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POINT-COUNTERPOINT

# Corporate influences on epidemiology

Neil Pearce

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Corporate influences on epidemiology have become stronger and more pervasive in the last few decades, particularly in the contentious fields of pharmacoepidemiology and occupational epidemiology. For every independent epidemiologist studying the side effects of medicines and the hazardous effects of industrial chemicals, there are several other epidemiologists hired by industry to attack the research and to debunk it as 'junk science'. In some instances these activities have gone as far as efforts to block publication. In many instances, academics have accepted industry funding which has not been acknowledged, and only the academic affiliations of the company-funded consultants have been listed. These activities are major threats to the integrity of the field, and its survival as a scientific discipline. There is no simple solution to these problems. However, for the last two decades there has been substantial discussion on ethics in epidemiology, partly in response to the unethical conduct of many industry-funded consultants. Professional organizations, such as the International Epidemiological Association, can play a major role in encouraging and supporting epidemiologists to assert positive principles of how science should work, and how it should be applied to public policy decisions, rather than simply having a list of what not to do.

**Keywords** Epidemiology, epidemiologic methods, ethics

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At 10.30 a.m. on Friday, April 8, 1988, I was sitting in my office in Wellington, New Zealand, when someone arrived unexpectedly and started talking about a drug called fenoterol which might be causing an epidemic of asthma deaths in New Zealand. Two years later, fenoterol had been restricted in New Zealand and the death rate had fallen by more than half.<sup>1</sup> The drug was also restricted in Australia and Japan, and the company which makes the drug had agreed to halve its dose in other countries. The United States Food and Drug Administration had held hearings into the safety of beta agonists (the class of asthma drugs that fenoterol belongs to). Editorials had appeared in some

of the major international medical journals calling for the safety of drugs like fenoterol to be reassessed.<sup>2–4</sup>

So it was a successful 2 years, but also a very difficult period in which our research came under intense pressure from the manufacturer of fenoterol (Boehringer Ingelheim), from epidemiologists who had been hired as consultants by the manufacturer, and also from clinicians who did not believe that the drug was dangerous and were very critical of epidemiology.<sup>5</sup> In the course of doing this research, and subsequently, I met many other colleagues who had similar experiences after having discovered that a particular drug or chemical was hazardous. I recently published a book on 'the fenoterol story'<sup>6</sup> that provided me with the opportunity to reflect on the whole experience. In this article, I reflect more broadly on the pressures on epidemiologists who discover that a particular drug or chemical is hazardous, and the resulting controversies. I will focus on the fields of pharmacoepidemiology<sup>7</sup> and

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Centre for Public Health Research, Massey University  
Wellington Campus, Private Box 756, Wellington, New Zealand  
E-mail: n.e.pearce@massey.ac.nz

occupational and environmental epidemiology,<sup>8</sup> since these are the fields in which these issues most often occur.

## Epidemiology

Why is epidemiological research so often full of controversy? The main reason, perhaps, is that epidemiology deals with hazardous drugs and chemicals for which it is unethical and impossible to do a randomized trial. Thus, it is impossible to do a perfect study, and epidemiologists must learn to review all of the available evidence rather than attempting to reach a decision on the basis of a single study. For example, the studies linking smoking with lung cancer were bitterly criticized by 'conventional' researchers who were not willing to accept evidence from studies where the exposure had not been randomized.<sup>9</sup> However, the preliminary evidence that smoking caused lung cancer<sup>10,11</sup> was eventually supported by hundreds more studies in other countries. More recently, we have seen similar controversies with regards to the health effects of passive smoking.<sup>12-14</sup>

Perhaps the most legendary critic of epidemiology was the late Alvan Feinstein at Yale University. Before his death in 2001, Feinstein disputed most of the major epidemiological findings in recent decades, including the established causal associations between smoking and lung cancer, between oral contraceptives and thrombo-embolism, between diethylstilbestrol and vaginal cancer, between aspirin and Reye's syndrome, between tampon use and toxic shock syndrome, and between estrogens and endometrial cancer.<sup>15</sup> In each instance, these controversies were eventually resolved with the vindication of the original studies, but the debates often lasted for many years, and the necessary safety warnings and regulatory procedures were therefore delayed.<sup>16</sup>

