LETTER

Epidemiological reasoning and biological rationale

Joshua E. Muscat

Studies in which the use of biomarkers results in faulty epidemiological reasoning are reviewed. The criteria for causal associations in science are discussed.

Keywords: *epidemiology, biomarkers, smoking, cancer.*

Epidemiological science has been intensely criticized recently both in the scientific literature (Tauber 1995) and in popular magazines (Ross 1995). The multitude of contradictory findings on numerous topics have left many questioning the value of epidemiological science. In 1965, A. Bradford Hill defined the paradigm that is commonly used to distinguish causal from non-causal associations in science (Hill 1965). The most relevant criteria included the strength of the association, consistency between studies, specificity of effect, temporality, and biological *plausibility*. With the recent advent of '*biomarkers*', a great deal of confusion has been created. It is the misunderstanding of this final criteria that has led to weak epidemiological reasoning in some instances.

Consider several examples. Cigarette smoking is not related to the risk of breast cancer except in a few studies. A few investigations found an increased risk which would be expected by chance. A larger number of studies have shown a reduced risk of breast cancer among smokers. In a review, Palmer and Rosenberg (1993) concluded that there was no evidence to support a positive association. This review did not include the many studies where the relative risks for smoking were not reported, presumably because there was no association. Doll and colleagues examined the mortality patterns of 6194 female British doctors and found no increased rates of breast cancer among smokers (Doll *et al.* 1980). Yet studies in 1978 and 1980 found that cigarette mutagens and nicotine were detected in breast fluid (Petrakis *et al.* 1980). Using molecular methods, DNA adducts of polycyclic aromatic hydrocarbons have recently been found in breast tissue (Petrakis *et al.* 1978). In another study, a large increased risk of breast cancer associated with genetic polymorphisms of genes that metabolize and detoxify polycyclic aromatic hydrocarbons was reported in one subgroup analysis (Ambrosone *et al.* 1995). Do these studies implicate smoking as a breast cancer risk factor? Clearly not. They simply show that using very sensitive laboratory techniques, low concentrations of certain compounds can be detected in breast tissue. This does not demonstrate causality. Unfortunately, there were no acknowledgements by the authors, either in their hypotheses or their conclusions, that decades of epidemiological research has not implicated smoking as a risk factor, or that the incidence rates of breast cancer continue to increase in women under 50 whereas the rates of lung cancer are slightly declining in younger women. This line of justifying epidemiological research based solely on biological data and ignoring epidemiology has led to its inevitable *reductio ad absurdum* with studies examining the risk of breast cancer in relation to environmental tobacco smoke.

A second example concerns the health effects of diesel engine emissions. Epidemiological studies have shown that truckers, miners and other groups that use diesel engines have an increased rate of lung and bladder cancers. These groups also have a higher rate of smoking cigarettes and it has not yet been possible to isolate the independent effects of diesel exhaust from smoking. The epidemiological studies often cite the experimental work which shows increased tumour burden in laboratory rates exposed to diesel exhaust. What is not discussed is that the levels of exposure in animal models are several-fold greater than that experienced by humans. In a recent series of experiments, the same incidence of tumours was found in rats exposed to diesel engine particulates minus the mutagenic organic fraction (Nikula *et al.* 1995). These studies suggest that the mechanisms for tumour induction was an irritant effect resulting from massive overload of particles; an overload not experienced by humans. The jury is still out in this complicated issue and more precise studies using markers of internal exposure would add significant knowledge in this area. But groups who are eager to implicate diesel exhaust as a causative agent often cite the International Agency for Research on Cancer (IARC) monograph on diesel exhaust (1989). In an otherwise excellent review, IARC concludes that 'there is limited evidence for the carcinogenicity in humans of diesel engine exhaust' and simultaneously that 'diesel engine exhaust is probably carcinogenic to humans'. This contradiction arises from another evaluation that 'there is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust'. While diesel exhaust causes lung cancer in rats, it does not necessarily follow that the experimental studies are appropriate models for human cancer, and especially not true that the results from experimental studies are more relevant to understanding human health than the human studies.

