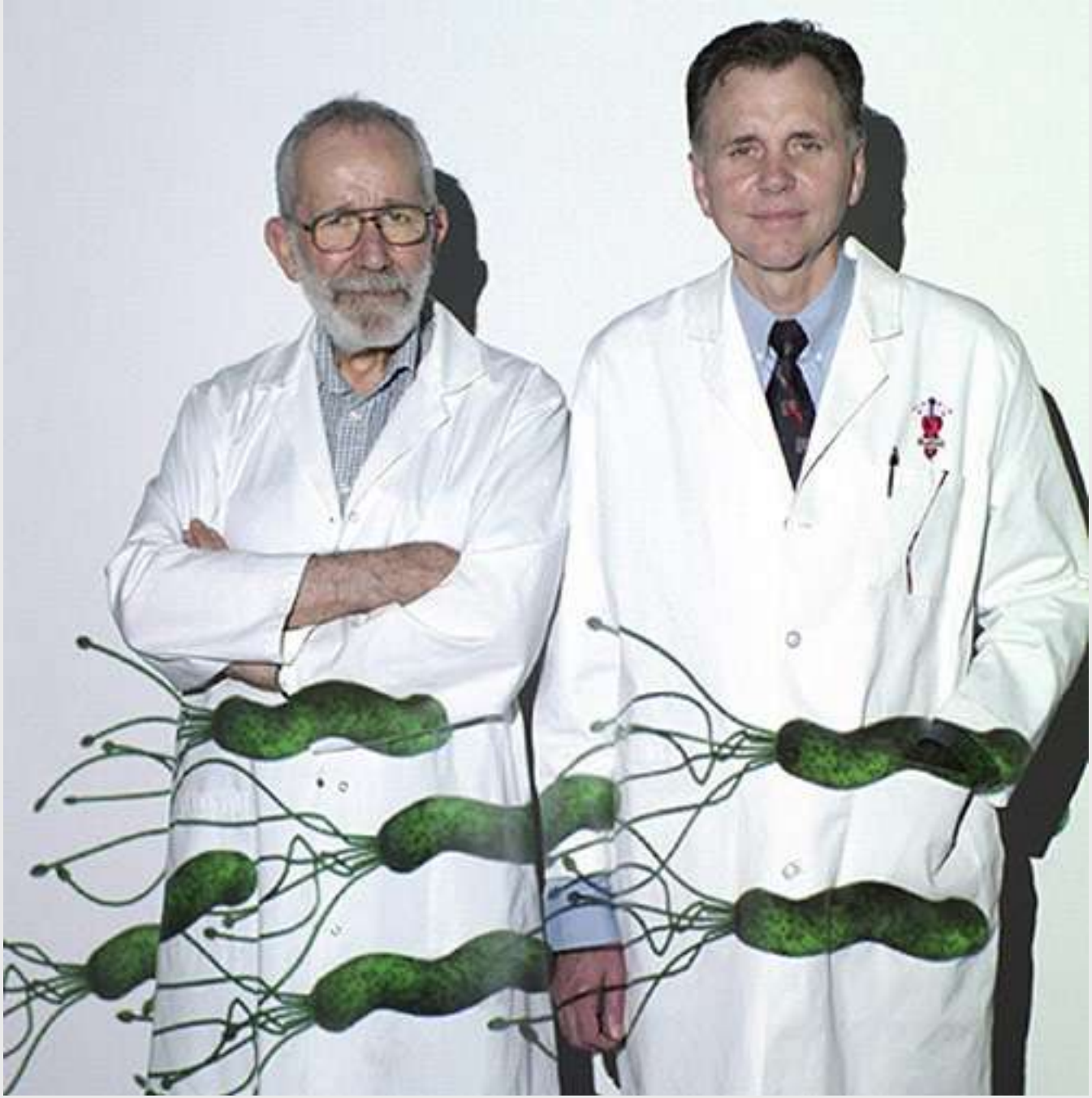
  - "Excess-acid theory" of peptic ulcer causation
    - Primarily due to diet and lifestyle factors
    - Non-specific causal mechanism
    - Symptomatic, chronic treatment (partially successful)
  - But, in 1979...







