Epidemiology: SECOND-RATE SCIENCE?

SYNOPSIS

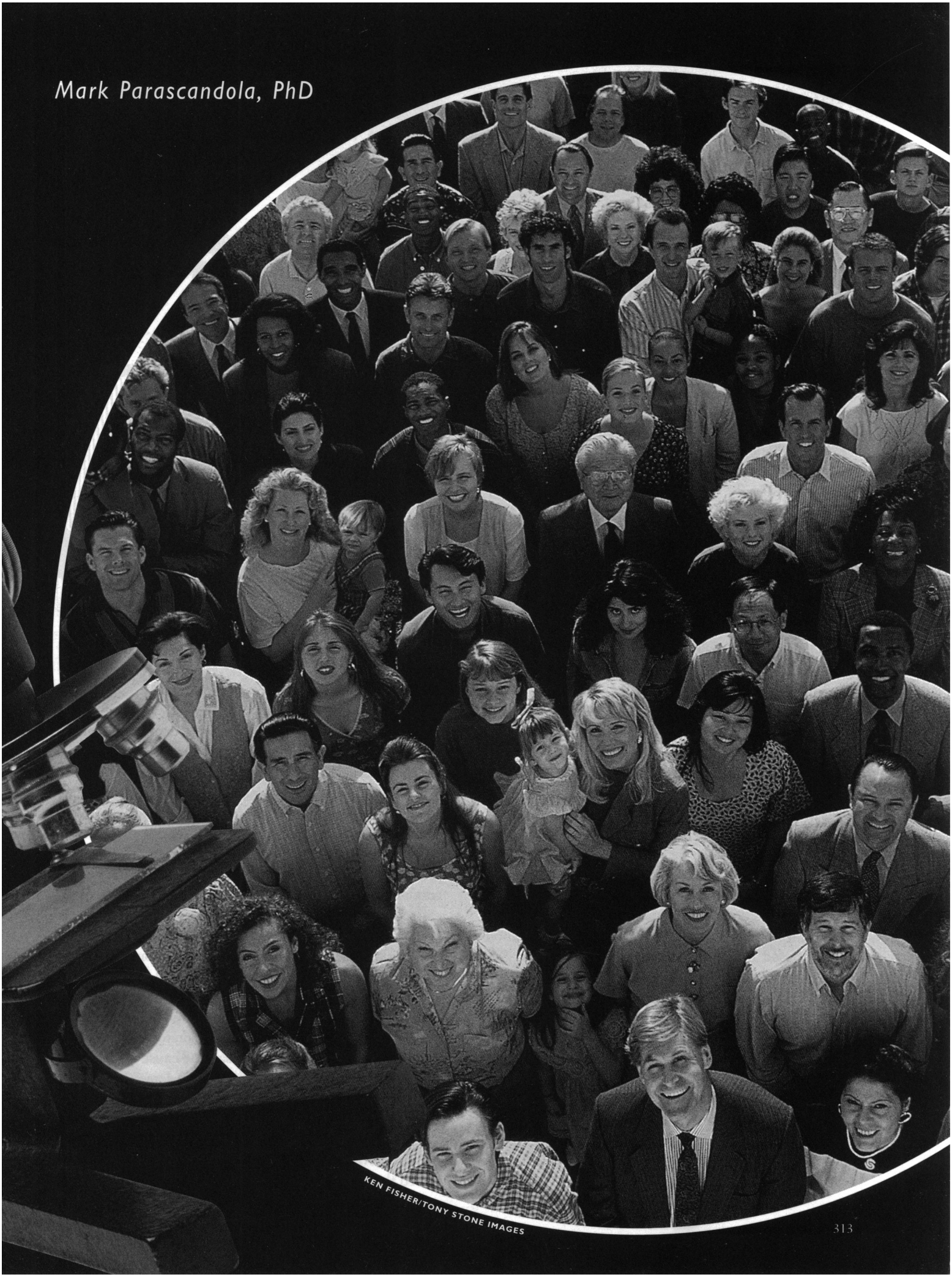
In recent years epidemiology has come under increasing criticism in regulatory and public arenas for being "unscientific." The tobacco industry has taken advantage of this, insisting for decades that evidence linking cigarettes and lung cancer falls short of proof. Moreover, many epidemiologists remain unduly skeptical and self-conscious about the status of their own causal claims.

