Mechanisms, Causation and the Russo-Williamson Thesis

Mechanism and Causality 2009

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UCL

The Russo-Williamson Thesis

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- Theoretical, rather than historical, thesis

The RWT as an empirical proposition

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- How well does the RWT conform to medical practice as seen in the recent history of medicine?

Why change the RWT?

- Causation without statistics
  - McArdle's syndrome
- Causation without mechanism
  - Hepatitis B infection and liver cancer
- Statistics and mechanism without causation
  - Non-causation of cervical cancer by herpes simplex virus

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1. That the requirement for statistical evidence needs weakening (to accommodate difference-making evidence)
2. That some account of the integration of mechanistic and statistical evidence might be given in terms of research methodology

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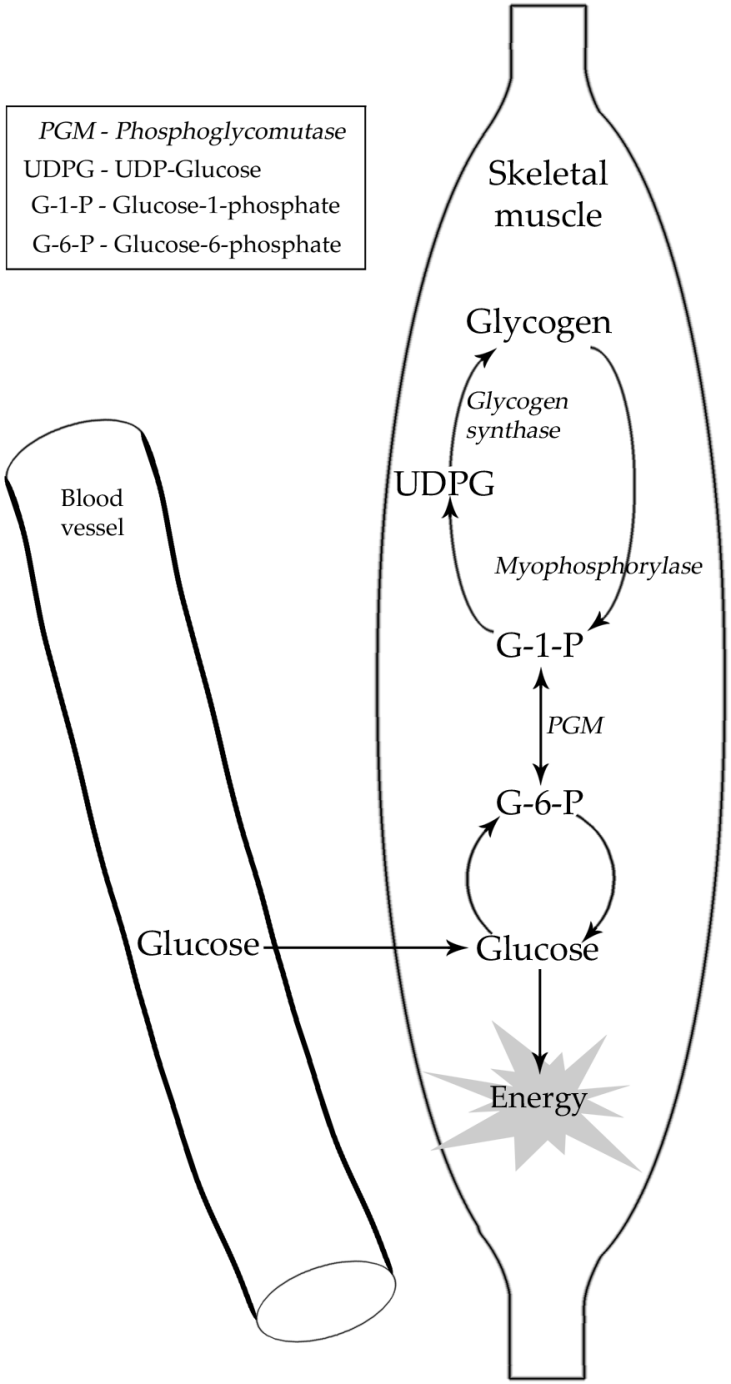
- Rare genetic disorder
- Tiredness and muscle pain on exertion
- Many (20+) mutations; one disease
- Caused by a functional absence of myophosphorylase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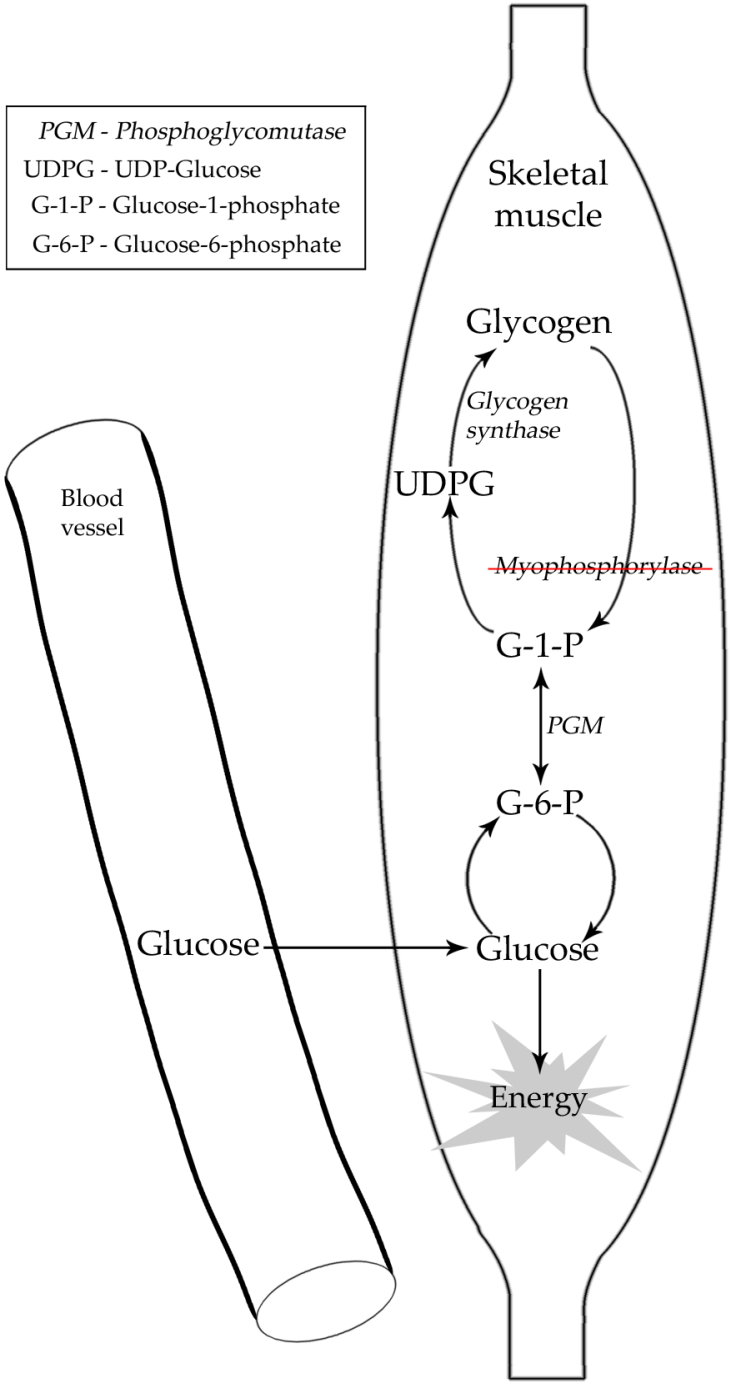
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- Larner and Villar-Palasi, 1959; Schmid and Mahler, 1959; Schmid et al., 1959; Schmid and Hammaker, 1961
  - Clinical course
  - Second wind phenomena
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- As an aside, this is a very similar position to early germ-theory causation, before developments in the importance of host factors in disease

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  - Of which statistical evidence will be the most common form

