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clear-cut than the 'tighter' results from animal experiments, there are increasing data on the human situation and I do feel that it is time that radiobiologists compared and contrasted their systems with the available clinical data.

The separate chapter on the immune system is a new idea that I have not seen given 'independent status' in other radiobiology texts and with the current realisation of differential radiosensitivity amongst lymphocyte sub-populations and the current clinical interest in total nodal irradiation as an immunosuppressant, I welcomed this section.

Overall, this book reviews a massive amount of data concerning primarily the response of normal animal tissues to radiation and cytotoxic drugs. Although it contains very little human data or comparisons, it will be of great interest to many oncologists, particulary those to whom an understanding of stem cells and tissue kinetics are important. The layout of text and figures is good, the index satisfactory and each chapter is liberally referenced.

P. N. Plowman

Principles of Animal Extrapolation. Edward J. Calabrese. John Wiley, Chichester, 1983, 603 pp., £57.75.

The title of this book examples the careless bastardization of the English language, which is all too often allowed to pass without comment. According to the Oxford Dictionary, extrapolation is 'the action or method of finding by a calculation based on the known terms of a series, other terms, whether preceding or following'. Rats in a maze who successfully find their way to the food basket or to their future marriage partner might do so by a process of extrapolation based on previous experience, but this book (which is dedicated to 'Brian') is not about that sort of thing. Instead it is concerned with the prediction of human responses to chemical agents from the results of tests conducted in laboratory animals. It is not, alas, a matter of mere pedantry for me to criticise the book's title in this way. There is the deeper problem that the serious misuse of words is all too often indicative of wrong premise and false logic.

The definition given above includes the words 'calculation based on the known terms of a series'. Data from laboratory animals frequently do not constitute any sort of series. I suppose if substance 'X' had been shown to cause effect 'Y' in say 3 different species, the odds might be that it would do likewise in a fourth species, e.g. man. Alternatively, if it is known that substances A, B and C all produce effect 'Y' in both rats and humans, then it may not be unreasonable to predict that if substance 'X' produces effect 'Y' in rats, then, it will also do so in man. But many of the contributors to this book are clearly quite happy to 'extrapolate' from observations in just one animal species and to predict how man will respond to a novel substance which does not form part of a series for which there is previous knowledge in both the test species and man.

Thus, the reader should not allow himself to be blinded by this compendium of facts, observations and hobby horses. Certainly much of interest has been

gathered under headings such as interspecies differences in absorption, microflora, tissue distribution, metabolism, and DNA repair; animal models for selected high-risk groups; models predictive for dermotoxicity, genotoxicity, teratogenicity, etc. However, at the end of the day, the basic difficulties and unreliability of predicting how man will respond to substance 'X' remain. Of course, similarities in pattern of response which transcend species differences are easy to find. Nor would one expect otherwise, given the nature of life and its development through the evolutionary process. But quantitative differences in response often masquerade as qualitative differences and, so disguised, give birth to myths. Also, too many would-be extrapolators overlook the limited extent of their data from animal studies and the artificiality of their test systems. It is not uncommon for control rats in present-day carcinogenicity studies to develop mammary, pituitary and other endocrine tumours in incidences of close to 100% and to be totally unlike man in terms of endocrine status throughout most of their lives. Recently in tests conducted under the National Toxicology Program in the USA, an outbreak of exocrine tumours of the pancreas has been found in animals orally exposed to test substances by gavage. The use of corn oil as the vehicle resulted in animals receiving the equivalent of a human drinking nearly 300 ml of vegetable oil every day! If these are the kind of observations from which predictions are to be made for man, then extrapolation can be no more than science fiction.

For all my scepticism, I have to say finally that there is too much information in this book and it is too well produced for me not to commend it!

Francis J. C. Roe

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Lead Versus Health: Sources and Effects of Low Level Lead Exposure. Edited by M. Rutter and R. Russell Jones. John Wiley, Chichester, 1983, 379 pp., £18.50.

The title is offputting; it suggests the kind of 'scare of the month' to which we have had to become accustomed. In fact it is an important book, first of all because the introduction and the summarizing chapters, both by Rutter, are magnificently written and raise issues which go far beyond the questions of lead.

The book starts with a series of reviews of the sources and routes of entry of lead into the population, especially in the United States and the U.K. Annest presents the results of very large surveys in the U.S.A. which show that the children of the disadvantaged, poor, black, inner city dwellers have considerably higher blood lead levels than others, with one in five children having a blood lead level over 30 mg/100 ml. There has been a consistent fall in blood lead levels over the last ten years, but in general these remain higher in the United States than in Germany or in the U.K. Moore from Glasgow describes the successful programme of reduction of lead intake from tap water by raising the pH in the city's supplies. As a result, the amount of lead in tap water has fallen and so have blood levels of lead. In general it seems that most of the lead intake for human populations arises from industrially produced lead either as lead pipes and so contamination of drinking water or else, and far more commonly, as lead in food, partly from solder in cans

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pentobarbitone anaesthesia (40 mg/kg, intraperitoneally) body temperature, heart rate, mean arterial blood pressure (MABP) and blood gases were monitored, and regional cerebral blood flow (rCBF) was measured with 4-[^{125}I]iodoantipyrine essentially as described by Ohno *et al.* (1979). Blood–brain barrier integrity and transport function were assessed by measuring [^{14}C]mannitol penetration and the unidirectional flux of D-[^{14}C]-glucose into regions of the CNS using a steady-state programmed tracer infusion technique (for methods see Pratt, 1984).

