HE WHO PAYS THE PIPER CALLS THE TUNE

In April of this year, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) disbanded an expert panel that had begun to review the safety record of selective serotonin reuptake inhibitors (SSRIs). This followed disclosures in the *Guardian* newspaper that two members of the 16-strong panel held shares in GlaxoSmithKline (GSK), the manufacturers of one of these compounds, paroxetine (Seroxat/Paxil). Significantly, GSK had paid out $6·4 million in the US to the family of Donald Schell, a victim in the killing spree, ended by suicide, of a patient on Seroxat. Over the last two decades there had been a large number of calls for both Seroxat and fluoxetine (Prozac) to be withdrawn from the market following allegedly similar incidents in the UK, involving either murder or suicide. The professional expert group had been constituted under the aegis of the MHRA and had observed the accepted rules of engagement for Section 4 Committees such as the Committee on the Safety of Medicines: all members are required to announce in advance and have registered any interest (either personal, non-personal, direct or indirect) in a medicine or group of medicines due to be discussed, and to exclude from the meeting any member with any personal and specific interest.

In disbanding the panel, the MHRA appears to have accepted that public opinion is increasingly suspicious of the influence of pharmaceutical manufacturers on doctors, and that proceeding with the same panel was simply going to be more trouble than it was worth. This occurred against a background of numerous warnings about conflict of interest in high-profile medical and scientific journals[1] over the past three years, not to mention stone-throwing by members of the profession from the safety of their glass houses. Presumably these missiles, spearheaded with phrases such as 'legal jeopardy' and 'In the grip of the python', are not intended to be ignored.[2,3] A more pragmatic and helpful article is entitled 'Dancing with the porcupine'.[4] Drs Arnold Relman and Marcia Angell,[5] two former editors of the *New England Journal of Medicine*, published late in 2002 a detailed and all-embracing account of the problems facing the medical profession, with the title 'America's other drug problem: the insatiable greed of the pharmaceutical industry'. A new concern is the purchase of for-profit clinical research organisations (CROs) by global advertising agencies handling pharmaceutical accounts.

Over the last three years, a large number of journal and newspaper editorials, systematic reviews and statements by professional societies and public bodies have emphasised the need for authors to declare in print any 'conflict of interest'. In their recent review, Bekelman *et al.*[6] define 'conflict of interest' from the literature: 'A set of conditions in which professional judgement concerning a primary interest (such as a patient's welfare or the validity of a research finding) tends to be influenced by a secondary interest (such as financial gain).' Financial interests are not the only, or necessarily the most powerful, secondary interest. Others include the desire of investigators and institutions for recognition, and, in the UK and elsewhere (e.g. Germany), to score highly in league-table exercises such as the Research Assessment Exercise (RAE) conducted by universities.[7]

For this paper, only a few controversies were selected, concerning the meaning of full disclosure, the commercialisation of our institutions and the need to introduce mechanisms to protect the individual clinical trialist from their employers and wealthy pharmaceutical companies. Deliberately avoided was any discussion of 'non-financial conflict of interest', which might be one explanation of investigator bias and false positive findings. The review by Ernst and Canter[8] is particularly poignant and relevant in this regard.

This editorial was prompted by indignation on reading the statements and editorials on conflict of interest of a number of journals managed by members of the medical profession, and then discovering, often in the same volume of the journal, papers in which one or other of the signatories gives accounts of clinical trials followed by a statement that the authors had 'no conflict of interests'. Is it really possible that they and their institutes received no financial benefit from these particular studies, and are the benefits they received for other studies funded by the same, or perhaps rival, sponsors for other more specific studies irrelevant? It appears essential that there should be a consistent approach to the declaration of any 'conflict of (financial) interest', and that full disclosure should, by and large, mean all the benefits received, including those that come to a department or institution by dint of the investigators' skills. Otherwise, the only option is for us all to ignore the requests of journals for conflict of interest statements and ensure that our own house is put in order by exhorting the universities to appoint appropriate overseeing committees. Hopefully, in time, the brief of such committees would include the control

of stone-throwers.

