Hierarchies of Evidence

Michael Rawlins

Honorary Professor, London School of Hygiene and Tropical Medicine

President, Royal Society of Medicine, London

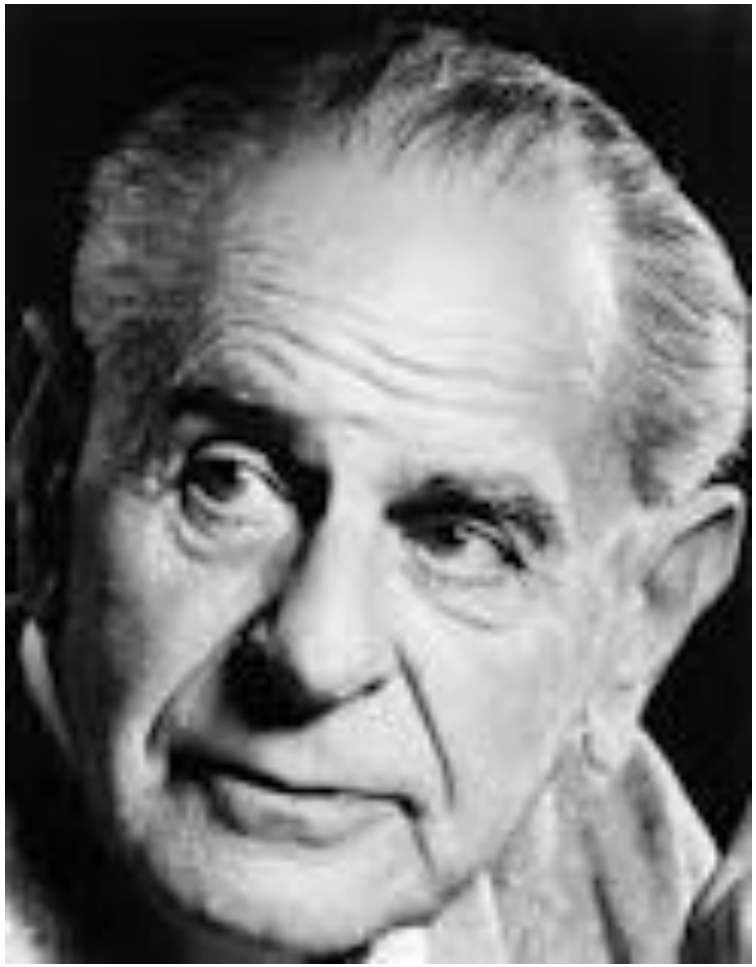
Experimentation-Deduction

Robert Hooke
1635-1703

Robert Boyle
1627-1691

Deductive Falsification

Sir Karl Popper
1902-1994

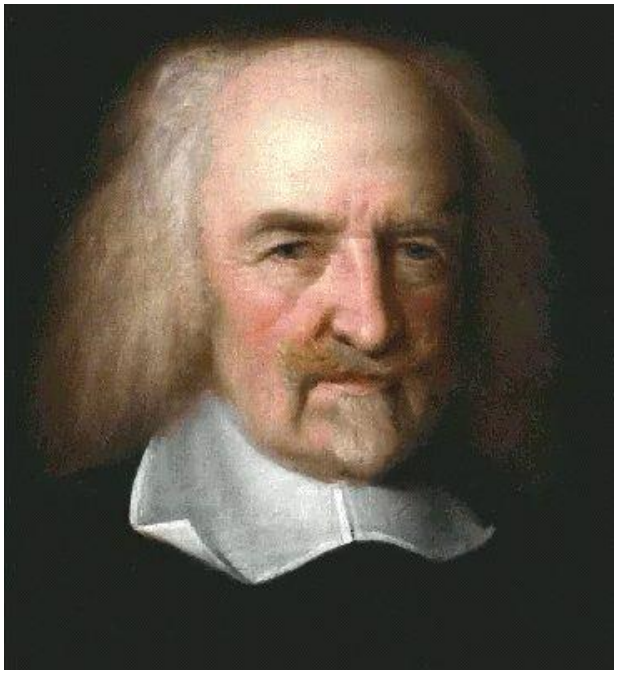