This situation persists in part because of a widespread belief that only the laboratory can provide evidence sufficient for scientific proof. Adherents of this view erroneously believe that there is no element of uncertainty or inductive inference in the "direct observation" of the laboratory researcher and that epidemiology provides mere "circumstantial" evidence. The historical roots of this attitude can be traced to philosopher John Stuart Mill and physiologist Claude Bernard and their influence on modern experimental thinking.

The author uses the debate over cigarettes and lung cancer to examine ideas of proof in medical science and public health, concluding that inductive inference from a limited sample to a larger population is an element in all empirical science.

AS TOBACCO LITIGATION has progressed, a clearer picture has emerged of the industry's campaign against the scientific evidence linking cigarettes and lung cancer. After nearly 50 years, the industry is still trying to cast doubt on epidemiologists' findings as "mere statistics," claiming that the studies suggest only a "risk factor" for disease while proof of causation remains elusive. Why have tobacco industry leaders and other opponents of epidemiologic evidence been able to push this strategy of denial for so long? In part, they have taken advantage of a widespread skepticism toward the science of epidemiology.

Criticism of epidemiology has been on the increase in the past decade.[1] In the courtroom, for example, epidemiologic evidence has become a scapegoat in debates over "junk science."[2] Practitioners of epidemiology have long been compared unfavorably to pathologists, who study disease through "direct" observation in the laboratory by looking for specific pathogens or other internal causes of disease. But it is not only epidemiology's critics who view its conclusions as second-rate. Epidemiologists themselves are unduly self-conscious and skeptical about their own methods.



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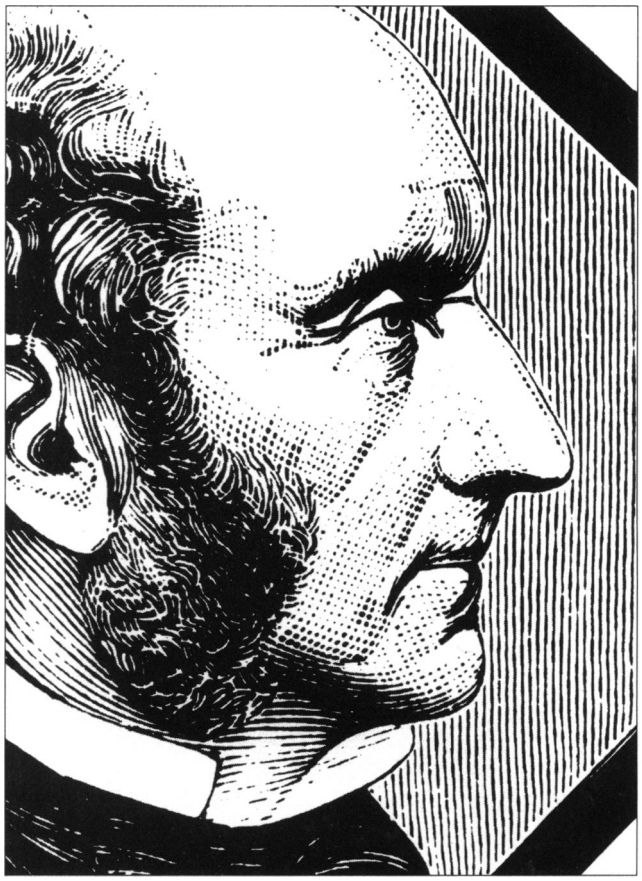
SEEING IS BELIEVING

Is there a justification for drawing a fundamental distinction between evidence from epidemiologic and laboratory studies? In answering this question, commentators often distinguish between observation and experiment. Critics of epidemiology emphasize that there are limits to what can be learned from field observations. In the laboratory, the investigator can alter the conditions of observations, repeat the experiment under different conditions, and compare the results of various trials. (Although some researchers consider clinical trials that employ experimental interventions part of epidemiology,[3] this is not the common view.) In this article I focus on that most maligned form of research—"observational epidemiology."

Yet the skeptical attitude toward epidemiology runs deeper than this distinction between experiment and observation. Some have argued (and many assume) that epidemiologists use a standard of proof less rigorous than the standard applied in laboratory medicine. The laboratory is commonly perceived as providing the opportunity for a direct view into causal mechanisms underlying disease, making laboratory researchers eyewitnesses to these phenomena, analogous to eyewitnesses in a court of law. And as in the law, eyewitness observation is often erroneously assumed to be infallible.