In the US, the current regulations of the Public Health Service and the National Science Foundation require medical schools and other research institutions to report conflicts of interest, but allow the institutions to manage conflict locally. In a survey of 127 medical schools, 170 research institutions, 48 journals and 17 federal agencies, it was shown that no policy on conflict of interest had been developed in five medical schools and ten research institutions. Ninety-one percent had adopted the federal declaration threshold of $10,000 in annual income or equity, or 5% ownership of a relevant company. Only 43% of journals and four federal agencies required disclosures of financial conflict of interest. The survey by McCrary *et al*.[9] draws attention to the great variability of institutional policies, the lack of external accountability and the absence of local schemes to manage conflict of interest. A much earlier attempt by the National Institutes of Health to tighten up its guidelines was withdrawn following an outcry: this recommended prohibition of holding equity in any company affected by an individual's research and disclosure of 'all financial interests' by the investigators regardless of the relevance of these finances to their research.

Complacent self-interest is not always the rule, however: the American Society of Clinical Oncology (ASCO),[10] with 20,000 members, has just reformed its existing policy on conflict of interest in which any financial interest is disclosed, including gifts and travel expenses from a project sponsor in excess of $100. The American Society of Clinical Oncology also suggests that certain financial inducements to participate in clinical trials should be banned, although they emphasise their willingness to help the individual physician who has difficulty abiding by these rules, to manage clinical trials provided steps are taken 'to ensure public confidence in their objectivity'. By adopting an exceedingly aggressive disclosure policy in which only payments of less than $100 are exempt, and defining the conditions for disqualification of an investigator, ASCO has deliberately set out to challenge all other players in clinical research to issue equally clear guidance on what must be disclosed. Their hope is that such policies will encourage patient participation in clinical trials by bolstering public confidence in the integrity of clinical research.

Earlier this year, a systemic review of the scope and impact of financial relationships between industry, scientific investigators and academic institutes was published in the *Journal of the American Medical Association* which identified 144 full papers potentially containing quantitative data and analysed 37 of these in depth. Bekelman *et al.*[11] concluded that approximately 25% of investigators had industrial affiliations and, rather surprisingly, roughly two-thirds of academic institutions held equity in start-up companies that sponsor research in these institutes. From an analysis of eight papers which evaluated 1,140 original articles, they came to the statistically valid conclusion that industrial sponsorship and a pro-industry conclusion went hand-in-hand. In addition, industrial sponsorship was associated with agreements that restricted publication and data-sharing. A new study, by Als-Nielsen *et al*.,[12] of Cochrane reviews of randomised drug trials has come to a similar conclusion: trials funded by for-profit organisations may be more positive due to biased interpretation of the results. Thus it is difficult to deny the financial relationships that exist between industry, scientific investigators and academic institutes, in the US at least, and that these conflicts of interest influence biomedical research. In the last two decades the percentage of biomedical research funded by industry almost doubled to 62% in the US (National Institutes of Health Extramural Data and Trends, 2000. Bethesda, Md: National Institutes of Health).[13, 14]

Recent figures from Centerwatch,[15] an independent monitor of clinical trials, suggest that the percentage of clinical trials organised by academic health centres on behalf of industry had dropped from 71% in 1991 to 36% in 2001. Centerwatch suggests that this is a result of academia shunning clinical trials funded by industry, in part due to potential conflicts with overbearing industrial sponsors. However, it acknowledges that this change has been accompanied by an increase in the number and size of the for-profit CROs. Although Paller *et al*.[16] suggest this is a result of greater academic integrity, a more cynical view would be that clinicians have found a more satisfactory way of working with industry, which avoids some of the irksome behaviour of their institutions towards conflict of interest on the one hand and sharing out the profit on the other. Industry may also take the view that this is the only way in which it can take ownership of the data and responsibility for its validity. It is difficult to believe, as implied by these authors, that a whole new generation of clinical investigators have appeared who work solely for these commercial concerns and are entirely divorced from academic institutes.