In the latent phase rCBF was reduced in all CNS regions compared with that in control, but the pattern of distribution was unchanged. Body temperature, heart rate, MABP, pH_a, Pa_{O_2}, Pa_{CO_2} were comparable in control and MeHg-treated rats. During the symptomatic phase rCBF appeared to be reduced in the hind brain where subsequently histopathological changes were most evident. Blood–brain barrier permeability to mannitol was unchanged at both periods, suggesting that barrier integrity was unaffected. However, glucose influx to the CNS was greater that in the control (at equivalent plasma glucose levels) during the latent phase of intoxication. The difference was significant in several regions. When the behavioural signs of neurotoxicity were present this trend was not significant.

The reduction in rCBF at a time of increased glucose uptake by the CNS suggests a disturbance of the normal relation between glucose supply, cerebral metabolism and blood flow. These findings suggest that there is a pathophysiological change in the CNS that occurs before signs of neurotoxicity appear.

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Germ-cell Responses after Dietary Restriction and Mutagen Treatment in CD-1 Mice

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In animal toxicity studies the highest dose of chemical used is often in the toxic range and one of the criteria used to determine toxicity is a reduction in body weight. The present study examines the effect of dietary restriction on various fertility and genetic parameters in sexually mature CD-1 mice.

Mice were fed a restricted diet for a week reducing body weight by about 25% after which body weight returned to control values. Maximal increases in sperm abnormalities were observed in weeks 3 and 4 but had returned to control values by week 5, suggesting that dietary restriction affects the early spermatid/late spermatocyte stage of spermatogenesis. Sperm counts were reduced for longer time periods.

In week 5 males were mated with the females and examined for dominant lethal effects. No differences were observed between control and dietary restricted animals. No abnormalities were observed in F_1 sperm. Ethyl methanesulphonate (EMS) treatment was superimposed on animals fed on a restricted diet for a week again reducing body weight by about 25% and the responses compared with those from animals fed on a restricted diet alone and control animals. Dietary restriction alone and EMS treatment alone produced the anticipated responses, but the combined treatment regimen appeared not to enhance the response and delayed it so that the effects were observed a week later (Anderson *et al.*, 1983).

Dominant lethal studies in weeks 3–6 again showed no effect with dietary restriction but gave anticipated responses in EMS-treated animals. With combined dietary restriction and EMS treatment, fertility was affected for longer than with EMS treatment alone.

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The effects of known pulmonary toxins, bleomycin, butylated hydroxytoluene (BHT) and paraquat and the structurally related diquat on a human lung tumour cell line (A549) were investigated. This cell line is thought to be derived from alveolar epithelial type II cells, which are the main site of action of paraquat *in vivo*. Bleomycin and BHT are believed to act primarily on type I pneumocytes which are derived from type II cells. Toxicity to the cell line was assessed by measurement of protein synthesis inhibition, vital dye exclusion, cell numbers and clonogenicity.

Considerable variation in the sensitivity of these methods of assessment was noted. The clonogenic assay was by far the most sensitive indicator of toxicity used in these studies. This assay measures the ability of individual cells to generate a colony containing approximately 100 cells.

The ID_{50} values for a given compound determined by the different methods were very variable, for example the value for bleomycin was >5000-fold higher as assessed by either Trypan Blue exclusion or protein synthesis assay compared with the clonogenic assay. The dye exclusion assay gives an indication of membrane integrity, whereas protein synthesis assesses the biosynthetic capability of the cell.

Athough the sensitivity of the different test systems to paraquat and diquat varied markedly, the toxicity of both compounds to a particular system was similar. These results indicate that the A549 cell line is not a good model for organ-specific toxicity, being unable to distinguish between the pulmonary toxin paraquat and diquat, a non-pulmonary toxic bipyridyl.

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Contamination in Rat Oral Toxicity Studies: an Assessment

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The use of powdered compound/diet mixtures in oral rodent toxicity studies has been recognized as posing a risk of animal-room contamination in addition to undesirable exposure of the compound to personnel and control animals (Sansone *et al.*, 1977). Pelleting the mixture might be expected to reduce the contamination as would oral dosing by gavage.

We investigated the contamination of the animal room, personnel and rats (dosed and undosed) with 1% (w/w) fluorescein/diet mixtures in both a powdered and pelleted form. Contamination was also assessed after gavage administration of equivalent doses of fluorescein.

For each mode of administration fluorescein was detected on the walls, floor and ceiling of the animal room and adjoining corridors. Contamination was also detected in the room filters and in the filters of ventilated helmets worn by the personnel as well as on their gowns and gloves. The contamination with powdered fluorescein/diet mixtures was generally five fold that of the other modes of administration, but significant and comparable levels of contamination, were also observed with the pelleted and gavage regimens.

One of the fundamental principles of toxicity testing is that the control group is not exposed to test compound. In this experiment, however, contamination of the undosed animals occurred in all three regimens: fluorescein was detected on their dorsal surface and statistically significantly higher fluorescence was measured in the plasma of undosed rats compared with blank rat plasma.

Fluorescein is excreted in high concentrations in rat urine and dust from fluorescein-contaminated bedding is likely to have been a major source of the generalized contamination. In the gavage group further contamination occurred from fluorescein-laden urine voided during dosing while the marked reduction in contamination in the pelleted, compared with the powdered, regimen is probably due to the containment of the compound within the pellet so reducing its spread into the animal room.

The compound/diet concentration and gavage dose levels used in this study are similar to those frequently used in routine toxicology studies. Although caution is necessary in extrapolating these findings to other compounds, or to rodents housed under different conditions, they demonstrate that significant contamination of the facility, personnel and control animals can occur in both diet and gavage dosing regimens. Further work is necessary to more closely identify the sources of contamination.

Reference

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