

activities both occupational and non-occupational. Nor are doctors practising in coastal areas the only ones who may be faced with diving accidents or a patient with the bends, as subaqua clubs may use inland waters and divers may be brought off an oil rig by helicopter and have travelled a considerable distance before having an attack of decompression sickness.

The author points out that the growth of underwater operations has been relatively slow compared with climbing and space travel, but his explanation that this is due to an instinctive and subconscious distrust of the sea derived from man's primitive origins is unconvincing. If man distrusts the sea it is surely because he has sound practical reasons for doing so. The hazards of the ocean are familiar and real for seafaring people. The descriptions of underwater accidents underline the need for strict training and discipline for subaqua enthusiasts in order to avoid errors which can so easily be fatal. This is essential reading for anyone concerned with the health and safety of a subaqua group especially as there is a tendency for them to go to greater depths than hitherto.

Decompression sickness in subaqua swimmers is always a possibility and it raises the problem of the general availability of compression chambers for emergency treatment. A list of such facilities available in Britain would be a useful appendix for the next edition. The chapters on the physiological effects of nitrogen, oxygen and carbon dioxide at raised ambient pressures summarize present knowledge clearly.

Work in compressed air in caissons or tunnels may be carried out anywhere in the British Isles. Doctors who are involved in the care of compressed air workers will find this book useful and particularly the section on decompression, although it deals mainly with divers. For the problems peculiar to caisson and tunnel workers it will be necessary to seek information elsewhere but the reference list is helpful here. There are useful lists of references for further reading at the end of each chapter.

R. I. MCCALLUM

Principles for the Testing and Evaluation of Drugs for Carcinogenicity. Report of a W.H.O. Scientific Group. (World Health Organization Technical Report Series No. 426. (Pp. 26; 4s.) Geneva: W.H.O. 1969.

Evaluation of the carcinogenic potential of a drug forms an important part of its safety evaluation. The test procedures adopted and the principles employed in assessing the results vary considerably and often lead to contradictory conclusions. A W.H.O. Scientific Group has reviewed in some detail the methods of testing commonly employed in animals. The Group also considered the relevance to man of demonstrating a true carcinogenic effect in animals. In its comments on the evaluation of results, attention is directed particularly to the controversial problem of sarcoma induction as an index of carcinogenic activity.

In the Group's view, long-term tests are essential for carcinogenicity testing, short-term tests, *in vitro* or *in vivo*, still being insufficiently developed to serve as an alternative. Among the general requirements for a valid carcinogenicity test, the identity and purity of the test material and a knowledge of its route of metabolism in

the test animals are of primary importance. The latter is especially valuable for a final evaluation of the carcinogenic hazard. Regarding the suitability of animal species, the Group considers that rodents (rats, mice and hamsters) are generally acceptable provided pathogen-controlled strains are used to ensure a sufficiently long survival. The dog is recommended for testing suspected bladder carcinogens of the aromatic amine group and the monkey is recommended for studying the carcinogenicity of certain hormone preparations. The use of newborn animals is not encouraged on the grounds that there is no clear indication that they are preferable to adults of the same species. Fish (trout) and birds are not recommended. Animal husbandry is not neglected and the Group makes a plea for the use of defined diets free of natural carcinogens, pesticide residues and food additives.

Turning to routes of administration the group emphasizes the need to administer the test compound by the route of intended clinical administration and to select a dose level that will ensure an adequate tissue concentration. Testing by the oral route meets these requirements in a substantial proportion of cases, but many drugs are given by subcutaneous injection, and the report pays particular attention to sarcoma induction in rats and mice by repeated subcutaneous injection. It is pointed out that local sarcoma induction by implantation of solids is determined by physical properties such as shape, size, smoothness of surface and whether or not the implant softens at body temperature. In the case of substances administered by repeated injection, the physical properties of injected solutions, such as hyper-tonicity, pH and surface activity, may play an important role in determining the onset of malignancy, while the injection of large doses in relation to the body weight of the animal may create other physical effects of which sarcoma production is the ultimate outcome. In such cases the local tumours do not reflect any chemical carcinogenic potential the test compound may possess. Chemical carcinogenesis is manifested by tumours of other tissues, including those remote from the injection site.

An important comment by the Scientific Group deserves to be quoted in full:

'Recognition of the part that may be played by the physical properties of a substance in the production of local sarcomas in the rat and mouse renders it difficult to interpret the significance of the induction of such tumours, especially if the substance is not carcinogenic when tested by other routes of administration. Detailed study of the nature and evolution of local tissue changes at the site of injection and of the mechanism by which they arise may help to resolve the problem.'

Another important aspect in evaluating results of carcinogenicity testing is the dose-response relationship. The Group considers that demonstration of such a relationship should be taken fully into account in the final assessment.

Should drugs that cause cancer in animals be allowed for administration to patients? Understandably, the Group is cautious in providing an answer. If a drug is to be used for short periods only, the risk involved may be justified; if the drug is one intended for prolonged administration, its use should be approached with greater caution. In the case of substances that produce local

sarcomas, their use by other routes of administration need not be precluded.