The growing commercialisation of our academic institutions is documented in a large number of reviews, one in particular dating back to 1918. Perhaps the most accessible of these sources is a new book, *Universities in the Market Place: The Commercialization of Higher Education*,[17] by Derek Bok, the outspoken former President of Harvard University and Dean of the Harvard Law School. Although the book reads like a series of after-dinner speeches, it is immaculately referenced and full of pragmatic solutions to many of the problems highlighted in this review. Bok's thesis is that the universities are the main source of the three ingredients most essential for continued growth and

prosperity: highly trained specialists, expert knowledge and scientific advances. Commerce, Bok argues, feels that its role is to transform these ingredients into valuable new products or life-saving treatments and cures. This recognition of the university's role in the nation's economic future has led to an increase in media interest, greater funding from government and charitable foundations, and a closer scrutiny by public officials. Rather ironically, the increased interest in their link with the economy has made the universities more aware of new opportunities to make money. In particular, they have discovered their ability to sell the expertise of their staff and the rights to use their scientific discoveries to the highest bidder. Bok also draws attention to the way in which the pharmaceutical industry is repeatedly invited to subsidise continuing medical education and suggests that the educators cannot afford to surrender this responsibility. Rightly, the public expects prescribing to be totally objective and reacts very badly to any suggestion that the profession is influenced by financial concerns, even if these are imposed by government bodies. Bok is rather pessimistic about the medical profession's ability to deal with this particular problem. He suggests other faculties may still have time to avoid greater entanglement with the commercial concerns anxious to place their teaching material on the web complete with logo.

This has engendered in the universities a new eagerness to earn even more, regardless of the possible compromise of the basic academic freedoms we all take for granted. As Bok points out, while none of these commercial practices are particularly new, the size and scope are unprecedented. Interestingly, he places a sizeable amount of the blame on the desire of senior university administrators for bigger and more powerful institutions. He pays only passing lip-service to the idea that government cutbacks may be a precipitating cause of the universities' desire to become more entrepreneurial. His comments about the desire of senior administrators, including presidents and deans, to enhance the assets of their institutions are well taken and the apparent hunger of these administrators for more power underlies his suggestion that the solution lies with subcommittees set up by the university trustees rather than senior academics. In all probability this approach would in turn require an in-depth review of the way trustees are selected. Often their wealth or business expertise is their major attribute, rather than their sense of public good.

In his review of Bok's book, David Baltimore[18] clearly admires the stance of Bok and the medical faculty in Harvard[19] but adopts an alternative argument and describes Bok as a 'purist'. He draws attention to the *Madey v. Duke University* (2002) case in which a federal appeals court decided that 'The correct focus should not be on the nonprofit status of Duke University but on the legitimate business Duke is involved in.' The Bayh–Dole Act was passed in 1980 specifically to speed the commercialisation of research and indirectly boost the sagging American economy by allowing universities to commercialise federally-funded research. In a recent Policy Forum article in *Science*, Thursby and Thursby[20] review the way universities in the US, between 1991 and 2000, have increased the number of inventions disclosed by 84%, new patent applications by 238%, license agreements by 161% and royalties by 520%. In 2000 the total revenue from this activity reported by 156 universities was $1·24 billion, i.e. about 4·7% of their total research expenditure. It should be noted when comparing this figure with the equivalent figures for the UK that in this American study this sum is net of the cost of arranging and managing the contract, while the UK figure includes 'overheads'. Importantly, Thursby and Thursby cite surveys to suggest that publications, meetings and consulting remain the major ways for industry to learn about academic research. This is understandable since the surveys they quote show that 46% of inventions and 72% of ideas supported by proof-of-concept studies fail to materialise. They also make a number of calculations which suggest that, on average, university technology transfer offices lose more money than they make, and rather naively go on to suggest that profits are not the sole goal of university efforts to promote commercialisation of research. They conclude finally that university licensing facilitates technology transfer with minimal effects on the research environment. Unfortunately, it is not clear without further surveys whether licensing and publishing go hand-in-hand or whether in some instances licensing has begun to replace publication.

