RISK: Health, Safety & Environment (1990-2002)

Volume 7 | Number 1 Article 3

January 1996

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When the results of epidemiological enquiries are published, enlightenment is often less than expected. Weak effects, inconclusive associations, other sources of apparent research ambiguity, and contradictions between studies, particularly, have been subjects for media debate and even popular satire. Society questions credibility, regardless of how rigorous or flawless the investigation.[1]

Over sufficient time, the accumulation of supportive findings can become substantial; Doll and Hill's first examination of the links between smoking and lung cancer[2] has been followed by perhaps a greater mass of corroborative evidence than in any other avenue of medical exploration. Yet, for less well-established research, society often fails to detect what it is looking for in published science — a clear, definitive conclusion that can inform decision making.

This paper identifies five sources of uncertainty and ambiguity in health and medical research that can interfere with that goal.

The Framework for Investigation: Equivocacy from the Search for Multiple Determinants

Awareness of the importance of environmental and social factors in human disease etiology dates from Hippocrates (circa 460–377AD). But by 1860, the peak of the industrial revolution in the U.K., this broad view was yielding to the emerging "germ theory" and the growing school of "contagion." This was strengthened by discoveries of

* I thank Jane Ying for insightful comments during preparation of this manuscript.

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1 *See also,* Which Scientist do You Believe? conference proceedings in 6 Risk 97–184 (1995).

2 Richard Doll & Austin B. Hill, *Smoking and Carcinoma of the Lung: Preliminary Report* Br. Med. J. ii 739 (1950).

Pasteur, Koch, von Behring and Erlich, demonstrating the microbiological root of the common diseases, and holding that this type of etiology was quite specific: *Disease could not occur in the absence of the agent, and the presence of the agent was always accompanied by the disease.* This was in full accord with the popular Cartesian reductionist viewpoint.

As the environmental and social focus lost ground, ill-health became purely biological. As Jones and Moon report,[3] medicine had turned almost exclusively toward allopathic principles,[4] and scientific medicine was assured dominance for the first half of the 20th Century. Whether accurate or not, scientific papers during this time were unhesitatingly confident. Yet, during the second half of the Century, other determinants of disease became more central, with illness increasingly seen as the product of several factors — societal, economic, behavioural and environmental — not a single biologic agent.[5]

While studies of specific agents usually follow a straightforward sequence of steps, with results that exonerate or condemn them, explorations into interdependent factors are complex in design, difficult in analysis and frequently enigmatic in outcome. As the base for enquiry has broadened, conclusions are increasingly equivocal.

Equivocacy Inherent in the Nature of Current Topics and their Risks to Environmental Health

Early investigations in epidemiology sought largely to identify and contain disease entities of an acute and infectious nature. Thus, Snow explored the relationship between water supplies and cholera;[6] Semmelweis, the etiology and concept of puerperal fever[7] and Chagas, a new disease entity that became known as trypanosomiasis.[8]

3 Kelvyn Jones & Graham Moon, **Health, Disease and Society** 1-37 (1987).

4 *Allopathic medicine* is the forerunner to modern orthodox medicine. Its distinctive feature is the use of large amounts of drugs to counteract symptoms.

5 *See* Rene J. Dubos, **Mirage of Health** (1959). *See also,* Thomas McKeown, **The Role of Medicine: Dream, Mirage or Nemesis?** (1979).

6 John Snow, *On the Mode of Communication of Cholera* (London 1855) in **Snow on Cholera** (1949).

7 Ignaz Semmelweiss, The Etiology, Concept, and Prophylaxis of Childbed Fever (K. Codell Carter, trans.) (1983).

8 Carlos Chagas, **Coletanea de Trabalhos Cientificos** (Universidade de Brasilia 1981).

Although infectious diseases still demand attention, cardiovascular diseases and cancers are the focus of much of today's epidemiology. Such may require ten to twenty years' worth of data. As our understanding of synergism and interaction between biologic, genetic and psychosocial factors increases, the results of research will inevitably appear more complex.[9]

Equivocacy from Conservative Approaches

The "scientific method" may be described as deductive, with inductive applications. Its credibility stems from the conservative statistical analysis by which hypotheses are tested. Instead of assembling supportive evidence to validate hypotheses, they are tested in a "null" form — that there is no effect, no difference or no association. Only when the null hypothesis is rejected at a satisfactory level of significance, can the original hypothesis be entertained.[10]

Such a process allows us to state, e.g., that *"the exposure and the outcome appear to be associated — but with a probability that this association might still have arisen by chance alone in up to 5% of repeated trials."* A result in this form alone, while accurate, remains inherently inconclusive for legal and other non-scientific arguments. Although the utility of results can be improved by measuring any gradients between exposure and outcome (or the strength of associations, e.g., by relative risk, odds ratio or attributable risk) and by assessing biological plausibility, inferences drawn from hypothesis testing can easily misinform laypersons.

Equivocacy Arising from Potential Emphasis, De-emphasis, Omission or Addition

Subtle adjustment of results from research sponsored by interested parties has been the subject of extensive examination by Salter.[11] Also,

[9] Professor Enrique Najera, who chairs Preventive & Social Medicine at the University of Sevilla, teaches causation theory using maraña (tangled web) not trama (web).

[10] This is analogous to verdicts in Scottish courts: Alleged offences are "proven" or "not proven," and the accused is never declared "not guilty." Doubt always remains.

[11] Liora Salter, Mandated Science: Science and Scientists in the Making of Public Policy (1985).

