

The value of a strong trials infrastructure in supporting evidence based medicine

Raising standards in UK policy evaluation: 'Learning from the last 10 years'
HM Treasury 7th October 2008

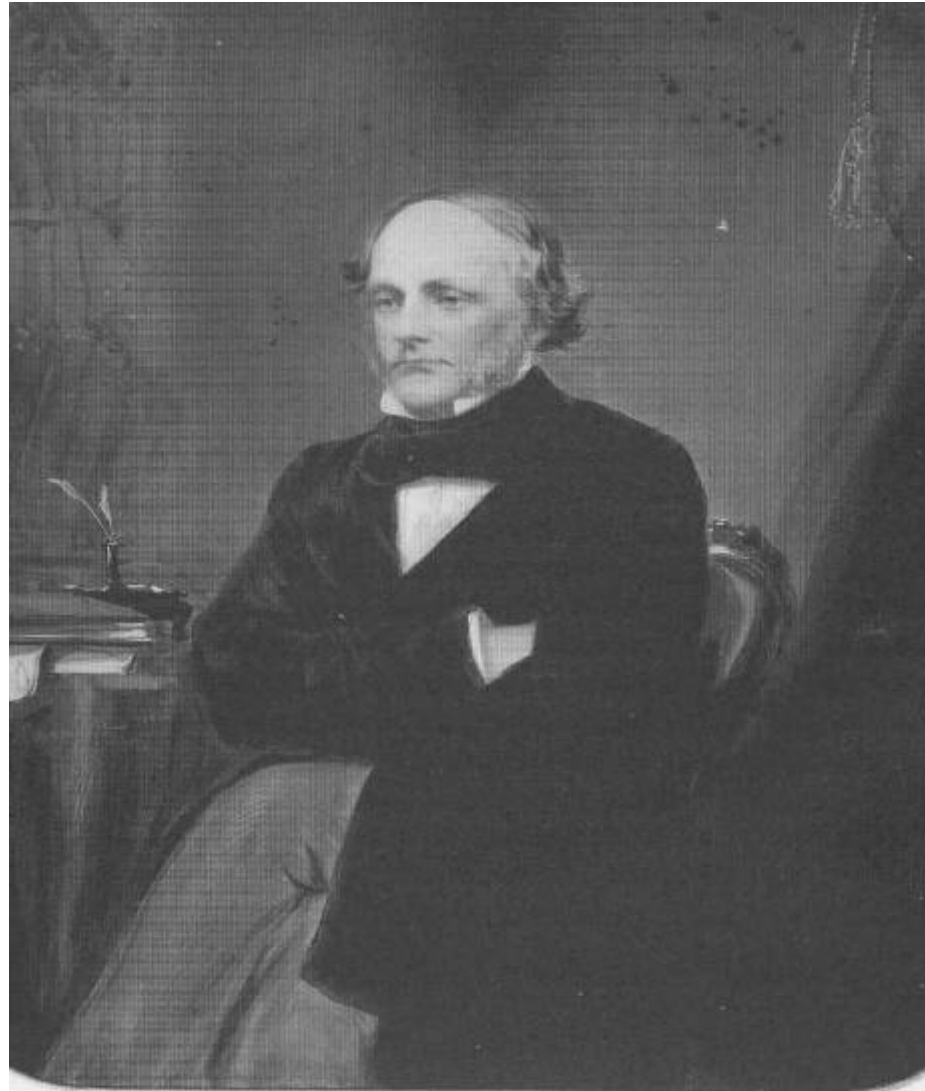
,

Professor Mike Kelly, PhD FFPH
Director, The Centre for Public Health Excellence, NICE