While the utility of epidemiology as a tool of public health is not in question, a tension exists within the discipline itself between epidemiology as a branch of the medical sciences and epidemiology as a tool for public health. On the one side are researchers who argue that "real science" requires more than "circumstantial" evidence for proof and that epidemiologic research does not meet the rigorous standards established for laboratory research. On the other side are those who contend that public health need not meet the evidentiary standards of laboratory science (which may not in fact be as rigorous a standard as some believe). What defines a method of investigation as "scientific"? Is it possible for epidemiology to succeed as part of the practice of public health and fail as science?

The traditional view of the experimental method is loosely based on what English philosopher John Stuart Mill, in his 1843 book *A System of Logic*, called the Four Methods of Experimental Inquiry (sometimes referred to in the epidemiology literature as Mill's Canons).[4] Specifically, according to Mill, an investigator can *only* infer causation when—while all else is held constant—alteration of a single factor results in a reproducible change in the effect. In practice, however, this more easily said than done. Mill's requirement for proof is far too strict to be realistic, even in the laboratory. At best, it might play the role of a heuristic device, offering an ideal model to strive toward.



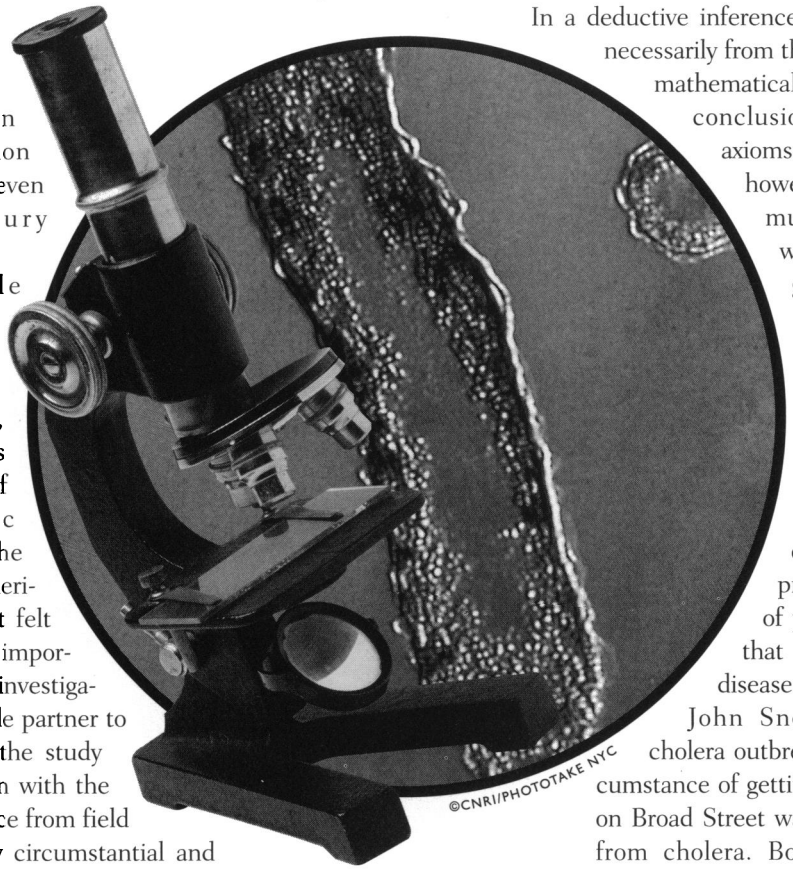
FROM HAFNER PUBLISHING CO. (NY) *JOHN STUART MILL'S PHILOSOPHY OF SCIENTIFIC METHOD*

John Stuart Mill (1806–1873) was a British philosopher who influenced later scientists' views of experimental method.

The roots of contemporary attitudes about standards of scientific proof in medical research can be traced to French physiologist Claude Bernard, a contemporary of Mill. Bernard's mid-19th century writings have had an overwhelming, yet often unacknowledged, influence on modern biomedical research methodology. Bernard insisted that for medicine to be truly scientific, it must be "based only on certainty, on absolute determinism, not on probability."[5] Bernard believed only experimental science conducted in the laboratory, typically invasive physiological study of animals, could meet this requirement. He contrasted experimental laboratory study with what he called "statistical" study, including observational studies of populations. Statistical methods, Bernard insisted, provided no explanations or certainties but only conjectures and probabilities: "Statistics can never yield scientific truth."[6] Experimental study in the laboratory could potentially provide absolute proof of, say, the cause of a disease, while statistical field studies could only demonstrate what *might* be the cause. Whether experimental laboratory science can live up to this generous promise is a matter to which I will return.