Observation-Induction

Francis Bacon
1561-1626

Rene Descartes
1596-1650

Thomas Hobbes
1588-1679



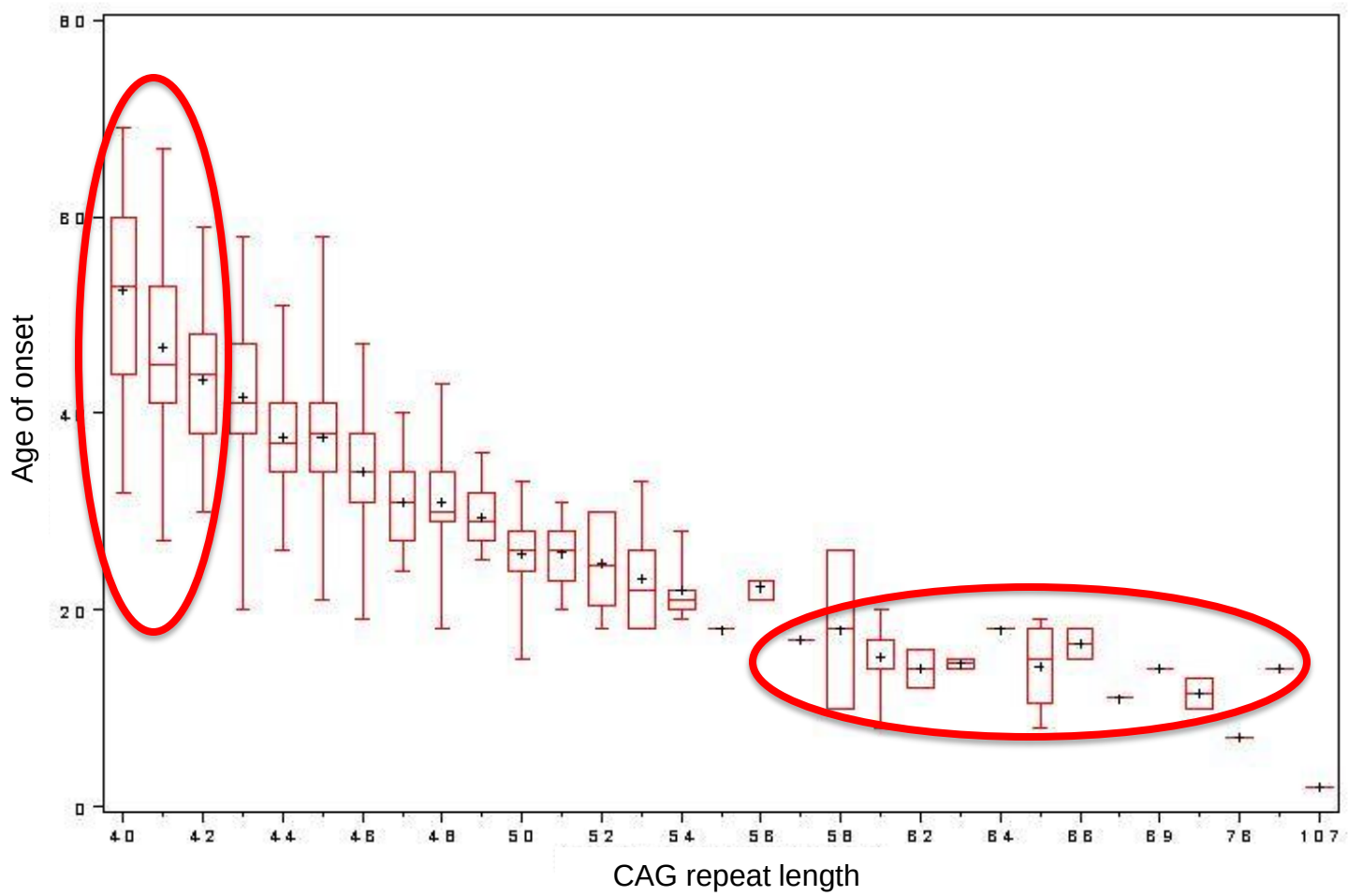
The Problem of Induction

"Probability is founded on the presumption of resemblance, betwixt those objects of which we have experience, and those of which we have not; and therefore 'tis impossible this assumption can arise from probability".

