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FOOD AND CANCER

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There are good reasons to suspect that the quantity and quality of food influe both the overall risk of development of many forms of cancer and the types o cancer which occur most commonly. The evidence is briefly reviewed and the kinds of mechanisms that may be responsible listed. The striking effects of dietary restriction on cancer risk in laboratory rats and mice and the possibilit that dietary restraint may be beneficial in man are discussed. Recent laborator evidence that carcinogens may be formed in food during cooking is mentioned Finally, the importance of avoiding mineral imbalance when conducting anima studies designed to evaluate the safety of food constituents and additives is stressed in relation to urinary-calculus formation and bladder-tumour risk.

Introduction

During the late 1950s and through the 1960s vast resources were devoted, especially in the United States, to the search for cancer-chemotherapeutic dru This research certainly led to greatly improved prospects for many cancer pati However, the era of this type of research ended with the realisation that furth major advances were only likely if research was based on more knowledge of t nature of cancer and of the mechanisms involved in its development.

Since attention is being increasingly focussed on food constituents, additive and contaminants in relation to cancer prevention, it is timely to consider the underlying philosophy and the quality of the evidence that should be required before introducing measures which alter in any major way the diets and food patterns of large numbers of people.

First however I should like to remind you of certain widely accepted facts. Cancers may, in theory, be caused by either genetic or environmental factors, but in practice, a combination of both is usually implicated, often with multip factors interacting with each other. Despite this, for most kinds of cancer, environmental factors figure more prominently as determinants of cancer risk than genetic ones. Especially persuasive are the results of studies on cancer incidence among migrants. Cancer of the stomach is about 5 times more prevalent in Japan than in the USA whereas cancer of the colon is seen almost times more often in the USA than in Japan. In Japanese who migrate to the USA and in their children and children's children the risk of stomach cancer fa and the risk of colon cancer rises to be more like the corresponding risks in white Americans (Haenszel & Kurihara, 1968).

The Registrar General's Decennial Supplement (Registrar General, 1961) recorded steep social class differences in England and Wales for cancer of the stomach in both sexes and also for cancers of the rectum, urinary bladder, lun and uterine cervix suggesting environmental factors in their causation. Howeve no such gradient was apparent for cancers of the colon (ie, excluding the rectu

nor for the prostate, breast, body of the uterus or brain.

A change in death rate with the passage of time also points to the importa of environmental rather than genetic factors. In North American and Northe Europe the death rate from cancer of the stomach has been falling in successi age-cohorts with birth dates in the present century, whereas there has been n change in either direction in the death-rate from cancer of the colon.

It is especially tempting to postulate that dietary factors are likely to be responsible for the changes in cancer incidence in Japanese migrants because the big differences between the kinds of food commonly eaten in Japan and kinds eaten in the USA. It is also tempting to regard factors associated with f as particularly likely candidates for suspicion in the case of cancers arising in tissues which come into direct contact with food.

Laboratory studies indicate that variations in the quality or quantity of fo can influence the risk of cancer development, not only in the gastro-intestina tract, but at any site in the body. It would, therefore, be naive to look only a incidence of gastro-intestinal tract cancers in assessing the likely contributior food to overall cancer risk in humans. The liver however is a favoured site fo the development of tumours in response to the oral administration of many known carcinogens in animals. It is, therefore, relevant to point to the low incidence of liver neoplasia in the developed countries of Europe and North America and reasonable to conclude that the diets consumed in those countr are free from significant concentrations of hepatocarcinogens.

Now this is surely an extremely important conclusion in view of the emph presently being placed by regulatory authorities on the possible carcinogenic dangers from nitrosamines, mycotoxins, pesticides and various chlorinated h carbons. The liver is one of the targets for many of the nitrosamines that ma formed in the acid pH conditions of the stomach by the interaction of secon amines (including food constituents and drugs) and nitrates (which may be present naturally in food as nitrates, or which may get into food as a result o the use of artificial fertilizers, or which may be added deliberately to food as preservatives). The liver is also a principal target for mycotoxins, such as afla first identified in ground-nuts, and for chloroform formed as a result of the chlorination of drinking water. DDT and dieldrin were banned from use as pesticides mainly because they increase the risk of liver tumour development laboratory rodents, and yet there has been no evidence of increasing risk of l cancer in humans, except very recently among women taking oral contracep