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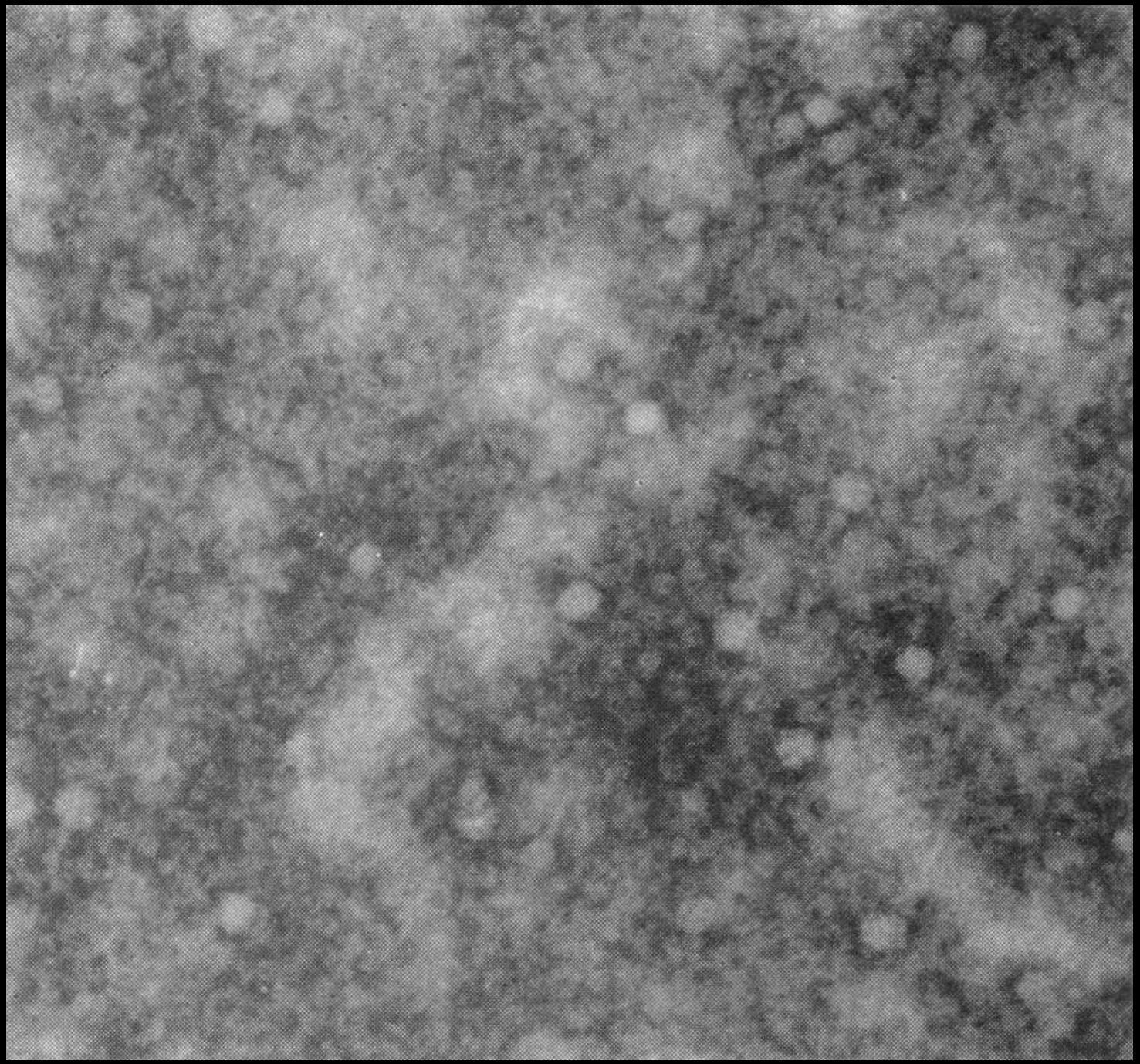