David Hume
1711-1778

Juvenile Huntington's disease

Age of onset of Huntington's disease



Richard Feynman

1918 - 1988

“Philosophers of science are as useful to science as are ornithologists to birds”

Hierarchies of Evidence

Level	Description
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1^{-}	Meta-analyses, systematic reviews of randomized controlled trials or RCTs with a high risk of bias.
2^{++}	High quality systematic reviews of case-control or cohort studies with a low risk of confounding, bias or chance and a high probability of causality
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a significant chance that the relationship is not causal.
2^{-}	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.
3	Non-analytical studies (for example case records, case series)
4	Expert opinion, formal consensus.

Harbour R, Miller J (2001)

BMJ

Helping doctors make better decisions

EDITORIALS

Observational evidence for determining drug safety

Is no substitute for evidence from randomised controlled trials

"Only properly randomised trials can provide truly reliable evidence on adverse events, just as these are the only convincing data on drug efficacy".

"Observational studies may provide some limited reassurance that a drug is safe, or they may provide an early indication of a problem, but by design they cannot provide reliable evidence on questions of drug safety".

Freemantle N, Irs A. BMJ 2008;336:627

Safety of thiazolidinediones

	Rosiglitazone (OR and 95% Cis)	e 5% Cis)
Death - all causes - cardiovascular causes	1.18 (0.8 1.64 (	.92 (0.76 to 1.11) -
Myocardial infarction	3 to 1.98)	0.81 (0.64 to 1.02)
Stroke	-	0.80 (0.80 to 1.04)
Compos troke)	-	0.82 (0.72 to 0.94)

and Wolski 2007; Lincoff et al 2007

Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE)

