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Bile Acids, But Not Neutral Sterols, Are Tumor Promoters in the Colon in Man and in Rodents

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Analysis of the etiologic factors and relevant mechanisms involved in carcinogenesis leads to a classification of agents involved in the carcinogenic process as genotoxic or epigenetic. Their mode of action is distinct, especially with regard to dose-response effects and reversibility. The genotoxic carcinogens for colon cancer are unknown, but mutagenic components found in fried beef and fish are under study. Epigenetic agents as promoting factors play a major role in the development of cancer of the colon. Specific nutritional elements associated with colon cancer risk are high fat diets, high cholesterol intake, and low fiber intake. The role of micronutrients as modulators and inhibitors needs to be explored. Through metabolic studies in diverse populations and in reliable animal models, it is now clear that dietary fat and cholesterol control the total flow of bile acids in lumen and a high-fat, high-cholesterol diet increases the total of bile acids in the gut. Bile acids but not neutral sterols have promoting effects and are related to colon cancer risk although bile acids by themselves do not act as complete carcinogens. The effect of dietary fiber such as cereal bran is to increase stool bulk which dilutes the concentration of bile acids. Reducing the concentration of bile acids either by lowering dietary fat and cholesterol or by increasing dietary fiber may effectively lower the risk for colon cancer.

Introduction

Various lines of evidence suggest that the majority of human cancers have complex, multifactorial environmental causes (*1-3*). In relation to the cancer question, "causes" are often thought to be ubiquitous chemicals, and, more specifically, those due to modern technology and industrial development. Certainly a number of food additives, pesticides, insecticides, and industrial chemicals introduced commercially in the last 40 years are carcinogenic in animal models (*4*). Historically, it is also true that chemical exposure due to occupation or to drugs has caused human cancers (*1-3, 5-8*). Cancer represents many diseases, and a detailed analysis of the often complex factors inherent in the occurrence of each specific type of cancer is essential to delineate those elements truly responsible for the occurrence of each kind of cancer.

In the last two decades it has been established that chemical contaminants in the environment, whether intentional or inadvertent, do not account for most of the main human cancers in the world. Worldwide statistics on time trends and the incidence of diverse cancers, as well as the altered risk for migrants from areas of high to low incidence over several generations and the corresponding analysis of data obtained under controlled conditions in animal models, outline the multiple causative factors involved in each of the main human cancers. Thus, it has been found that individual and national, traditional lifestyle, as related to the use of tobacco and broad nutritional factors, is of great significance (*9*). It will be useful to consider current concepts of the mechanisms of carcinogenesis, and then see how these can be applied to an evaluation of the role of nutritional factors in the causation of an important type of cancer in the Western world—colon cancer.

Mechanisms of Carcinogenesis

Considerable advances have been achieved in studies on the mechanisms of carcinogenesis. Can-

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cer causation and development involves a series of essential steps. It is likely that an early event in neoplasia depends on a somatic mutation involving an alteration of the genetic material (*10-12*).

We have classified chemical carcinogens into eight classes that, in turn, belong to two main groups: genotoxic carcinogens and agents operating by nongenotoxic or epigenetic pathways such as promotion (*13*). In relation to an understanding of the relevant mechanisms, this classification is important in dissecting the complex causes of diverse kinds of cancer and arriving at a delineation of the role of each agent—genotoxic carcinogen, cocarcinogen, or promoter—in the overall carcinogenic process for each kind of cancer.

Genotoxic Events

A change in the genetic material can arise through a number of mechanisms: (1) through a direct attack by (a) radiation, (b) chemicals, or (c) viruses, which may result in the mispairing of bases during DNA replication, or by viral insertion of new DNA segments to yield abnormal DNA; (*2*) through defective operation of DNA polymerase during synthesis; (*3*) through errors introduced by DNA repair enzymes.

Nongenotoxic or Epigenetic Events

Abnormal DNA obtained by any mechanism is only the first step in a long sequence of events terminating in a malignant invasive neoplasm. An important element is the ability of an abnormal cell population to achieve a selective growth advantage in the presence of surrounding normal cells. The process of cell duplication is highly dependent on a number of endogenous and exogenous controlling elements operating by epigenetic mechanisms. Two such elements are promoters and inhibitors of growth, which either enhance or retard the process. In addition, during the multiple generation steps, early tumor cells can undergo phenotypic changes of expression, perhaps as a result of faulty steps in differentiation.