Anyone who has tried to carry out a dietary study in humans will know h exceptionally difficult it is to obtain reliable information about current eatir habits, let alone past eating habits. We recently attempted (A. Gregor, P.N. I F.J.C. Roe, M.J. Wilson & A. Melton, Unpublished) to compare the past consumption of vitamin A-rich foods (eg liver and carrots) and vitamin A-containing medicines among patients with lung cancer and control subjects matched for age and smoking habits. Like Bjelke (1975), we found that, in males, past vitamin A consumption was apparently lower in the lung-cancer group than in the controls. However, an opposite pattern was seen in female would need a much larger study of the same kind to establish that vitamin A past diet has had a protective effect. Indeed probably a protective effect cou

only be demonstrated satisfactorily in a large-scale long-term prospective study such has recently been organised in the USA by Dr Michael B. Sporn.

The difficulaties in obtaining accurate dietary histories, and the fact that 20 more years are likely to elapse before the effects of introducing a carcinogen in food are detectable by epidemiologists, spell out a need for extreme caution in the interpretation of epidemiological studies relevant to cancer and food. News paper headlines and public scares have often been based on epidemiological studies that have not been properly designed or executed, are of too short duration, or which involved too few people. An example was a claim that fluoridation of drinking water is associated with increased cancer risk (Burk & Yiamouyiannis, 1975). Unfortunately suspicions raised on poor foundations persist despite clear demonstrations of their deficiencies (Doll & Kinlen, 1977; Fredrickson, 1976; Hoover, McKay & Fraumeni, 1976).

Possible ways in which food may influence cancer risk

Food is but one aspect of the environment which may influence the risk of cancer, and the potentiality for the environment to influence cancer risk begins as the moment of conception. Food components, drugs, alcohol, contaminants in water, contaminants in air, tobacco smoke, hair dyes, background ionising radiation, cancer viruses to which the pregnant mother is exposed, may reach the developing fetus. Transplacental carcinogenesis has been demonstrated repeatedly in the laboratory. The same array of environmental factors may influence cancer risk more directly after birth. Wynder & Gori (1977) expresse the view that food factors are implicated in the aetiology of 60 per cent of cancers in women and more than 40 per cent in men. Table 1 shows some of th mechanisms whereby food could influence cancer risk.

Table 1. Ways in which food may influence cancer risk

1. Food may contain a carcinogen or a co-carcinogen
   (a) as an ingredient
   (b) as a natural contaminant (eg aflatoxin) or man-made contaminant (eg agrochemical, processing or packaging chemical)
   (c) as a food additive
   (d) produced during cooking.
2. Food may provide one or more of the raw materials for the endogenous production of carcinogens by gut flora or in the liver (eg production of nitrosamines from nitrates and secondary amines).
3. Deficiency in essential ingredients (eg trace minerals, Vitamin A) may enhance cancer risk
4. Excess of certain food ingredients (eg fat) or of food generally (overnutrition) may enhar cancer risk or general dietary restriction may reduce cancer risk by changing corticosteroid status.

Here, I will discuss three aspects of nutrition and cancer, namely: (1) the effects of overnutrition in increasing the risk of cancer in laboratory rats and mice; (2) the formation of bacterial mutagens some of which may be carcinogens, during cooking, and (3) the influence of crystalluria and calculus formati on bladder tumour risk in animals fed on diets improperly balanced with regar to certain minerals or on diets which disturb mineral balance.

Enhancement of cancer risk by overnutrition

Five years ago, relying heavily on Mary Tucker's work at Imperial Chemical Industries Ltd. (Roe & Tucker, 1974), I drew attention to the fact that the incidence of neoplasms in animals fed on restricted diets was as much as eight times less than in *ad libitum* fed animals, many of which were grossly obese. S then Tucker (1979) has confirmed her previous findings in mice and shown tl the same is true for rats (Table 2). Further confirmation has come from a car fully conducted mouse study carried out by G. Conybeare (personal commur cation) (Table 3).

Table 2. Effects of dietary restriction on tumour incidence in specified-pathogen-free Wistar rats. (Tucker, 1979)

	Males		Females	
	Ad lib	20% restricted	Ad lib	20% restricted
Survival to two years (%)	72	90	68	88
Tumour bearing at or before two years (%)	66	24***	88	56*
Number of tumours per rat (mean)	0.94	0.27***	1.18	0.76**
Rats with pituitary tumours (%)	32	0***	66	39**
Rats with mammary tumours (%)	0	0	34	6***

*=$P<0.05$, **=$P<0.01$, ***=$P<0.001$. Statistical significance (ignoring better survival of diet - restricted groups).