Obtaining the figures for the value of industrial contracts to universities in the UK was harder than anticipated. For instance, one assumes that all the data collected during the last RAE[21] for the five-year period from 1995–2000 would be freely available on a website: this is not the case. If they were available, these figures could be quite revealing. Looking solely at money that was awarded to named individuals in Unit of Assessment 3 (Hospital-Based Clinical Subjects) from 'UK Industry, Commerce and Public Corporations' in the 27 universities with medical schools throughout the period of the study, the sum totalled £147 million, equivalent to about 12% of their research spend. This excludes similar awards from the European Union (EU) and overseas, including the US. In addition, it does not include money contracted to commercial companies operating within a single university whose profits are donated to the university, or contracts awarded to hospital trusts but funding work directed by university staff. Since most universities thought it would be to their advantage in terms of RAE scores to maximise this figure, one must assume it contains a number of costs that are not included in the figures for Research Council-funded

research or the American studies discussed earlier. It is important to note that the influence of this money within individual departments and faculties is often much greater than the overall figure of 12% suggests. Its expenditure is usually authorised by a small group of individuals, and it can be used in ways that differ from those usually associated with funding from the Research Councils and the charities. Unfortunately, there is also a risk that this money will receive undue weighting by senior administrators when individuals are considered for promotion and/or distinction awards. In other words, this funding is highly prized and has an undue impact on the kudos of individual departments, and indeed of individuals.

Clearly the interactions between industry and academic institutions have boosted medical advances, have led to the introduction of many essential new technologies and have provided new financial support for education. There is, however, a danger that the failure to disclose unrecognised conflicts will lead to public anxiety about the influence of money on the research process. In the UK, this anxiety extends well beyond the public. For instance, the Royal Society has just published a study entitled 'Keeping science open: the effects of intellectual property policy on the conduct of science', which asks universities to refrain from aggressively seeking so many patents. One member of the study panel, Roger Elliot, a theoretical physicist at the University of Oxford, commented to *Science*,[22] 'What concerned us most was the drive towards research aimed at creating intellectual property.' However, in a recent submission to Parliament, the Royal Society stated in paragraph 28 in the section on 'The Future Development of University Research': 'Our major charities . . . have a significant role to play in the development of research capability. This is also true of our innovative firms . . .which should seek out the most appropriate university research partners . . .'[23]

Earlier this year Colin Blakemore, Chief Executive Designate of the Medical Research Council, and Sir Paul Nurse, Nobel Prize winner and spokesman for Cancer Research UK, took part in an interview on BBC Radio 4,[24] essentially to discuss the trustworthiness of scientists and the necessity for press releases that extol the value of new research findings and increase prematurely the expectations of patients. They both seem happy with the idea that scientists working on basic research in our universities funded by public money and scientists working on developments and applications in industry live on different planets. It is hard to believe that the sole purpose of these press releases is to encourage patients and benefactors rather than to increase the likelihood or value of licences or patents. This ambiguous approach by the Royal Society and by senior figures involved in the public funding of research makes it difficult to believe that even these august bodies would be able to organise the nationwide management of conflict of interest in the UK.