As numerous experiments documenting this phenomenon indicate, promoters do not lead to the production of an invasive cancer in the absence of an antecedent cell change (*12-16*). Thus, in exploring the causes of any specific human cancer, consideration must be given both to the agents leading to an abnormal genome and any other agents possibly involved in the growth and development of the resulting abnormal neoplastic cells and their further progression to malignancy.

Genotoxic Carcinogens for Cancer of the Colon

Until recently there were no data as to the genotoxic carcinogens responsible for nonoccupational human cancer in the general public in western countries, except for those found in tobacco smoke (2, *16*). This is especially so for nutritionally linked cancers such as colon, breast and prostate.

It was discovered that charcoal broiling of meat or fish yielded mutagenic activity for *Salmonella typhimurium* TA-98 (*17, 18*). Since mutagenic activity is often an indicator of carcinogenic activity, studies on the effects of mode of cooking of foods are taking place (*19*). One mutagenic component found in fried sardines and in fried beef, 2-amino-3-methylimidazo-[4,5-d]quinoline, is similar sterically and structurally to known homocyclic carcinogenic arylamines, such as 3, 2′-dimethyl-4-aminobiphenyl, which are colon, mammary gland, and prostate carcinogens in rodents (*19*). The main mutagens in fried meat or fish most probably do not derive only from the pyrolysis of amino acids or peptides but also from the formation of heterocyclic compounds from carbohydrate components and amino acids, as formed in a model system for browning reactions involving the reaction of sugars with ammonium ions (*20, 21*).

Nongenotoxic or Epigenetic Agents in Nutritionally Linked Cancers

Delineating the relevant epigenetic promoting effects for cancer of the colon is important because whether or not overt invasive disease is seen depends a great deal on these epigenetic promoting factors. Epigenetic agents play a major, perhaps decisive, role in the development of cancer of the colon, and incidentally also of the breast, and prostate. These stem from the intake of appreciable amounts of dietary fat which are responsible for the endogenous production of specific nongenotoxic, epigenetic agents associated with increased risk.

For colon cancer, the specific dietary elements, relevant through studies in man and in animal models, are the amount of dietary fat and fiber (*22, 23*). One of the best arguments for these concepts is the changing incidence of colon cancer in Japan in recent years as the Japanese nutritional intake has become progressively westernized (*24*). In addition, in many areas of the world, an association exists between colon cancer and coronary heart disease, where the amount of dietary fat and cholesterol have been shown to relate to risk for heart disease.

An interesting exception to this rule is Finland, where the risk for heart disease is high and that of colon cancer low; we, as well as the IARC, have obtained some evidence that the lower risk of Finnish people for colon cancer despite a high fat intake is attributable to their consumption of foods high in fiber, especially bran fiber (*23*, *25*).

Laboratory research by a number of groups, particularly by Reddy (*23*) and by Nigro (*26*), yields insight into the mechanism whereby fat and cholesterol promote colon cancer risk and fiber inhibits colon carcinogenesis. The main effect of dietary fat appears to reside in a direct association between endogenous cholesterol biosynthesis, which when combined with exogenous cholesterol intake, in turn, leads to increased bile acid biosynthesis and excretion through the intestinal tract (Table 1). Certain bile acids and neutral sterols were of interest because they induced sarcomas but not carcinomas at the injection site in experimental animals (*28-30*). However, this evidence of oncogenic effect does not implicate them or their metabolites in carcinomas in the large bowel. Instead, this reaction represents an instance of "solid-state" oncogenesis, yielding tumors in the mesenchymal tissue, and must be considered quite unrelated to the effect of neutral sterols and bile acids in colon cancer causation. Rather, certain bile acids have been shown to be colon tumor promoters in both germ-free and conventional rats (Tables 2 and 3). Bile acids do not act as complete carcinogens, and their role would seem to be to act as epigenetic agents in the overall carcinogenic process. (*23*, *30*). At the same time, the cholesterol metabolites, including the α-epoxide, or neutral sterols, not only did not by themselves, or by their metabolites produced by colonic bacteria, induce tumors in the colon or germ-free and conventional rats but also had no promoting activity (*30*, *31*).

The colonic cells during neoplastic transformation undergo a similar sequence of changes which lead to uncontrolled proliferative growth in the development of colon cancers in humans and rodents treated with colon carcinogens (*32*). Further studies are needed on the mechanisms whereby bile acids enhance cell proliferation and possibly also affect the functional differentiation of colonic cells during their upward migration in a crypt.