It should be stressed that there are also plenty of examples, as in other sciences, where epidemiologists have got it wrong, and the findings of epidemiological studies have been contradicted by subsequent randomized trials. Examples include studies of beta carotene and cardiovascular disease, hormone replacement therapy, vitamin E and vitamin C intake in relation to cardiovascular disease, or fibre intake in relation to colon cancer.<sup>17</sup> However, these examples of 'epidemiological failures' primarily involve studies of lifestyle factors (particularly diet). These are notoriously difficult to study, since the 'exposed group' (e.g. those with high beta carotene levels in their diets) will often be markedly different from the 'non-exposed group' with respect to many different lifestyle factors. Furthermore, the multiple exposures considered in many epidemiological studies means that such studies frequently produce chance findings which may be widely reported in the press, but which are not replicated in subsequent studies.

This has led to some well-justified, and some less-justified, criticisms of epidemiology as being an unreliable science that frequently produces spurious findings.<sup>18,19</sup> However, these problems with epidemiological studies of lifestyle risk factors can, to some extent, be overcome by requiring replication of study findings, and by adopting a 'lifecourse approach' which takes account of the interconnections between different exposures and exposures contexts.<sup>17</sup> Furthermore, problems of multiple comparisons are not unique to epidemiology and apply to other areas of research, particularly genetic research.

More importantly in the current context, there are some areas of epidemiological research which are less prone to error. Ironically, these are often the areas in which there is the most controversy. In particular, there are usually only relatively minor problems of confounding in occupational epidemiology, since there are usually only minor differences in smoking, diet, etc between different groups of workers.<sup>20</sup> The situation is less consistently clear with regards to pharmacoepidemiology studies. Clearly there is a risk of 'confounding by indication' when studying the effects of a particular class of drugs (i.e. that patients with more severe disease may be more likely to be prescribed a particular type of drug), whereas there may be fewer potential problems of confounding when comparing the effects of different drugs within the same class.<sup>21</sup>

Thus, there are no universal rules about the reliability of epidemiological studies—it depends on the hypothesis being investigated and the study design being used to address it. Many of the criticisms of epidemiology as being inherently unreliable are applicable to studies of lifestyle factors, but are less applicable to pharmacoepidemiology and occupational and environmental epidemiology studies.

## Clinicians

It is often particularly difficult for epidemiological findings to be accepted by clinicians when these relate to methods of treatment. Almost all major discoveries in medicine have been met with bitter criticism and lasting controversy as leaders of the medical establishment have found their traditional ideas and world-view threatened by new ideas. In many ways, this parallels the situation in other fields of science, but there are some features of clinical research, which can make the struggle between new and old ideas particularly difficult and bitter.

One reason is that most methods of treatment have grown from a tradition of summarizing the clinical experience of individual doctors. This often amounts to no more than the 'gut feeling' of an eminent doctor based on their experience of treating individual patients. Although such practical experience can provide great insight, it can also be misleading, because every patient is different and the experience

of an individual doctor is often too limited to draw general conclusions from. For example, the average general practitioner would have only one asthma death in their practice every 10 years. If a new drug is introduced that doubles the risk of dying from asthma, the average GP would have two deaths in their practice every 10 years rather than one—they would probably not even notice that the death rate had changed, and would certainly not notice that deaths were more common in people using the new drug. Similarly, most GPs do not even know their patient's work histories, and are very unlikely to detect increases in risk of rare diseases that are associated with a particular occupational exposure.

But that is not the only problem. Even when established treatments have been tested in randomized trials and clearly shown to be ineffective or dangerous, doctors have been reluctant to accept the evidence. There are many such examples from the history of medicine, but one of the most famous is that of Ignaz Semmelweis, who discovered that puerperal fever ('childbed fever') could be prevented by requiring doctors to wash their hands in chlorinated lime before entering the ward, and between each examination.<sup>22</sup> His findings were not accepted by most of his medical colleagues, who took offence at the implication that they had been killing their patients with their unhygienic practices. Semmelweis was denied promotion, eventually became mentally ill and died in a mental hospital of 'childbed fever' contracted when he cut himself during his last obstetric operation. It was another 30 years before his ideas were revived and began to gain acceptance.