The development of the germ theory of disease reinforced the central role of the laboratory. The theory essen-

tially held that each disease is caused by a specific microorganism. Identifying the microorganism for the disease in question was deemed equivalent to finding the cause. In the 1880s, German bacteriologist Robert Koch proposed a set of requirements to guide researchers in making these causal inferences.[7,8] Koch's approach demanded that investigative work be carried out in the laboratory, with the investigator isolating the causative agent and observing its presence under the microscope for each case of the disease. Others soon recognized that Koch's strict requirements could not be met for every disease and offered revised sets of criteria to meet new challenges.[9] Yet faith in laboratory investigation has remained strong, even among 20th century epidemiologists.



In 1921, Wade Hampton Frost became the first Professor of Epidemiology in the United States, seated at the Johns Hopkins School of Hygiene and Public Health. Writing in the formative years of American epidemiology, Frost felt the need to defend the importance of epidemiologic investigations as an indispensable partner to laboratory research in the study of disease. Yet he began with the assumption that evidence from field investigations is merely circumstantial and secondary to observations made in the laboratory. He described two distinct approaches to developing a theory of the spread of a given disease, one based on inductive and the other on deductive reasoning.

> One approach.... proceeds *inductively*, by the accumulation of observations, to build up a chain of associations between the occurrence of the disease and certain related conditions and combinations of circumstance. If the specific microorganism has not been identified and experimentally established as the causative agent, its existence and certain of its essential characteristics may be inferred from such *circumstantial* evidence....The other approach begins with *direct observation* of the specific microorganism itself, ascertaining something of its actual distribution in nature and of its reactions under controlled experimental conditions. From these observations inferences are drawn by an essentially *deductive* process as to the life history and behavior of the microorganism under the more complex conditions of nature.[10] *(emphases added)*

Eyewitness observation is often erroneously assumed to be infallible.

In a deductive inference the conclusion follows necessarily from the premises, such as in a mathematical argument in which a conclusion follows from basic axioms. In inductive inference, however, there is a "leap" that must be made, such as when one draws a broad generalization based on a few observations.

Frost agreed with Bernard's view that the laboratory investigator's experimental reasoning is deductive. Both noted that the epidemiologic approach relies primarily on observation of particular circumstances that may be correlated with disease outcomes. For example, John Snow noticed during a cholera outbreak in 1854 that the circumstance of getting water from the pump on Broad Street was associated with death from cholera. Both Frost and Bernard pointed out that investigators in the field are required to make risky inferential leaps from population-level data to individual-level causation. In contrast, a laboratory investigator can, with the aid of a microscope, actually see the microorganism that caused a particular individual's disease and observe its behavior.

Nevertheless, Frost defended epidemiology by asserting that "circumstantial" evidence could be useful. Population-level studies could, for example, provide information about disease patterns that could not be observed in the laboratory. Such studies also sometimes uncovered important facts about the spread of a disease decades before the responsible

organism was "seen" in the laboratory, as in the case of cholera. He emphasized the value of epidemiology for disease prevention and for the practice of public health; however, its value was primarily a pragmatic one and, in his view, epidemiologic knowledge ultimately remained second rate.

THE SMOKING HYPOTHESIS

The long-lasting controversy over the relationship between smoking and lung cancer demonstrates the tenacity of a disparaging view of epidemiologic evidence. In 1950, the preliminary reports of two large-scale epidemiologic studies—by Ernest L. Wynder and Evarts Graham in the United States[11] and by Richard Doll and Bradford Hill in England[12]—showed an association between cigarette smoking and lung cancer. However, these researchers were cautious about asserting a causal link, and throughout the rest of the decade there was substantial controversy over the significance of their findings. Critics pointed out that no known human carcinogen had been found in large quantities in cigarette smoke and that nonsmokers developed the disease as well as smokers. The best epidemiologic findings could do, according to these skeptics, was to strengthen the call for further research. But further research failed to resolve the debate over causation.

Is it possible for epidemiology to succeed as part of the practice of public health and fail as science?

In 1958, the *British Medical Journal* noted that "the fact that experimental work has not provided complete and irrefutable proof of [the] conclusion [that smoking causes cancer] has tended to hinder its whole-hearted acceptance."[13] Two prominent statisticians, Joseph Berkson and R. A. Fisher, voiced strong opposition to the causal hypothesis, further complicating the debate. Berkson maintained that the observed association between smoking and lung cancer was likely to be due to bias and called for more evidence, particularly at the level of biological mechanisms.