The effect of some dietary fibers (Table 4), such as cereal brans, is to increase intestinal and stool bulk, thereby reducing the concentration of promoters, effectively lowering the risk for development of colon cancer incidence in populations such as the Mormons and the Finns, who consume fried meat and other sources of genotoxic carcinogens and appreciable amounts of fat which lead to promoters but who also eat sizable amounts of cereal grains, may thus be explained by stool bulk acting as a modulator of promotion by reducing bile acid concentration (Tables 5 and 6).

More research is also needed on modulators and inhibitors, such as micronutrients, that would eventually find application in lowering human disease risk. The role of yellow-green vegetables, especially from the Brassica family, in apparently lowering the colon cancer risk remains to be defined. It is not clear whether the active ingredients in such vegetables modify the metabolism of the genotoxic carcinogens associated with colon cancer, whether they play a role in bile acid

Table 1. Effect of type and amount of dietary fat on fecal acids in rats.[a]

	Fecal bile acids, mg/kg/day[b, c]			
	5% Corn oil control (8)	20% Corn oil control (8)	5% Lard control (8)	20% Lard control (8)
Cholic acid	0.68 ± 0.08[b,1]	0.64 ± 0.07[1]	0.74 ± 0.06[1]	0.86 ± 0.10[1]
β-Muricholic acid	0.82 ± 0.05[1]	0.98 ± 0.08[1]	0.80 ± 0.07[1]	0.88 ± 0.11[1]
3α.β.12α-Trihydroxy-5β-cholanic acid	0.11 ± 0.02[1]	0.10 ± 0.01[1]	0.10 ± 0.01[1]	0.13 ± 0.01[1]
Chenodeoxycholic acid	0.12 ± 0.01[1]	0.15 ± 0.01[1]	0.13 ± 0.02[1]	0.16 ± 0.03[1]
Hyodeoxcholic acid	2.76 ± 0.12[1]	2.73 ± 0.16[1]	3.14 ± 0.18[1]	2.73 ± 0.17[1]
Ursodeoxycholic acid	0.10 ± 0.2[1]	0.10 ± 0.02[1]	0.15 ± 0.09[1]	0.08 ± 01[1]
Deoxycholic acid	2.53 ± 18[1]	4.80 ± 0.23[2]	2.61 ± 0.220[1]	4.54 ± 0.30[2]
Lithocholic acid	0.83 ± 0.11[1]	1.98 ± 0.16[2]	1.00 ± 0.10[1]	2.84 ± 0.13[2]
12-Ketolithocholic acid	0.44 ± 0.03[1]	0.77 ± 0.07[2]	0.51 ± 0.18[1]	0.77 ± 0.02[2]
7-Ketodeoxycholic acid	0.14 ± 0.02[1]	0.08 ± 0.01[1]	0.16 ± 0.02[1]	0.06 ± 0.01[1]
Other bile acids	1.93 ± 0.10	2.52 ± 0.25	1.92 ± 0.16	2.51 ± 0.19
Total bile acids	10.45 ± 0.20[1]	14.86 ± 0.41[2]	11.24 ± 0.49[1]	14.91 ± 0.62[2]

[a]Weanling female F344 rats were fed an experimental diet containing either 5% or 20% corn oil or 5% or 20% lard, and individual daily fecal samples were collected 14 weeks later for 5 days. Fecal samples from each animal were subjected to bile acid analysis. From Reddy et al. (*23*, *27*).

[b]Mean ± SEM. Units: mg/day/kg body weight.

[c]Mean ± with a common number superscript between groups in a horizontal row are not significant: $p > 0.05$.

production or further metabolism, or in the metabolism of other, as yet unknown, epigenetic promoting agents 1, 2, 3 (*35-37*).

Since these elements operate through epigenetic mechanisms, their action is, by definition, dose- and time-dependent. Thus, a reduction in effective dose, by whatever means, would be expected to lead to rather rapid lowering of risk, and hence of incidence. This applies even to patients with such diseases, where dietary intervention promises to be an effective adjuvant therapy. When the postmenopausal use of estrogen drugs such as premarin was discontinued, there was a rapid decline in endometrial cancer, indicating that epigenetic phenomena are reversible.

