Nutrition and Experimental Carcinogenesis: A Review

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Summary

Restriction of the total diet or the number of calories fed to rats and mice inhibits the formation of tumors in several tissues. Unless animals are fed equivalent levels of food, or attain equivalent body weights, it is difficult to assess the significance of the effect of other nutritional modifications on carcinogenesis. The effects of altering the levels of protein or fat are much less than those seen with dietary restriction. Feeding a protein-free diet is tolerated for a limited period and can alter the metabolism of carcinogens. It may thus affect the tumor incidence induced by one-shot carcinogens. Vitamins have specific effects on the activity of certain carcinogens, the fullest information being available for vitamin A, which has been shown to inhibit or enhance carcinogenesis, and vitamin C, which by reducing sodium nitrite, prevents nitrosation of secondary and tertiary amines occurring in acidic conditions of the stomach. Inorganic substances, such as iodine (thyroid) and copper (liver), may affect the tumor incidence in specific tissues. The metabolic activation of carcinogens is modified by enzyme induction and the administration of antioxidants. The relevance of these results to the induction of cancer in humans is briefly discussed.

Introduction

Carcinogenesis may be affected by nutrition in 2 ways. Food or drink may be contaminated by carcinogens, or the composition of the diet may impose upon the host patterns of enzyme activity and other factors that dictate the yield of naturally occurring or induced tumors. The deliberate addition of carcinogenic additives to food should diminish, as a result of worldwide governmental action. Nevertheless, the control of naturally occurring carcinogens in food presents difficulties, especially for technically developing countries. The most studied naturally occurring carcinogens include aflatoxins B₁ and G₁, sterigmatocystin, and other mycotoxins (40). There is presumptive evidence that aflatoxins are carcinogenic in humans (67). Also to be considered are the carcinogens present in bracken fern (20–22, 64), cycasin (42), the nitrosamines, especially those formed from nitrite and secondary or tertiary amines (53, 79), environmental goitrogens, and hormones, and other dietary carcinogens. Besides their possible carcinogenic actions in man, the presence of these substances may considerably modify the response of experimental animals in carcinogenicity tests.

Changes in tumor incidence may also be brought about by altering the composition of the diet. In some cases, especially in that of chemical carcinogens, there is knowledge of the mechanism by which these changes arise. Modifications of the metabolic activation of carcinogens by controlling the levels of cofactors or by inducing different patterns of metabolizing enzyme activities are well documented. On the other hand, those factors which regulate tumor development, such as different levels of cellular proliferation or immunological control, do not appear to have been as amenable to study.

This presentation will illustrate the way in which nutritional differences can affect tumor incidence in experimental systems. Wherever possible, the mechanism by which these changes are mediated will be discussed.

Dietary and Caloric Restriction

The demonstration from actuarial records that overweight or obese men had a higher cancer mortality than normal or underweight men led Tannenbaum (93) to investigate the effect on the development of spontaneous and induced tumors of a restricted dietary intake in mice. Dietary restriction reduced the incidence of mammary tumor virus-induced tumors in DBA and C3H mice, spontaneous lung tumors in Swiss and ABC mice. B(a)P²-induced skin tumors and, to a lesser extent, s.c. sarcomas induced by B(a)P (Chart 1) (94, 95). Similar effects have been observed in rats. As in mice, underfeeding greatly increased the life-span (45) and led to a lower tumor incidence than that found in animals that received ad libitum supplements 74, 80). In these underfeeding studies, the amounts of the various dietary components were reduced proportionately to each other.

An alternative to underfeeding is caloric restriction, in which the amount of carbohydrate is reduced, while other components are maintained at a constant level. Calorie-restricted diets also lessen the incidence or delay the appearance of certain tumors, such as mammary tumors in DBA mice (Chart 2) (97). In this example, the inhibition was apparent, even if the restricted diet was not instituted until the mice were 9 months old.

The mechanism by which dietary restriction inhibits

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¹ The abbreviations used are: B(a)P, benzo(a)pyrene; DAB, 4-dimethylaminoazobenzene; DMN, dimethylnitrosamine; MCA, 3-methylcholanthrene; DMBA, 7,12-dimethylbenz(a)anthracene; FAA, N-2-fluorenylacetamide; BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene.

