DETECTION OF DRUG-INDUCED DISEASE

Our former clinical pharmacology group at the Massachusetts General Hospital cannot reasonably be described as critics of the Boston Collaborative Drug Surveillance Program, as Dr Lawson does in his informative survey (1979). As one of the 'collaborators' for many years before leaving Boston in 1975, I cannot even be accused of being objective: 'the enormous amounts of data collected, the sophistication of data storage and analysis, and the kinds of questions about drug effects that can be answered, fully justify the high regard in which this program is held internationally' (Koch-Weser, 1976).

Lawson (1979) also writes that our study at the Massachusetts General Hospital during 1972 (Koch-Weser, Sellers & Zacest, 1977) demonstrated 'how there is great variability both between and within observers in the reporting of adverse drug effects even within a single study'. In fact, we did not study the reporting of adverse drug effects but compared the independent evaluation by three clinical pharmacologists of 500 untoward clinical events reported as adverse drug reactions by practising physicians. We were prudent enough not to test variability within anybody. We did find that the three evaluators more often than not disagreed with each other and with the reporting physician about whether any drug had been responsible for the event and that, when they agreed about the occurrence of an adverse drug reaction, they very commonly disagreed about the drug responsible and about the characteristics and consequences of the reaction. We concluded that suspected adverse drug reactions are usually ambiguous clinical events and that attribution of responsibility for such an event is a highly subjective judgement. This is precisely the conclusion reached by Karch, Smith, Kerzner, Mazullo, Weintraub & Lasagna (1976) after studying sixty selected cases. There is nothing surprising about it, since wide divergence of judgements about the same clinical data made by independent observers have been clearly documented in many other areas of medicine (Elstein, 1976). Nevertheless, much of what has been written in the last two decades about the frequency and importance of adverse drug reactions implies that in this field causation can be established by intuition or revelation.

The findings of our and of Lasagna's group (Karch *et al.*, 1976) do not constitute a criticism of the

Boston Collaborative Drug Surveillance Program. That information about suspected adverse drug reactions based solely on clinical observation under uncontrolled circumstances is relatively 'soft' has, to my knowledge, never been questioned by anybody connected with this program. The data are not 'hardened' if all suspected adverse drug reactions are accepted or rejected independently by 'experts' who are distant from the event in time and place and have only second-hand information (Koch-Weser, 1977). Unlike several other programs, the Boston Collaborative Drug Surveillance Program has never fallen into this self-deceptive trap. It has shown, however, that judgemental information painstakingly collected from many sources and skillfully analyzed can greatly increase qualitative and quantitative knowledge about adverse effects of specific drugs and develop risk figures in terms of patient characteristics, specific diseases and concomitant therapy with other drugs.

Finally, our comparison at the Massachusetts General Hospital from 1966 to 1968 of 2000 spontaneous reports with surveillance studies (Koch-Weser, Sidel, Sweet, Kanarek & Eaton, 1969) did not, as Lawson (1979) states, show that physicians report allergic drug reactions in preference to others. We did not then and I would not now presume to exclude or implicate an allergic mechanism (whatever that means) in many adverse reactions to drugs. We did find that physicians reported a far higher percentage of reactions that were not related to the expected pharmacologic actions of the drug than of those that were clearly due to excessive doses. More importantly, many other characteristics of the reaction, the drug, the patient and the physician were found to influence the completeness of reporting. How many and which reactions physicians reported also depended on what feedback they received and on what happened to be 'fashionable' in adverse drug reactions. We concluded that the ability to generate meaningful incidence figures is not one of the many virtues of spontaneous reporting programs.

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DETECTION OF DRUG-INDUCED DISEASE

The intention of my review entitled 'Detection of Drug-Induced Disease' (Lawson, 1979) was to bring together a vast number of diverse studies into a form which was coherent to the practising clinician, indicating the strengths and weaknesses of the various research strategies used. If in doing so it has appeared that I regard Dr Koch-Weser primarily as a critic of the Boston Collaborative Drug Surveillance Program (Koch-Weser, 1979), this impression requires correction. As he states, his group at the Massachusetts General Hospital contributed substantially to that program and have been active over many years in analysing the accumulated data (Greenblatt & Koch-Weser, 1973, 1974; Pfeifer, Greenblatt & Koch-Weser, 1976a, b, 1977). Nevertheless, I think it is true to state that his article emphasizing the considerable disagreement between clinical pharmacologists when assessing the likelihood of a given event being drug-related has been used by others, although not perhaps by himself, to question the relevance of the type of information collected by the Boston group and other similar programmes. Therefore, I welcome his firm statement that judgemental information, painstakingly collected and analysed can be of value in providing knowledge both of the frequency of adverse drug effects and of subgroups of the population at greatest risk of developing them.

In my view the majority of the problems that have arisen in the last two decades about interpreting published information on the frequency and importance of adverse drug effects are due to unwarranted extrapolation of information beyond the frame of reference within which it was collected. It is this, rather than the 'softness' of the information input or disagreements between individual doctors about specific events in individual subjects, that leads to incorrect inferences about the magnitude of the problem.

In a review published in 1974 Feinstein stated that 'After we work our way through all the majesty of the computer print-out and the glory of the statistics, we find that the decision-making mechanism for identifying adverse reactions.... depends upon the vagaries of clinical judgement of an array of unstandardized physicians'. Of course it does! We knew that long before the computer in-put was

generated far less needing to wait until the output was produced. This is a fact of life and if we fail to undertake surveillance studies either because the data are 'soft' or by insisting upon much more rigorous definitions of adverse reactions, involving definitive cause and effect relationships and multiple confirmations by independent 'experts' we will cause much more harm than arises as a consequence of accepting the current imperfect arrangement and making the most of it.

Koch-Weser (1979) is however correct in pointing out that his 1972 study looked only at inter-observer variations in interpreting data on adverse effects, not intra-observer variability. This latter aspect has been the subject of an unpublished study which I incorrectly attributed to his group.

Koch-Weser's comments on his paper published in 1969 are more difficult to understand. In the section of my review dealing with spontaneous reports of adverse drug effects I emphasized that there was definite selection on the part of physicians as to the type of reaction they report. This is well known and generally accepted, however in view of the interesting and relevant study of this area undertaken by Koch-Weser's group, it seemed appropriate to quote his work. In the results section of this paper it is emphasized that the presumed mechanism of a reaction 'greatly influences the decision whether or not to report (it)'. Only 22% of pharmacological reactions (i.e. reactions that are dose-dependent and related to the basic pharmacologic actions of the drug) were reported. In marked contrast, physicians spontaneously reported 42% of all non-pharmacologic (allergic or idiosyncratic) reactions.' My summary, albeit brief, accurately reflects the spirit of this part of his paper. It was not intended to summarize the entire paper—merely that part which I regard as being particularly of interest and importance. His conclusion that in general spontaneous reporting systems do not generate meaningful incidence figures of adverse drug effects accurately summarizes the views expressed by many other workers (Doll, 1971) and reflected in my article.

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