The findings summarised in Tables 2 and 3 are, of course, by no means fundamentally new. Beneficial effects of dietary restriction in the form of be survival and reduced tumour incidence have previously been recorded in mic Tannenbaum, alone and together with Silverstone, in a series of papers publi between 1940 and 1951 (Tannenbaum, 1959 for review). McCay & co-work (1939) recorded increased survival and reduced tumour incidence in rats fed a restricted diet. More recently Rowlatt, Franks & Sheriff (1973) reported reduced incidences of mammary and liver tumours in diet-restricted mice. R Bras (1965) recorded both better survival and reduced tumour incidence in r given fewer calories or diets containing reduced concentrations of protein or hydrate. Gellatly (1975) saw a markedly higher incidence of liver tumours in fed on a high fat diet than in mice fed on the same diet with lower fat conte

Two important questions arise from these observations in rats and mice, f 'Which is the more artifical circumstance for these animals - *ad libitum* feedi or a diet-restricted regime?', and secondly, 'Does dietary restriction reduce c risk in humans?'.

The gross obesity of many *ad libitum*-fed rats and mice provides a persuas

Table 3. Effect of simple dietary restriction on survival and tumour incidence in Swiss mice fed on commercially supplied cubed diets. (G. Conybeare, 1979, personal communication

	Males		Females	
	Ad lib	25% restriction	Ad lib	25% restriction
Number of mice	160	160	160	160
Survival to 83 weeks (%)	58	66	62	77*
Any tumour at any site (%)	44	22.5**	31	11***
Any malignant tumour at any site (%)	11	4**	14	4***
With lung tumour (%)	19	12*	15	5***
With liver tumour (%)	29	7.5***	4	0.6***
With lymphoma (%)	2.5	0.6**	7	2.5***
With other tumours (%)	5.0	2.5*	7.5	2.5**

*=$P<0.05$, **=$P<0.01$, *=$P<0.001$. Statistical significance (ignoring better survival of diet-restricted groups)

common sense answer to the first question. Unlimited food supply would rare prevail in the wild and, in any case, slow-moving obese animals would be pick off by predators. It has become traditional to feed laboratory rats and mice *a libitum,* mainly because it is convenient; animals can be left without supervisi for longer periods. But in my view the practice ought long ago to have given w to controlled, slightly restricted, feeding regimes. In most laboratories where or monkeys are used for toxicological purposes, it is not the practice to feed animals *ad libitum* since obesity is recognised as a potentially seriously interfe problem. The obesity which occurs in laboratory rodents fed *ad libitum* can b just as marked but, for historical reasons, is ignored.

There is, almost certainly, more to dietary restriction than mere reduction caloric intake. Under conditions of starvation, circulating cortico-steroid level rise and the whole hormonal status of animals changes. When an animal is giv a ration of food, even though the amount provided is almost as much as it wo eat during 24 hours if fed *ad libitum,* it tends to gobble up the whole ration a then spend the rest of the day regarding itself as being starved. Consequently, is likely that diet-restricted animals have a diurnal hormone pattern quite different from that which characterises *ad-libitum*-fed animals. Of course, starvation is not the only factor which effects cortico-steroid status. Anxiety fear due to noise, fighting, or to some experimental procedure may have the effect. My colleagues and I, therefore, were not unduly surprised to see significantly fewer mammary tumours in female rats exposed to tobacco smo which they found irritant, than in comparable rats exposed to air. The daily stress of being exposed to the irritant had the same effect on mammary tumo

incidence as dietary restriction (Davis *et al.*, 1975). This finding was, of cour potentially very misleading, because if it were extrapolated to humans witho the role of stress being taken into account, the conclusion to be drawn woul that smoking protects women from breast cancer, and as far as I know, there not a scrap of evidence for this.

Another difference may be that under conditions of starvation the upper p of the gastro-intestinal tract is both empty and sterile, whereas in continuou feeding animals, bacteria are to be found throughout the gut. Diet-restricted *ad libitum*-fed animals are, therefore, liable to differ in their gut flora during at least, some periods of each 24 hours.