The TIDE study

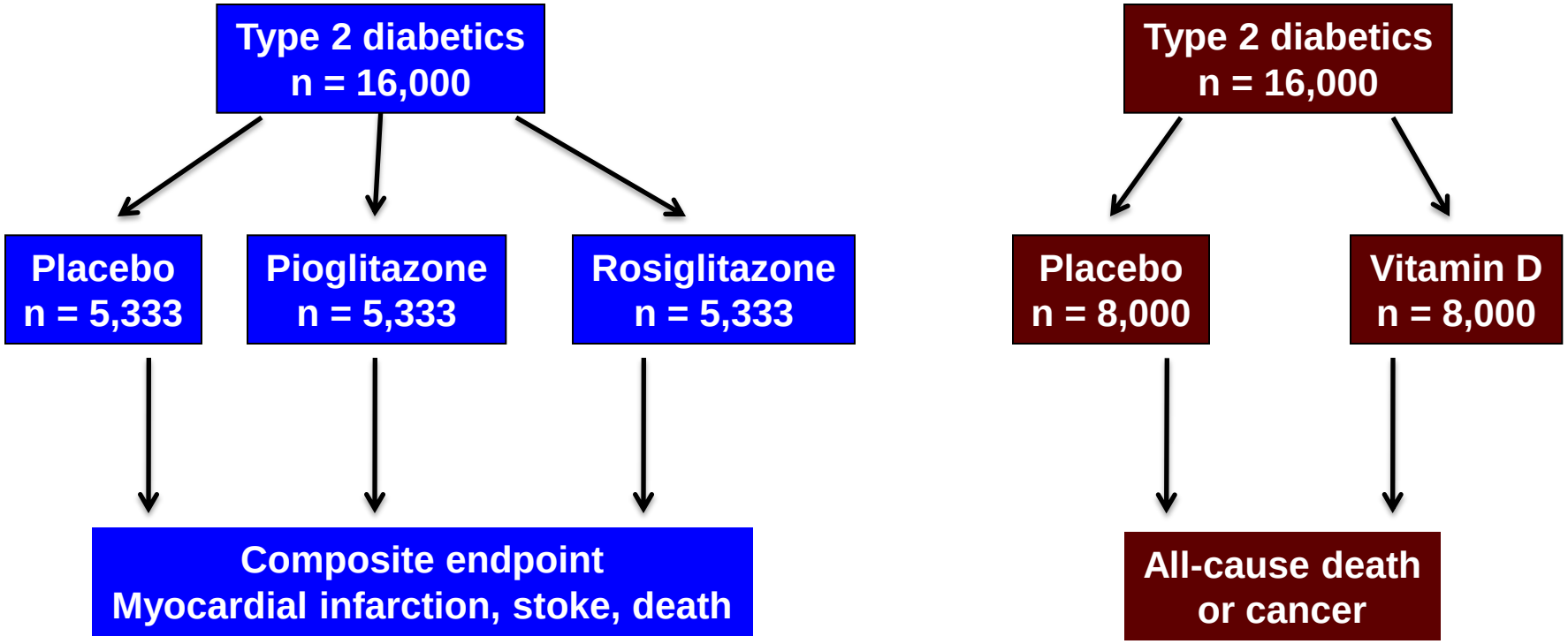
Primary objectives

1. To test the cardiovascular effects of long-term treatment with rosiglitazone or pioglitazone.

2. To compare the effects of long-term vitamin D supplementation on death and cancer.

The TIDE study

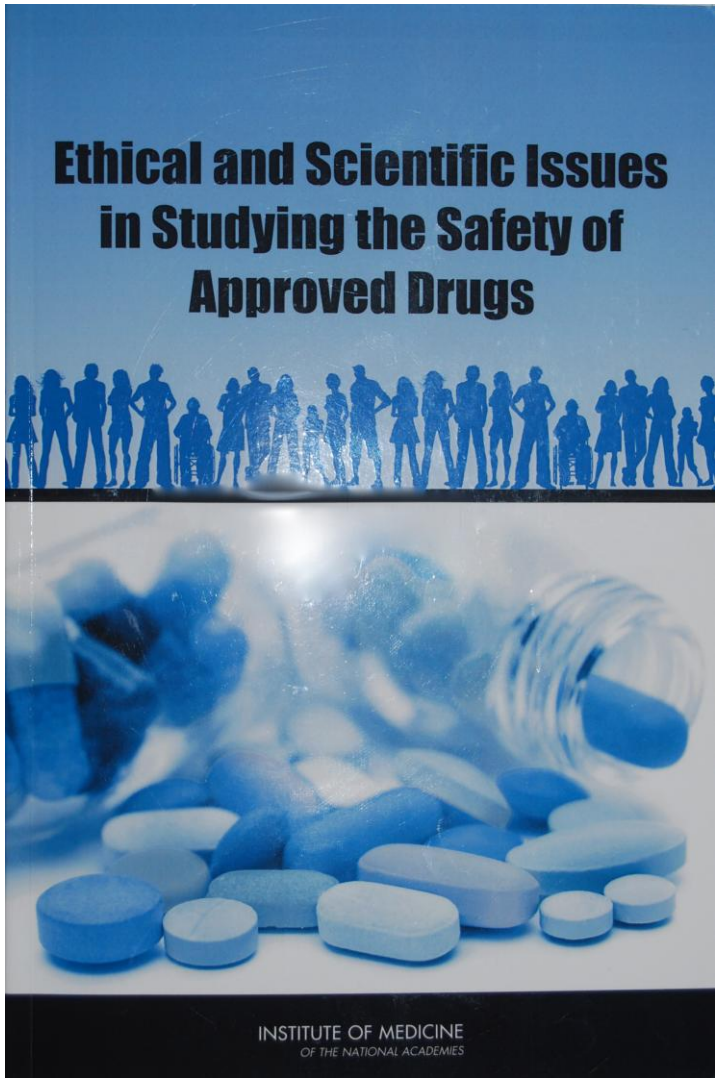
Design



The IoM Review

Such trials only justified if:

- they answer critically important public health questions;
- the potential risks are acceptable and minimised;
- there is explicit informed consent.



