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Plausible but not very probable

An assessment of Dr Shamberger's hypothesis by Dr Francis Roe, a London consultant in toxicology and adviser in experimental pathology and cancer research.

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IN a paper with T. L. Andreone and Dr C. E. Willis published in the Journal of the National Cancer Institute (Volume 53, pp 1771-3) in December, 1974, Dr Raymond J. Shamberger reported that malonaldehyde is capable of initiating tumour formation in mouse-skin and also of giving rise to internal tumours when applied to mouse skin.

They were not surprised at this finding because, according to them, malonaldehyde resembles two known carcinogens, glycidaldehyde, and β-propiolactone.

Now, Dr Shamberger has pointed out that malonaldehyde is readily formed in common foodstuffs, as a result of oxidation during storage.

It is also formed in the tissues of animals fed on diets deficient in antioxidants. Antioxidants such as vitamins C and E or selenium prevent its formation.

During his life-time a non-vegetarian may eat as much as 75 grammes of malonaldehyde (ie just over 1g per kg).

By comparison, Shamberger *et al* found in their experiments that as little as 5 mg malonaldehyde was enough to initiate skin tumour formation and to produce liver and rectal cancers in mice.

Dr Shamberger cites epidemiological evidence in support of his view that malonaldehyde is probably a cause of gastro-intestinal cancer in humans.

The questions are "Is Dr Shamberger likely to be right?" and "If so, why hasn't his 1974 paper attracted more attention?"

It is true that β-propiolactone and glycidaldehyde have been shown, in several laboratories, to be carcinogenic in laboratory animals although the latter compound appears to be only weakly active as such. The experiments with malonaldehyde on mice reported by Shamberger and his colleagues in 1974 are the only relevant studies so far recorded.

Although the description of the experiment is difficult to follow, it seems clear that, like β-propiolactone and glycidaldehyde, malonaldehyde is able to initiate skin tumour formation in mice, that is to say that mice which receive a single application to the skin of malonaldehyde followed by repeated applications of the tumour-promoting irritant, croton oil, developed skin tumours.

Far less convincing is the evidence that malonaldehyde caused liver and rectal cancers in mice. As far as one can tell from a very poor description of the experiment, 30 mice were treated with applications of 12 mg malonaldehyde to the dorsal skin daily for nine weeks and then with 0.36 mg daily for 39 weeks (total dose = 756 mg during the first nine weeks plus 98.3 mg during the next 39 weeks = 854 mg per 40g mouse = 21g/kg).

No tumours were seen in 12 animals which died between four and six weeks but five out of six mice which died between six and nine weeks had tumours, four in the liver and one in the rectum.

This left 12 mice still alive to continue on the 0.36 mg malonaldehyde per day regime. None of these died with neoplasms between nine and 48 weeks, although what happened thereafter is not reported.

Only two of 30 control mice died during the same 48 week period, both without tumour.

Before one can interpret these findings it is necessary to know what tumours, if any, were present in the 12 treated and 28 control animals that were still alive at 48 weeks. Relatively slow growing liver tumours may occur in up to 100 per cent of untreated mice and the one rectal cancer is the one swallow that doesn't make a spring, anyway.

The most unbelievable features of the results, however, are the shortness of the latent interval in the five cases of internal cancer and the absence of any further cases of death from cancer after nine weeks.

The 12 mice from the treated group which survived from the ninth to the 48th week had received more malonaldehyde by nine weeks than those that had died between six and nine weeks.

The nature of malignant cancer is firstly that it takes a long time to produce (usually much longer than six to nine weeks in mice) and secondly that, once it has been produced it usually progresses despite cessation of exposure to the agent which produced it.

In short, no experienced cancerologist would accept that malonaldehyde can produce liver and rectal cancers in less than nine weeks in mice solely on the basis of the available evidence.

In some ways the hypothesis that Shamberger has proposed is plausible. It probably is true that meat-eaters are at higher risk of gastro-intestinal cancer than vegetarians and that the falling incidence of gastric cancer in the USA and Europe is associated with better refrigeration and dietaries more adequate in antioxidants.

But associations do not constitute cause-effect relationships. In any case liver cancer incidence has always been low and rectal cancer in humans is neither increasing nor decreasing in incidence.

Shamberger's "malonaldehyde theory" is thus, but one of many theories that seek to relate epidemiological observations on human gastro-intestinal cancer rates with diet.

I have little doubt that other workers will in due course confirm that malonaldehyde is an initiator of skin tumour formation in mice.

I am far more doubtful, however, that malonaldehyde will be found to be a cause of liver or gastrointestinal cancer in mice. If not, then malonaldehyde will simply take its place alongside the increasing number of other potential carcinogens which we now know we have to live with.

But if someone confirms that malonaldehyde can cause gastrointestinal cancer then the possibilities Shamberger has put deserve urgent investigation.