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CRITICAL REVIEW

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In reviewing Dr Wagner's paper, Dr Roe raised the following points:

(1)
In so far as the whole approach to the safety evaluation of drugs is questionable, it is unreasonable to criticise the rat animal model on its own in relation to the prediction of carcinogenic risk. To give very high doses of pharmacologically active compounds and then express suprise that tumours develop is patently foolish. Additionally, the traditional overfeeding of laboratory animals, particularly rats, is apt to make them into 'endocrinological cripples', with high incidences of a variety of endocrine tumours. If these incidences rise further in response to drug treatment then they become end-points in carcinogenicity tests. Improved animal models should take account not only of the amount of food given but also differences in composition between the diets fed to laboratory animals and those consumed by humans.

(2)
To appraise spironolactone adequately, one needs to take account of all the evaluable data – including mutagenicity and long-term mouse data. Long-term safety in a second rodent species is desirable.

(3)
Pharmacology can be considered simply as the lower end of a continuous spectrum with toxicology at the other end. Many drugs produce their desired effects via a hormonally-mediated mechanism and when given in high doses produce hormonally-mediated toxic effects. Since the pituitary exerts a controlling effect on many endocrine glands one kind of endocrine disturbance often leads to others. Thus, if a drug (such as spironolactone), which affects hormonal status, is given in high doses, it is unlikely to affect just one aspect of the endocrine system. Most probably it will affect other endocrine functions.

(4)
Chemical structure is not a good predictor of biological effect. It is therefore not surprising that, despite some similarity in their formulae, spironolactone and potassium canrenoate exhibit different effects *in vivo*.

(5)
The proposed explanation of the difference between spironolactone and potassium canrenoate in respect of risk of myelocytic leukaemia depends heavily on the quality and compatability of the long-term data for the two compounds. Although Dr Wagner stressed the differences between the effects of the two compounds, the similarities in the profiles of their effects could also be emphasised e.g. the thyroid, mammary gland, testes and, arguably, the liver were target organs for both compounds. Also there is some evidence of activity of spironolactone in human mammary tissue. It is necessary to see the results of both short-term and long-term studies in which rats have been exposed, under identical conditions, to the two agents.

(6)
The effects of spironolactone on the liver, thyroid, mammary gland and testes ought to be regarded separately from the granulocytic leukaemia. The hypothesis is that all the former effects are hormonal and that the granulocytic leukaemia effect is due to the two mutagenic metabolites of potassium canrenoate. Putting all the carcinogenic

effects of the latter compound together could obscure this distinction.

(7)
Enzyme induction in the liver increases the metabolism of T^3 or T^4 and this lack of thyroxine stimulates the production of TSH leading to increased stimulation of the thyroid and the associated histological changes. There was nothing in the data presented to suggest that this mechanism was not operating here and, if this is so, it should be made clear.

there are no comparable insights into the hormonal mechanisms of tumorigenicity and carcinogenicity, and there must be concern about grouping the genotoxic and hormonal mechanisms together. The implications of each mechanism are very different both for risk assessment and for regulatory purposes. While the metabolic hypothesis may be useful to explore from the perspective of the leukaemia end-point, it may be less meaningful when assessing endocrine tissues.

The need for appropriate tests of the genotoxic hypothesis described and evidence for *in vivo* epoxide formation are important issues. There is a need for such studies to be as truly comparative as possible. The historical progression from the early 1960s has already been described and involved changes in regulatory requirements and acceptable standards and although the data presented have become more comparable, these new studies should be established on as comparable a basis as possible so as to avoid some of the obvious pitfalls in this type of extrapolation. In terms of clinical endpoints and clinical utilisation, metabolic and pharmacokinetic criteria are important in reducing the subjective element in judgemental extrapolation from animals to man. Further studies and more detailed information are needed in order to resolve finally some of these important issues.

Additional comments from Dr Roe

1. It is dangerous to assume that the same mechanism is responsible for positive genotoxicity and positive carcinogenicity. By the same token, a positive result in a long-term carcinogenicity test does not have to be paralleled by positive genotoxicity test data. The *in vivo* effect may have been mediated by a non-genotoxic mechanism.
2. The studies based on the use of the double-labelling technique may not prove that mutagenic or leukaemogenic metabolites are not produced from spironolactone.
3. There has been elegant detective work to explain the difference in activity between spironolactone and potassium canrenoate but virtually all the evidence has been used to generate a hypothesis and this now needs to be tested. One way to test it would be to see if granulocytic leukaemia could be produced with one or other of the epoxides derived from potassium canrenoate, and it is possible that one really large intravenous dose may be enough for this purpose. Finally it would be extremely helpful to know from an *in vivo* study whether spironolactone can prevent potassium canrenoate-induced leukaemia in rats.