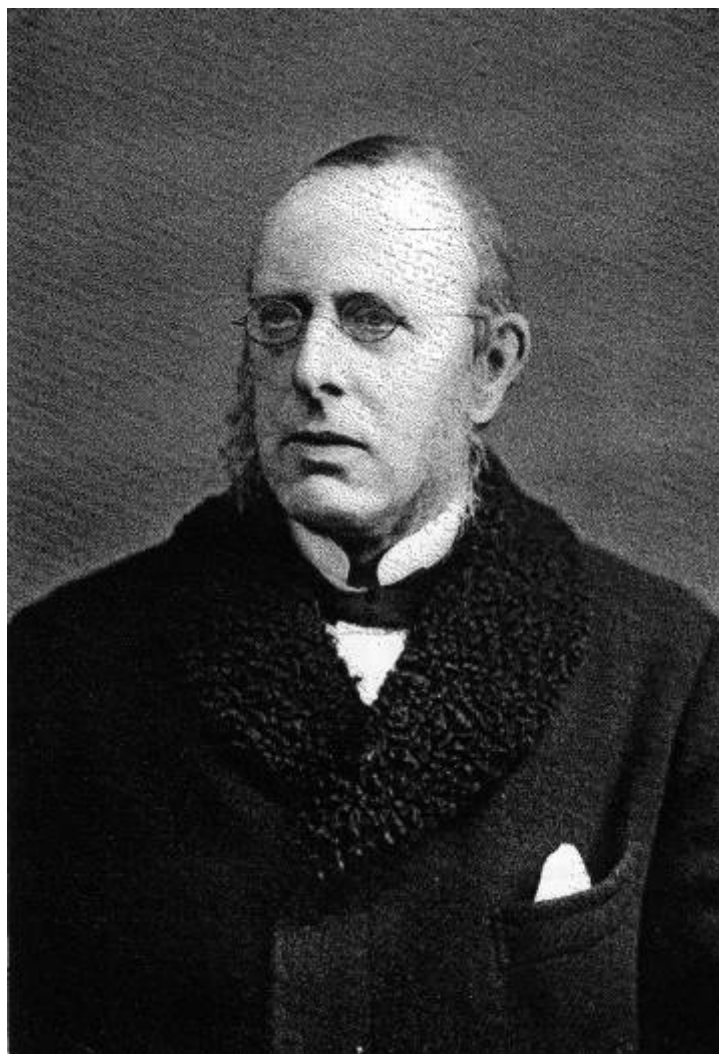
The clinical trial and the development of evidence based medicine

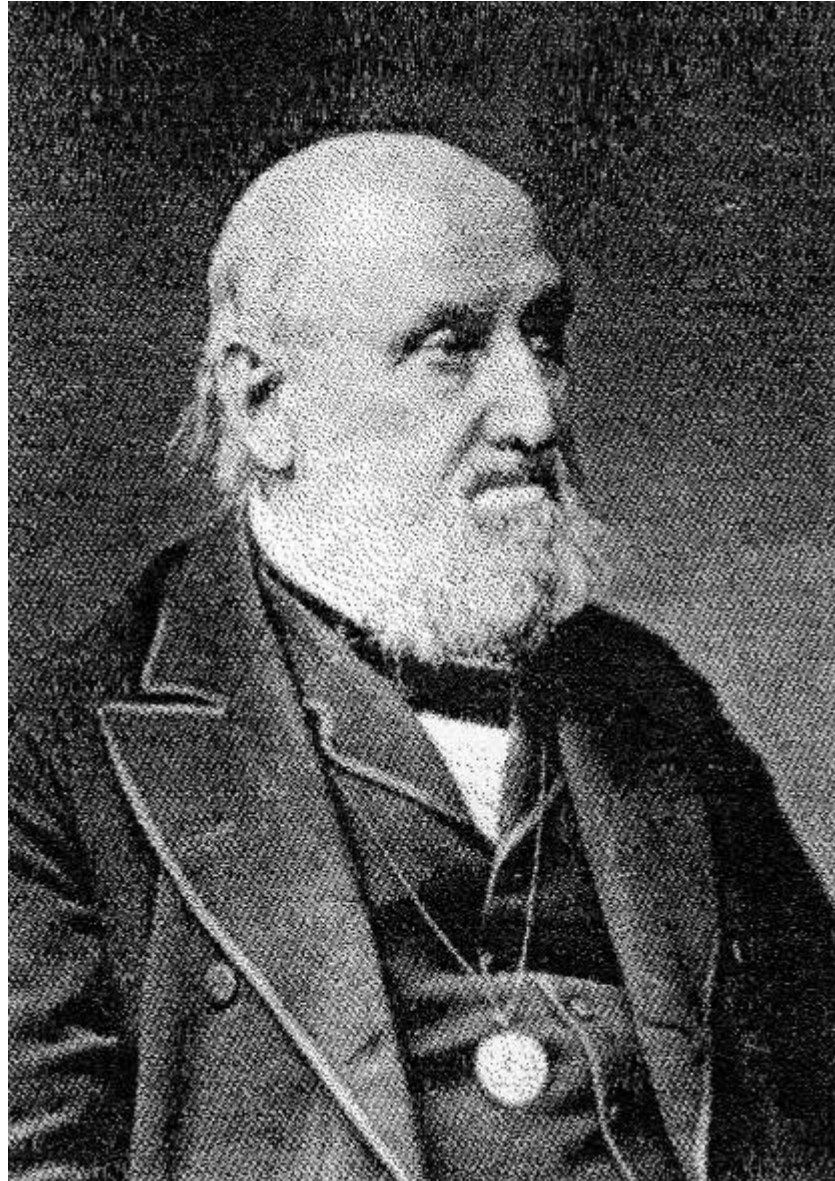
- The early pioneers - John Snow, William Tennant Gairdner, William Duncan, Edwin Chadwick, William Farr.