In the 1970s, Archie Cochrane, in a BBC documentary, described the reluctance of doctors to accept the findings of a randomized trial of coronary care units compared with home care for patients who had suffered a heart attack. The trial eventually found that patients cared for at home had a slightly lower death rate in the first year after their heart attack than the patients cared for in hospital. Cochrane had great difficulty getting permission to conduct the trial, which was considered unethical by coronary care doctors. Eventually it was allowed to proceed, provided that the progress was regularly reviewed. The initial results showed a slightly smaller number of deaths in the group with home care (six deaths) than in the group with hospital care (eight deaths):

'Just for fun I reversed the table, showing more deaths at home than in hospital... I showed it to some of the consultants before the meeting and there was an absolute uproar... 'that trial is unethical, it must be stopped'... so I let them go on a bit and blow their tops, and when they were calming down a bit I apologized that I had shown them the wrong table. I then showed them the

correct table, and said didn't they think it was unethical to continue with coronary care units, but I was unable to convince them... it does make the point that there is an enormous amount of emotion about coronary care units.'<sup>23</sup>

## Links between industry and clinicians

The difficulties of having evidence accepted that medicines in common use may be worthless or even dangerous, are strengthened by the close relationship between clinicians and drug companies.<sup>24</sup> The drug company 'sponsorship' of doctors has included not only direct advertizing, but also countless free gifts, ranging from pens and prescription pads to free meals, bottles of wine, cellular phones, holidays and educational seminars in exotic locations. Most doctors are unwilling to reveal the extent of their gifts from the pharmaceutical industry. Privately, many of them argue that they are unaffected by such gifts and that it would be foolish (rather than moral) to reject them. However, as a 1989 article in the *Journal of the American Medical Association* pointed out:

'Inherent in the relationship is an obligation to respond to the gift; this obligation may influence the physician's decisions with respect to patient care or possibly even erode the physician's character... The companies are, of course, motivated by profit, not altruism... Also, the fact that many physicians are not seasoned business people who are aware of subtle but compelling sales techniques probably contributes to the success of these marketing tactics.'<sup>25</sup>

Despite continuing concern about these issues over the last few decades, the influences of industry on undergraduate and postgraduate medical education continue to be strong and pervasive.<sup>26-30</sup> These influences are particularly strong in developing countries where most continuing medical education is funded by pharmaceutical companies.<sup>31</sup> Journals may also be strongly influenced by industry funding for advertizing.<sup>32,33</sup> For example, in 2004, an editorial questioning the benefits of an increased dose of Epogen in patients with renal disease was rejected by a journal because it went 'beyond what (the) marketing department (was) willing to accommodate'.<sup>34,35</sup>

## Industry consultants

These 'natural' tendencies for epidemiological research findings to be regarded with some scepticism, particularly by clinicians, are exacerbated by the activities of companies, which have produced a drug or chemical that is suspected of causing disease

or death. The usual approach is for the company concerned to hire epidemiologists as consultants to criticize the research publicly, either when it appears in print, or even prior to publication, as well as appearing as expert witnesses once the research has been published.<sup>36</sup> In recent years, these efforts have been further developed and refined with the use of websites and publicity that stigmatizes unwelcome research findings as 'junk science'.<sup>37-40</sup> In some instances these activities have gone as far as efforts to block publication.<sup>6</sup> In many instances, academics have accepted industry funding which has not been acknowledged, and only the academic affiliations of the company-funded consultants have been listed. This issue has recently received particular attention because of the controversy regarding Sir Richard Doll's undeclared acceptance of consultancy fees from Monsanto during the 1980s, with some condemning this outright,<sup>34</sup> while others have argued that different rules of disclosure prevailed at the time and that in any case, Doll's opinions are unlikely to have been affected by the acceptance of such fees.<sup>41</sup>