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The feeding of isocaloric diets containing levels of protein ranging from 9 to 45% failed to influence the incidence of mammary tumors in DBA and C3H mice, and that of hydrocarbon-induced skin tumors and s.c. sarcomas. Spontaneous hepatomas in C3H mice occurred less frequently when the 9% protein diet was fed (100). This was due to a diminution in the concentration of the essential sulfur-containing amino acids, cysteine and methionine. The addition of sufficient protein, freed from these amino acids, to raise the protein level from 9 to 18%, failed to affect the incidence of spontaneous hepatomas, whereas addition of the calculated amounts of these amino acids did so (88).

High protein levels, however, protect the rat liver against carcinogenesis by DAB. Adequate dietary casein, even with low levels of riboflavin (see below) protects the rat liver against this chemical. The reason for this phenomenon is not known. Tannenbaum and Silverstone (104) suggested that the high-protein diet might be protective because it enabled the liver to store and utilize riboflavin more efficiently.

Ross and Bras (75) fed diets containing 10, 22, or 51% casein on either a restricted (equicaloric) or an ad libitum basis. The dependence of the genesis of induced skin tumors on the caloric intake during different stages of carcinogenesis is summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Diet</th>
<th>10-wk painting period</th>
<th>50-wk development period</th>
<th>No. of mice</th>
<th>% tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F*</td>
<td>F</td>
<td>49</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>R</td>
<td>50</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>R</td>
<td>50</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>F</td>
<td>50</td>
<td>55</td>
</tr>
</tbody>
</table>

* From Ref. 95

* F, full diet; R, restricted diet.
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regimen to rats. Longevity increased from the group of rats fed 10% casein *ad libitum* to that fed 51% casein restricted, and tended to increase with the amount of protein in the diet. The most common tumor in the high-protein groups was papilloma of the urinary bladder (Table 2). Urinary stone formation was not described (13). Possibly, this is an effect of the increase in the amount of the essential amino acid tryptophan administered in the protein. It has been suggested that the urinary output of those tryptophan metabolites on the niacin pathway is higher in some patients with nonoccupational bladder cancer than in normal subjects (9, 68). Furthermore, feeding a 7-fold excess of DL-tryptophan to dogs led to hyperplasia of the urinary bladder (69). An increase in the proliferation of the rat bladder epithelium has been reported on a similar regimen (56). The metabolites of tryptophan responsible for these effects have not been identified. They might be N-hydroxylated derivatives of the amino acid and its metabolites. The previously suggested o-aminophenol derivatives (68), which have, as yet, given little satisfactory evidence of biological activity in the bladder, are unlikely to be the carcinogenic factor.

Very low levels of protein can be sustained for short periods of time, but are not compatible with the survival required for most carcinogenesis tests. The advent of single-dose carcinogens has made it possible to maintain animals on a very low protein diet during administration of the carcinogen and then return them to an adequate diet for the remainder of their lives. Swann and McLean (92) showed that feeding a protein-free diet for only 7 days led to a 45% inhibition of liver metabolism of DMN in vivo, but that kidney metabolism was unaffected. In liver slices, this pretreatment led to more than a 50% inhibition of metabolism. The amount of 7-N-methylguanine formed in liver RNA and DNA was little affected by the protein-free diet, while that in the kidneys increased 3-fold. The overall effect of the low-protein diet was to decrease hepatotoxicity and increase the dosage that is lethal to 50% of the animals, thereby enabling more chemical to be administered in a single dose. Thus, by giving the maximum tolerated dose, it was possible to increase the incidence of kidney tumors induced by a single administration of DMN (30, 46, 92). Very-low-protein diets or starvation for a limited period will thereby enable more chemical to be administered in a microsomal metabolizing enzymes (47). No effect of very-low-protein diets or starvation has been observed in the induction of esophageal (107) or nasal epithelial tumors (62).

The possibility that protein from various sources may influence carcinogenesis has not been studied. It may be minimal in view of the hydrolysis of protein to amino acids before ingestion. Such experiments are required to assess the significance, for example, of beef consumption in the etiology of human colon cancer (2).