WILLIAM HENRY DUNCAN, M.D.
Medical Officer of Health, Liverpool, 1847–1863

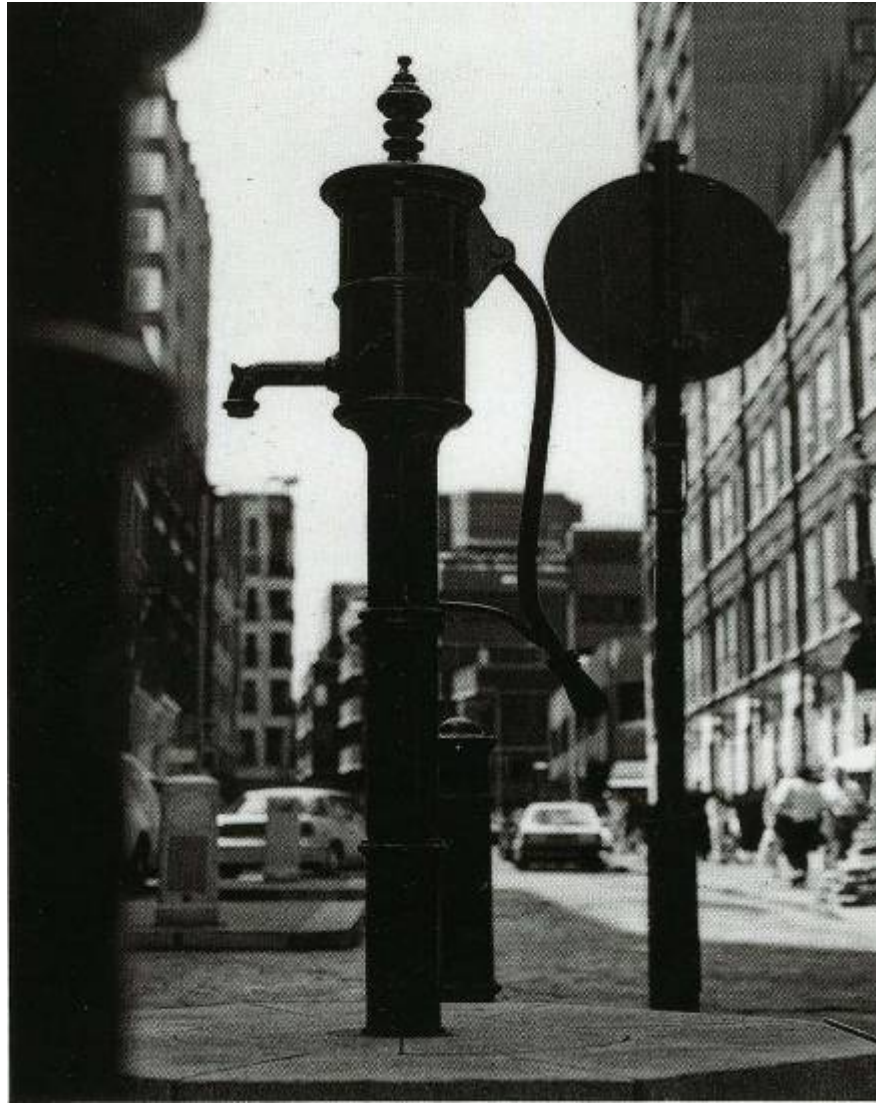






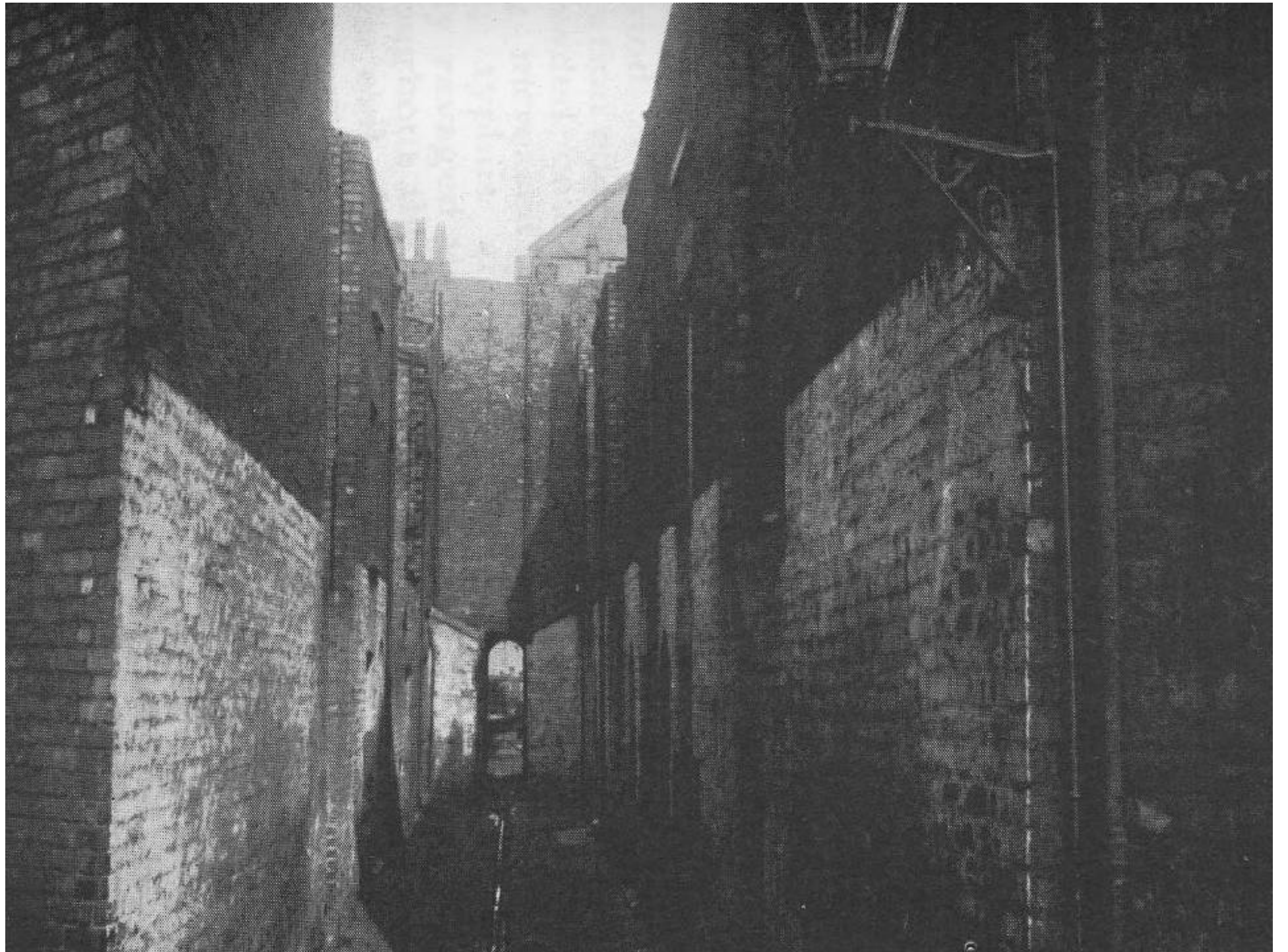
The classic period of public health

- **The development of causal models without necessarily understanding the mechanisms involved because empirical observation had yet to reveal the underlying causes (Snow, Duncan and cholera) .**
- **Social deprivation was seen both as a confounder and as a cause in itself (Chadwick, Gairdner) .**





A COURT FOR KING CHOLERA.



- **The statistical patterning of mortality and morbidity revealed major geographical differences (William Farr).**
- **The measurement of occupations and households from 1911 demonstrated health inequalities**