Berg (1975) dismissed the laboratory findings of reduced tumour incidenc in response to diet restriction in an unjustifiably cavalier fashion. The only relevant animal study he referred to was that of Ross & Bras (1965) but he nevertheless concluded: 'The diets are much too drastic to be used on humar and in any case the extrapolation to humans is doubtful.' Many of us who ha actually conducted dietary restriction studies in animals could not agree witl this. In the first place the restriction does not have to be severe in terms of c intake. Thus, in the earlier mouse study by Mary Tucker (Roe & Tucker, 19 restriction of food intake from 5.77 g per day consumed by *ad libitum*-fed animals to 5 g per day was associated with a dramatically-reduced tumour incidence. Moreover, in that and nearly all such studies, restricted animals bc look sleeker and healthier and survive significantly better. Berg's idea that di restriction may reduce tumour incidence by rendering animals slightly defici in some essential factor is clearly nonsense in relation to all the experiments which I have been associated.

The question of whether dietary restriction would reduce cancer risk in hu is difficult to answer. In developed countries virtually all of us can eat as mu we want to eat. However, humans are not generally-speaking confined to uni cages without the possibility of exercise and with nothing to amuse them ap from food. It is thus difficult to identify groups of humans who are the cour parts of either the *ad libitum*-fed or diet-restricted groups in the animal studi Nor can we turn to developing countries for an answer; because, there, reliab on cancer incidence and mortality are not available, early death from non-cancerous disease is common, and there is uncontrolled exposure to known carcinogens in food such as does not occur in developed countries.

However, some evidence that overfeeding increases cancer risk in humans has been forthcoming. Wynder & Mabuchi (1972) reviewed epidemiological evidence suggesting that overnutrition increases the risks of cancers of the br ovary and endometrium in women and the risk of cancer of the prostate in n Cheraskin, Ringsdorf & Aspray (1969) recorded a general association betwee obesity and incidence of cancers of all types, and the actuaries of the Metrop tan Life Insurance Company of New York (Metropolitan Life, 1960) observe 16 per cent excess of cancers among men more than 20 per cent overweight a 13 per cent excess of cancers among similarly overweight women. Other stu have found specific associations between obesity and breast cancer and obesi and endometrial cancer (De Waard & Baanders-van Halewijn, 1974; Dunn & Bradbury, 1967).

At this stage, it would seem that much of the dramatic effect of simple diet restriction on cancer incidence in laboratory animals is dependent on the high artificial circumstances associated with keeping animals in cages and feeding th *ad libitum*. Nevertheless, I am convinced that there is much waiting to be discovered concerning the effects of food patterns, overeating and caloric restraint and discipline on cancer risk in humans. Research orientated solely towards the identification of carcinogens in food will not lead to discoveries in this area. Furthermore, laboratory investigations confined to over-fed obese ra and mice might well be giving us a very distorted view of carcinogenic hazards from food.

Formation of carcinogens during cooking

Cancer of the colon is commoner in man than in other animal species. Could this be because man is the only species who regularly consumes cooked food? The last decade has witnessed a flurry of interest in possible causes of cancer o the colon. Burkitt, Walker & Painter (1972) studied the effects of dietary fibr on the consistency of stools and transit times. They pointed out that diseases such as appendicitis, diverticulitis and cancer of the colon are rare in countrie (eg in Africa) where transit times are short and high where (eg Northern Europe and USA) they are long. Burkitt's work in this area has stimulated mu research including research directed towards the possibility that the high fat content of Western-type diets stimulates the excretion of bile acids, and that carcinogens are formed from bile acids by the action of bacterial enzymes in t gut (Reddy & Wynder, 1978). Another possibility is that cooking methods us for Western food might introduce carcinogens not present in the uncooked, o less-cooked, foods consumed in low colon-cancer-risk countried.