Recent examples include attempts to influence studies on the toxicity of benzene<sup>42</sup> and diesel particulate matter,<sup>43</sup> and the various industry efforts over many years to influence the conduct and interpretation of research into the health effects of dioxin.<sup>34</sup> Perhaps one of the worst such examples has been the industry campaign to undermine an OSHA chromium (VI) standard<sup>44</sup> and corporate infiltration of a panel convened to set standards for chromium (VI) in California.<sup>45</sup> This involved the ghostwriting of an article,<sup>46</sup> which was later retracted by the journal,<sup>47</sup> which claimed that a Chinese scientist had re-evaluated his findings and reversed his conclusions on elevated cancer risks in residents of Jinzhou, China, who were exposed to chromium (VI) in water.<sup>45</sup>

Many leading epidemiologists would argue that they are not influenced by industry funding. They study the evidence objectively, and then make their opinions known for the benefit of society, and if they receive some funding along the way, then that is entirely appropriate.<sup>48</sup> In fact, although such consultants are invariably paid well, this is usually not necessarily their main motivation, and the pressures on them are usually more subtle than this. This is typified by remarks from an American lawyer, John C Shepherd of St Louis, who was President of the American Bar Association in 1984-85:

'The first thing you need to get along with your expert witness is money. But the hiring and successful use of an expert may not be that easy—a lot of good experts are rich. Although you will eventually be talking about money with your expert, it is wiser to begin on another tack. Tell your expert how justice will be served if he will testify on your side of the case. Remind him how the unfortunate situation in our courts today can

be improved if we have people of his caliber to help in the administration of justice. That ploy will impress even the rich expert.'<sup>49</sup>

A second line of defence of their activities that is often offered by 'modern epidemiologists' involves a relatively crude (and convenient!) interpretation of the (already crude) Popperian philosophy of science.<sup>50</sup> It is argued that 'science is about criticism' and that by being critical of colleagues' work corporate-funded epidemiologists are simply doing their duty as scientists—who pays them for it is irrelevant.<sup>48</sup> However, there is substantial evidence that the source of funding strongly influences the conclusions that are reached, e.g. in the cases of tobacco<sup>51</sup> and calcium-channel antagonists.<sup>52</sup> This makes it essential that any sources of funding, and potential conflicts of interest are declared. Nevertheless, it has been argued that the declaration of conflicts of interest is 'the new McCarthyism in science',<sup>53</sup> and the requirement that at least one investigator who is independent of any commercial funder should take responsibility for the integrity of the data and the accuracy of the data analysis is 'unfair—and absurd'.<sup>54</sup>

It should be emphasized that a company clearly has a right to argue against what it believes are weak data or incorrect conclusions, and it is not in the interests of society or the company to withdraw a drug which has been wrongly accused.<sup>55</sup> However, equally clearly, a company has a moral obligation to seek the truth of the matter when obtaining advice from consultants, rather than just preparing the 'case for the defence'. The latter usually occurs, even if the hired consultants are relatively neutral in the dispute and merely sit on an 'expert panel'. This is not to imply that deliberate corruption is a common occurrence. However, a company which intends to prepare the 'case for the defence' may seek out academics who (usually because of sincerely held beliefs) have been very critical of similar studies in the past. Thus, the shaping of the 'case for the defence' usually involves 'selection' rather than 'coercion' of experts. As Paul Stolley has observed:

'If you hire somebody to look at a paper which has a new discovery, and there have been obvious difficulties in doing the study, and this guy doesn't believe that DES [diethylstilboestrol] causes cancer of the vagina, that there's not enough evidence to implicate tampons with toxic shock, that there's not enough evidence to believe estrogens are related to uterine cancer, has even questioned the cigarette smoking/lung cancer association. If that's the guy you hire, you don't have to be a genius to figure out where he's going to come down on this issue'.<sup>6</sup>

It should be stressed that criticism plays an important role in science, and even very biased critics may make important points. However, an overemphasis on criticism can lead to the dismissal of almost any scientific

study as being 'fatally flawed'. At a conference on ethics in epidemiological research, I once presented a satirical set of guidelines for a 'corporate epidemiologist' who is asked to review a study:

- (1) Consider only the specific study that you have been asked to review. Don't consider supporting evidence from other epidemiologic or experimental studies.
- (2) There are three possible questions you could consider: (i) is there any chance that the study findings are right? (ii) is there any chance that the study findings are wrong? (iii) what is the balance of evidence? Restrict yourself to the second question.
- (3) Prepare a list of possible biases. Do not comment on the likely direction or magnitude of the biases. Conclude that there are many 'fatal flaws' in the study and it is therefore uninterpretable.
- (4) Decline to comment directly on policy, but insist that further studies must be undertaken which avoid the biases identified in step 3.
- (5) Go back to step 1.