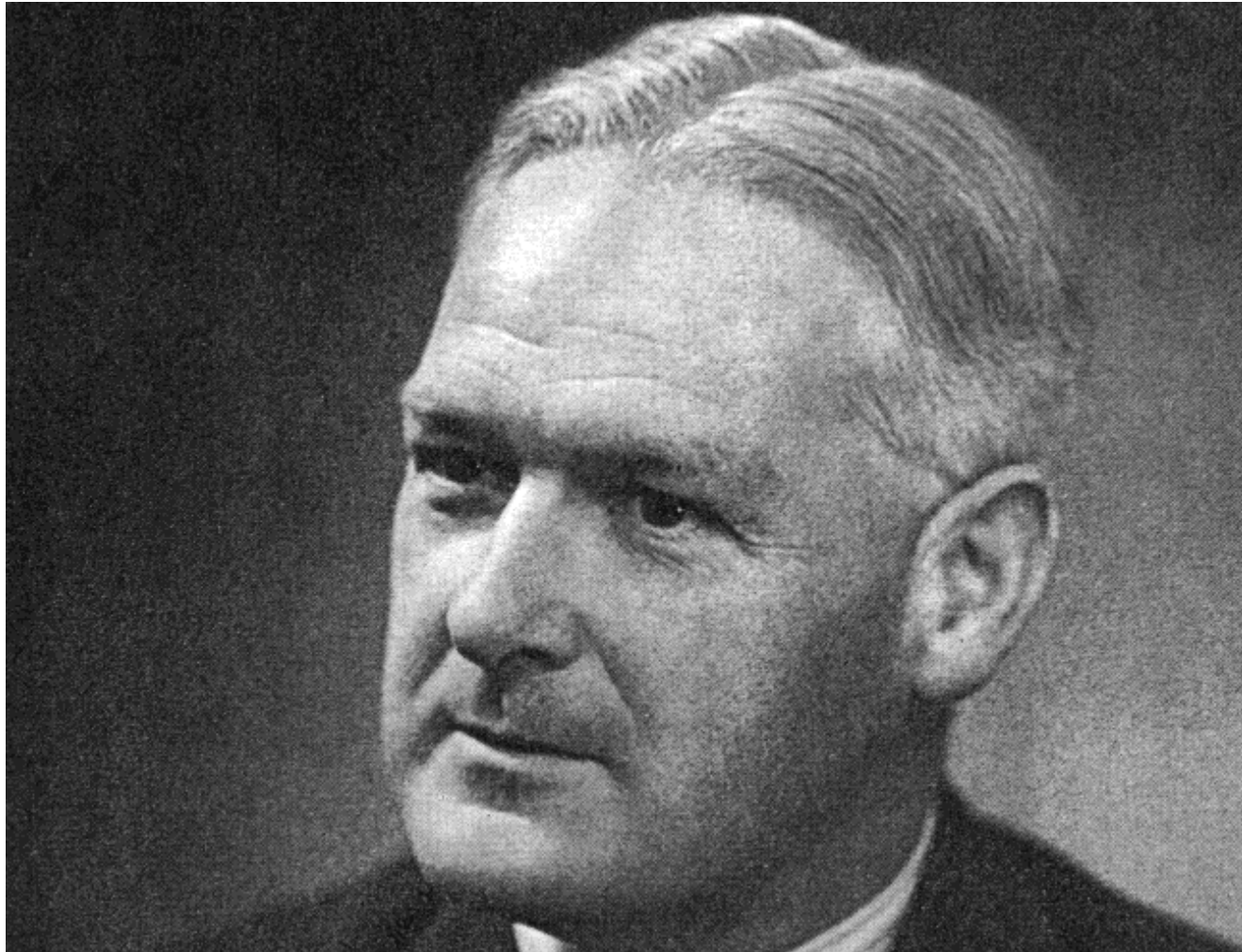
Implications

- **Causal agents**
- **Patterning by time place and person**

The emergence of epidemiology: time, place and person

- **Smoking and lung cancer Doll and Hill 1952**
- **Exercise and heart attack Morris et al 1953**
- **Asbestos and lung cancer Doll 1955**

Austin Bradford-Hill



Evidence based principles

- **Temporal sequence**
- **Strength of association**
- **Dose response relationship**
- **Replication.**
- **Biological plausibility.**
- **Alternative explanations.**
- **Cessation of exposure.**
- **Coherence with other knowledge.**
- **Specificity**