The possibility that carcinogens may be formed during cooking has stimula research for many years. However, much of this research was conducted wher only a relatively few kinds of chemical carcinogen had been recognised and methods for analysing food for known carcinogens were comparatively primit Thus, much of the early research sought to relate the levels of 3,4-benzpyrene in smoked foods with the risk of cancer of the stomach (Roe, 1967 for reviev

Research recently reported by Sugimura and his colleagues in Japan (Sugimura *et al.*, 1977*a,b*) *may* mark the start of an era of better understandi of the importance of cooking procedures in relation to cancer risk. I say '*may* advisedly since it is arguable that the laboratory 'cooking' procedures used by these investigators would rarely be mimicked in the kitchen. However, I feel i is too early to dismiss their work on these grounds. Sugimura *et al.* (1977*a,b*) and Yamamoto *et al.* (1978) reported the isolation of bacterial mutagens fro pyrolysates of L-glutamic acid, tryptophan and phenylalanine, and postulate structures for the mutagenically-active constituents which they had isolated. The demonstration of mutagenicity for bacteria provides grounds for suspicic of carcinogenicity. It will, therefore, be of great interest to see whether studi designed to test the putative active constituents in the pyrolysates for carcinogenicity give positive results. If so, and if it is clear that the condition required for the formulation of the active principles are fulfilled during ordin cooking procedures in the home, then obviously a whole new area of researcl

will have been opened up. Indeed the whole approach of regulatory bodies to safety assessment of foods and food additivies will need reappraisal to take th effects of cooking into account.

Crystalluria, calculus formation and bladder cancer

Cyclamate was banned because rats fed on diets containing high concentratio of it developed bladder tumours. Rats fed 5 per cent or 7.5 per cent saccharir also develop bladder cancers and regulatory bodies are presently trying to dec whether they should ban saccharin too. Both substances increase the incidenc of calculi in the renal tract, and although calculi have not been seen in all the rats which developed tumours, it is possible that in some cases calculi present one time were passed *per urethram* or that crystalline deposits too small to b seen by the naked eye were present. There is abundant evidence that the pres of solid objects, such as paraffin-wax pellets or glass beads, within the urinary bladder predisposes to tumour formation (Ball *et al.,* 1964). There is also increasing evidence that other substances which predispose to stone-formatio also predispose to bladder tumour formation (eg polyethylene glycol in rats, xylitol in mice).

Recently I have had occasion to survey the literature relating to nephro-calcinosis in laboratory rats and have come to the conclusion that many of th diets currently used in laboratories all over the world contain inappropriate amounts of various minerals. The rat requires less calcium than man and has difficulty in dealing with excess amounts of it in the diet. Many laboratory animal diets contain too much calcium, too much phosphorus, too little magnesium and a too low Ca:P ratio. These defects manifest themselves in th deposition of minerals in the cortico-medullary region, particularly in female and in increased mineral deposition in the pelvic region of rats of both sexes. More extreme defects in dietary mineral formulation can lead to acute tubula nephrosis or stone formation. Some laboratory diets are also marginally defic in vitamin B_6 and this predisposes to oxaluria and oxalate-stone formation. Calcium is normally absorbed along with monosaccharides, such as glucose, ir the jejunum. When diets contain carbohydrates which are not broken down t absorbable sugars by the time the food reaches the duodenum, calcium is carried down to the ileum and caecum. If, in these parts of the gut, the carbo hydrates are broken down - possibly through the intervention of bacterial enzymes - to absorbable monosaccharide units, then calcium absorption takes place here and for some reason the overall calcium absorption is then *greater than normal.* The feeding of lactose, for example, in all species, increases calc absorption from the gut. This, of course, is of importance to the young growi animal which needs extra calcium for bone building. But when diets containir high concentrations of lactose (eg 25 per cent) are fed to rats, especially if th diets contain supra-optimal levels of calcium, then a variety of forms of nephrocalcinosis, including stone-formation occur. I do not know if bladder tumours having arisen in lactose-fed rats with bladder stones, but I do not do that such animals would be at increased risk of bladder-tumour development.

The importance of these facts is two-fold. First, I suspect that rats given hi doses of cyclamate or saccharin have increased calcium absorption and excret

turn predispose to tumour development. It may be that all these findings are dependent on artificial laboratory conditions, and that the same sequence of events would not occur in man. As far as I know, no research has related specifically to these possibilities. Secondly, I believe that the mineral requirements of laboratory animals under test need to be considered very seriously. It is not good enough to be satisfied that the minimal requirements of animals are covered; attention should be paid to providing minerals in *optimal* concentrations and ensuring a proper balance between them.

The situation with regard to risk of urolithiasis in humans is an odd one. Oxalate stone-formation used to be common in this country, but disappeared very suddenly about the time of the first World War. Oxalate stone-formation is presently endemic in Thailand, but nobody knows why. There is probably a very association between stone-formation and risk of cancer of the renal pelvis and bladder in humans. The situation in Thailand offers the possibility of defining the association more precisely, but as far as I know, this has not yet been done.

