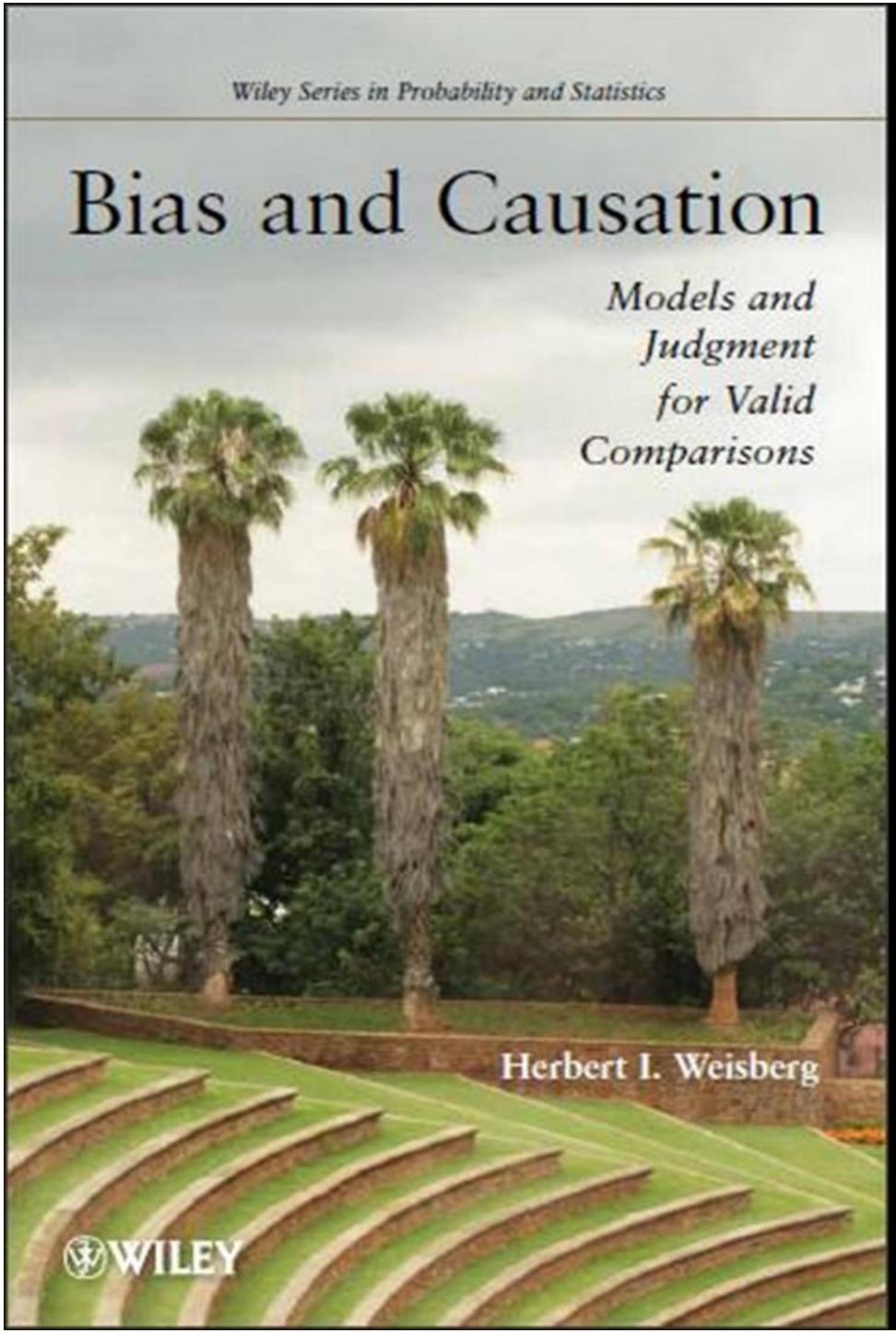
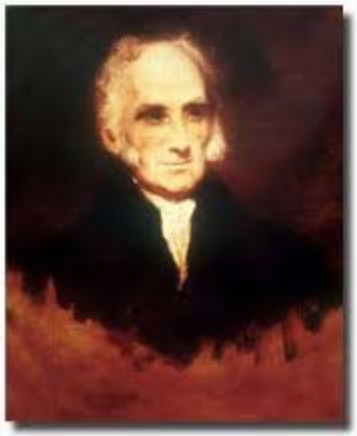


Medical Statistics and Causation

Past, Present & Future

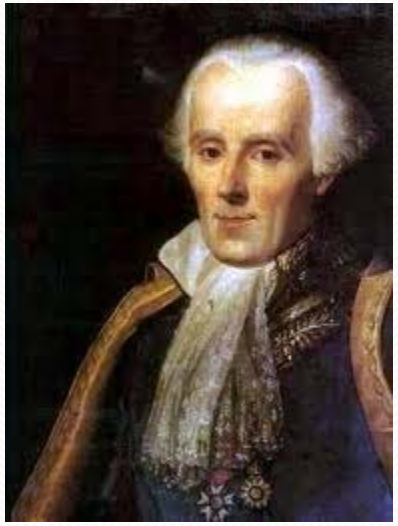
Herbert I. Weisberg, Ph.D.
Correlation Research, Inc.