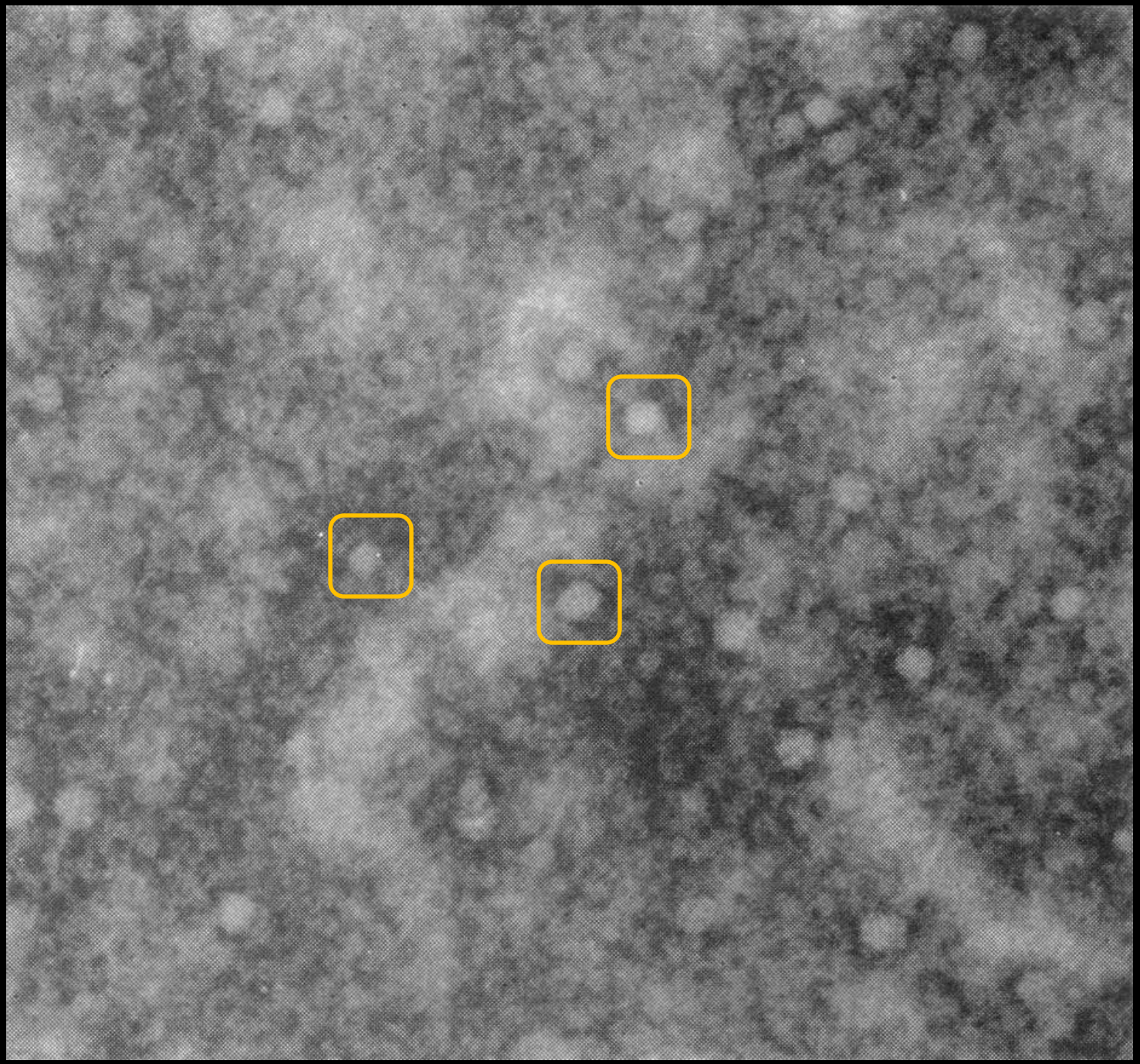

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  - Statistical correlation between HBV and HCC in diverse circumstances

Summary of epidemiological evidence for HBV causing HCC

- 1956 – first anecdotal report of correlation between HBV and HCC
- 1970s – correlation between chronic HBV infection and HCC statistically investigated
- Mid-1970s – complications: aflatoxin, direction of causation
- 1981 – RR of HCC given HBV vs no HBV 233:1
  - 22707 male HBV +/- Taiwanese civil servants [Beasley et al, 1981]

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http://en.wikipedia.org/wiki/File:Closeup_groundhog.jpg

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  - No specific oncogenic mechanism identified