**Lipotrope Deficiency**

Lipotropic substances are those which prevent or correct fatty liver due to choline deficiency. Lipotrope-deficient diets are low in choline and methionine. Choline-deficient diets *per se* in rats, and in chickens surviving beyond 78 weeks, led to fatty livers and to liver tumors (17, 78). More recent confirmation of the latter result is lacking (58), and the possibility cannot be excluded that the liver tumors were a consequence of the interaction of the hepatotoxic diet (59) and adventitious contamination with a natural carcinogen, such as aflatoxin B1. Nevertheless, there is evidence that lipotrope-deficient diets enhance hepatocarcinogenesis by aflatoxin B1, diethylnitrosamine, and DBN (58, 71). In the latter 2 examples, the latent period of the tumors was diminished. Esophageal cancer induction by diethylnitrosamine was possibly also enhanced. Other tumors were not affected (73). The lipotrope-deficient diets have been demonstrated to reduce the activity of hepatic metabolizing enzymes, such as aminopyrene demethylase, p-nitroaniline demethylase, and B(a)P hydroxylase (72), and also to increase the mitotic rate in the liver (71).

**Lipids**

Both the amount and nature of the lipid component of the diet may vary. The high caloric value of fat makes it essential to feed equicaloric amounts of each diet. An early experiment in which tumors were produced by skin painting with B(a)P, MCA, or dibenz(a,h)anthracene showed that, in the case of each of 5 different fats, 3 different basal rations, and 2 strains of mice, the tumor incidence increased when the dietary level of fat exceeded 15% (35). The result could have been due to the fat content of the diet, or to the resultant higher energy content that led to increased body weight. Tannenbaum (96, 98) and Silverstone and Tannenbaum (86, 88) showed by using equicaloric diets that a regimen that contained enhanced levels of fat increased the

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Life expectancy (days)</th>
<th>Tumor-bearing rats (%)</th>
<th>No. of bladder papillomas</th>
<th>Life expectancy (days)</th>
<th>Tumor-bearing rats (%)</th>
<th>No. of bladder papillomas</th>
<th>Life expectancy (days)</th>
<th>Tumor-bearing rats (%)</th>
<th>No. of bladder papillomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad libitum</td>
<td>540</td>
<td>25.6</td>
<td>3</td>
<td>585</td>
<td>28.8</td>
<td>9</td>
<td>614</td>
<td>28.0</td>
<td>19</td>
</tr>
<tr>
<td>Restricted</td>
<td>692</td>
<td>11.4</td>
<td>5</td>
<td>838</td>
<td>19.2</td>
<td>9</td>
<td>934</td>
<td>21.6</td>
<td>13</td>
</tr>
</tbody>
</table>

* From Ref. 98.
incidence of B(a)P-induced skin tumors in Swiss, C57 Black, and DBA mice, and of naturally occurring hepatomas in C3H mice. With mammary tumors in DBA mice, either the latency was reduced or the number of tumors increased. There was no effect on s.c. sarcoma or lung adenoma induction. The positive effects were of a lower order than those seen with caloric restriction, which led to the suggestion that they may have been due to different "energy values" of fat and carbohydrate and that caloric intake is an imprecise parameter in this type of work (7).

The importance of the type of fat in the diet is well illustrated by the induction of hepatomas in rats fed DAB. Substitution of hydrogenated coconut oil for corn oil reduced the number of hepatomas obtained at 6 months (50), although the more potently carcinogenic 3'-methyl derivative did not show the effect (28). The fatty acids obtained from hydrogenated coconut and corn oils gave rise to similar tumor yields in the experiments involving DAB (38). Other oils used in similar experiments gave variable hepatoma yields (39, 51). It has been suggested that the tumor-inhibitory fats enable the liver to store riboflavin more efficiently and that this leads to the greater activity of detoxifying enzymes, for which riboflavin is part of a cofactor (52).

Beef fat (35% of diet) enhances the yield of intestinal tumors induced by azoxymethane in rats (60). The body weight of rats treated with this compound in normal and beef fat diets was similar, although those treated with beef fat diets without carcinogen were heavier. The enhancement may therefore be a direct result of this fat supplement, but it is unclear as to whether only beef fat is effective or if other fats could be substituted. Other aspects of experimental intestinal cancer have been discussed by Weisburger et al. (70).

Cyclopropanoid fatty acids may be derived from raw cotton seed oil or Sterculia foetida oil. These substances act as cocarcinogens in hepatocarcinogenesis by aflatoxin B1 in rats (61, 89). The effect on diethylnitrosamine carcinogenesis in rats was much smaller (61).