Sir Gilbert Blane (1785)



There is . . . a great difficulty attending all practical inquiries in medicine; for in order to ascertain truth, … there must be a series of patient and attentive observations upon a great number of cases, and the different trials must be varied, weighed, and compared, in order to form a proper estimate of the real efficacy of different remedies and modes of treatment.

Pierre-Simon de Laplace (1825)



Thus, to discover the best treatment to use in curing a disease, it is sufficient to test each treatment on the same number of patients, while keeping all [other] circumstances perfectly similar. The superiority of the most beneficial treatment will become more and more evident as this number is increased.

Claude Bernard (1865)

The results of statistics, even statistics of large numbers, seem indeed to show that some compensation in the variations of phenomena leads to a law; but as this compensation is indefinite, even the mathematicians confess that it can never teach us anything about a particular case.

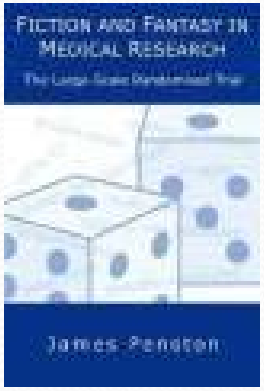
R.A. Fisher and A.B. Hill (1925-)

Sir Austin Bradford Hill

Randomized Controlled Trials

Tests of statistical significance

James Penston (2003)

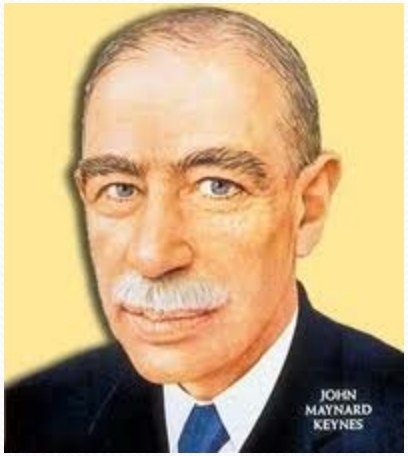


…we should place more emphasis on the identification of relevant variables…Step by step more homogeneous groups of patients would be available for recruitment to clinical trials…This approach…would tend to produce more homogeneous study populations, thus allowing trials of new drugs to demonstrate large, clinically meaningful differences…Defenders of the status quo would , no doubt, assert that it is not possible to identify the relevant variables …Yet this is a sad indictment of current medical research and ought to provide the impetus for change.

Causality

- Individual effects vs. population “average”
- The underlying causal process
- Asking better questions
- The relevant reference class for an individual

John Maynard Keynes (1921)



…we must be clear as to what we mean by saying that a probability is *unknown*. Do we mean unknown through lack of skill in arguing from given evidence, or unknown through lack of evidence? The first alone is admissible, for new evidence would give us a new probability, not a fuller knowledge of the old one.

Jacob Bernoulli (1713)

Remote and universal arguments are sufficient for making judgments about universals, but when we make conjectures about individuals, we also need, if they are available, arguments that are closer and more particular to those individuals.

Individual Response Patterns

	Treated	Untreated
Doomed:	**Bad**	**Bad**
Causal:	**Bad**	Good
Preventive:	Good	**Bad**
Immune:	Good	Good

Distributions of Response Patterns

	Study Groups	
	Treatment	**Control**
Doomed	p□	p□
Causal	p□	p□
Preventive	p□	p□
Immune	p□	p□

Causal Effect in Population

	Outcome		
	Bad	Good	
Treated	$N_T\,(\boldsymbol{p_1 + p_2})$	$N_T\,(p_3 + p_4)$	N_T
Control	$N_C\,(\boldsymbol{p_1 + p_3})$	$N_C\,(p_2 + p_4)$	N_C

$$RD = p_2 - p_3$$

$$RR = (p_1 + p_2)/(p_1 + p_3)$$

Expected Observable Data

Outcome

	Bad	Good	
Treated	20	80	100
Control	20	80	100
	40	160	

$$RD = 0\%$$

$$RR = 1.0$$

Expectation: "Sharp-Null" H_0

	Study Group	
	Treatment	**Control**
Doomed	20	20
Causal	0	0
Preventive	0	0
Immune	80	80

Expectation: Possible "Dull-Null" H_0

	Study Group	
	Treatment	**Control**
Doomed	**10**	**10**
Causal	**10**	10
Preventive	10	**10**
Immune	70	70

Is there really no effect?

	Outcome: Bad	Outcome: Good	
Treated	**20**	80	100
Control	**20**	80	100
	40	160	

$$RD = 0\%$$

$$RR = 1.00$$

Herb Weisberg (2011)

Ask not whether the drug works. Ask what the drug can do for (or to) *you*. Researchers must learn how to link individual characteristics with efficacy and safety estimation.

Example: Aspirin and MI Prevention

- Recommended for most men over 50
- Questioned for *primary prevention* in 2009
- Variable causation: Does one size fit all?
- Can “recognizable” subgroups be identified?
- Specification of a “causal mechanism”

Toward a New Approach

- Expect *effect variability*
- Never stop *conjecturing*
- Trust but *verify*
- Generate *evidence* not answers
- Try to stay *humble*

Wall Street Journal (2011)

In a recent article about the FDA's rejection of an anti-cancer drug for insufficient average efficacy:

"According to the data, I should have been dead years before," said a breast cancer patient who had survived for several years on the drug---

"***I'm not just a statistic, and it's in your hands to ensure I don't become one***."