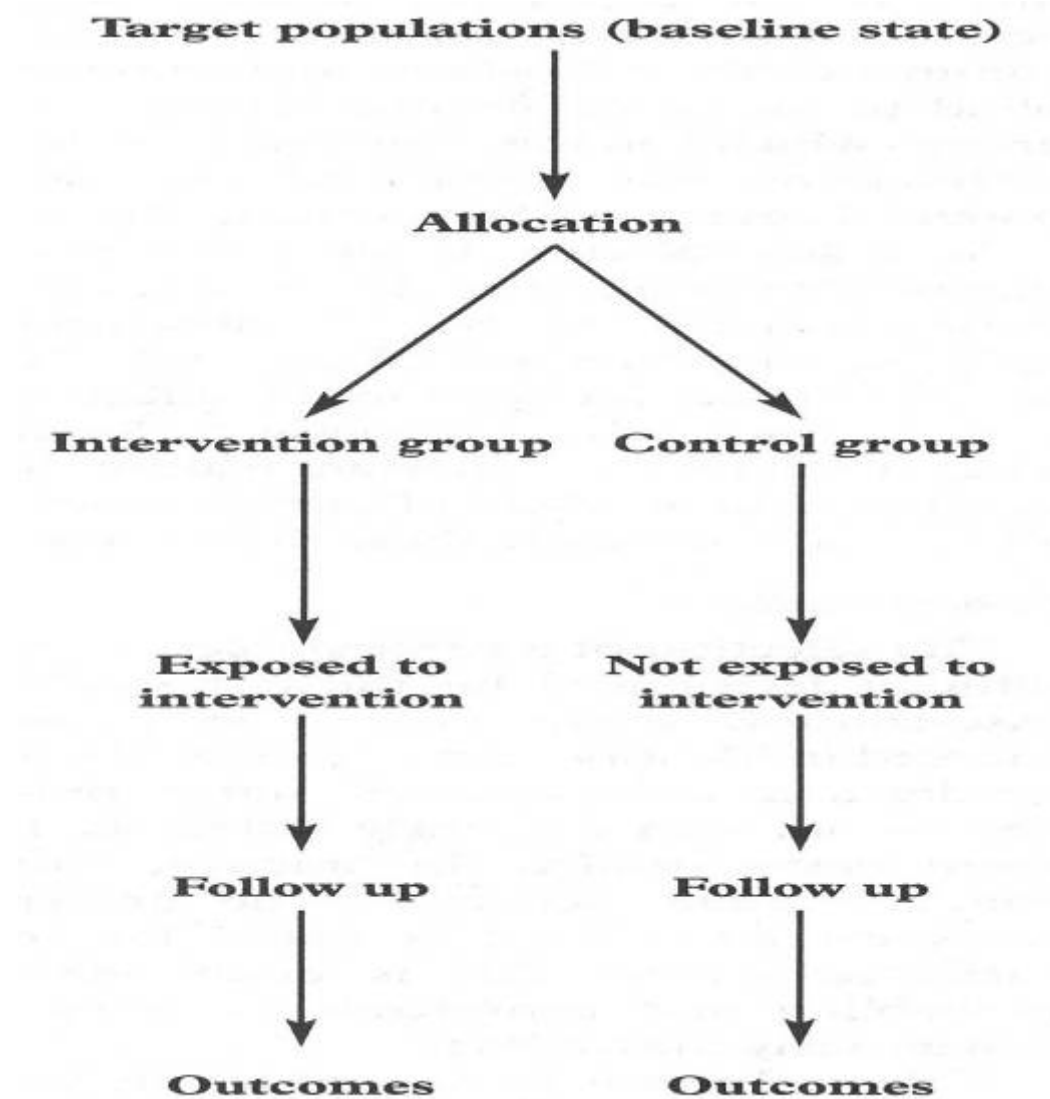
The Randomised Controlled Trial: Definition

- “A carefully and ethically designed experiment which includes the provision of adequate and appropriate controls by a process of randomisation, so that precisely framed questions may be answered”
A. Bradford-Hill

RCT: Principles

- **To evaluate a specific intervention or treatment.**
- **Individuals are assigned randomly to intervention or control group.**
- **This assures exposure is unbiased and comparability between the groups.**
- **Subjects and medical or other staff should be blind as to who is in the intervention group or the control group**