Randomised Controlled Trials

Randomised Controlled Trials

Strengths

1. Minimises bias
2. Minimises confounding
3. Minimises random error

Alfie

Randomised controlled trials

Weaknesses

1. Statistical issues
2. Generalisability
3. Resource implications

Statistical Issues

The Frequentist Approach

The null hypothesis is tested by estimating the probability of obtaining a result as extreme or even more extreme, as the one observed, were the null hypothesis to be true.

Statistical Issues

The null hypothesis

1. **Definition of "extreme"**
   - Arbitrary
   - Inconsistent

2. **Ignores previous studies**
   - Drug development
   - Previous trials

3. **Clumsy**
   - Equivalence
   - Non-inferiority
   - Futility (!)

Statistical Issues

Multiplicity

Multiple testing:

- Interim analyses
- Subgroup analyses
- Safety analyses

Generalisablity

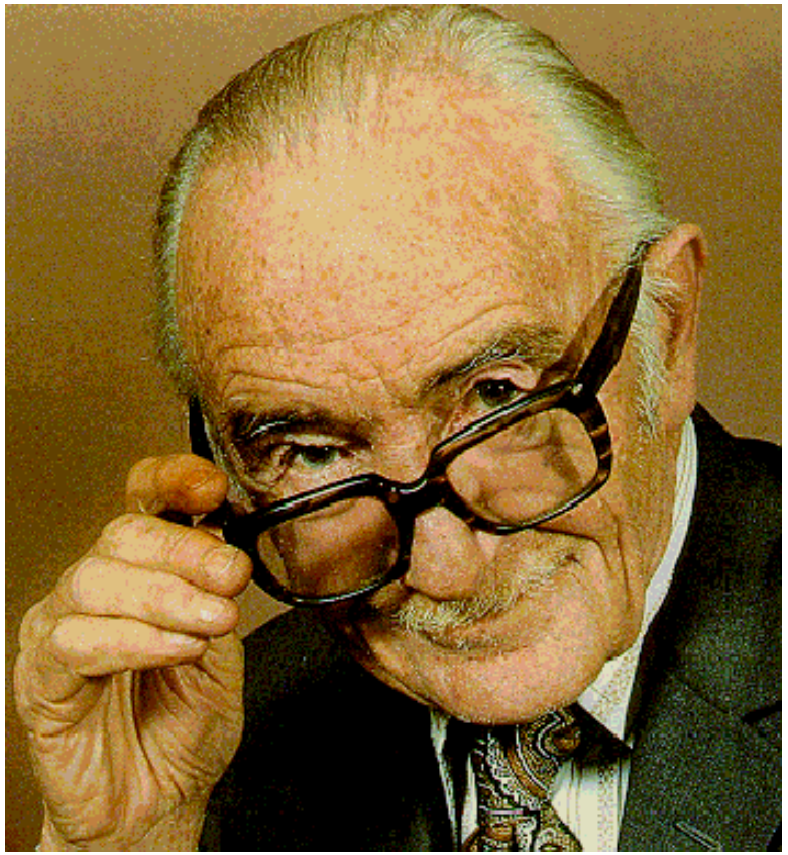
Main problems:

1. Relatively small patient numbers
2. Homogeneous patient population
3. Limited period of time
4. Under-representation
   - Young
   - Elderly
   - Ethnic minorities
   - Co-morbidity

Archie Cochrane

(1908-1988)

