ABSTRACT

What is a carcinogen?
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RSM - 1 December 1988

A carcinogen is quite simply any agent which, under natural conditions of exposure, enhances the age-standardized risk of cancer development in man or other animal species compared with unexposed but otherwise identical controls.

This definition, although precise, is of little value as a guide to how best to prevent cancer.

The concept that most cancers are caused, not by bad genes or bad luck, but by environmental factors became dominant in the mid-1960's. But many who held it at that time imagined that only xenobiotic environmental agents could be incriminated since God would never have allowed naturally-occurring substances to be carcinogens. Nowadays all except the most bone-headed of us know that some of the most potent carcinogens are of natural origin, and also that factors which cause prolonged irritation or disturbance of physiological status - especially of hormonal status - can also act as carcinogens.

The two-stage theory of carcinogenesis, which was mainly founded on the basis of stereotyped experiments in mouse skin with simple benign warts as the end-point, has served as much to confuse as to advance our understanding of carcinogenesis. That the so called initiating stage which involves damage to the genome has to occur first, and that

any non-genotoxic agent which causes cancer must be a tumour-promoter which acts by stimulating previously initiated cells to proliferate became tenets of faith. Carcinogens present naturally in the environment, such as radon and cosmic rays, and/or man-made carcinogens occurring as environmental contaminants, were held responsible for the pre-existent state of tumour initiation. Unfortunately this possibility could neither be confirmed or refuted.

For a theory of carcinogenesis to be robust it must take into account all the known facts and not just those that are easy to explain on the basis of popular paradigms. Neither the two-stage theory nor the idea that only xenobiotic agents can be carcinogens are consistent with the following facts:-

(1) Simple ovariectomy followed by the implantation of one ovary into the spleen leads to neoplasia both in the pituitary gland and in the implanted ovary, even though no external environmental agent is involved. (2) Potentially DNA-damaging electrophiles are produced during ordinary metabolic processes. (3) By simply reducing the food intake of laboratory rats and mice, which are normally grossly overfed, the incidence of both benign and malignant tumours can be highly significantly reduced.

The things that seem certain about carcinogenesis are that cancers involve the proliferation of genetically-altered or genetically-unstable cells. Gene-mutation, defective cell division at the chromosome level, inherited cancer genes (oncogenes) or reverse transcription following infection with RNA viruses may be implicated. However a host of other, non-genotoxic factors may, by a wide variety of mechanisms, seemingly cause cancers to appear. They may do this, for instance, by

stimulating the proliferation of mutant cells, by increasing the rate of generation of electrophilic metabolites, by interfering with negative feedback processes involved in normal homeostasis, or by numerous other mechanisms. These two kinds of activity may reasonably be referred to, respectively, as genotoxic carcinogenicity and non-genotoxic carcinogenicity. Natural hormones, such as 17β-oestradiol and natural foodstuffs, such as lactose, are good examples of non-genotoxic carcinogens.

Two practices more than any others have posed problems for the pharmaceutical industry in relation to the need to ensure that carcinogenic drugs are not marketed. The first is the Regulatory requirement to undertake in vivo carcinogenicity tests at maximum tolerated doses such that gross disturbances of physiological status are bound to occur. The consequence of this is that the way is opened up for a wide variety of non-genotoxic carcinogenic mechanisms to operate. The second is the tradition of maintaining laboratory animals in a continuous state of overnutrition such that both control and drug-exposed animals prematurely develop all manner of degenerative diseases, multiple disturbances of endocrine status and a greatly enhanced risk of developing tumours. At best this does no more than muddy the waters but very often it also introduces the possibility of false positive and false negative results in the tests.