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Letters

Valium and cancer

Your refer to some remarks by myself about Dr Horrobin as constituting "below-the-belt bitchery" and "attempted character assassination" (This Week, 8 January, p 53). I should like to make it clear that when I described Horrobin as "basically brilliant" I was being wholly genuine and that I was sad to learn that he presently finds himself without a job or funds for research. On the other hand, I believe it was scientifically unjustifiable for him to cause a sensation in the lay media about possible cancer hazards from Valium (diazepam).

A subheading in Colin Tudge's article in the same issue (p 80) reads "How promoters work", but what follows bears little or no relationship to what most specialists in the field of carcinogenesis understand by the term tumour-promotion. Furthermore, TPA (112-tetradecanoyl-13-phorbol-acetate), which Horrobin compares with diazepam, is a phorbol ester which is completely unrelated chemically to diazepam. It is categorised as a tumour promoter because it promotes the development of skin tumours in mice previously exposed to a sub-carcinogenic dose of a carcinogen. I am not aware of any evidence that TPA can promote the growth of either transplanted or primary mammary tumours.

The statement that diazepam is 10 000 times more potent than saccharin as a promoter is as misleading as it is emotive. The promoting activity of saccharin, *if any*, is confined to the enhancement of the incidence of tumours of the urinary bladder in rats exposed to doses of a known bladder carcinogen, *N*-methyl-*N*-nitrosourea (MNU), that are within the carcinogenic range. I say "*if any*" because Green and others (*Food and Cosmetics Toxicology*, vol 18, p 575) recently reported no significant enhancement by saccharin of MNU-induced bladder cancer.

Colin Tudge refers to three studies by Horrobin of the effects of diazepam on the growth of transplantable tumours. In the reports of these studies, Horrobin claims to have demonstrated a "dose-related" effect of diazepam on tumour growth, when in reality he has simply not done so in any of them. Indeed one of the most statistically significant effects he saw was reduced tumour growth in response to diazepam in one of the studies.

Colin Tudge argues that there is theoretically no reason why bell-shaped curves should not occur in carcinogenensis and tumour promotion. In fact it is very much the rule in carcinogenesis, as in toxicology and pharmacology generally, that high doses exert bigger effects than low ones. To be sure, one can find examples of plateauing of effect above a certain maximal-effect dose-level, but bell-shaped curves in carcinogenesis are rare.

The studies on the effects of diazepam on metabolic cooperation between two lines of cells in culture by Trosko and Horrobin (IRCS *Journal of Medical Science*, vol 8, p 887) are interesting but uninterpretable in terms of prediction of tumour-promoting activity. The authors claim that diazepam, like TPA, blocked metabolic cooperation between two cell lines grown together in culture. There is simply no body of experience of the relevance of this test system to the prediction of any kind of tumour-enhancing effect *in vivo* and no information on the activity of other drugs and chemicals in this system.

The results of a conventional two-year carcinogenicity study in large groups of rats carried out at the Huntingdon Research Centre (HRC) and commissioned by Hoffmann-La Roche were submitted to the US Food and Drug Administration and to the Committee on Safety of Medicines (CSM) in the UK during 1980 and will be submitted for publication soon. Not only were the results of this study completely negative for carcinogenicity at all sites, but in my view they go a long way towards disproving Horrobin's theory that diazepam may promote breast cancer development. Females of the rat strain used in the HRC study were, like females of most other strains, fairly prone to the spontaneous development of mammary tumours. If diazepam had been a promoter of mammary tumour development one would have expected to see evidence of it in this study. In fact there was no enhancement of mammary tumour incidence in response to any of the three dose levels of diazepam studied (1, 15 or 225 mg/kg/day). The highest dose was associated with significantly better survival, significantly reduced incidences of hyperplasia and galactocele formation and a lower incidence of mammary tumours than in controls.

Further evidence that diazepam is not a tumour promoter is provided by a study in gerbils (Green and Ketkar, *Z. Krebsforch*, vol 92, p 55) in which diazepam failed to enhance the carcinogenic activity of diethylnitrosamine. Horrobin refers neither to this nor to the results of two relevant epidemiological studies. Friedman and Ury (*Journal of the National Cancer Institute*, vol 65, p 723) observed no excess cancer risk in over 12 000 valium users, and no excess risk has been found so far in a study by the Boston University Drugs Epidemiology Unit.

On 9 January, responding to an inquiry, the Food and Drug Administration in the US replied: "Present information before FDA does not suggest an association between Valium and breast cancer. FDA continues to monitor data on breast cancer and its possible association with Valium or any other drug."

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Useful inflation

I would like to correct a factual error in the otherwise excellent article on high-altitude ballooning ("Around the world in a balloon", by Ted Stevens, 18/25 December, p 817). A balloon holding 80 000 cu.m of gas is very far from being the biggest in the world. When I worked at the National Scientific Balloon

Grimbledon Down — Bill Tidy