Personal Paper

"Me-toos," "me-agains," and the risk of drugs

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In 1969 the family and I made a double move—from London to Basle and from university to industry. When asked why we had moved I sometimes answered, "After failing for 15 years to persuade medical students not to prescribe drugs, why not try to persuade the manufacturers not to make them?"

But even without my help the drug industry nowadays is coming under more and more pressure not to make drugs. In the past ten years a steadily increasing proportion of the time, resource, and effort of many members of a productive industry has been spent in responding to the ever more clamorous demands of consumers as well as regulatory authorities. In part the problems arise from failure—so far—to deliver from pain and unforeseeable diseases the aging population that is to a certain extent a consequence of the industry's own earlier efforts, and in part from the earlier practices of some of the members of that industry. Although the phase in which even large companies sometimes neglected ethical questions is over, vigilance is still required, as it is for the activities of any productive member of society—academic, bureaucrat, or industrialist. But delayed pursuit of the previously unsatisfactory may inhibit current research on the promising.

Defensive research

Although some outsiders may appreciate the ever more demanding requirements of regulatory authorities, they perhaps remain largely unaware of the magnitude and consequences of the resulting effort on new and future products. Because the continually increasing time needed to bring a new drug to market comes out of the limited period in which it remains in patent, smaller resources are available for the fundamentally new. Thus it may be safer for a company to spend on "me-toos," or "me-agains" (me-toos made by the same company); only maintaining or increasing the market share can bring the returns on investment necessary to maintain the research base. Those so engaged sometimes have difficulty in accepting that support of the research base by working to preserve the market share represents the best use of their time, especially if this entails mainly so-called "defensive" research.

Any report that a marketed product has been suspected to cause a major toxic effect—usually tumorigenesis—in a laboratory species or in an epidemiological study rightly requires an adequate response. (Most large companies probably survey information about their products as a routine without waiting for external stimulation.) Previous reports—experimental and clinical—must be checked for relevance, completeness, and accuracy; and additional scientific work may be needed to clarify obscure points. There will subsequently be much labour in keeping regulatory authorities informed and meeting their requests for a change in the indications or for a warning to be inserted in the package leaflet.

The latency of chemically induced human carcinomas may be about 15 or 20 years or even more; so, not surprisingly, epidemiological methods have been brought to bear on drug problems of this kind only in the past few years. These methods can rarely be experimental; usually they violate the basic experimental necessity that the chances of individual allocation to treated and control groups be equal. Although suspicion of a causal relation needs experimental support, prospective studies can seldom be carried out in man because the required time is long and the numbers are large; there are often important ethical impediments too. The relevance of some of the animal models that take their place, such as the use of the beagle dog for studying oral contraceptives, is being questioned or has even been rejected.

Drug-effect epidemiology

I am not qualified to comment on events in the animal laboratory, and scarcely more so on epidemiology. Such even-handed ignorance allows me to express the belief that a toxicologist can as easily convince an epidemiologist about the soundness of his work as the reverse. Either can convince the other more easily than he can one of his own colleagues. Nevertheless, some drug-effect epidemiology of recent vintage seems to me to have been unworthy of laying down.

Surely investigating alleged drug-related illness requires the reliability of data about drug consumption to be as carefully established as that about the illness; yet some publications are not reassuring. Valid inference is also sometimes in short supply. For example, retrospective case-control studies generally allow calculation of the *relative* risk, compared with controls, that those who had a given illness will have been exposed to a given agent. Such a calculation can lead to a suspicion that the risk of acquiring the disease is increased by taking the drug, but it can never establish a causal connection and seldom makes possible an estimate of any increase in the risk of acquiring the disease associated with having taken the drug. This estimate, the *attributable* risk, is the ratio that matters clinically and socially, and it can be obtained only from prospective inquiries or adequately designed retrospective comparisons against base populations. Yet the relative risk is often either mistaken for or taken to be a direct estimate of the attributable risk by many who should know better.