Writing in 1960, Berkson expressed disappointment with the direction of lung cancer research at the time. In commenting on one study, he described what he saw as a gap in the evidence:

> Here I expected to find the presentation of individual cases, perhaps of long-time smokers with a history of smoker's cough or bronchitis with later development of lung cancer, and for whom a study of the tissues at necropsy exhibited evidence of the development of the cancer in or contiguous with the tissues showing inflammatory changes due to smoking, and in such a way as to suggest that one developed from the other, or some things of this sort.[14]

Berkson was calling here not so much for an explanation of mechanisms as for an observable marker that could be implicated as a necessary cause because it shows up in every case of the disease.

An influential 1959 paper by Jacob Yerushalmy, a biostatistician at the University of California at Berkeley, and Caroll Palmer of the U.S. Public Health Service, pointed to limitations of epidemiologic methods.

> In many of the important chronic diseases we are not yet at the stage of attempting to identify a definite, final, and single entity as a causal agent. Rather we are concerned with the investigation of conditions, often environmental, which may be involved in the causation of a given disease. These conditions, however, may, at best, be looked upon only as vectors or vehicles which may contain the specific causative agent.[15]

They saw smoking as not itself a cause of cancer but merely a pathway

through which some final specific cause (perhaps a carcinogenic molecule) acts on the body. A 1962 editorial in *The Lancet* still referred to "a slight nagging uncertainty as to the evidence" because no carcinogenic agent had been identified in sufficient amounts in tobacco smoke and the disease had not been successfully reproduced experimentally.[16]

From the skeptics' point of view, epidemiologic studies can at best offer circumstantial clues to guide laboratory scientists in looking for "real" causative agents. These clues may be extremely useful—suggesting, for example, an environmental influence or genetic predisposition that would not be immediately obvious to an observer of individual cases. Yet the charge against epidemiology remains that scientific "proof" is beyond its reach.

Different Standards of Proof

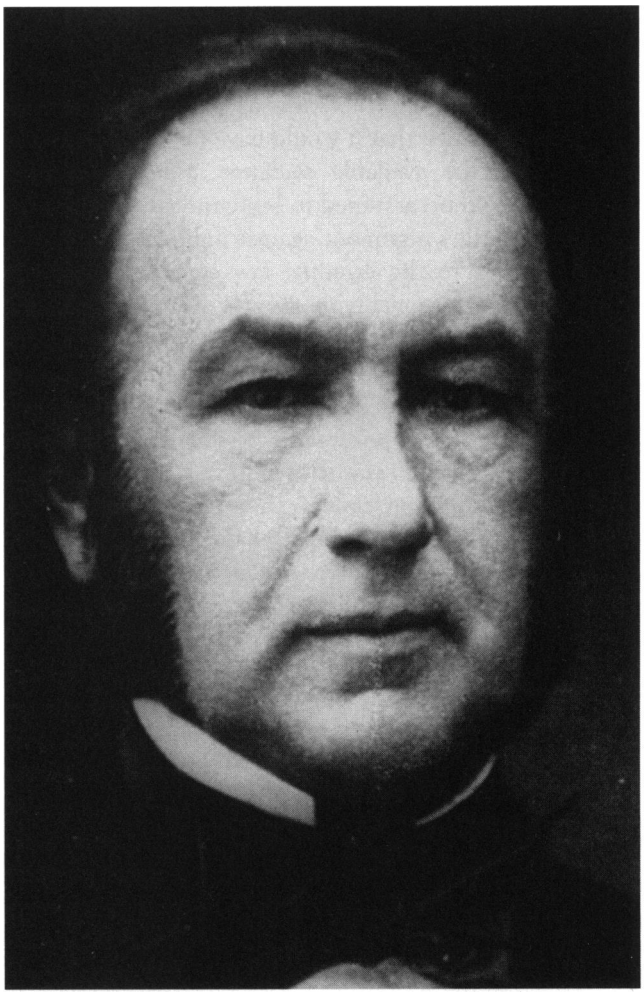
The realms of science and of public policy demand very different standards of proof. While those who view themselves as pure scientists would, to paraphrase an old saying, rather let 10 true hypotheses go unproven than "prove" one false hypothesis, protectors of the public health cannot wait for all the evidence to come in.

Many of those who supported use of health warnings against smoking noted gaps in the evidence but argued that certainty was not required to justify protective actions. In 1959, a response to skeptics was authored by a group of leading investigators from schools of public health and cancer research centers:

> As in other fields of science, new findings lead to new questions, and new experimental techniques will continue to cast light on old ones. [However, t]his does not imply that judgment must be suspended until all the evidence is in, or that there are hierarchies of evidence, only some types of which are acceptable.[17]

According to these scientists, while no single cause could be found to account for all lung cancer, the data implicating smoking were sufficient to plan and activate public health interventions.