Main conclusions

(1) Very great care needs to be exercised in extrapolating from the results of studies in laboratory animals to man, especially in feeding studies where the compositions of diets are grossly distorted from normal. More care also needs to be directed towards the formulation of animal diets, particularly with regard to the levels of minerals in them.

(2) The relationship between food and cancer is not solely dependent on the presence or absence of carcinogens or co-carcinogens in food. *Ad libitum*-feeding of laboratory rats and mice, which is unnatural for these species, leads to obesity and to very high incidences of benign and malignant neoplasms compared with diet-restricted animals. The problem is probably not simply one of excessive intake of energy. There is already evidence that overnutrition increases cancer in humans, particularly cancers of the breast, endometrium, ovary and prostate, but more research is urgently needed on the effects of overnutrition and different dietary patterns on human cancer incidence.

(3) Ascertaining the current consumption of different foods by individuals is subject to great difficulty and gross inaccuracy. The reliability of data on present dietary habits is extremely low. These difficulties make it very difficult to study the relationship between food and cancer risk in man. Nevertheless, there is an urgent need for properly conducted prospective epidemiological studies which seek to relate cancer incidences with dietary habits ascertained as accurately as possible in people while they are still well.

(4) Despite all the scares about hazards from food, food additives, food contaminants etc., which have confronted us during the past decade, it would my plea and strong recommendation that dietitians should, in their work, remain moving very far off the path which their basic knowledge, experience and common sense dictate. They should never respond precipitously to scare-mongering. Two quotations are relevant:

An article of food and drink which is slightly worse, but more palatable, is to be preferred to such as are better but less palatable. (Hippocrates c. 400 B.C.)

One swears by wholemeal bread, one by sour milk; vegetarianism is the only road to salvation of some, others insist not only on vegetables alone, but on eating those raw. At o time the only thing that matters is calories; at another time they are crazy about vitamins about roughage.

The scientific truth may be put quite briefly; eat moderately having an ordinary mixed diet, and don't worry. (Sir Robert Hutchison, Newcastle Medical Journal, Vol. 12, 1932)

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ROLE OF BACTERIA IN HUMAN CARCINOGENESIS

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The bacterial hydrolysis of conjugated carcinogens, production of potential carcinogens from amino acid metabolism, formation of *N*-nitroso-compound and production of carcinogens from bile salt metabolism are discussed. The limited evidence implicating these compounds in the causation of bowel, gast bladder, biliary tract and cervical cancer is presented. Although there is no example of a proven role for bacteria in the causation of any human cancer, t are many leads currently under investigation. They have exciting implication for prevention.

Introduction

It is generally accepted that most cancers in humans have at least an environmental component in their etiology and that environmental factors are of ma importance in the causation of a high proportion of them. This contrasts witl for example, the mouse or cat where many of the cancers appear to have a vi etiology. One of the most intimate parts of our environment is our bacterial flora; because of its distribution and its high metabolic activity it is, in my opinion, very unlikely that the flora has no role to play. The nature of this ro has still, however, to be determined.

Many cancers appear to be diet-related (eg, stomach, oesophagus, colorectu breast, endometrium, ovary, prostate, pancreas and kidney) and although carcinogens, such as *N*-nitrosamines, aflatoxin, polycyclic aromatic hydrocarb are often present in the food the relationship can rarely be ascribed to these p formed carcinogens. The gut bacterial flora is ideally sited to play a key intermediary role in this relationship between host and his diet. In this paper I wil first describe some of the carcinogens or promoters produced by bacterial act on benign substrates, and then go on to give some of the evidence that these substances are important in human carcinogenesis.

Bacterial production of carcinogens and promoters

As the production of carcinogens, promoters and mutagens by bacteria has nc been widely studied, the data available at present are limited. In this section I will discuss some of the examples for which data are available.

The hydrolysis of conjugated carcinogens

Cyasin, a plant glucoside derived from the cycad nut, is the β-glucoside of methylazoxymethanol (MAM). Although cycads are a major starch source in p of Southeast Asia they must first be soaked repeatedly in water to leach out t cycasin, which is hepatotoxic in man. When fed to rats, cycasin, gives rise to tumours in the intestine, liver and kidneys (Laqueur & Spatz, 1968); however