On the whole, this document marks an important advance in our approach to carcinogenicity testing. Recognition of the importance of metabolic studies in the test animal and possibly also in man mark a major step forward in placing carcinogenicity testing on a firm scientific basis. Equally important is the emphasis laid on prospective epidemiological studies when a new drug is placed on the market. In a third major advance, subcutaneous sarcoma induction has been placed in its proper perspective. Against these achievements there are some major omissions. For example, the Group failed to examine the significance of benign tumours as an indication of carcinogenic potential. Such an examination could not have failed to take into account the controversy regarding the meaning of pulmonary tumour induction in mice. Nor did the Group consider the problems of co-carcinogenesis as manifested in the skin and vesical epithelium of the mouse. These are problems that demand an urgent answer and should not be shelved for future generations.

P. GRASSO

Occupational Disease in California Attributed to Pesticides and Other Agricultural Chemicals – 1967. (Pp. 35; 12 tables; copies obtainable free on request from the State of California Department of Public Health, 2151 Berkeley Way, Berkeley, California 94704, U.S.A.) State of California Department of Public Health. 1969.

A previous statistical record of this kind (for 1965) was reviewed at length in the April 1968 issue of the *Journal* (vol. 25, p. 157). The present record deals with 1,400 reports compulsorily notified under the State Labor Code by the attending doctor. A perfunctory attitude by the medical profession to recording and notification is apparently universal, and the value of this survey has been much reduced by failure to specify the chemical involved in 29% of cases. The survey reveals no new or unexpected patterns of hazard. Organo-phosphate pesticides remain the most important single group in producing serious occupational poisoning, accounting for 22% of all reports but 83% of systemic poisonings (240).

The incidence of poisoning episodes among staff engaged in aircraft spraying operations – labourers and flagmen, as well as pilots – increased in both 1966 and 1967, and the contribution of pesticide exposure to pilot error in aircraft spraying accidents is being made the subject of special study by the Bureau of Aviation Safety and the U.S.D.A. Community Studies on Pesticides programme. Only two ‘occupational’ fatalities occurred in 1967 – one through a farm labourer accidentally drinking parathion, not strictly an occupational casualty in the more usual sense of exposure occurring during preparation or application of a pesticide; the other casualty was an aircraft pilot who was contaminated by TEPP (tetraethylpyrophosphate) when his aircraft crashed after failing to take off because it was overloaded. Some of the information in the 12 reference tables will

be of little interest outside California, and the general presentation is not much improvement on the 1965 survey.

A. A. B. SWAN

Principles for First Aid for the Injured, 2nd ed. By H. Proctor and P. S. London. (Pp. 264; illustrated; 40s.) London: Butterworths. 1968.

The first edition of this book published in 1962 proved to be of great value to those concerned with the initial management of injuries, and also to those with a responsibility for first aid training. The second edition has been revised to take account of recent advances in knowledge. The section dealing with asphyxia due to drowning has been re-written. A discussion of the management of exposure, and of the principles in the use of inflatable splints, are introduced into this edition.

The almost indiscriminate use of the word ‘shock’ in first aid practice causes great confusion in the minds of first aid workers. The authors’ clear thinking and clarity of expression are nowhere better seen than in the revised chapter on shock and injury. The shock syndrome is precisely defined and classified in terms of the circulatory changes. This presentation should make for easier understanding and improved first aid teaching of this complex subject.

The revised second edition will continue the tradition of the first as an important book of reference for all doctors and nurses working in industry.

J. D. CAMERON

Toxic Properties of Inorganic Fluorine Compounds. By R. Y. Eagers. (Pp. 152; 55s.) Barking: Elsevier. 1969.

This monograph summarizes the various aspects of poisoning with inorganic fluorine compounds. It is divided into three sections, the effects on humans, the effects on animals, and ‘other effects’. The latter include the insecticidal and bactericidal effects of some of the compounds, and a chapter titled ‘physiological effects’ which describes research on enzyme inhibition by soluble fluorides and the changes which occur in carbohydrate metabolism and in the calcium balance.

The first section gives an account of methods of absorption, followed by descriptions of outbreaks of acute fluoride poisoning due to accidental absorption, gassing or to burning with liquid compounds. Case histories with pathological reports are quoted and treatment schedules are given. The importance of the administration of calcium gluconate by intravenous infusion, or by local injection in the case of burns, is stressed.

The sections on endemic fluorosis of both man and animals are of particular interest. In an Indian village where the fluoride content of the water varied from 1.2 to 162 ppm, 204 of the 208 inhabitants of the village over the age of 6 years had evidence of chronic fluorosis. The teeth showed mottled enamel and brown staining, there were pathological changes at the roots of the teeth, and cases of pokerback, with narrowing of the canal of the spinal cord causing neurological changes, were seen.