If current research does document further that the mode of cooking, especially frying and broiling, yields carcinogens for colon cancer, means are available to lower the formation of such agents. Furthermore, and importantly, if colon cancer risk is indeed associated with the level of dietary fat and inversely with the amount of cereal fiber, with the

Table 2. Colon tumor incidence in germfree rats treated with intrarectal MNNG and/or bile acids or neutral sterols[a]

Series[b]	Group[c]	No. of rats	Animals with tumors	Tumors/rat		
				Total	Adenoma	Adenocarcinoma
I	CA	10	0	0	0	0
	CDC	10	0	0	0	0
	MNNG	22	27	0.27	0.13	0.14
	MNNG + CA	24	50	0.63	0.34	0.29
	MNNG + CDC	24	54	1.08	0.79	0.29
II	LC	12	0	0	0	0
	MNNG	24	38	0.67	0.42	0.25
	MNNG + LC	24	79	1.42	1.00	0.42
III	Cholesterol	15	0	0	0	0
	Epoxide	21	0	0	0	0
	Triol	15	0	0	0	0
	MNNG	24	46	0.63	0.50	0.13
	MNNG + cholesterol	24	46	0.67	0.42	0.25
	MNNG + Epoxide	24	58	0.71	0.54	0.17
	MNNG + Triol	24	46	0.54	0.46	0.08

[a]Data from Reddy et al. (*23*).

[b]In Series I, the CA or CDC group received intrarectally 20 mg of sodium salt of respective bile acids 3 times weekly for 48 weeks; MNNG group received intrarectally 2 mg of MNNG twice a week for 2 weeks, followed by vehicle for 46 weeks; MNNG + CA or MNNG + CDC group received intrarectally MNNG for 2 weeks and bile acids thereafter for 46 weeks. In Series II and III, the MNNG group received 2.5 mg MNNG twice a week for 2 weeks and the vehicle thereafter for 46 weeks. The experimental protocol for the bile acids and cholesterol metabolite administration is the same as described for Series I.

[c]CA, cholic acid; CDC. chenodeoxycholic acid; LC. lithocholic acid) Epoxide, cholesterol-α-epoxide) Triol. cholestane-3, 5, 6-triol) MNNG, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.

Table 3. Colon tumor incidence in conventional rats treated with intrarectal MNNG and/or bile acids or neutral sterols[a]

Series[b]	Group[b]	No. of rats	Animals with tumors	Tumors/rat		
				Total	Adenoma	Adenocarcinoma
I	CA	12	0	0	0	0
	CDC	12	0	0	0	0
	MNNG	30	37	0.55	0.23	0.32
	MNNG + CA	30	67	0.87	0.24	0.63
	MNNG + CDC	30	70	1.23	0.27	0.96
II	LC	12	0	0	0	0
	MNNG	24	54	1.00	0.75	0.25
	MNNG + LC	24	83	1.83	1.50	0.33
III	Cholesterol	15	0	0	0	0
	Epoxide	21	0	0	0	0
	Triol	15	0	0	0	0
	MNNG	24	71	1.29	0.96	0.33
	MNNG + cholesterol	24	71	1.04	0.67	0.38
	MNNG + Epoxide	24	58	1.08	0.71	0.38
	MNNG + Triol	24	58	0.96	0.75	0.21

[a]Data from Reddy et al. (*27*).

[b]The experimental protocols and abbreviations are the same as described for Table 2.

Table 4. Intestinal tumor incidence in rats fed diets containing pectin, alfalfa or wheat bran and treated with AOM.[a]

Diet[b]	Animals with colon tumors		Colon tumors		Total number of colon tumors per group by tumor classification			No. of animals with duodenal tumors
	No.	%	Per rat	Per tumor-bearing rat	Adenoma	Carcinoma in situ	Adeno-carcinoma	
Control (30)	17	57	0.8	1.5	14	5	6	2
Pectin (30)	3	10*	0.1	0.1	0	0	3	0
Alfalfa (30)	16	53	0.7	1.3	8	3	10	6
Wheat bran (30)	10	33**	0.4	1.2	3	1	8	2

[a]Weanling female F344 rats were fed semipurified diets containing 0 or 15% pectin, alfalfa, or wheat bran. At 7 weeks of age, all animals except vehicle-treated controls received azoxymethane (AOM) SC at a dose rate 8 mg/kg body weight/week for 10 weeks. All animals were necropsied 30 weeks later. Data from Watanabe et al. (*33*).

[b]Effective number of animals in each group is shown in parentheses.

*Significantly different from the groups fed the control diet, alfalfa diet, or wheat bran diet by x^2 test ($p<0.05$ or better).

