pendent risk factor for heart disease.[4] If physical activity and dietary fat indeed are inversely related, then the two-fold increased risk of coronary heart disease observed among sedentary persons[3] could be an overestimate, due to confounding by dietary fat.

Because uncontrolled confounding is a major threat to the validity of epidemiologic findings, it is imperative that adequate information be collected to allow for control of potential confounders. The difficulty, however, lies in the fact that for most exposure-outcome hypotheses, we simply do not know all the variables, or their exact component(s), that could potentially confound. We cannot control for a potential confounder that we cannot identify or measure. In the example of physical activity and coronary heart disease, we suspect that "dietary fat" may be a potential confounder. However, the precise components of dietary fat that are relevant (e.g., total fat? saturated fat? monounsaturated fat?) must be identified if they are to be measured and controlled for. Therefore, our ability to adequately control for confounding is, to a great extent, dependent on the current state of knowledge. As knowledge regarding the predictors of an outcome unfolds, our ability to eliminate confounding as a possible alternative explanation increases, allowing us to assess with more confidence the validity of an observed association.

Thus, Simoes et al. have added an important piece of information to studies on physical activity by suggesting that dietary fat must be considered as a potential confounder in these studies. It is important, however, to recognize that while physical activity and dietary fat were inversely associated in the study by Simoes et al., it does not mean that dietary fat always will confound physical activity in studies evaluating all diseases or outcomes. Neither does it mean that the results from any study of physical activity that did not control for diet are necessarily confounded. By definition, for dietary fat to confound an association with physical activity, two conditions must be met: (1) There must be an association between physical activity and dietary fat in the specific population under study; and (2) Independent of physical activity, dietary fat must be a risk factor for the outcome of interest. If either of these conditions is not met, dietary fat will not be a confounder. Thus, although data from the 1990 Behavioral Risk Factor Surveillance System indicated an inverse relation between physical activity and dietary fat, this association may not necessarily hold, or hold as strongly, in a different population. This may explain why, in the few studies of physical activity and colon cancer that have controlled for potential confounding by diet,[5] diet did not appear to confound the association. In a population-based case-control study of physical activity, diet, and colon cancer conducted in Utah, for example, the investigators reported that as physical activity increased, total caloric consumption also increased, but the proportion of total calories as fat did not vary across activity categories for either cases or controls.[6] Thus, dietary fat would not be a confounder of the physical activity–colon cancer relation in this situation. Similarly, in studying the relation of physical activity and osteoporosis, while specific components of the diet, such as calcium intake, clearly need to be considered, there is no known relation between dietary fat and osteoporosis. Therefore, when evaluating the association between physical activity and osteoporosis, dietary fat is unlikely to be a confounder of this hypothesis.

Perhaps, then, the salient message to anyone analyzing or interpreting data on physical activity is the following: Be cognizant of dietary fat. It may not turn out to be an actual confounder of the hypothesis under study, but it certainly must be evaluated. □

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Annotation: Protection of the Public Interest, Allegations of Scientific Misconduct, and the Needleman Case

To understand why and how the lead industry was able to use the ill-formed National Institutes of Health (NIH) Office of Scientific Integrity process to hobble a highly accomplished researcher and terrorize those who might be inspired to emulate him, it is important to go back a bit in history. The lead industry has mobilized against the advances of science for nearly 100 years, since Turner and colleagues in 1894 first reported on cases of childhood lead poisoning due to lead-based paint in Brisbane, Australia.[1] As early as 1920, the primary lead extracting and smelting industry (some of whose members also owned paint companies—e.g., Dutch Boy was owned by National Lead) had organized itself to control the incorporation of research findings on lead hazards into public policy. The Lead Industries Association (LIA), incorporated in 1928, succeeded in blocking US adoption of an international convention against the use of white lead in paint; LIA campaigned to prevent cities and states from restricting the use of lead in plumbing and residential paints.[2] But LIA's greatest triumph was in 1925, when it overrode opposition to the introduction of tetraethyl lead as a gasoline additive.

In its campaigns LIA adopted a two-pronged strategy toward medical research, which reached its zenith in the Needleman persecution. On the one hand, LIA and later the International Lead Zinc Research Organization (ILZRO)

funded lead research—at Harvard, Johns Hopkins, and the University of Cincinnati—to such an extent that until the 1970s, their support dominated the field of lead research.[2,3] On the other hand, LIA developed to an art the use of the bullying response to intimidate independent researchers. Alice Hamilton and Yandell Henderson, who testified before Congress against tetraethyl lead, were vilified as hysterical and anti-progress.[3] In 1943, LIA pulled out the media stops to attack Randolph Byers, who published the first report on long-term neurological sequelae of early childhood lead poisoning; Byers was also threatened by LIA with legal action.