RCT Design



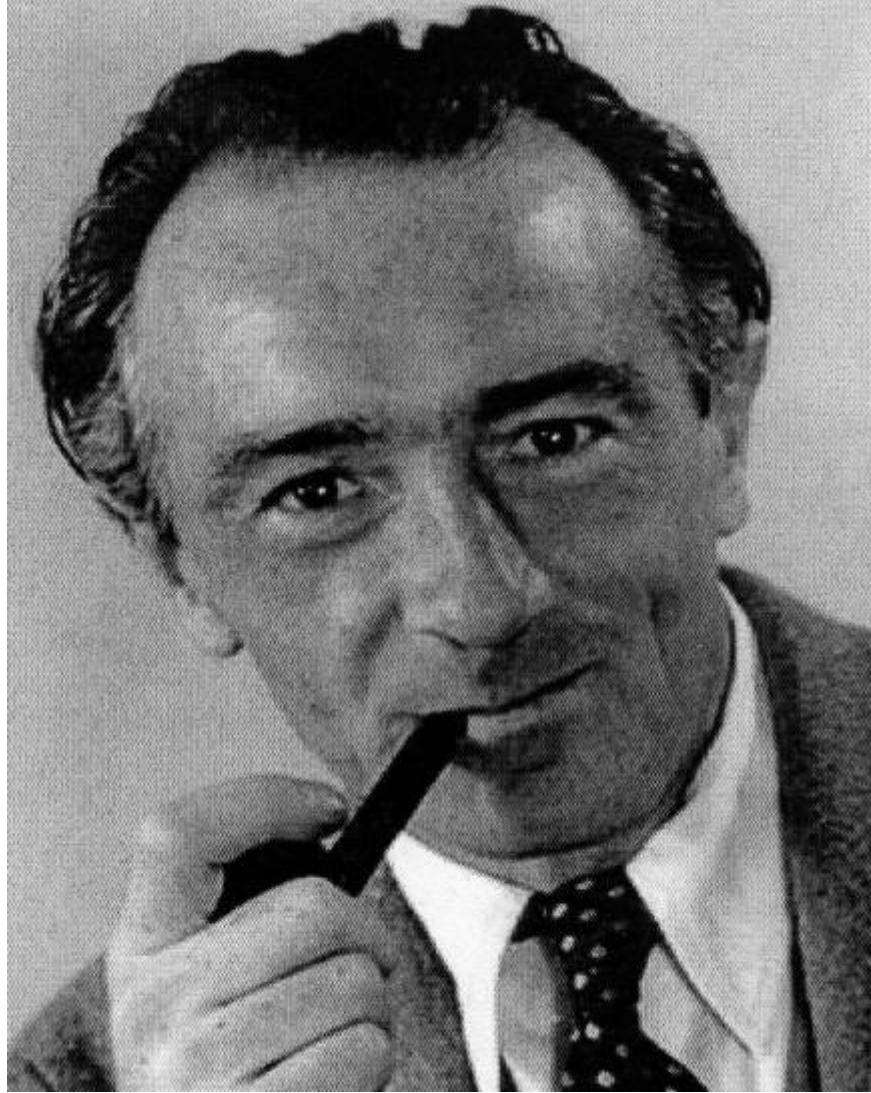
Assessing the results of an RCT

- **Was the allocation to intervention or control random?**
- **Was the allocation concealed?**
- **Were the intervention and control group similar in terms of factors that might affect the outcome?**
- **Were the health workers blinded as to which group was which?**
- **Apart from the intervention were both groups treated in the same way?**
- **Was analysis done on all subjects at the end?**

The early trials

- **Streptomycin for Pulmonary Tuberculosis 1948**
- **Whooping cough vaccine 1951**

Enter Archie Cochrane



- Cochrane, A.L.(1972) *Effectiveness and Efficiency: Random Reflections on Health Services*, British Medical Journal/Nuffield Provincial Hospitals Trust, London.

Archie Cochrane's recommendations

- The best care available to all
- The need for a means to determine what was the best treatment
- The importance of rooting out harmful or useless practice using scientific methods
- The solution – the RCT
- The necessity of ascertaining costs and benefits.
- The solution - health economics.

The legacy

- **The Cochrane (and Campbell) Collaborations**
- **NHS Centre for Reviews and Dissemination**
- **Health Evidence Bulletins Wales**
- **NICE**
- **The Cochrane Controlled Trials register**
- **Fast electronic search engines**
- **Systematic review and meta analysis**

Principles for building the trials evidence base

- **Cumulation**
- **Methodological rigour by reducing bias based on internal validity**

The hierarchy of evidence

- Systematic review and meta analysis
- RCTs
- Cohort studies
- Case control studies
- Cross sectional surveys
- Case reports
- Expert opinion

The value of the trials data bases

- **Data source independent of the pharmaceutical companies' evidence.**
- **Provides potential comparisons for new technologies.**
- **The fundamental building block for developing clinical guidelines.**
- **Helps to identify gaps in the evidence.**
- **Easily accessible to medical and other professionals.**
- **Can be used to inform practice and local decision making.**
- **Can be used to inform policy.**