In the mid-1950s an American Cancer Society epidemiologist argued that implementation of public health measures need not wait for all the evidence to come in: "[i]n human affairs, important decisions must necessarily be based upon the preponderance of the evidence."[18] Public health, he maintained, should rely on the evidential standards of civil law, not criminal law. The standard of proof applied in criminal law—"beyond a reasonable doubt"—is assumed to apply to scientific research as well; no one wants to send an innocent person to jail or accept a false hypothesis. Yet applying that standard of proof is not always practical or useful from a public health perspective; to safeguard people's health it is often more appropriate to use the standard applied in civil law, which bases decisions on the "preponderance of evidence"—of two competing stories, the more plausible wins out.



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Claude Bernard (1813–1878) was a French physiologist who argued that, to be scientific, medicine must be based on laboratory experimentation.

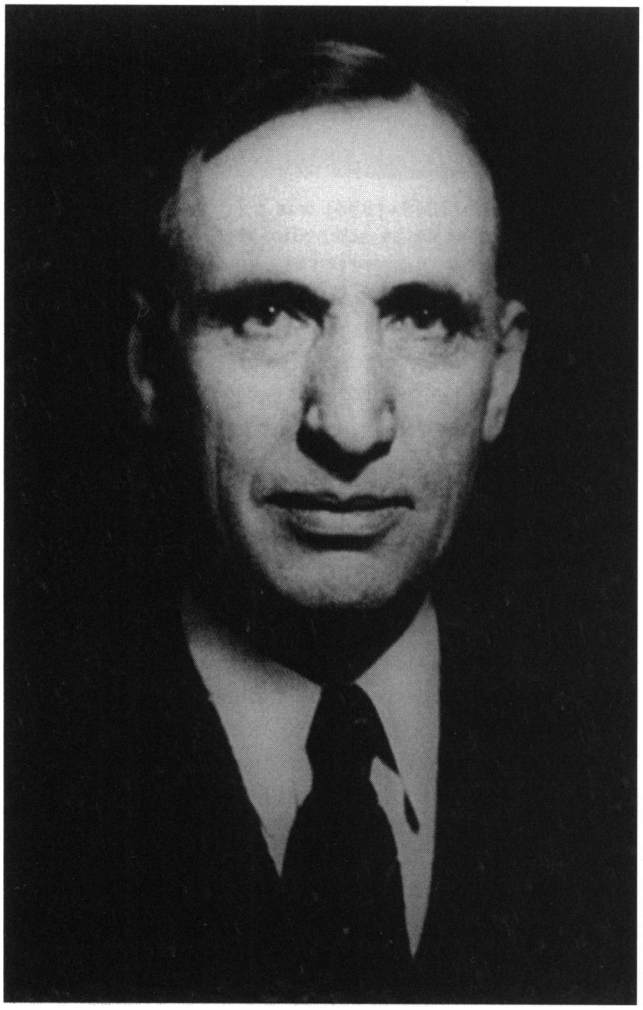
Despite the scientific controversy over causation, the link between smoking and cancer was clear enough from the public health perspective by the late 1950s. A substantial public health response was eventually mounted, and a consensus emerged among physicians that smoking should be discouraged. In 1959, U.S. Surgeon General Leroy E. Burney implicated smoking as "the principal etiological factor in the increased incidence of lung cancer"[19] and concluded that the most effective means of reducing one's risk was to stop smoking. How could scientific skepticism exist side-by-side with a recommendation against smoking?

Clarence C. Little, Scientific Director for the Tobacco Industry Research Committee, debated appro-

priate standards of proof with Ernest Wynder in the *New England Journal of Medicine* in 1961.[20,21] Little believed there was no obligation to warn of possible dangers. In fact, he maintained that it would have been irresponsible to do so on the available evidence and that tobacco smoking should be assumed to be harmless until proven otherwise. Little's argument against public health action was analogous to the criminal law standard, requiring proof beyond a reasonable doubt and putting the burden of proof on the accuser.

The 1964 Surgeon General's report on *Smoking and Health*[22] attempted to balance the need for public health warnings with the requirements of science. The report admitted that while statistics showed an association between smoking and cancer, they could not establish proof of a causal relationship. Yet the Surgeon General took the position that "[w]hen coupled with the other data, results from the epidemiologic studies can provide the basis upon which judgments of causality may be made."