Vitamins

Variation in the level of the vitamin B complex in the diet from the minimum required to keep the animals healthy to 9 times the level did not influence the yield of mammary tumors in DBA mice or of induced skin tumors in C3H or DBA mice (102). Diets low in vitamin B complex had little, if any, inhibitory effect on skin tumor induction in mice (8). Nevertheless, in specific situations, changes in the level of certain vitamins may alter the carcinogenic response.

**Vitamin A.** A deficiency of this vitamin leads to squamous changes in the respiratory and lower urinary tracts (32, 114). The influence of this deficiency on carcinogenesis has not been studied, possibly because of the difficulty in maintaining the health of the test animals. However, there has been interest in the apparent protective effect of high levels of this vitamin since Chu and Malmgren (12) first indicated that it protected against hydrocarbon-induced tumors. Feeding 0.5% vitamin A palmitate to hamsters inhibited formation of dyskeratotic lesions, as well as carcinomas of the forestomach and small intestine, induced by DMBA and B(a)P, and against esophageal dyskeratotic lesions induced by the former hydrocarbon. A considerable volume of evidence on the protective effect of dietary or topical vitamin A on skin tumor production in mice by hydrocarbons, often in combination with croton oil promotion, has been obtained (4–6, 18, 83). Shamberger (83) showed that topically applied β-carotene, a vitamin A precursor, which is converted to vitamin A in the intestine, enhanced the incidence of papillomas induced by DMBA and croton oil, whereas retinyl acetate and retinol inhibited papilloma formation. Retinol also inhibited papillomas induced by the hydrocarbon and phenol, as a promoting agent. It was shown that lysosomal labilizers, such as filimarisin, a polyene antibiotic, and vitamin A, had a considerable protective effect, whereas the lysosomal stabilizers, chloroquine and hydrocortisone, enhanced the tumor yield. The inhibitory effect of vitamin A on carcinogenesis was suggested to be due to the destabilization of the lysosomes of "premalignant" cells.

Schmähle et al. (81) failed to demonstrate any protective effect of vitamin A (palmitate and acid) on the induction of tumors by painting B(a)P on mouse skin. This experiment and another on injection site fibrosarcomas induced by the same chemical may be criticized, because the short latency of the induced tumors indicates that a massive carcinogenic stimulus was used, and that may have overridden any protective effect of vitamin A. In the hamster cheek pouch, topical application of DMBA and vitamin A was shown to induce more tumors per animal and a greater volume of tumor tissue than the hydrocarbon alone (43). The number of animals used was small.

The effect of vitamin A derivatives on bronchial carcinogenesis is confused. Original observations indicated that dietary retinyl palmitate inhibited induction of lower respiratory tract tumors by B(a)P and ferric oxide dust in the hamster (77), but a recent experiment has produced an enhancement rather than an inhibition (90). An inhibition in lung tumor incidence followed feeding high levels of retinyl acetate to rats given 2 intratracheal instillations of MCA (15). The appearance of squamous cell carcinomas was increased in lung tissue fragments treated with MCA and transplanted i.m. into syngeneic BALB/c mice (91). A failure to protect against carcinogenesis has been observed for vitamin A in the induction of neurogenic tumors by nitrosomethylurea and of squamous cell carcinomas of the bladder epithelium and liver tumors by dibutylinosamine (81).

The utility of vitamin A as an anticarcinogenic treatment is problematical in view of those experiments producing enhancement. Besides the lysosomal labilization reported by Shamberger (83), Hill and Shih (33) have shown that 14 vitamin A derivatives inhibited the metabolic activation of B(a)P and other polycyclic aromatic hydrocarbons by liver microsomes. The extent of inhibition varied with the derivative. It is clear that only further critical experimentation can clarify the present confusion.

**Thiamine (Vitamin B1).** This vitamin is destroyed by
thiamase present in bracken fern. When rats were fed dried bracken fern (33% of the diet), all the animals developed intestinal tumors, and 2 of 22 developed bladder tumors. When a supplement of thiamine (2 mg weekly) was provided, the intestinal tumor incidence was unaffected, whereas bladder tumors were induced in more than 50% of the rats. There were no differences in average daily food intake up to 6 months and no significant differences in survival rates (65).

Riboflavin (Vitamin B₂). Riboflavin inhibited formation of hepatic tumors induced by DAB (36). It is an essential constituent of certain cofactors of detoxifying enzymes (52) and is considerably less effective against the 3'-methyl derivative. Riboflavin analogs (7-ethyl-8-methyl- and 8-ethyl-7-methyl-10(8-ribityl)-isoalloxazine) are more effective than the parent compound against 3'-methyl-4-dimethylaminoazobenzene and 3'-methyl-4'-ethyl-4-dimethylaminoazobenzene (41).

