

Cornfield, the CDP, the UGDP,

Janet Wittes
Statistics Collaborative, Inc.

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Who was he...

“The cover of the New Yorker is from May of '07. It absolutely reminded me how Jerry's office looked through a kid's eyes; dominated by a blackboard covered with numbers.”

Ann Cornfield



Principles of Research

“On being asked to talk on the principles of research, my first thought was to arise after the chairman’s introduction, to say, “Be careful”, and to sit down.”

Am J of Mental Deficiency 64: 240-252 (1959)

Articulation

The degree of articulation of a field is measured by the extent to which the phenomena with which the field is concerned are potentially capable of being explained and predicted in terms of a small number of fundamental concepts and constants.

High vs. low articulation

- **High: physics**
- **Low: biology**

Low articulation

The language that has been developed for discourse about variable phenomena, the hallmark of fields of low articulation, is, of course, the language of statistics.

Abstraction

- “The danger of abstraction lies in the possibility that it may leave behind an essential part of the original intuition”
- The results of quantification “must be checked constantly for correspondence with the ‘short, small and haphazard’ events that it purports to describe.”
- A Jerryism: **SHOW ME THE DATA.**

Topics

- **Diagnosis (now “sensitivity and specificity”)**
- **Relative vs. absolute measures**
 - Which of the two possible quantifications is correct?
 - “It is ...senseless to ask which of the two apparently contradictory quantification is correct,
 - because they both are.”
- **Randomization**
- **Choice of control (specificity)**
- **Generalizability**

Randomized trials vs. observational studies

- He distinguished not between the methods
- but between the “kinds of inferences” supported

- “If important alternative hypotheses are compatible with available evidence,
- then the question is unsettled,
- even if the evidence is experimental.”

Discovery vs. proof

- Our “hypothesis-generating” vs “confirmatory”
- Who is concerned with what?
 - Mathematician: correctness of proof > truth of theorem
 - Statistician: validity of inference > proposition itself
 - Researcher: discovery > proof

UGDP

(University Group Diabetes Program)

- Did ↓ blood sugar ↓ sequelae of diabetes (esp CV)?
- Study designed in 1960
- First patient enrolled: 1961
- Follow-up between 5 and 8 years
- Data collection completed: 1975
- Published report: 1982

Design

- **Mild, adult-onset diabetes**
- **Groups**
 - Tolbutamide
 - Phenformin
 - Diet alone
 - Diet+tolbutamide
 - Diet+phenformin

Interim results (CV mortality)- 1970

- Tolbutamide: 26/204
- Diet alone: 10/205
- Diet+treated: 13/210 and 12/205

- Tolbutamide arm stopped
- Later phenformin stopped
- Bitter, long debate re safety of oral hypoglyemics

Cornfield's contributions

- A sensible, intelligent voice
 - RBOs (Bayes factor) for interim analysis
 - Used raw data to analyze the numbers
 - Q: Were results due to baseline imbalance
-
- Selected references
 - UGDP Diabetes 19 (supp 2), 747-830 (1970)
 - Cornfield: JAMA 217:1676-1687 (1971)
 - Schor: JAMA 217:1671-1675 (1971)
 - Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. JAMA 231: 583-608 (1975)
 - Bradley, MD. Settling the UGDP controversy. *JAMA* 232:813-817 (1975)

CDP (Coronary Drug Project)

- 1966 to 1974
- Randomized, double-blind, placebo-controlled
- 8341 men with previous MI
- Primary outcome: all-cause mortality
- 5 lipid-modifying agents vs. placebo
 - High dose estrogen (5.0 mg/day)
 - Low dose estrogen (2.5 mg/day)
 - Dextrothyroxine sodium (6.0 mg/day)
 - Clofibrate (1.8 mg/day)
 - Niacin (3.0 gm/day)
 - Placebo (3.8 mg/day lactose)

Results relative to placebo

- Hi dose estrogen – stopped early for adverse effects
- Lo dose estrogen – stopped early for adverse effects
- Dextrothyroxine – stopped early for adverse effects
- Clofibrate – did not show benefit
- Niacin
 - ↓ CV events (mean fu 6.2 years)
 - ↓ all-cause mortality (6.2 yrs + 9 yrs post-treat fu)

Cornfield's contributions

- **A sensible, intelligent voice**
- **Used RBOs (Bayes factor) for interim analysis**

- **Selected references**
 - Cornfield: Recent methodological contributions to clin trials. Am J Epi 104:408-21 (1976)
 - CDP Research Group: The CDP: Design, methods, and baseline Results (AHA Monograph No. 38). Circulation, 47(suppl 1):11-150, 1973.
 - CDP Research Group. Practical Aspects of decision-making in clinical trials. The CDP as a case study. Contol Clin Trials 1:363-76 (1981).
 - For more, go to clintrials.gov and you'll find lots

Other contributions

- **Subgroups (see all the RBO papers)**
 - Bayesian estimation for higher order cross-classifications - *The Milbank Memorial Fund Quarterly* 48: #4, Part 2:., pp. 57-70 (1970)
- **Multiplicity (Bayes papers)**
- **Competing risks**
 - The estimation of the probability of developing a disease in the presence of competing risks. *AJPH*: May, 601-607 (1957)
- **Safety**
 - Cornfield, Halperin, Moore. Some statistical aspects of safety testing the Salk poliomyelitis vaccine. *Pub Health Rep* 71:1045-1056 (1956)

Conclusion of the Prin of Research

The statistician functions as a devil's advocate against the admission of new evidence, and, in this capacity, has an important influence on the quality and cogency of the evidence submitted.

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**The investigator must pay close attention to this advocate,
but it is his and not the advocate's responsibility
to decide when he must stop listening.**

So why don't we refer to him more?

- There came a pharaoh who knew not Joseph.
- Those who cannot remember the past are condemned to repeat it.-Santayana
- He was modest...
 - On being asked to talk on the principles of research, my first thought was to arise after the chairman's introduction, to say, "Be careful", and to sit down."
- And generous

Strong recommendation

- Read (and reread) as many of his papers you can
- They are models of
 - Clarity
 - Wit
 - Insight
- “No matter what his interests, one cannot help but gain from this paper a wholesome caution about accepting seemingly obvious assumptions”
 - From the competing risks paper

And how I remember him...