**Significantly different from the groups fed the control diet or alfalfa diet by x^2 test ($p<0.05$ or better).

Table 5. Fecal bile acids of healthy male subjects from Kuopio (Finland) and New York metropolitan area.[a]

Bile acids	Average as mg/g[b]		Average as mg/day[b]	
	Kuopio (15)	New York (20)	Kuopio (15)	New York (20)
Cholic acid	0.20 ± 0.06	0.24 ± 0.04	12 ± 2.9	6 ± 1.4
Chenodeoxycholic acid	0.13 ± 0.03	0.23 ± 0.03	8 ± 1.3	5 ± 1.1
Deoxycholic acid	1.72 ± 0.16*	3.74 ± 0.26	104 ± 12	88 ± 5.1
Lithocholic acid	1.40 ± 0.16*	3.27 ± 0.15	84 ± 5	77 ± 4.5
Ursodeoxycholic acid	0.08 ± 0.02*	0.13 ± 0.01	5 ± 1.1	3 ± 0.3
3α,7β,12α-Trihydroxy-5β-cholanic acid	0.04 ± 0.01*	0.12 ± 0.01	2 ± 0.8	3 ± 0.3
12-Ketolithocholic acid	0.06 ± 0.02*	0.13 ± 0.01	4 ± 1.0	3 ± 0.2
Other bile acids	0.93 ± 0.08*	3.8 ± 0.26	56 ± 5.0†	89 ± 6.0
Total	4.59 ± 0.42	11.7 ± 0.54	277 ± 22	275 ± 14

[a]Data from Reddy et al. (*34*).

[b]Averages ± SEM.

*Significantly different from New York, $p<0.05$ or better.

Table 6. Epidemiology of large bowel cancer.[a]

	Dietary factors[b]			Fecal constituents		
				Stool bulk,	Promoters (bile acids)	
	Fat	Beef	Fiber	g/day	mg/g	mg/day
High risk						
United States	+ + +	+ + +	+	22	11.7	275
Low risk						
Finland	+ + +	+ +	+ + +	60	4.6	277
Japan	+	+[c]	+	23	4.8	110

[a]Data from Reddy et al. (*34*).

[b]The following score has been assigned based on nutritional data available: + + +, high dietary intake; + +, moderate dietary intake; +, low dietary intake.

[c]Fiber intake in Japan is slightly higher than United States.

Table 7. Comparison of high and low risk dietary factors for cancer in the colon.

Organ	Lower risk		Higher risk	
	Population	Dietary factors	Population	Dietary factors
Colon	Japan	Low fat diet	USA, Western Europe, New Zealand, Australia, Scandinavia	High fat and cholesterol, low fiber, diets; fried food
Colon	Mormons	Higher fiber	USA in general	High fat and cholesterol, low fiber
Colon	7th Day Adventists	Low or no fried food, higher fiber	USA in general	High fat and cholesterol, low fiber
Colon	Finland	Higher fiber, lower fried food	USA in general, Denmark	High fat and cholesterol, low fiber

Table 8. Current concepts on colon cancer causation and development.

Risk factors
Diets high in fat, cholesterol, fried foods
Diets low in fiber, yellow and green vegetables
Established mechanisms
High fat → High cholesterol biosynthesis → High gut bile acid levels
High dietary cholestrol ——————↑
Low fiber → High concentration of gut bile acids
(low dilution through lack of bulk)
High bile acid concentration → Promoting effect in colon carcinogenesis
Mechanisms under study
Fried food → Mutagens → Colon carcinogens?
Role of micronutrients (vitamins and minerals) and different types of fiber in production and metabolism of carcinogens, bile acids, promoters?
Mechanisms of promotion?

[a]Data of Weisburger et al. (*38*).

concentration of bile acids as the crucial element in the promoting process, this evidence can be the basis for suggesting relatively minor alterations in dietary habits involving mainly a lower fat intake and a higher fiber consumption as tools to lower disease risk (Table 7).

Along these lines, research on optimal levels of vitamins, minerals and other micronutrients as well as antioxidants and certain indoles, in the current diet would provide a broad basis for chemoprevention. Over the last several years, research has provided new perspectives on the causes and modifiers of the main premature killing diseases. Data in the current paper specifically record experimentation designed to yield understanding of underlying mechanisms as a sound reliable basis for prevention of an important kind of human cancer, colon cancer and for the long-term goals of disease prevention (Table 8).

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