Wade Hampton Frost (1880–1938), the first Professor of Epidemiology in the United States, argued that "circumstantial" evidence could be useful in public health.



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The Ongoing Search for Biological Causation

While the "preponderance of evidence" was sufficient for the public health community, the medical community continued its search for biological causation. Through the 1960s and 1970s, motivated in part by the tobacco industry's insistence that the biological link between smoking and cancer had not been firmly established, scientists continued their searched for the "first cause" of lung cancer. In a 1981 editorial, the editors of *Nature* pointed out:

> It is...now to be taken as a fact that people who smoke cigarettes are more likely than others to develop lung cancer. The habit of smoking cigarettes is thus in some sense a cause of lung cancer. The link is clear enough for individuals prudently not to smoke cigarettes and for governments to encourage abstention. Yet the habit of smoking is not a first cause of lung cancer. That distinction no doubt lies with a group of chemicals not yet conclusively demonstrated.[23]

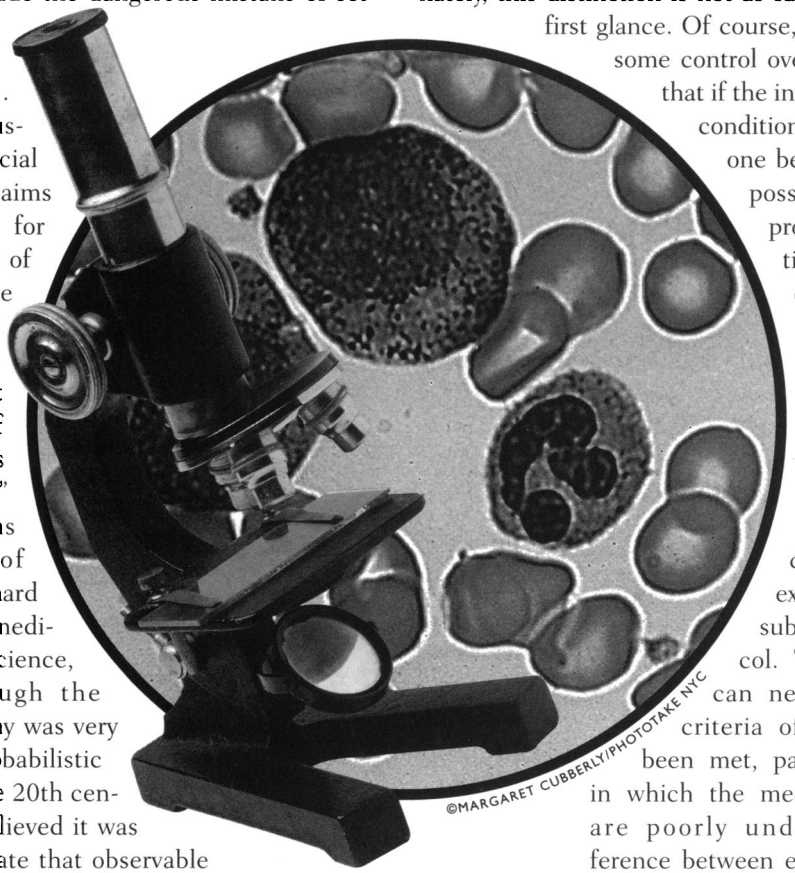
Like Yerushalmy and Palmer, *Nature*'s editors were hoping to find a molecular agent that could be observed in the laboratory to affect the cells of the lungs in a particular way, providing in the right circumstances a necessary and sufficient cause of lung cancer.

In late 1996, controversial new laboratory findings were hailed as providing a "direct link" between smoking and cancer.[24,25] Researchers reported that sites on the P53 gene which are mutated in some cases of lung cancer are the same spots that tend to bind with a tobacco carcinogen molecule named BPDE. But a one-to-one correspondence between a P53 mutation and cancer has not been shown, and the action of BPDE remains unclear. A skeptic might say—as has been said of epidemiologic studies—that this is a case of "guilt by association."

Future investigations at the molecular level will substantially improve our understanding and may even lead to novel preventive strategies. We should not assume, however, that investigators will uncover a necessary and sufficient cause to explain every case of cancer. The more we learn about biology, the more we find that it is rarely so neat and simple. In fact, there has been much debate among biologists about whether causal relationships observed at the level of whole organisms—as in epidemiologic studies—can be fully reduced to the molecular level.[26] The long-term effects of smoking and the development of cancer are likely to be too complex to allow for identification of a single event that could be termed a "first cause" of cancer.