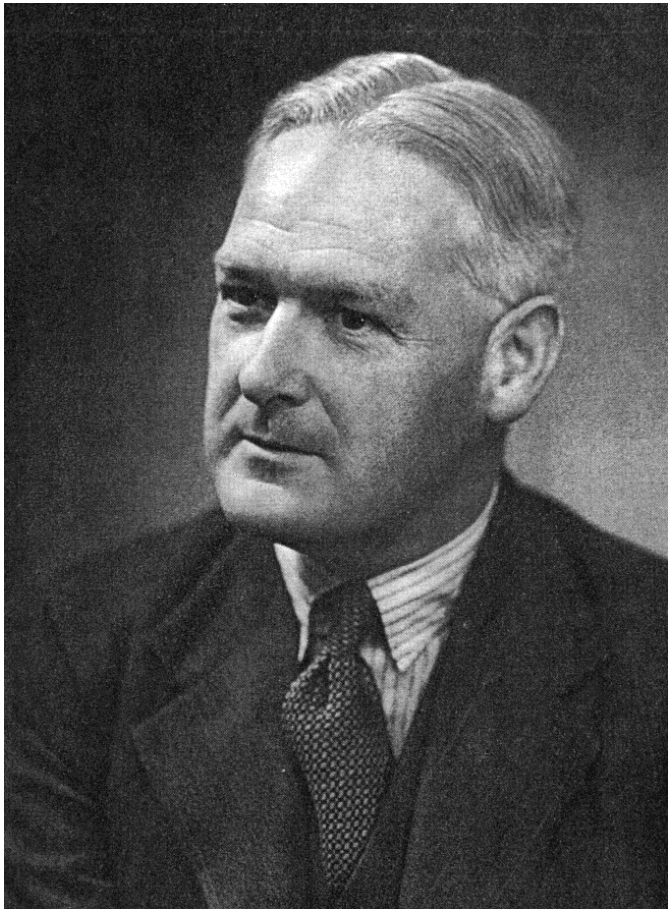
"Between measurements based on randomised controlled trials and benefit in the community there is a gulf which has been much under-estimated".



Sir Austin Bradford Hill

(1897-1991)

"Any belief that the controlled trial is the only way would mean not that the pendulum had swung too far but that it had come right off the hook".



Solutions?

1. Pragmatic trials.
2. More active comparator trials.
3. Greater use of Bayesian approaches.
4. Increasing dependency on observational studies (pharmacoepidemiology)

Thomas Bayes

(1701-1761)

Bayesian Statistics

What's the Problem?

1. Statistical prejudice
2. The concept of subjective probability
3. Establishing priors
4. Computationally difficult
5. Drug regulatory authority resistance
6. Some statisticians can’t do it

Observational approaches

1. Historical controlled trials
2. Case-control studies
3. Concurrent cohort studies
4. Before-and-after designs
5. Databases/registries
6. Case reports

Observational Studies
Strengths

- Assessment of benefits
- Assessment of harms
- Generalisability

Observational Studies
Weaknesses

- Selection bias
- Confounding by indication

Historical Controlled Trials

Comparison(s) between:

- A group of patients treated with a (usually) new intervention
- A “historical” cohort (implicit or explicit)