## Regulatory authorities

The selection, by a company with a vested interest, of a few scientists who follow the 'guidelines' given above, and are hypercritical of others' work can therefore result in massive pressure on regulatory authorities. This pressure is particularly effective because it seems to come from independent scientists—it would not be taken so seriously if it came directly from the company. In this sense, the company's consultants have the privilege of acting as 'lawyers for the defence' while maintaining the image of being an 'independent jury'.

However, this is not an insurmountable problem provided that regulatory agencies maintain a strict independence from industry (and from other influences), recognize the pressure from industry consultants for what it is, and hire their own independent consultants. Unfortunately, in recent years the threats to the integrity of science have come from government as well as from industry.<sup>56</sup> For example, Clapp *et al.*<sup>57</sup> cite a recent report of the US Congress which cited a number examples of how the current administration has manipulated scientific review procedures, including 'inappropriate questioning of prospective members of scientific review committees about their political views; removal of long serving members on the basis of political litmus tests; and blocking research funding and the publications of research results, when these appeared to reflect badly on economic interests supporting the administration'. In particular, the recent public-health catastrophe of the licensing of Vioxx, and its continued use after evidence had appeared of its cardiovascular side effects has indicated 'lethal weaknesses' in the US Food and Drug Administration.<sup>58,59</sup>

## Epidemiological organizations

So what can be done about these pressures from industry, and in some instances from governments, to obstruct or influence the conduct, publication and policy response to research that shows that particular drugs or chemicals may be hazardous? There are things that we can do collectively as epidemiologists, and also things that we can do as individuals.

With regards to what can be done collectively, there is no simple solution. However, for the last two decades there has been substantial discussion on ethics in epidemiology,<sup>60-63</sup> partly in response to the unethical conduct of many industry-funded consultants.<sup>64</sup> A number of websites (e.g. [http://www.ucsu.sa.org/scientific\\_integrity/](http://www.ucsu.sa.org/scientific_integrity/) and <http://www.cspinet.org/integrity/>) are now devoted to fostering integrity in science, and the International Epidemiological Association has issued a report on 'good epidemiological practice'.<sup>65</sup> Recently there have been renewed calls for scientists to 'engage in processes to assert positive principles of... how science should work, and how it should be applied to public policy decisions' rather than simply having a list of what not to do. This will require 'strong pressure from within the scientific community for codes of ethics conduct and financial conflict of interest'<sup>57</sup> with the goal, not of restricting what people can do, but to ensure complete transparency 'through full declaration of potential sources of conflicts of interest'.<sup>66</sup> For example, Vallance has recently suggested that full disclosure of conflicts of interests should form the opening sentences of any publication, rather than being buried in small print in the acknowledgements.<sup>67</sup>

## Researchers

However, these are developments that, if they succeed at all, will take some years to bear fruit. In the meantime, what can be done by researchers who have discovered evidence that a particular drug or chemical may be hazardous? In theory, any evidence of hazard should be made immediately available to the scientific community, and should have some influence on public health decision-making. In practice, researchers who have discovered evidence that a particular chemical or drug may be hazardous require very strong evidence, perseverance, a sense of humour and a good lawyer.<sup>5</sup> Even then, there is the danger that, despite the best of intentions, researchers may overreact to the resulting wave of criticism and may tend to overstate the case against the chemical or drug, particularly if they consider that the criticisms of the corporate-funded consultants are trivial, irrelevant or incorrect.