In the 1970s the stakes shifted, as did the stakeholders. From 1971 to 1980, the US government began to invest in environmental health research, including research on lead poisoning.[4] Under the leadership of David Rall, the National Institute of Environmental Health Sciences supplanted LIA and ILZRO as a major source of research funds, with no strings attached. At the same time, the government began to restrict the use of lead in gasoline and paint.

Dr Herbert L. Needleman, a pediatrician and psychiatrist, participated in these two changes: his research first at Harvard and then at the University of Pittsburgh was funded through the competitive grants process of NIH, and he was an outspoken advocate for scientifically based public action to remove lead from gasoline and ban the use of lead-based paints. Industry-supported researchers could not disprove his early findings; in fact, the burden of scientific evidence from 1972 to 1980 shifted substantially toward the opinion that lead at low levels was dangerous to young children.[4] Needleman's 1979 *New England Journal of Medicine* article was influential, but not alone in this process. The mood of the country made it less likely that a media campaign would succeed in slowing the movement toward change. The industry continued to fight, but increasingly it had to take on the Public Health Service, the American Academy of Pediatrics, and the petroleum and automobile industries. An early attempt in 1983 by the lead industry to discredit Needleman's research was dismissed, after careful analysis, by an Environmental Protection Agency expert advisory committee.

In the 1990s a new weapon was at hand. The NIH Office of Scientific Integrity provided the industry a possible weapon with which to intimidate one of its most accomplished critics. Because of the confused mission and inchoate processes of the Office of Scientific Integrity, the industry may have perceived that it could use an allegation of scientific fraud and misconduct to regain some control over public policy on lead. The industry's success—defeat came only at the end—must raise troubling thoughts in all of us who participate in science. The ability of parties at interest to manipulate the Office of Scientific Integrity must cause us to reexamine the utility and reliability of the institution we are putting in place to protect ourselves and the public. The Needleman case, now resolved, must make us ask the following hard questions:

1. *What is the basis for a charge of scientific fraud or misconduct?*

Surely something more than suspicion must be required to put a costly and time-consuming process into action, yet Needleman's accusers admitted during the course of hearings at the University of Pittsburgh that they had no specific grounds for their accusations, only a desire for NIH to investigate the possibility of fraud or misconduct. In a similar hearing that I chaired at the University of Maryland, I dismissed a preliminary investigation when the accuser made a similar admission.

2. *Who should investigate charges of fraud and misconduct?*

Placing universities in the position of conducting the first round of adjudication of their own employees is like forming a grand jury composed of the defendant's friends and family. It is impossible for them to find the defendant innocent for fear that others will see such a finding as confirmation of institutional bias. Hence these early rounds, which are supposed to select out only valid and serious cases for NIH investigation, actually serve to reverse the presumption of innocence so that the responsibility for real investigation can be passed as soon as possible outside the university.

3. *How should such investigations be conducted?*

One of Needleman's significant accomplishments in this process was his victory in ensuring the right to an open and public process and the right to legal counsel. Surely after the Magna Carta, the Star Chamber, and the Inquisition, we know enough to be suspicious of claims that closed processes are necessary to protect the rights of accused and accuser? Yet Needleman had to gain the support of his faculty and the intervention of colleagues around the world to assert this right.

4. *What, after all, was the Needleman investigation about?*

On the surface, the issues in contention were, if anything, matters of disagreement in methods of data analysis. No fraud, no misconduct. Several reanalyses of Needleman's data (e.g., that conducted by Schwartz[5]) have found it even more robustly supportive of an association between low-level lead exposure and neurobehavioral deficits in children. Studies conducted around the world over the past 15 years have followed his work and have gone on to replicate his methods and conclusions and to extend our concern to even lower levels of exposure.[6]

But data analysis is not what the investigation was really about. It was about the power of a few to manipulate institutions imperfectly designed to protect the public from the misuse and abuse of science. Those of us who need this protection—as we all do, researchers, taxpayers, doctors, and patients—must learn from the Needleman story. We are fortunate this time that a courageous man of intellectual integrity defended his rights and ours. The next time we may not be so fortunate. □

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