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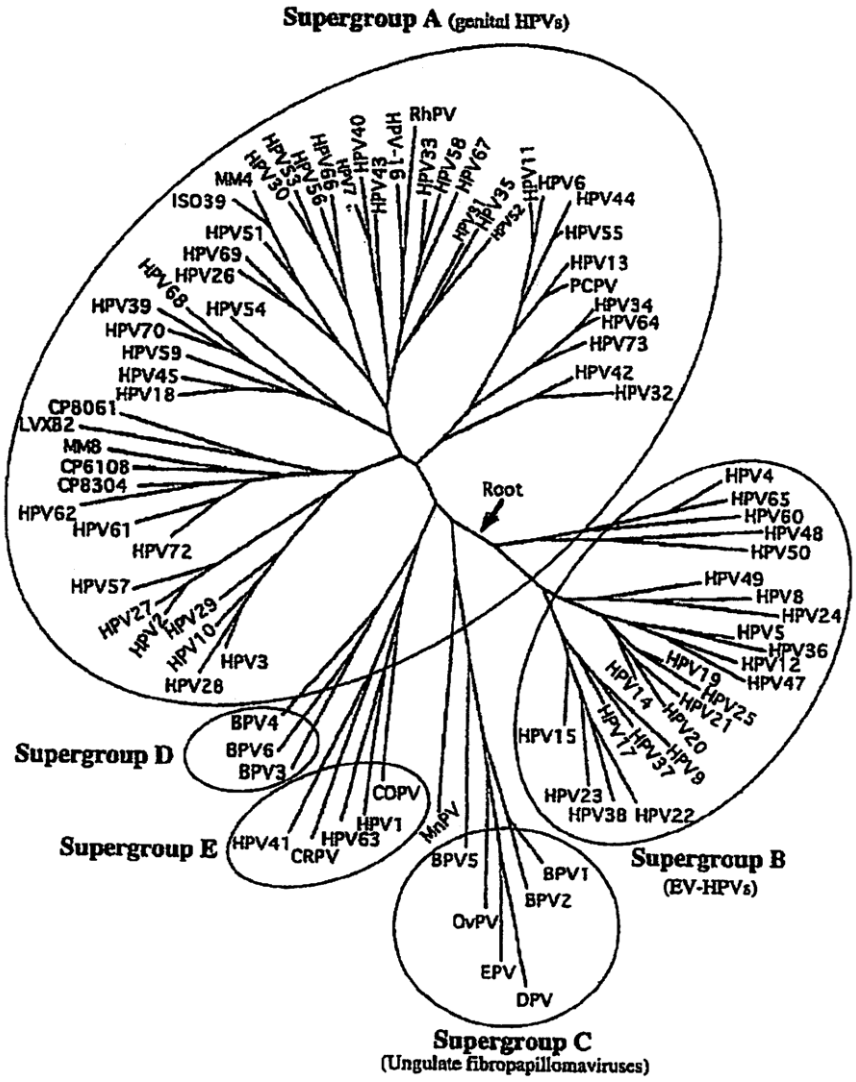
Example 3: Mechanism, statistics but no causation
Cervical cancer 1966—1983

HPV and cervical cancer [Lowy and Howley, 2001: 2232]



- Caused by infection with the human papillomavirus (HPV)
- Complex biology:
  - More than 110 types identified with varying propensity to cause cervical cancer
  - High-risk types
    - **16, 18, 31, 45**

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Phase 2: Evidence for herpes simplex virus as cause of cervical cancer

[Alexander, 1973: 1486]

1. HSV is a commensal organism
2. HSV is transmitted venerally
3. HSV is compatible with known risk factors, including:
    1. First coitus at early age
    2. Multiple sexual partners or promiscuity
    3. Low socioeconomic status
4. Herpes viruses are implicated in similar disease states
5. HSV is recoverable from some tumour cells

Phase 2: Herpesviridae cause many tumours

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)

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- Suggestion that the causal virus is HSV, partly by analogy with properties of other herpesviridae
- Attempts to generate evidence linking HSV and cervical cancer

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  - But not worse than many apparently correct causal claims (HBV-HCC...

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  - Publication bias renders much of this confusion invisible
  - Research programmes develop, but do not pose each other answerable questions

Ideally...

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- Integration of laboratory and epidemiological investigation in a recursive, interdependent process:
  - laboratory work guides epidemiology
  - epidemiology guides laboratory work
- Production of interdependent mechanistic and statistical evidence is required

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- Blind luck?
- Specific interventions versus general interventions

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(useful review text on the biomedical issues in viral oncogenesis)

Interaction: From mechanism to statistics

- Mechanisms give us grounds to epistemically partition our data
- Thus, features arising from mechanistic inquiry suggest the direction that statistical work should take
- Help with confounding

Interaction: From statistics to mechanism

- In turn, statistical results inform us of the applicability of our mechanisms
- For instance, is a (mechanistically discovered) aetiological pathway clinically significant for disease causation?