Pyridoxine (Vitamin B₆). A deficiency of pyridoxine protects the rat liver from injury by FAA and permits the animals to survive longer and thus to develop bladder tumors (48). The pyridoxine deficiency may influence tryptophan metabolism (see above).

Ascorbic Acid (Vitamin C). Because of its ability to inhibit hyaluronidase, ascorbic acid may strengthen the ground substance of the tissues. This has been postulated to inhibit cell proliferation and lead to the suggestion that a very high intake of ascorbic acid may aid in cancer prophylaxis (10). This idea requires confirmation.

Ascorbic acid reduces sodium nitrite to nitrogen oxides. It thus inhibits the in vivo and in vitro nitrosation of secondary and tertiary amines, amides, and ureas to form potently carcinogenic nitrosamines and nitrosamides (53–55). This action of ascorbic acid assumes considerable importance in light of the use of nitrite as a food preservative and because certain drugs may be readily nitrosated (26, 44). Some foods, e.g., milk, have been shown to retard the nitrosation reaction (23).

Inorganic Constituents

When the proportion of a balanced mineral supplement in the diet was altered, the incidence of naturally occurring mammary tumors and hepatomas, or of induced skin tumors in DBA mice was not affected, provided isocaloric diets were used (103). Nevertheless, specific alterations in the levels of certain constituents of the mineral mixture may have a profound effect on carcinogenesis.

Iodine. Iodine deficiency, or the administration of goitrogens, may lead to thyroid tumors. In the presence of a carcinogen such as FAA (3), or of thyroid irradiation (19), high yields of malignant thyroid tumors may be obtained. Goitrogens or iodine deficiency lead to a lowering of thyroid hormone levels in blood with a consequent homeostatic increase in the levels of thyroid-stimulating hormone. This, if continuous, results in thyroid adenomas and, with a carcinogenic stimulus, in thyroid cancers.

Copper Salts. In excess, copper salts have been shown to delay azo dye hepatocarcinogenesis. The earlier observations (34, 37, 66, 84) are suspect, as the body weight of the rats was not recorded. Liver tumors induced by 3-methoxy-4-aminoazobenzene and its N-methyl derivative were inhibited by the incorporation of 0.5% cupric oxacetaate in the diet. The excess copper did not, however, affect the incidence of ear duct tumors. The rats in the different groups consumed equivalent amounts of food (24). In a further small experiment, it was shown that the same level of cupric oxacetaate did not affect induction of skin tumors by painting 3-methoxy-DAB (25). In diets containing either 1 ppm copper (deficient) or 800 ppm copper (excess), little difference was found in the induction of liver tumors by FAA, although the incidence of tumors of other sites was diminished (11). An earlier experiment failed to show that copper affected 2-fluorenylamine carcinogenesis (29). DMN-induced kidney neoplasms were frequent on a copper-deficient diet but were absent on an excess copper-containing diet (11). However, the latter induced toxicity and reduction in body weight, and thus interpretation of these observations is difficult. There is a need for further critical observations in this area.

Selenium. An essential trace element, selenium, on feeding at toxic levels, has given rise to hepatomas (57). These may be a consequence of cirrhosis due to levels of 5, 7, or 10 ppm ammonium potassium selenide or, possibly, because of a chance carcinogenic contaminant in the diet. An attempt to repeat this observation cannot be considered adequate, because of the failure to report on controls (105).

Selenium is a powerful antioxidant and may therefore be expected to inhibit carcinogenesis (see below). Clayton and Baumann (14) reported a reduced liver tumor incidence at 20 weeks when 3'-methyl-4-dimethylaminoazobenzene was fed to rats for the 1st and 3rd 4-week period of the experiment, and when a diet containing 5 ppm selenium instead of the basal diet was fed in the 2nd 4-week-period. This effect was confirmed and body weight data were given. Shamberger (82), using sodium selenide or selenate, showed that selenium supplementation had, at best, a weak and inconsistent effect on polycyclic aromatic hydrocarbon-induced cutaneous cancer in mice. No significant effects were obtained with MCA painting; the use of DMBA and croton oil or croton resin gave variable results while, with B(a)P, fewer tumors were obtained. With FAA, higher levels of selenium (2.50 and 0.50 ppm) apparently protected against tumors as compared with rats given toxic selenium-deficient diets (0.10 and 0.00 ppm) (31). Body weights unfortunately were not discussed, and therefore the significance of this observation is in doubt. The effect of dietary selenium is obscure.