Historical Controlled Trials

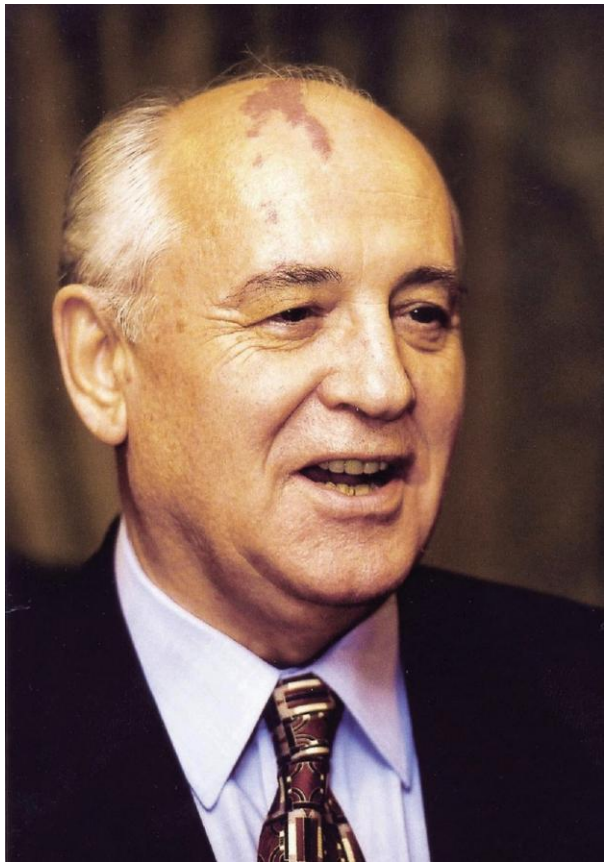
Evidence of Benefit

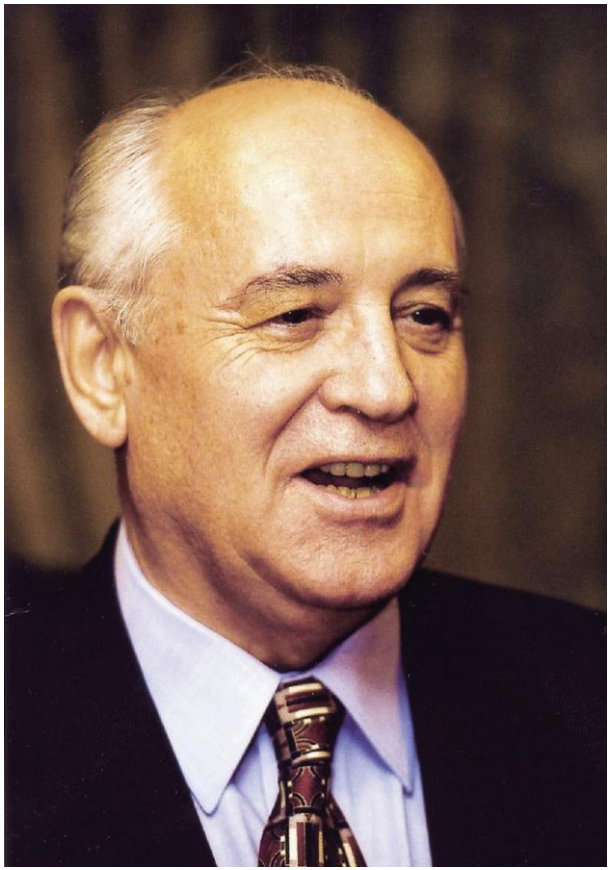
Intervention	Indication
Thyroxine (1891)	Myxoedema
Streptomycin (1948)	Tuberculous meningitis
Defibrillation (1948)	Ventricular fibrillation
Ganglion blockers (1959)	Malignant hypertension
Oestrogen + progestogen (1960)	Oral contraception
N-acetylcysteine (1979)	Paracetamol poisoning
Ganciclovir (1986)	CMV retinitis
Imiglucerase (1990)	Gaucher's disease
Laser therapy (2000)	Port wine stains
Imatinib (2002)	Chronic myeloid leukaemia
Imatinib (2005)	Gastrointestinal stromal tumours

Cytomegalovirus retinitis

Ganciclovir

Port wine stains





Historical Controlled Trials

Criteria for Acceptance

1. Biological plausibility
2. No reasonable comparator
3. Predictable natural history
4. Adverse effects not expected to compromise benefits
5. Substantial effect size (signal-to-noise ratio)

Case-control studies

Harms

Intervention	Harm
Oral contraceptives	Venous thromboembolism
Diethylstilboestrol in pregnancy	Genital tract cancer (in offspring)
Non-steroidal anti-inflammatory drugs	Upper gastro-intestinal bleeding
Aspirin in children	Reye's syndrome
Hormone replacement therapy	Venous thromboembolism
Hormone replacement therapy	Breast cancer
Anticonvulsants	Stevens-Johnson syndrome
Olanzepine	Diabetes mellitus
Fluoroquinolones	Ruptured Achilles tendon
Biphosphonates	Atypical femoral fractures