WHAT IS "PROOF" ENOUGH?

While it is clear that public health practice should demand a different kind of proof than is required in the laboratory, we should not relinquish too quickly the scientific status of epidemiology. The smoking to cancer link, for example, is a paradigmatic instance of good scientific inference. To say that the connection has not yet been scientifically proved would be absurd. Over the course of a century, theorists have attempted to place a wedge between epidemiology and laboratory science. In doing so, they have made the dangerous mistake of setting the standards for experimental science unrealistically high. Not only is there no justification for this artificial distinction, but the claims that have been made for the unique guarantee of the laboratory are unfounded.



Reacting to vitalists who did not believe in laws of nature and systematists who derived all "truths" from intuitive axioms without any form of experimentation, Bernard wanted to show that medicine could be a true science, like physics (although the physics of Bernard's day was very different from the probabilistic quantum physics of the 20th century). To do this he believed it was necessary to demonstrate that observable biological phenomena could be reduced to deterministic causal mechanisms. Or, to bring the science up-to-date, that the statistical relationship between smoking and cancer would reduce to molecular interactions that could be described with a few simple nonstatistical laws. Central to his view was the belief that science could, and must, deliver certainty. That naive hope still exerts substantial influence on scientists.

What do those who claim that epidemiology cannot "prove" causation mean? Do they mean that epidemiology fails to provide deductive certainty? If so, then *no* empirical method can prove causation because any empirical science relies on induction to make broad generalizations from limited experience. Contrary to Bernard's view, inference in the laboratory, as in the field, is primarily *inductive*. Data, even from a number of experiments, do not *determine* the theory one should adopt. Results must be interpreted, and researchers may disagree over the significance of observations.

Perhaps epidemiology's critics mean to draw a distinction between observation and experiment instead of between inductive and deductive reasoning. Unfortunately, this distinction is not as satisfying as it appears at first glance. Of course, the laboratory gives us some control over conditions. Mill said that if the investigator could hold *all* conditions constant except the one being tested, it would be possible to prove (or disprove) causation. In practice, the "controlled laboratory" is not totally within the investigator's control. The ability to manipulate and create phenomena does not guarantee the absence of hidden confounders such as differences between experimental subjects or subtle differences in protocol. Thus, the investigator can never be sure that the criteria of Mill's Canons have been met, particularly in situations in which the mechanisms under study are poorly understood.[27] The difference between epidemiologic and laboratory studies then is one of degree and not the fundamental distinction often invoked.

The realms of science and of public policy demand very different standards of proof.

Just as important, further uncertainties complicate efforts to extrapolate results from the laboratory to a population. Understanding how a particular molecular mechanism operates is of little use unless something is known about where and how frequently the phenomenon occurs among a group of people. As its advocates argued earlier in the century, epidemiology may provide this essential information that cannot be obtained by other means.

In response to these many uncertain-

ties, philosopher Karl Popper has urged scientists to turn their backs on induction; his ideas have had a substantial influence on scientists, epidemiologists among them.[28,29] Popper wrote that using inductive reasoning to make broad generalizations from limited experience is never warranted, even in experimental science. In my view, his position should be rejected along with Bernard's. If we truly limit ourselves to deductive reasoning, we will be forced to throw away most of our beliefs about the world and to give up all hope of knowledge of nature, not to mention any hope for improving peoples' health.

Careful use of inductive inference is what has made empirical science so successful. For example, Claude Bernard used inductive inference in suggesting that the effects of poisons on whole organisms in the world outside the laboratory would be similar to their effects on tissues in the laboratory.

There is no absolute proof in science, and there are no hard and fast rules for what is "good" inductive practice. Much is left to the investigator's judgment, and the best check on poor judgment comes from the watchful eye of fellow investigators. The fact that epidemiologic studies are often accompanied by daunting debate over issues of protocol and study design is a healthy sign. Textbooks of epidemiology routinely include a chapter devoted to causation and causal inference, but, sadly, the same is not the case in other disciplines within the biomedical sciences. Perhaps researchers in those other disciplines have a thing or two to learn from epidemiology.

It remains now for epidemiologists and other public health researchers to take the lead in defending their practices and, most importantly, to communicate a realistic vision of what empirical science can and cannot achieve. While the validity of epidemiological studies on smoking are no longer contested, the negative health consequences of many other environmental factors—air pollution and fatty diets being prominent among them—are being hotly debated and need our attention.

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