Another area of confusion includes research on alcohol consumption and pancreatic cancer. Most studies have been negative, and some have been positive because heavy drinkers also smoke cigarettes. The lowest rates of pancreatic cancer in Europe are in France and Italy, which have the highest *per capita* consumption of alcohol. Because there is a 'biological rationale' to support such an association (alcohol affects insulin release in experimental studies and can impair the immune system) investigators continue to justify further studies.

The criteria of judgement offered by Bradford Hill was published in 1965. With the extraordinary advances made in new and more sensitive analytical chemical and molecular techniques over the past three decades, and the huge increase

Joshua E. Muscat *is at the American Health Foundation, 320 East 43rd Street, New York, NY 10017 (212) 551–2530, USA.*

1354–750X/96 $12.00 © 1996 Taylor & Francis Ltd

in the number of basic science and medical journals, the concept of biological plausibility has perhaps lost its original intent. With a careful search of the scientific literature, it is too easy to justify epidemiological findings by a *post-hoc* search through the experimental or basic science literature. The criteria 'biologically plausible' should be refrained to 'biologically probable'. The definition of 'biologically probable' needs to be worked out but perhaps should include consistent findings in toxicology, physiology, and biochemistry. There needs to be more careful consideration of interpretation of the results from very sensitive laboratory instruments. Simply detecting the presence of a chemical or genetic alterations caused by that chemical in human tissue does not necessarily infer that the chemical is a carcinogen for that specific tissue. We need to relate the quantity of DNA adducts to the risk of cancer in a meaningful way. In this way, epidemiologists can hold themselves to a higher standard and ensure that the results from other branches of medical and basic science are not too liberally used to overinterpret epidemiological associations. It also needs to be kept in mind that epidemiology does not always require biological explanations. Large relative risks or strong ecological correlations often provide important clues to the causes of disease even in the absence of a known biological mechanism. A stricter standard in defining biological causation cannot compensate for inherent epidemiological study biases. It can provide a basis for a more thorough evaluation of scientific studies.

References

AMBROSONE, C. B, FREDENHEIM, J. L., GRAHAM, S. *et al.* (1995) Cytochrome P450A1 and glutathione S-transferase (M1) genetic polymorphisms and postmenopausal breast cancer risk. *Cancer Research*, **55**, 3483–3485.

DOLL, R., GRAY, R., HAFNER, B. AND PETO, R. (1980) Mortality in relation to smoking: 22 years' observations on female British doctors. *British Medical Journal*, **280**, 967–971.

HILL, A. B. (1965) The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, **58**, 295–300.

NIKULA, K. J., SNIPES, M. B., BARR, E. B., GRIFFITH, W. C., HENDERSON, R. F. and MAUDERLY, J. L. (1995) Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. *Fundamental and Applied Toxicology*, **25**, 80–94.

PALMER, J. R. and ROSENBERG, L. (1993) Cigarette smoking and the risk of breast cancer. *Epidemiologic Reviews*, **15**, 145–156.

PERERA, F. P., ESTABROOK, A., HEWER, A. *et al.* (1995) Carcinogen DNA adducts in human breast tissue. *Cancer Epidemiology Biomarkers & Prevention*, **4**, 233–238.

PETRAKIS, N. L., GRUENKE, L. D., BEELEN, T. C. *et al.* (1978) Nicotine in breast fluid of nonlactating women. *Science*, **199**, 303–304.

PETRAKIS, N. L., MAACK, C. A., LEE, R. *et al.* (1980) Mutagenic activity in nipple aspirates of human breast fluid (Letter). *Cancer Research*, **40**, 188–189.

ROSS, P. E. (1995) Lies, Damned Lies and Medical Statistics. *Forbes*, August 14, pp. 130–135.

TAUBES, G. (1995) Epidemiology faces its limits [news]. *Science*, **269**, 164–169.