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Editorial

Bile acid receptors and large bowel cancer

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There has been longstanding interest in the role of the diet in the aetiology of cancer. Potential dietary causes include naturally occurring carcinogens in food, carcinogens produced by cooking, by organisms infecting foodstuffs or factors affecting the transport, activation or deactivation of ingested carcinogens. One important factor, the effect of overnutrition per se (Doll and Peto 1981) has been well documented in animals (Roe 1981), although obesity as a risk factor appears to cause little concern in man. However, it is noteworthy that in a recent case control study (Bristol et al. 1985) energy intake has been shown to be 16% higher in bowel cancer patients.

The incidence of large bowel cancer varies considerably in different countries and correlates not only with fat consumption but also with meat, sugar and total energy intake (Armstrong and Doll 1975; Drasar and Irving 1973). Low dietary 'fibre' intake has also been considered a risk factor (Burkitt 1975). A role for the bacterial flora of the bowel interacting with the rate of excretion of cholesterol and bile acids has been proposed. The hypothesis could be simply stated in this way: – A particular substrate is acted on by bacteria in the bowel to produce a carcinogenic product. Diet is important in determining the concentration of the substrate and will also affect the composition of the bacterial flora (see Hill 1985). Thus cholesterol and bile acids may be acted on by colonic bacteria to produce carcinogens that act locally – or may be absorbed and act elsewhere. Bowel transit time, affected by fibre, will affect exposure to any active compounds produced.

Local effects are probably those which should cause concern. Although it is clear that dietary cholesterol ultimately reaches the blood and the faeces there is no evidence that the blood levels of any form of the lipid are correlated with the risk of developing cancer. Indeed, some evidence suggests that those with low cholesterol levels have a high mortality from cancer at a variety of sites.

Reports of the presence of bile acid receptors in colorectal cancer (Summerton et al. 1983) have led to suggestions that bile acids may have a critical role. Summerton et al. examined the cytosol from normal mucosa, adenomas and carcinomas. They suggested that specific receptors existed if total binding of C^{14} deoxycholic acid (specific and non-specific) exceeded the non-specific binding in duplicate assays (the data given in their paper do not permit the avidity of binding to be evaluated). Autoradiography was used to evaluate cell binding morphologically. Just under a third of carcinomas had apparent binding sites. There was no correlation with differentiation; advanced tumours – assessed by clinical staging – were more likely to be receptor positive. Only two cases showed autoradiographic positivity. Hill et al. (1987) have used these data together with their observations that faecal bile acid concentrations (FBA) were higher in patients with carcinoma or dysplasia than in patients without these changes, in support of the theory that bile acids "are causally related to colorectal cancer". This paper has been criticised on technical grounds (Lewin and Clark 1987) including possible sampling errors for the FBA's and the wide variation in total and individual bile acid excretion which are known to occur day by day, but there are broader problems with this type of evidence.

Recent developments in studies of the genetics of colonic cancer (Bodmer et al. 1987; Solomon et al. 1987) have localised the gene for familial polyposis coli to chromosome 5 (5q21–q22) and suggested that becoming recessive for this gene may be a critical step in the progression of any colonic lesion to carcinoma in these patients. In studies of ras gene mutations Bos et al. (1987) and Forres-

ter et al. (1987) have demonstrated these mutations in 40% of colorectal tumours; they were never identified in normal mucosa from the same patients. In eight tumours the residual adenoma in the specimen could be separated from the carcinoma and in seven of these cases the adenoma cells contained the same mutation as the carcinoma. The mutation is thus a step on the road to malignancy, rather than a determinant. These studies suggest that a number of highly specific genetic steps occur in the progression of changes in the mucosa leading to colorectal carcinoma and that these steps may vary, thus offering a number of possible pathogeneses.

Receptor induction is apparently not a necessary event in carcinogenesis since it is manifest very late in the process. It is probably an epi-phenomenon, a view supported by the fact that cytosolic binding is not ubiqitous in the tumours. An analogy with oestrogen receptors in carcinoma of the breast could be drawn (Panahy et al. 1987) but is not exact since a role for oestrogen receptors in the metabolism of the cells of the breast is established; no functional role is proposed for large bowel bile acid receptors.

What alternative modes of action, other than an effect on 'receptors' may there be for bile salts? Moorehead et al. (1987) have found an increased proportion of chenodeoxycholic acid in duodenal bile in patients with adenomas and carcinomas when compared with controls. Should the properties of particular constituents of bile as substrates for bacterial genesis of mutagens in the gut be evaluated? Fahrig (1987) has used a yeast system – S. cerevisiae – to examine the problem. In his system the spontaneous frequency of mutation in the yeast is dependant on the concentration of cycloheximide in the culture medium. Suppression of mutations leads to enhancement of recombinations, while suppression of recombinations leads to enhancement of mutations. In this system bile acids showed weak mutagenic activity alone but had additive effects when tested with an alkylating agent. Both antimutagenic (lithocholic acid) and comutagenic (cholic acid) effects were seen. In complex mixtures of bile salts (ox gall) antimutagenic/corecombinogenioc effects predomonated. These data suggest little risk from bile salts, but can only be considered as an indicator. It is difficult to see how in vitro studies will help in the face of great natural variability in the composition of bile and the effects of common food stabilisers, emulsifiers and thickeners in increasing faecal bile acid excretion (for example, xanthan gum, Eastwood et al. 1987). However, if it becomes clear that a particular set of genetic events are necessary to induce a colorectal neoplasm it may be possible to identify those types of mutagen which can produce them. This, in turn, may make it possible to pick the needle out of the haystack.

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