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EDITORIAL

From epidemiological association to causation

The fundamental objective of epidemiology is the identification of the causes of disease through the appropriate study of the distribution of cases within groups of humans with a range of identified characteristics, such as different levels of exposure to some agent, for example, a chemical. However, epidemiology is predominantly an observational (i.e. non-experimental) science that draws its data from the uncontrolled conditions of everyday life, and this greatly complicates the interpretation of the findings of epidemiological studies—to the play of chance must be added the real possibility of bias and confounding as alternative explanations to a causal relationship for the statistical associations thrown up by epidemiological studies. As a consequence, it is often very difficult to arrive at a reliable interpretation of an epidemiological association, a matter often considered in some depth by expert review groups, such as those convened by the International Agency for Research on Cancer. Much has been written on this subject, but some 40 years ago Sir Austin Bradford Hill [1] wrote a seminal paper on the interpretation of epidemiological findings that is still worthy of reading and reflection today.

Hill set out nine 'viewpoints', or guidelines, against which an epidemiological association might be assessed when attempting to reach an appropriate conclusion. Among the more important of these are strength of association, consistency of results, dose–response and (more important today than 40 years ago because of advances in the understanding of mechanisms) biological plausibility. Hill noted:

> None of my nine viewpoints can be indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?
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> No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis.

Hill's wise words need to be borne in mind today, with the tendency of some researchers to employ computers to trawl through epidemiological data in search of 'statistically significant' associations that then frequently become treated as if cause and effect relationships have been established.

Having carefully weighed the evidence and arrived at the inference that a given epidemiological association is causal, how may one judge whether a specific case of the disease in question was caused by the particular exposure? The methodology of assigned share, or probability of causation, allows a weight to be attached to the conclusion that a specific case has been caused by the exposure of interest—an assigned share in excess of 50% is usually regarded as having met the criterion of the balance of probabilities that the case has indeed resulted from the exposure. Compensation schemes based on the assigned share methodology have been adopted in the assessment of the role of occupational exposure to ionizing radiation in causing particular cases of cancer, for example, in the UK and the USA [2]. Such schemes are based on the reasonable assumption that cause and effect relationships between ionizing radiation and most forms of cancer have been established, and use sophisticated models that relate the risk of radiation-induced cancer to the recorded level of exposure (the radiation dose), as modified by factors such as sex, age at exposure and time since exposure.

In the UK, the Social Security Contributions and Benefits Act 1992 requires that a disease may only be prescribed if there is a recognized risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in individual cases. In order for a disease to be prescribed under the industrial injuries disablement benefit scheme, there has to be robust epidemiological evidence of a doubling of the risk, for a particular occupational circumstance, thus providing the framework for a decision on compensation, for individual cases, on the balance of probabilities [3].

Those assessing individual cases of cancer in terms of the likelihood that they were caused by particular exposures such as ionizing radiation are fortunate in that they are dealing with an established causal relationship, detailed radiation risk models and a widely accepted methodology for attaching weight to the conclusion of an exposure–disease link in a specific case. Thus, the only issue in an individual case is whether the relevant exposure is sufficient. What is to be done under circumstances that are not so accommodating? In this issue of *Occupational Medicine*, Guidotti [4] considers the example of compensating Canadian firefighters for cancer, and this illustrates well the difficulties encountered and the consequent compromises that must be made. Firefighters are exposed, to a greater or lesser extent, to a variety of

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carcinogenic exposures, and it is reasonable to expect that some cancers that develop in current or former firefighters are caused by these occupational exposures. The question is, of course, which cases? In the situation described by Guidotti, it is assumed that any one of eight types of cancer that develops in a firefighter has been caused by occupational exposure unless there is compelling evidence to the contrary (e.g. a lung cancer in a smoker). The eight cancers are identified by a review of the epidemiological literature concerning firefighters. Here, we encounter a major problem, in that judgement is based upon occupation (i.e. firefighter) rather than exposure (e.g. a specific chemical)—it is presumed that all firefighters will have experienced occupational exposure to the carcinogenic agent that is responsible for the epidemiological association between firefighting and the particular type of cancer (under the assumption, of course, that this association is actually causal). Then there is the difficulty of accounting for level of exposure—if exposure to an agent is not assessed, then low (or even no) exposure will have to be considered as likely to have caused the cancer as heavy exposure.

All this illustrates the difficulties of determining the appropriate balance in assessing the degree to which a particular cancer is likely to have been caused by a previous occupational exposure. For ionizing radiation and for a good number of cancer types, and for those cancers compensated under the industrial injuries disablement benefit scheme, causal relationships are reasonably well established and quantified, and this permits an identification of cases of cancer that are likely to have been caused by exposure, whatever the occupation (although there are likely to be other factors that enter into a judgement as to whether compensation is to be awarded or not). For firefighters, with much cruder methods of assessing the likelihood of a causal link, it is inevitable that compensation will be awarded to more (perhaps many more) individuals than actually suffered the cancer as a result of occupational exposure. That is not necessarily a bad thing, and society may well judge that any individual who may have been adversely affected by performing a courageous and worthy job such as firefighting should be adequately compensated; but the fundamentally uncertain nature of compensation under these circumstances must be recognized. The paper by Guidotti demonstrates the difficulties encountered in attributing causation under conditions that are far from ideal—practicalities dictate that something must be done by way of compromise, but this should not eclipse the real challenges to scientific interpretation that underlie the *realpolitik* of awarding compensation.

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