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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.

D.H. LAWSON

Royal Infirmary, Glasgow G4 0SF

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CHLORDIAZEPOXIDE IN ACUTE ALCOHOLISM

In a recent article Whiting, Lawrence, Skellern & Meier (1979) claimed that in patients acutely intoxicated with alcohol the elimination half-life of chlordiazepoxide was prolonged and its clearance from plasma was reduced. Unfortunately, the design of their study renders the data difficult to interpret. The effect of variable age on chlordiazepoxide disposition was not controlled in the paper of Whiting *et al.* (1979). The mean age of their control subjects was 31.2 years while for the alcoholic subjects it was 51.6 years. Recently, both Roberts, Wilkinson, Branch & Schenker (1978) and Shader, Greenblatt, Harmatz, Franke & Koch-Weser (1977) have reported a significant age-dependent alteration in chlordiazepoxide disposition. From the data of Roberts *et al.* (1978) the estimated half-life in normal

subjects at 31 years would be 5 h and at 52 years it would be 22 h; clearance of chlordiazepoxide would fall from 30 to 19 ml/min, respectively. These figures are similar to the actual changes observed by Whiting *et al.* (1979) and attributed solely to the effects of alcohol. Before that interpretation can be accepted as valid, carefully age-matched subjects must be compared for the single variable (i.e., alcohol) being evaluated.

PAUL V. DESMOND & STEVEN SCHENKER

Vanderbilt University School of Medicine & Nashville V. A. Medical Center, Nashville, Tennessee 37203, USA

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CHLORDIAZEPOXIDE IN ACUTE ALCOHOLISM

We would like to acknowledge the points made in Desmond & Schenker's (1979) letter about the age-dependency of chlordiazepoxide disposition. Unfortunately, our data was insufficient to show this but we did emphasize that the increased variability associated with the alcoholic data may have been partly due to age. Our inability to show any

significant correlation between age and chlordiazepoxide half-life or clearance in the controls or in the alcoholics, or in the group as a whole, prompted us to analyse the data in terms of alcohol as the single most important variable. Recently, Sellers, Greenblatt, Zilm & Degani (1978) have also shown that alcohol causes alterations in chlordiazepoxide pharmaco-