Applying the principles more widely

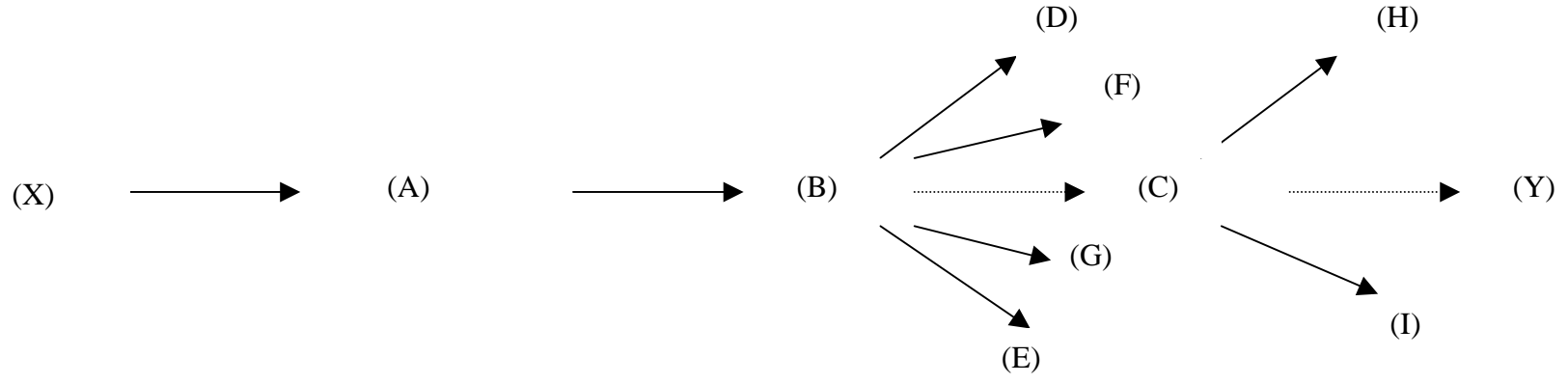
- **Evidence based public health.**
- **Where the causal relationship between the intervention and the outcome is distal**
- **Complex interventions in complex settings.**

The practical problems of applying the existing hierarchy of evidence in public health.

- **Very few Randomised Controlled Trials to go at the top of the hierarchy**
- **External validity at least as important in public health as internal validity**
- **Very difficult to measure the strength of evidence on a single dimension.**
- **At the very least we needed multiple hierarchies of evidence.**
- **The need to deal with theoretical evidence.**

The relationship between interventions and outcomes

- **Where X is, for example, advice about the dangers of being overweight and Y is weight loss.**



The relationship between interventions and outcomes

- **Long causal chains.**
- **Importance therefore of developing logic models to describe the relationship between interventions and outcomes.**
- **The existing evidence base silent on large tracts of the logic models.**
- **Key points in the logic model involves evidence of a type that had never been near an evidence hierarchy.**

Conclusion



“First come I; my name is Jowett.
There’s no knowledge but I know it.
I am master of this college:
What I don’t know isn’t knowledge.”

The Masque of Balliol
Revd. H.C. Beeching

- It is very important not to get stuck in a very narrow interpretation of what evidence based medicine means.
- Must not fall into the trap of assuming the evidence speaks for itself...

Because

- **All evidence requires interpretation.**
 - **Absence of evidence of effect does not necessarily mean there is no effect.**
 - **Strong evidence of effect may not relate to the important issue.**
-
- So.....

Interpreting the evidence of complex interventions requires an assessment of:

- **Plausibility: a scientific assessment – biologically, organizationally, socially, psychologically.**
- **Likelihood of success: the nature of local conditions married to tacit knowledge of practitioners**

And it is therefore important to:

- **Embrace a range of evidence**
- **Evidence from trials and from other sources of systematic investigation**
- **Evidence from practice**

But this is not new!!!!



Demonstrative reasoning and factual reasoning: Hume's fork

- **Demonstrative reasoning is deductive and involves relations between ideas and moral reasoning.**
- **This type of reasoning can proceed with absolute certainty based on the logical relations between ideas.**
- **Factual reasoning is inductive and involves drawing apparently reasonable but not logically certain conclusions based on the evidence, experience or testimony.**

- **To learn from what we have observed we must extrapolate beyond experience to draw out factual or inductive inferences from that which we have observed to that which we have not.**
- **Such inferences are contingent because the future may not resemble the past.**

- **In turn that is why guidance production in which demonstrative reasoning – the hierarchy of evidence and certain mathematical techniques masquerade as factual reasoning causes so much difficulty; and**
- **It is therefore an unsuitable basis on its own for making real world recommendations.**
- **So the building blocks of evidence based medicine are of fundamental importance, but we must not confuse their *a priori* principles with empirical observation and interpretation.**