Doll and Peto considered reported estimates of mortality for cancer among workers in selected industries[12] to be as much as ten times too high.[13] They speculate that the report was written "for political purposes, and it will undoubtedly continue in the future as in the past to be used for political purposes...."[14]

Equivocation from Poor Study Design and Implementation

Insufficient attention to study design, sampling or data gathering, analysis and interpretation can suggest weak or ambiguous findings when results should have been quite definite — or strong associations when in reality there were none. Both circumstances are unacceptable and can be expected to increase apparent inconsistencies between studies. Several criteria with potential for weakening the validity and accuracy of studies in the chronic, non-infectious realm are discussed below and have been adapted from Taylor & Wilkins[15] and Susser.[16]

Are Exposures and (Health) Outcomes Identified, Explicit and Adequately Measured?

What was the exposure; when; and what was its amount? Many, but by no means all risk factors for non-infectious diseases are known. For example, carcinogenic risk from synthetic pesticides are likely insignificant compared to risk from background levels of natural pesticides.[17] Exposure factors are elusive, and confident results can often only stem from large, well-organized, expensive studies that run for considerable time.

Exposures and outcomes are sometimes relatively well defined and specific, such as in the relationship between angiosarcoma and exposure to vinyl chloride monomer in industrial settings[18] or the relationship

12 Kenneth Bridbord et al., Estimates of the Fraction of Cancer in the United States Related to Occupational Factors (Nat'l Cancer Institute, Env'l Health Sciences and Nat'l Institute, Occupational Safety & Health (1978).

13 Richard Doll & Richard Peto, The Causes of Cancer 1238-1265 (1981).

14 *Id.* at 1241.

15 S. Martin Taylor & Peter A. Wilkins, *Health Effects* in Transportation Noise Reference Book 4.1–4.12 (P. Nelson, ed. 1987).

16 Mervyn Susser, Epidemiology, Health and Society 82–93 (1987)

17 Bruce N. Ames, Renae Magaw & Lois S. Gold, *Ranking Possible Carcinogenic Hazards*, 236 Science 271 (1987).

18 Albert W. Barnes, *Vinyl Chloride and the Production of PVC*, 69 Proc. Roy.

between mesothelioma and exposure to respirable asbestos fibres,[19] but more often exposures being sought may have been spread through a wide temporal and spatial landscape. What, for instance, are contributing factors for prostate cancer, and when might exposures have taken place? As Doll and Peto remind us, cancer seldom develops until one or more decades after exposure.[20]

Is the Sample Size Adequate?

Investigations must consider not only the principal variables hypothesized as causative, or at least contributive, but also a cascade of potential confounders, any one of which could eliminate the study's credibility if not taken into consideration, and control for confounders during analysis will demand larger numbers. When studies run for years, subjects "lost-to-follow-up" can also endanger the required "N" for statistical power and confidence with which results can be reported.

Are Measures and Terminology Inconsistent?

When differing measures, terms, definitions and criteria are used to determine exposures or outcomes, resulting variations can obscure potentially important findings. Deaths in Britain from coronary heart disease had been found more prevalent among the professionals than among "lower" classes. Yet, Abraham Lillienfeld found that deaths from degenerative heart disease were greater among the working classes, observing that, when combined, the rates were the same. Confusion arose because professionals had better-educated doctors who were conversant with more precise terminology, whereas lower classes were seen by older generalists who had always called their condition "degenerative heart disease."[21]

Have All Reasonable Sources of Bias Been Addressed?

Sources of bias in analytic research are numerous, and observational studies are particularly vulnerable, as are long-term investigations.[22]

Soc. Med. 277 (1976).

19 Edward D. Anderson & Michael J. Gardner, *The Ill-Effects of Asbestos on Health* in Asbestos (vol. 2), Final Report, Advisory Committee, (U.K.) Health & Safety Comm. (1979).

20 Doll & Peto, *supra* note 13.

21 *See, e.g.,* Milton Terris quoted in Pan-American Health Organization, The Challenge of Epidemiology: Isssues and Selected Readings 154–155 (1988).

22 *See, e.g.,* David L. Sackett, *Bias in Analytic Research,* 32 J. Chronic Dis. 51

Was the Strength of Association Measured as Well as the Simple Probability Stated?

This could be accomplished by means of regression, relative risk/odds ratio measures, goodness-of-fit tests, confidence limits, etc.

Does Any Association Satisfy a Plausible Temporal Sequence?

That is, does the exposure appear to precede the outcome?

Are Extrapolations Appropriate, Reliable and Valid?

Extrapolations from high to low doses are not always linear, and characteristics of effects at the near-zero dose levels are highly variable.

Extrapolation between species is often unreliable. For instance, the lethal dose of TCDD (dioxin) is thousands of times less for guinea pigs than for hamsters. Its effects upon humans, on the other hand, range from unobservable, to some reports of rare cancers.[23]

Final Considerations

Many other questions can be asked: Was the statistical "power" adequate? Is the sample representative? Are confounders addressed? Was the analysis appropriate and correctly implemented? Were "gradients" or "dose-responses" observed and recorded? Are findings congruent with other studies and consistent with current epidemiologic or biologic wisdom? Are specificity and sensitivity arguments satisfied?

Yet, even with optimal data and analysis, conclusions "beyond all reasonable doubt" cannot always be attained. Burdens of "proof" should be weighed against those of "prudence."[24]

As stated by a former U.S. Surgeon General:[25] "In protecting health, absolute proof comes too late. To wait for it is to invite disaster or to prolong suffering unnecessarily." Thus, awaiting incontrovertible proof may be irresponsible and unethical.

(1979).

23 Kathryn Harrison, *Between Science and Politics: Assessing the Risks of Dioxins in Canada and the United States,* 24 Policy Sci. 367 (1991).

24 *See, e.g.,* Taylor & Wilkins, *supra* note 15.

25 William H. Stewart, quoted in U.S. Environmental Protection Agency, Office of Noise Abatement and Control, Noise: A Health Problem 23 (1978).