In a 'Sounding Board' article, 'Academic Freedom in Clinical Research' in the *New England Journal of Medicine*,[25] Weatherall of Oxford and Nathan of Boston summarise the well-publicised dispute between Nancy Olivieri and one of the manufacturers of deferiprone, a bivalent iron chelator.[26, 27] Olivieri, a professor at the University of Toronto's Hospital for Sick Children signed a contract with a Canadian pharmaceutical company to perform clinical trials on a drug to treat thalassaemia. When her findings showed the drug not only to be less effective than originally thought but potentially hazardous, she published her results against the express wishes of the company. The company accused her of deviating from their agreement, cancelled her contract and tried to discourage her reporting her findings by threatening to take her to court. A faculty associate sought to discredit her results by writing anonymously to colleagues and the media, and publishing contrary findings without disclosing that his work was funded by the same company. The hospital suspended Dr Olivieri for failing to observe hospital regulations, and directed her and her colleagues not to discuss the matter publicly. The University of Toronto made no effort to intervene despite a flood of unfavourable publicity about the treatment of Olivieri. It then became known that the University had for sometime been in discussions with the same pharmaceutical company about a sizeable donation. Only after the intervention of a number of distinguished American and British clinicians did the University initiate negotiations with the Sick Children's Hospital that restored Olivieri's position and allowed her to resume her research. Interestingly Bok[17] suggests that John Le Carré's novel, *The Constant Gardener*, is a fanciful but thinly disguised account of this and similar tales of woe involving woman scientists and leading universities.

Weatherall and Nathan were particularly incensed by the failure of the Hospital for Sick Children and the University of Toronto to support Dr Olivieri. They draw attention to the review by the Canadian Association of University Teachers,[28, 29] and use this case to make a plea for changes that might preserve the academic freedom of the individuals in disputes with commercial concerns and their employer, university or hospital, which may have a general or specific financial interest. Academic freedom is required at the very least to ensure honest reporting and, indirectly, the safety of patients. The article opens by making the point that new therapies will only arise from the human genome project through increasingly effective partnerships between academia and industry. Their plea is for additional measures to protect clinical investigators from the enormous legal and financial power of the pharmaceutical industry which may be thrown at them when the outcome of a particular study becomes controversial. This could be achieved by recognition, in the original contract for the clinical trial, of an independent external review panel to

mediate in cases of scientific disagreement about the outcome of a particular study. Although this sounds straightforward at a local level, they argue such a panel would have more teeth if it were to be established as an independent national panel. Interestingly, the pharmaceutical company concerned replied by publishing a letter, in the same journal, suggesting that Nathan had not disclosed the full extent of his own financial interests.[30]

Several reviewers of Bok's book, discussed earlier, have suggested it should be required reading for heads of universities, their trustees and deans of medical schools. However, one could go further and suggest that all those involved in medical research should read Dr Relman's review of the book in the *New England Medical Journal*.[31] Relman, who has been fighting this battle for at least 20 years,[32] very effectively uses his account of Bok's book to argue:

> If a handful of the most prestigious and influential medical schools were to adopt new guidelines that drew clear and reasonable limits to protect research and education from the worst effects of corporate influence, we would be well on the way to a solution.

It is difficult not to conclude that effective policing of financial conflict of interest in clinical and biomedical research is, and will be, extremely difficult. The safety of patients and volunteers must be an overriding concern. Bias must be eliminated, and not just by good experimental design; yet innovation must not be stifled. Unfortunately, management of financial conflict of interest cannot be entrusted to academic or professional institutions which in one way or another stand to gain from the commercialisation of research. Efforts to respond to this situation by professional societies and journals has shown a remarkable but perhaps understandable variability; some pressing for prohibition of certain financial relationships while others favour full disclosure with some arbitrarily set limits. Perhaps the first step is for academic institutions and peer-review journals to ensure that investigators have full access to their study data and have a contractual right to publish the final outcome unhampered. However, even this commitment will not deal with publication delays resulting from the desire of institutions, charities and individuals to pursue patent applications and exploit intellectual property. Attempts to use definitions of disclosure of 'conflicts of interest' that are ambiguous and fail to change current practice will need to be actively discouraged. Meanwhile, the public and the press would be wise to accept that quangos such as the MHRA can hardly be expected to do any better than their masters in the House of Commons in operating a policy of full but limited disclosure!

CONFLICT OF INTEREST STATEMENT

The writer holds a single consultancy with an overseas pharmaceutical company. He and his family hold equity in a number of pharmaceutical companies and are directors of a small limited company. His past employer continues to benefit from his past associations with industry. Full details of these activities have been declared to the College.

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