Reasons for the Successes and Failures of Specific Models in Drug Epidemiology

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Several constituencies are interested in the safety of drugs, and therefore in the discovery of adverse effects and in valid estimates of their incidence, which are the main objectives of drug surveillance. The constituencies include government regulatory agencies, pharmaceutical manufacturers, academic scientists and the medical community at large, and the public.

In the 1960s, when the perception first became widespread that often we lack reliable information on adverse drug reactions, the different constituencies frequently were seriously at odds with each other. Some of the protagonists were so deeply engrossed that they sometimes forgot that the advent of drugs has had incalculable benefits for society; that adverse effects are an inevitable consequence of administering pharmacologically active substances; and that the proper concern, from a public health point of view, is how simultaneously to maximize the benefits and minimize the risks of drug use.

Despite this inauspicious start, however, a great deal of progress has been made, and there have been notable changes within the various constituencies. Within the industry, some manufacturers (but not all) have recognized increasingly that long-term profitability and productivity are best assured by identifying and quantifying the adverse effects of their products as early as possible – and by taking appropriate action when needed, including the withdrawal of drugs from the market. Accordingly, several manufacturers now have their own epidemiology departments, and no doubt more will follow.

Within regulatory agencies, professionalism has increased. In the United States, the Food and Drug Administration, for instance, has in recent years recruited skilled and enthusiastic epidemiologists.

In the public arena progress has been more erratic, but I believe that public interest advocates have on the whole attempted to make more sophisticated distinctions between genuine adversity and spurious associations. In addition, the quality of communication to the public, by journalists and others, is a great deal better than it used to be; at least, this appears to be the case in the United States. I should add that vigilant consumers and journalists continue to bring to light drug hazards that

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might otherwise remain hidden. However, whatever one may feel about the pressures from the public arena in general, there is one specific respect in which conditions have become worse, and that is in the field of litigation, particularly in the United States. No one, I think, would question the right of a person to legal redress if he has suffered injury as a result of criminal acts; but what we are witnessing in America of matters of science being decided in courts of law, with arguments sometimes conducted by unscrupulous and misinformed protagonists. The decision by Merrill-Dow to remove Bendectin from the market not because of scientific evidence but because of mounting legal costs is one of the most striking recent examples.

In the academic arena drug surveillance has undergone substantial development. It is appropriate to review its evolution, and to understand its strengths and weaknesses.

**Spontaneous Reports**

The starting point for any review, of course, is the spontaneous reporting of adverse drug reactions. In a sense, this approach to surveillance has been in existence as long as pharmacology itself. In the era of drug monitoring it is generally conceived of as occurring at several levels: as case reports published in the medical literature and as reports submitted to governments, international agencies, or manufacturers.

We have now had sufficient experience to judge the value of spontaneous reports. To begin, I hope it is generally accepted that it is virtually impossible to obtain reliable incidence rates. What we should consider here is the utility of this approach in discovering cause and effect relationships.

Some of the conditions under which spontaneous reporting is effective in documenting causation are well-known (Louik et al. 1985): for example, short time intervals between exposure to the drug and onset of the adverse effect; common and easily discernible patterns in populations exposed to specific drugs; exaggerations of pharmacological actions; and not least, recurrence of an effect on rechallenge. Outcomes such as headache, nausea, metallic taste, insomnia, nightmares, impotence, amnesia, drug rashes, idiosyncratic reactions, and bizarre effects such as deafness, have all been correctly identified by means of spontaneous reports. This is a domain that many critics of spontaneous reports tend to overlook, and this technique of surveillance remains one of the most important means by which adverse effects of this type are identified. Case reports are vital to surveillance and are likely to remain so.

Other conditions under which causation can be inferred from spontaneous reports are perhaps less well-known, but nonetheless compelling. When considering outcomes much more serious than metallic taste, rashes, etc. (e.g., hepatic failure), several spontaneous reports of the same association are least subject to error when the disease of interest is rare and when the drug is rarely used, since multiple coincidences are exceedingly unlikely. In that circumstance, the evidence for causation can be convincing: for example, the occurrence of benign and recurrent hepatic tumors in relation to the use of oxymetholone (WHO 1977), or the occurrence of