Disclosure of Financial Interests

Joseph Friedman, MD, and spouse/significant other. Consultant: Acadia Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers' Bureau: Astra Zeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, Glaxo Smith Kline, Neurogen, and EMD Serono.

Conflicts: In addition to the potential conflicts posed by my ties to industry that are listed, during the years 2001-2009 I was a paid consultant for: Eli Lilly, Bristol Myers Squibb, Janssen, Ovation, Pfizer, makers of each of the atypicals in use or being tested.

From Sequence to Consequence

A stranger walks down a country lane and sees a small farmhouse at the margins of a plowed field. He wonders: "Did that visibly fertile field attract the farmer who then built his dwelling next to the field?" Or, alternatively, "Did the farmer, inheriting the farmhouse from his parents, then clear the adjacent woodland to make a meadow capable of growing a crop?" A farmhouse and a plowed field: which came first? And did the farmhouse "cause" the plowing? Or did the fertile field "cause" the farmer to construct his farmhouse beside this obviously fecund field? Or, perhaps, was there no causal relationship between the two physical entities?

A tourist from the States visits Stonehenge in southern England and exclaims: "Wasn't it thoughtful of those early Druids to build their primitive monument next to an accessible highway and parking lot!" Or an equally credulous tourist in Virginia questions: "How come so many Civil War battles were fought in National Parks?" People take two or more disparate things and speculate about their interrelationships, wondering, sometimes, if one came about because of the other.

Before they perceive the rudiments of language, young children learn the fundamentals of causal relationships. One of the first principles that they learn is the temporal connection between causes and effects: if A truly causes B, then A must precede B. A baseball game is not rained out if it rains the next day. Eating forbidden cookies comes before a spanking – not after (except, perhaps, in dysfunctional families.)

Nature respects the rules of causality but displays a cosmic indifference to how the many and varied consequences are perceived. It acknowledges neither penalties nor prizes, just outcomes.

But how reliable is a temporal relationship in assigning causality when the outcome is a complexity such as a human disease? For example, most people with Alzheimer's disease have grey hair; furthermore, the grey hair almost always precedes the development of dementia. Can we conclude then that the grey hair "caused" the dementia? Or will we require more stringent evidence to indict greyness as the etiologic agent? How might innocent sequence be separated from evil consequence?

The time is 1942 and a healthy man works in a New England shipyard constructing ocean-going freighters to sustain the war effort. His job is to coat the many interior pipes with an insulating sludge containing asbestos. Many years later, after an interval during which he held many diverse jobs and smoked countless cigarettes, he developed difficulties in breathing, lost weight and was diagnosed as a victim of the lung cancer mesothelioma. In the year 2011 we now recognize that inhaled asbestos particles may eventually lead to this unusual form of malignant tumor. The time interval, the latent phase, was not minutes but decades, and so much transpired in the interim. A child touches a hot stove and a fraction of a second later feels the pain. If the interval between touching a hot surface and experiencing pain had been many days, the likelihood of the child, or the adult, learning something from the experience is probably lost. And with the many shipyard workers it required much painstaking epidemiologic inquiry and laboratory research to indict asbestos finally as the cause of mesothelioma.

It also required over a century of research to convince the conservative medical profession that microscopic organisms – called microbes – might cause human distress, even fatal illness. And further, that each strain of bacteria generally causes its own specific, often idiosyncratic infection. It didn't seem reasonable to most physicians that an invisible organism could fell a 200 pound adult. A German physician named Robert Koch (1843 - 1910) assembled a sequence of laboratory steps, now called Koch's postulates, to provide proof of causality.

First, the suspect microbe must be consistently associated with the specific disease. Second, the suspected microbe must be isolated from one or more organs and grown in pure culture. And third, a healthy susceptible host (an experimental animal such as a mouse) when inoculated with the putative microbe will then develop the disease. A fourth proviso was later added: the same microbe must be re-isolated from the experimental animal.

As clinical medicine learned more of the intricacies of infectious disease, some of these postulates have been modified; but Koch's postulates, recognizing that the world is awash with bacteria and other risks – some of which may be harmful to humans – still offer a rational means by which disease-producing germs might be distinguished from non-disease-producing germs: a laboratory method effectively separating the innocent microbiologic bystanders from the hostile invaders.

As water runs downhill so, too, does effect follow cause. Some relationships never seem to change.

– Stanley M. Aronson, MD

Stanley M. Aronson, MD is dean of medicine emeritus, Brown University.

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Stanley M. Aronson, MD, and spouse/significant other have no financial interests to disclose.

Correspondence

e-mail: SMAMD@cox.net