Editorials

Quality Assurance in Toxicology

There is general concern in the profession that new drugs should be subject to a rigorous series of tests for their safety before they are released to trial on human beings. These toxicity tests are carried out in laboratory animals and are often very elaborate, lengthy and costly. In many countries, including the United States and the United Kingdom, the results of these tests have to be submitted to a government regulatory agency to obtain clearance before the drug can be tried in man or eventually marketed. In the last two or three years the American drug regulatory agency, the Food and Drug Administration, have discovered that the data submitted by some of the larger pharmaceutical companies have been imperfect in several respects. Largely as a consequence of this discovery the Food and Drug Administration (FDA) have over the past year or two been developing standards of procedure for the conduct of toxicity tests that they call Good Laboratory Practice. The detailed proposals by the agency were published in the Federal Register on 19 November 1976, and have excited considerable interest and great concern in the pharmaceutical companies and other companies with material commitment to the conduct of toxicology.

This subject was considered at a symposium held at the Royal Society of Medicine on 31 January and 1 February 1977. This symposium, sponsored by a British contract research company, Inveresk Research International, was addressed by a number of experts in the field, including the Acting Commissioner of the Food and Drug Administration in the United States, a representative from the Swedish drugs control authority and a representative from the Medical Secretariat of the British Committee on the Safety of Medicines, as well as scientists from universities and industrial toxicology laboratories.

It appeared that the practice in the best laboratories already considerably exceeded that required by the standards suggested by the FDA. Procedures have been suggested to ensure that valid and reliable data can be obtained from those laboratories where standards are less rigorous.

However, one major innovation is proposed by the FDA that has much wider implications than any of the other detailed proposals. This is the suggestion, indeed possibly to become a legally binding regulation in the United States, that laboratories conducting toxicity studies should have an internal quality assurance unit. The function of this quality assurance unit will be to ensure that the scientists and technicians conducting the experiments in a particular laboratory are doing so strictly in accordance with the laid down protocol and with the other general provisions in the Code of Good Laboratory Practice. Much debate at the meeting centred on what qualifications such quality assurance inspectors should have, since it was felt on the one hand that if they were scientists they would not only inspect compliance with protocol but also feel free to criticize the protocol; whereas if they were not scientists they might well not have a sufficient understanding of all that was being undertaken to enable them to determine whether there was compliance with the protocol.

There was keen discussion on the issue that, as proposed by the FDA, a corps of external inspectors should visit laboratories and be vested with the power to disqualify from submitting data those laboratories that did not meet the established standards. Again great concern was expressed about the training of these individual inspectors, especially since it seemed that they would be released into enacting an inspectorial role after their three weeks' training in the American Centre for Toxicological Research in Arkansas. Much apprehension was expressed that such relatively unskilled people might be placed in a position of criticizing and eventually disqualifying the work of highly qualified scientists. The acting Commissioner of the FDA, Mr Sherwin Gardner, endeavoured to assure those expressing concern that the only function of these inspectors would be to ensure that the scientists were doing what they said they would do rather than to make any criticism of their proposed experiments. The remainder of the debate was probably only of interest to active toxicologists.

There are now, of course, in medicine plenty of examples of regulation and the practice of peer-review, although not common in the United Kingdom, is very widely accepted in the United States. Until now, however, while the lay community at large has often been concerned about the effects of scientific and medical practice, it has not felt able to inspect the manner and quality of its performance. The proposed regulations of Good Laboratory Practice aim to reassure the public not

only about the results of research but also about the manner in which such research is carried out. Unfortunately, it seems likely that such intervention by the community may be counter-productive. Most of the great toxicological calamities, such as thalidomide, or vinyl chloride, or asbestosis or industrial bladder cancer arose not because the relevant experiments were badly carried out but because these experiments were not carried out at all. Once the hazard was considered it proved fairly easy to detect the changes in experimental animals. The more the community concerns itself with the details of established methods the less likely it may be that scientists will have the time and indeed even the inclination to think more widely about toxicological problems. It is one thing to do well-conducted experiments and it is quite another to do meaningful ones.

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Medical Research, Reading, Speaking and Writing

There are those who don't understand research in medicine. Some refute the need for further research, arguing correctly that we have now more knowledge than we can use. They plead for more development, forgetting that research and development are tied together intimately in medicine. Others believe that research can only be done at centres of excellence. There is no simple definition of excellence, but there is a simple definition of research – active curiosity. Wide curiosity is man's happiest endowment.

Research exists to be enjoyed not just evaluated. It also has an educational value which is not always appreciated (Welbourn 1966). To set up an hypothesis and dig deep to support or refute it, has importance out of proportion to the findings. The scientific method (of observation, hypothesis, verification, prediction, further observations, etc.) is a powerful tool for logical thought even though Medawar (1965) has confounded most of us by stating that things do not happen in that order. Maybe not, but ideas have to be put through this logical sequence of explanation even if this is subsequently devised to make them intelligible and credible to others. Observations without hypotheses are of little value. It is the application of research that is the essence of technology, and medicine is no more than that. We also imply that research cannot be taught, yet how can anyone learn? There are principles of research and its problems (Calnan 1976) which can be inculcated before, during and after quite a small project: the project and the result are of enormous educational value to the individual. A third value, one only half-recognized, is that research matures the individual in ways that are difficult to quantify but evident enough a decade later. Perhaps this personal developmental growth, more than any other, deserves particular attention at times of economic poverty when everyone is looking for methods of saving money. The man who encourages others to do research has several responsibilities: he must ensure value for money for the grant-giving body, he has to provide time, equipment and encouragement for the work to get done and lastly he has to furnish the right environment for development of the research.

Reading provides intellectual nourishment, as essential for the mind as food is for the body. The art of reading can be lost if the coordination of eye, hand and brain is not practised daily. There are the competing attractions of radio and television which should be allowed to supplement but never to replace reading. Today, some 50% of doctors are functionally illiterate, that is they can read but don't; Leggett (1976) puts the figure higher for engineers, but we should not be proud of that. Throughout the ages the three great liberal professions (the Church, Law and Medicine) have always been proud that their members were educated, if not learned, and education demands wide knowledge of the written word. Research demands of its practitioners constant reading and of the thesis writers wide reading. Yet how many people just scan journals, picking the meat off the bones. Admittedly the first reading of papers and books should not be intensive, but rapid to grasp the main theme. But often I wonder how many people reread for depth of understanding.

Research without publication is sterile, for knowledge has to be disseminated as well as discovered. In medicine the IMRAD structure (introduction, material and methods, results and discussion) is the usual format for reporting. It allows the busy reader to decide from the title whether the subject is important to him, from the results whether the data are new, from the discussion whether to read the whole offering. Because all papers follow the same structure no time is lost during a quick survey. Some authors complain that formal medical writing is unduly restrictive; perhaps it is to those who can and do write well, but for the vast majority intelligibility is difficult enough even within such guidelines. Bradford Hill's five questions (1965), enunciated a decade ago – What did you do? How did you do it? Why did you do it? What did you find? What does it mean? – seem to have fallen on stony