Many other colleagues of mine have also had their research attacked by vested interests. When asked, I always give them two pieces of advice.<sup>6</sup> First, don't take the criticisms personally, even if the attacks are

personal—if you get emotional and respond emotionally, you will always regret it the next day. Second, no matter how much you think your critics are bending the evidence, don't ever exaggerate the evidence that supports your case—keep to the facts and don't try to stretch them, try to be balanced, and be self-critical of your work, even if you know that your opponents will misuse this. As Paul Stolley has written:

'The pharmacoepidemiologist must develop a thick skin; this is not a field for timid souls. More important, the pharmacoepidemiologist must have some historical and ideologic anchorage and perspective to be able to understand the nature of the attacks. The history of drug regulation, the battle for effective drug efficacy and safety standards, and the connection of drug regulation with the sanitary movement of public health are all a part of the progressive tradition we have inherited as epidemiologists.'<sup>7</sup>

Ultimately, the best approach for researchers is to address any criticisms in subsequent studies. It is important to remember that epidemiological research is usually a marathon rather than a sprint, and that to the extent that debates ever get settled, this happens

over many years. When you are involved in a major controversy it is important to ignore temporary problems and criticisms—real or imaginary, justified or unjustified—and to concentrate on the research. How is the controversy going to be viewed in 15 years time? How will you feel about it and about yourself? If education is what is left once everything we learned at school is forgotten, research is what is left when individual studies and publications are forgotten, or languish uncited in the archives. The stakes involved make it even more important not to get side-tracked and to focus on doing more research and better studies. Most of the time, science wins in the end, but there are things that we can do as epidemiologists, both individually and collectively, to increase the chances of this happening.

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### KEY MESSAGES

- Corporate influences on epidemiology have become more pervasive in the last few decades.
- These influences are major threats to the integrity of the field.
- In response to this there has been substantial discussion on ethics in epidemiology.
- Professional organisations can play a major role in encouraging and supporting epidemiologists to assert positive principles of how science should work and how it can be applied to public policy.

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# Commentary: Epidemiology and the pharmaceutical industry: an inside perspective

Joanna Haas

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Neil Pearce's impassioned comments on 'Corporate Influences on Epidemiology'<sup>1</sup> are designed to raise awareness of industry activities that he believes 'are major threats to the integrity of the field, and its survival as a scientific discipline'. He argues that 'for every independent epidemiologist studying the side effects of medicines there are several other epidemiologists hired by industry to attack the research and debunk it as "junk science"'. While we recognize his depth of feeling, passion may nurture bias of its own. The relationship between science and industry is complex, and the role of epidemiologists in the pharmaceutical industry is not limited to debunking 'junk science'. Balanced evaluation and discussion are necessary to provide accurate safety information to physicians and patients. Unfortunately, such temperate interchanges rarely make headlines and seldom sell books.<sup>2</sup>

According to Dr Pearce, the tobacco industry, the pharmaceutical industry and all the industries studied by occupational epidemiology should be grouped together as the 'corporate influences' that threaten

the discipline of epidemiology. Quite apart from the tobacco industry and smoking-related diseases, the issues related to occupational epidemiology are very different from those related to pharmacoepidemiology, both with respect to regulatory framework and critical methodological challenges. Epidemiology is a core discipline for the development of medicinal products; this is not the case for the tobacco industry or for other industries. Dr Pearce seems deeply aggrieved and doubtless feels justified in pooling together the corporate enemies; however, we suggest that discussion is better served by assessing these very different groups separately. Since we are epidemiologists working within the pharmaceutical industry, our remarks are best confined to our area of expertise: epidemiology in relation to medicinal products.

## The role of epidemiology in drug development

Epidemiological investigation has become an essential component in the development of pharmaceutical and biological products. Characterization of target medical conditions with respect to occurrence, natural history, outcomes, related costs and the medical context in which they are managed frequently involves epidemiological analyses. While some of these issues reflect

MD, MSc, Vice President, Pharmacovigilance, Genzyme Corporation, For the Pharmaceutical Research and Manufacturers of America (PhRMA) Pharmacovigilance and Epidemiology Group, 675 W Kendall Street, Cambridge MA 02142, USA. E-mail: joanna.haas@genzyme.com