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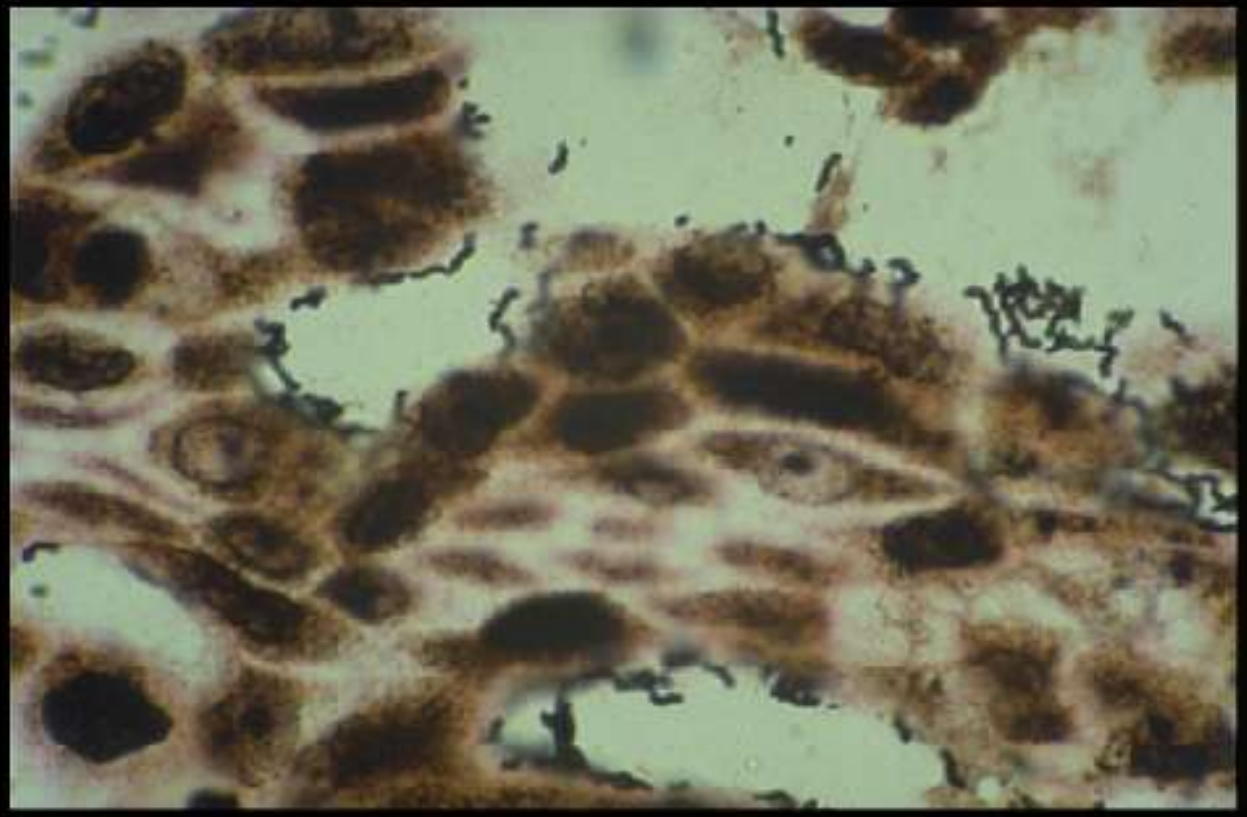
Case 2: *Helicobacter Pylori* and peptic ulcers

- Pre-1983
  - "Excess-acid theory" of peptic ulcer causation
    - Diet and lifestyle factors alone
    - Non-specific causal mechanism
    - Symptomatic, chronic treatment (partially successful)
  - But, in 1979...
    - *H. Pylori* discovered in gastric biopsies
    - ?causal...

Case 2: *Helicobacter Pylori* and peptic ulcers



Marshall, B.J., Armstrong, J.A., McGechie, D.B. and Glancy, R.J. 1985. "Attempt to Fulfill Koch's Postulates for Pyloric *Campylobacter," Medical Journal of Australia*. **142**: 436—9.

Case 2: *Helicobacter Pylori* and peptic ulcers

- So *H. Pylori* was determined to be the cause of many peptic ulcers
  - and netted Marshall and Warren the 2005 Nobel prize for Physiology
- But the causal mechanism was initially considered highly implausible...

Elements of implausibility

- Facts
  - No bacteria were detected in gastric tissue
- Mechanism
  - Existing treatments were partially successful, implying that the excess acid mechanism was correct
  - Other differences between gastric and duodenal ulcer pathophysiology count against common aetiology
- Generalisation
  - Bacteria can’t survive in the hostile environment of the stomach
  - Bacteria can’t cause this type of chronic disease, much less cancer