Few cases have been squarely laid against marketed drugs either by epidemiological or by toxicological endeavours. With some important exceptions the attributable risk, if calculable, has been small and has usually been considered to be outweighed by benefits from continued use of the drug. Nevertheless,

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changes in labelling or package inserts have often been required even though questions about their relevance have been simultaneously permitted. Consequently, in the interests of regaining time and perhaps achieving other economies, I recently circulated among some colleagues a proposal for a universal package leaflet. It was received so stonily that I realised I had been serious by accident, and therefore decided to submit the proposal to a serious journal. Here it is:

The universal package leaflet

(1) The active principle of this drug will doubtless at some time in the future be shown to be highly toxic to one or more bacterial or other species, if indeed this has not already happened.

(2) A group of epidemiologists will also demonstrate that people who are ill are more likely than those who are not to have taken drugs. This discovery will be interpreted by some to mean that taking *this* drug has caused you to be sick with the disease for which you are taking it.

(3) Because patients find it as difficult to understand the relevance of such findings as the finders do to admit their irrelevance to patients, you are strongly recommended to *take this compound only if it is essential that you do so.*

The last sentence contains advice with which, surely, no one will quarrel.

Today's Treatment

Uses of anaesthesia

The anaesthetist in the accident and emergency service

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The basic training of the anaesthetist in the operating room is orientated around secure airway control, artificial ventilation, monitoring and support of the circulation, and the relief of acute pain. It is precisely these skills that are essential in managing the suddenly ill and seriously injured patients cared for by the accident and emergency services and departments (fig 1).

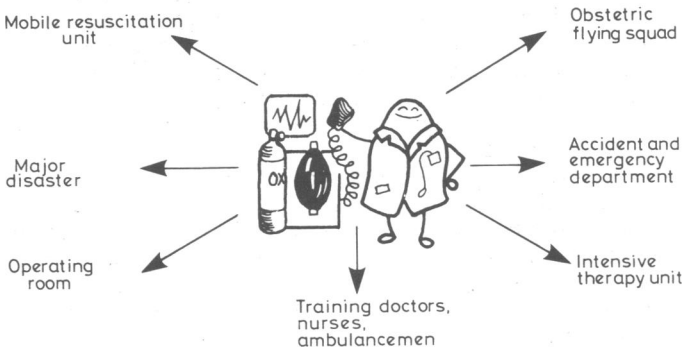

FIG 1—Roles of the anaesthetist.

Prehospital care

Increasing awareness in several countries of the world of the value of expert prehospital care has led to the development in Britain of schemes designed to bring skilled assessment and treatment to the patient on site and during transport to hospital. In certain rural areas general practitioners[1] have organised on-site immediate care schemes. Through training in hospital with anaesthetists in the anaesthetic rooms, operating theatres, and recovery rooms they have acquired the skills of intravenous cannulation and transfusion, airway control using endotracheal intubation, and reliable artificial ventilation with a self-inflating bag or mechanical resuscitator. In urban areas general-practitioner schemes are not so practical, and several centres[2 3] have now followed the United States practice of training selected ambulance personnel to a paramedical standard, which includes the practical skills mentioned above combined with a thorough knowledge and understanding of the systematic assessment and monitoring of the seriously ill patient.[4]

All of these paramedical schemes rely on anaesthetists for a large part of their training and, in several instances, the entire scheme has been masterminded and organised by anaesthetists working in collaboration with their colleagues in the accident and emergency department and in the ambulance service. There are now moves to improve the efficiency of the emergency side of the ambulance service in Britain by separating this part away from the routine transport service, thereby creating a top tier of highly trained men to concentrate on the patients requiring skilled emergency care. As this development is adopted by more and more centres, so anaesthetists will become increasingly concerned. It is important, however, that they do not confine their participation to training only. They should also work on site from time to time with the trainees in their own environment to appreciate the problems of attempting resuscitation away from the complex and organised surroundings of their hospital.

Obstetric flying squad

With improving antenatal care by general practitioners and obstetricians and the increasing trend towards hospital rather than domiciliary confinement, the need for obstetric flying

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