Some pharmacogenetic associations

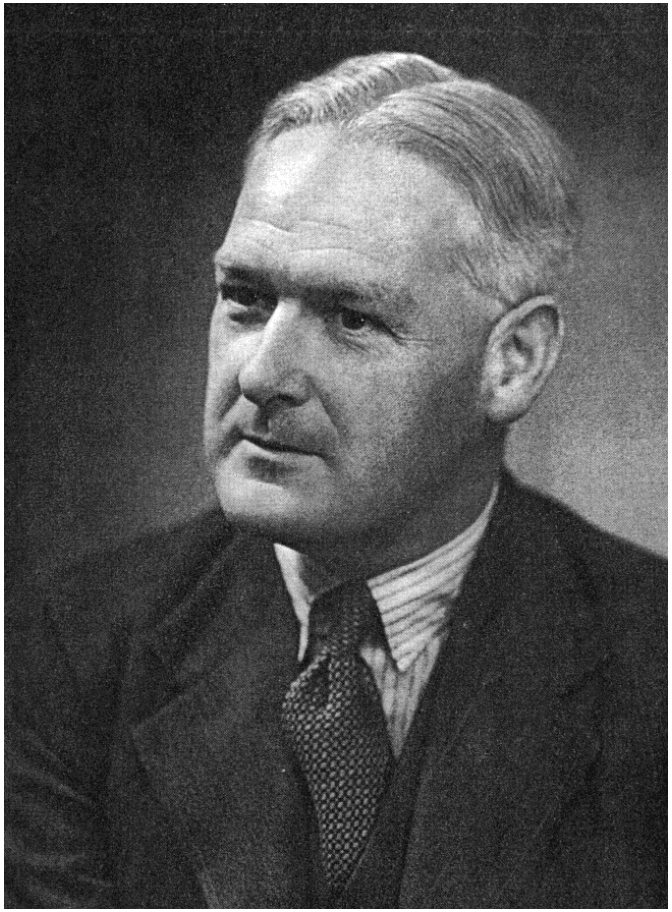
Genetic marker	Population prevalence	Drug	Adverse reaction
HLA-B*3101	2-5%	Carbamazepine	Hypersensitivity
HLA-B*5701	5-9%	Abacavir	Hypersensitivty
HLA-B*5701	5-9%	Flucloxacillin	Hepatitis
HLA-DRB1*1501	21.4%	Co-amoxiclav	Cholestasis
HLA-B*1502	5-12% (Asians)	Carbamazepine	Stevens-Johnson syndrome
HLA-B*5801	0.2%	Allopurinol	Stevens-Johnson synrome Toxic epidermal necrolysis
m.1555A>G	0.2%	Aminoglycosides	Permanent deafness
Factor V Leyden mutation	≈5% (Caucasians)	Oral contraceptives	Venous thromboembolism

Sir Austin Bradford Hill

(1897-1991)

“I cannot be certain that the sun will rise every morning for the next month.

But I am sufficiently confident to have purchased a monthly season ticket to get me to work each day”.



Hierarchies of evidence

Level	Description
1a	Systematic review of randomised controlled trials with homogeneity
1a-	Systematic review of randomised controlled trials worrisome heterogeneity
1b	Individual randomised controlled trial with narrow confidence interval
1c	All or none effects
2a	Systematic review of cohort studies with homogeneity
2a-	Systematic review of cohort studies with worrisome heterogeneity
2b	Individual cohort study including randomised controlled trials with < 80% follow-up
2c	Outcomes research or ecological studies
3a	Systematic review of case-control studies with homogeneity
3a-	Systematic review of casecontrol studies with worrisome heterogeneity
3b	Individual case-control studies
4	Case series and poor quality cohort or case control studies
5	Expert opinion without explicit critical appraisal; or based on physiology or “first principles”

William Blake

(1757-1827)

"God forbid that truth should be confined to mathematical demonstration"