Enzyme Inducers and Antioxidants

The alteration in the relative levels of metabolizing enzymes, known as induction, may be brought about by a wide variety of substances, including certain polycyclic aromatic hydrocarbons, quinones, chlorocarbons, and barbiturates. These substances, whether carcinogens or not, may profoundly influence carcinogenesis induced by another agent (1, 16, 49), but will not be discussed here as they
are the subject of another paper in the symposium (112).

The antioxidants provide a similar group of chemicals whose effects in the diet have been extensively investigated. The number of lung adenomas induced in female strain A mice by either diethylnitrosamine or 4-nitroquinoline 1-oxide was significantly reduced by feeding BHA or ethoxquin (108). BHA and BHT inhibited the formation of DMBA-induced forestomach tumors in female HA/ICR mice, mammary tumors in female Sprague-Dawley rats, and adrenal necrosis and general toxicity in rats (109). In further studies on strain A mice, BHA was given from 3 weeks before treatment with the carcinogen to the end of the experiment. The number of lung tumors/mouse induced by B(a)P, DMBA, urethan, and uracil mustard was reduced. On feeding dibenz(a)anthracene, DMBA, or 7-hydroxy-methyl-12-methylbenz(a)anthracene in diet, fewer lung tumor-bearing animals and fewer tumors/mouse were found in the presence of BHA (110). FAA carcinogenesis was likewise inhibited by BHT, but not by a different type of antioxidant, p-phenylenediamine (106), and BHT delayed the appearance of rat liver tumors induced by DAB and reduced the level of protein-binding (27). These antioxidants provide one of the more consistent and hopeful examples of carcinogenesis inhibition. Their mode of action remains to be elucidated, but Wattenberg (111) has postulated that BHA and BHT may act partly through an enzyme-inductive effect and partly through their antioxidant properties.

Discussion

This review emphasizes the extent to which changes in nutrition may affect the incidence of tumors induced by even the most potent carcinogens. The overriding factor is the dependence of the yield of many tumor types on the caloric value of the diet or on body weight. Although this fact has been established for many years, it is apparent that some investigators have not realized its significance in determining the influence of other dietary changes on cancer formation. The other important factor in the study of the effect of diet on chemical carcinogenesis is to avoid too high a level of carcinogen, which may obscure more subtle changes induced by certain dietary modifications.

Under appropriate conditions, changes in the nutritional state of test animals may considerably alter the incidence of tumors. If the same is true for man, it is pertinent to inquire whether some tumors which appear to be influenced by environmental factors are dependent on the nutritional status of the population, rather than on exposure to tissue-specific carcinogens. For example, stomach cancer in the United Kingdom is more prevalent among the lower income groups.

Certain aspects of nutrition and experimental cancer require further study. The effect of cooking food has been largely ignored, with the exception of the possible formation of carcinogens in heated fat (63). Also, some individuals, from an early age, have a choice in the type, as well as the quantity, of food which they consume. An experiment designed to study this (76) consisted of feeding Charles River COBS rats on 1 of 4 regimens. Three groups received 10, 22, or 51% casein in the diet; the other was offered a choice of these diets in separate feeding pots. The rats in the latter group each consumed different proportions of the 3 diets. This group developed significantly more benign, but not malignant, tumors, severe glomerulonephrosis, severe myocardiofibrosis, and prostatitis, than those rats that received one of the other diets (Table 3). The significant excess of lesions was reported to remain even after correction for latency, age-specific morbidity rates, population size, and length of life. Although the rats given a free choice of diet had an elevated body weight, this was not enough to explain the differences. The significance of these results is, as yet, unclear. Nevertheless, if the actual choice of diet, even on a genetically determined basis, influences tumor incidence, this has considerable importance in the human situation.

The most clearly understood effects of alteration in nutrition in experimental carcinogenesis are on the metabolic activation of chemical carcinogens. In order to permit conclusions from animal experiments to be applied to man, there is a necessity for the effects of diet on other facets of the carcinogenic process to be elucidated.

References


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