The influence of big pharma

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Wide ranging report identifies many areas of influence and distortion

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> . . . he would have us believe that his drug has been discovered by chemical research of alchemical profundity, and is produced by a process so costly and elaborate that it can only be sold at a very high price.[1]

A report published last week on "the influence of the pharmaceutical industry" describes a strong United Kingdom pharmaceutical industry, whose net exports are worth over £3bn ($5.6bn; €4.3bn) annually.[2] The industry's declared goal is "to bring patients life-enhancing medicines," a goal "not only necessary but noble." The House of Commons health committee examined the means used to achieve this noble end. They found an industry that buys influence over doctors, charities, patient groups, journalists, and politicians, and whose regulation is sometimes weak or ambiguous. For example, the Department of Health, responsible for a national health service that spends £7.5bn on drugs annually, is also responsible for representing the interests of the pharmaceutical industry.

The committee described how the industry taints doctors. Over half of all postgraduate medical education in the UK, and much education of nurses, is funded by the pharmaceutical industry from its annual marketing budget of £1.65bn. The Department of Health spends just 0.3% of this on publishing independent information on drugs. "Key opinion leaders" may receive £5000 for giving an hour's lecture. The committee found this surprising. Their report recommends that the General Medical Council maintain a register of "all substantial gifts, hospitality, and honoraria received by members." In this way, professional self delusion that "marketing does not influence us" may bring outside regulation.

The industry spends £3.3bn annually on research in the UK, financing about 90% of all clinical drug trials, but develops few truly innovative drugs. It influences the interpretation and reporting of results of trials. Negative results can be dismissed as erroneous ("failed trials"), whereas positive ones can be published repeatedly in different guises.[3] The committee report recommends establishing an independent register of clinical trials, containing full information and available at the time of product launch, as a condition of authorisation for marketing. Registering all trials at their inception might be better so that "failed" trials can also be scrutinised.

The committee noted that drug advertising deliberately associates brands with attributes that satisfy the emotional needs of the professionals—the "strategy of desire."[4] The report recommends closer scrutiny of advertisements and limits to promotion aimed at inexperienced prescribers. It also recommends that medical undergraduates learn more about clinical trials, adverse drug reactions, and marketing by drug companies. Unfortunately, clinical pharmacology has disappeared from many medical school curriculums and will need active resuscitation.[5] The report also suggests that marketing and prescribing be limited when a product is first licensed, to allow experience to accrue. The idea of a probationary period is attractive, but formal trials of relative efficacy within the NHS would be better.[6]

Companies can only market products if they have authorisation to do so from the Licensing Authority. The Medicines and Healthcare Products Regulatory Agency (MHRA) is its executive arm, with an annual income of £65m derived entirely from licensing fees. The committee thought that the need to attract pharmaceutical business could conflict with the MHRA's primary task of protecting the public. They also questioned the thoroughness with which the MHRA reviewed data submitted for licensing, and its ability, after licensing, to detect adverse drug reactions and act on them.

As evidence, the report cites the fact that "only 19 drugs have been withdrawn between 1993 and 2004," but "medicines can be licensed in the absence of adequate data or investigation into possible adverse reactions. . ." The MHRA cannot win with this analysis: if it withdraws drugs, it has failed in the first place to obtain adequate information to predict adverse reactions; and if it does not, then it has failed to detect adverse reactions. The committee chose rofecoxib as an example. We now know from a large randomised trial that this coxib probably increases the risk of thromboembolism by 1:140 patient years, less than twice the background incidence.[7] To confirm such small increases is notoriously difficult.[8 9]

The spontaneous adverse drug reaction reporting scheme using yellow cards is also criticised. Many reactions go unreported, and increasing their reporting rates would be good.[10] However, spontaneous reports describe association, not causation, and rarely provide sufficient evidence for regulatory action. Even with good data on benefit and harm, pharmacovigilance is rarely straightforward—the US Food and Drug Administration may yet agree to re-licence rofecoxib.[11] The report urges greater efforts to investigate signals of possible problems, but does not suggest how to

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command the necessary resources. Matters would improve if the MHRA could require companies to undertake specific studies as a condition of renewal of a marketing authorisation.

The last health select committee report on the pharmaceutical industry was published on the day World War I was declared,[12] and its far sighted recommendations such as the registration of all manufacturers, remedies, and therapeutic claims, were ignored in the aftermath. The current wide ranging report correctly identifies many areas of pharmaceutical influence, and the distortions they introduce. The report does not identify the resources to assure that an independent David triumphs over the pharmaceutical Goliath. Unbiased clinical trials, objective drug data, and perfect pharmacovigilance are desirable but probably illusory and certainly expensive.

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Reducing mortality in myocardial infarction

Treatment in specialised angioplasty centres should follow rapid prehospital thrombolysis

Restoring blood flow promptly in an occluded coronary artery by either thrombolysis or angioplasty reduces mortality in myocardial infarction with ST elevation. With both treatments, the faster reperfusion is achieved, the greater the reduction in mortality.[1 2] The relative merits of thrombolysis in hospital and angioplasty have recently been debated in this journal,[3 4] but in most developed countries the debate is largely over. Meta-analysis of trials comparing the two treatments showed a reduction in reinfarction and stroke and a small reduction in mortality in favour of angioplasty.[5] Guidelines from the European Society of Cardiology now state that primary angioplasty is the preferred therapeutic option when it can be performed "within 90 minutes after the first medical contact."[6]

In the United Kingdom no special funding exists for primary angioplasty: thrombolysis in hospital remains the standard treatment. Things may be about to change, however. The Department of Health has earmarked £1m ($1.89m; €1.46m) "to pilot the possibility of providing a national 24/7 primary angioplasty service," even though such a service would require enormous reorganisation of services and considerable additional investment. Patients with acute myocardial infarction would bypass their local hospitals and go to specialist centres providing a 24 hour angioplasty service. This proposal entails daunting logistical and financial challenges, and the prospect of large numbers of emergency procedures, many of them performed out of hours, raises questions about the quality of such a service.

There is, however, a "third way" that might deliver equivalent or even better results than primary angioplasty while avoiding many of the associated problems. This is the strategy of rapid, prehospital thrombolysis followed by transfer to angioplasty centres.

Although primary angioplasty can deliver highly effective reperfusion, it is often delayed by slow transport for patients and by lack of available time in catheter laboratories. In essence, prompt reperfusion is sacrificed for effective reperfusion. By contrast, patients can have thrombolysis administered by medical or paramedical staff at first contact before admission to hospital, and there is strong evidence that early administration improves outcome. The association between lives saved and time to thrombolysis is not linear: treatment in the first three hours after infarction is three times as effective as later administration.[1]

Meta-analysis shows that, compared with thrombolysis in hospital, prehospital thrombolysis is associated with a 17% reduction in mortality.[7] In the PRAGUE II study, when thrombolysis was given within three hours of the onset of symptoms, mortality was no higher than that associated with primary angioplasty (7.3% *v* 7.4%).[8] In the CAPTIM study, patients with myocardial infarction and ST elevation were randomly allocated within six hours of the onset of symptoms to receive either primary angioplasty or prehospital thrombolysis coupled with, if thrombolysis failed,

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