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Nutrition and carcinoma of the large intestine

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Based on various lines of evidence and multi-disciplinary approaches, it has been suggested that nutrition and specific nutritional components, as well as dietary habits, in various parts of the world may play an important role in the causation and development of a number of major types of cancer. Nutrition may relate directly to the occurrence of 30–40% of cancers in men and 50–60% of cancers in women in the USA and other Western countries (Hiatt *et al.* 1977; Doll & Peto, 1981; Magnus, 1982; Wynder *et al.* 1983). We have dissected the overall carcinogenic process into a number of sequential steps, all of which are necessary for a clinically invasive cancer to occur (Fig. 1) (Weisburger & Horn, 1981; Weisburger & Williams, 1981). This sequence has been demonstrated in numerous studies in animal models, and there is no reason to assume that this sequence would not also hold for the initiation, development, and progression of human cancers. In this scheme, the early events are the result of specific molecular changes caused by genotoxic carcinogens in cellular systems for cancers of the colon, breast, prostate, and perhaps even pancreas. We have noted that mutagens and also carcinogens are seen at the surface of fried or broiled foods such as meat or fish (Barnes *et al.* 1983; Sugimura *et al.* 1983). This concept, however, needs further validation through research currently being performed in a number of laboratories in Japan, Europe, and the USA. Gastric cancer, on the other hand, appears to be associated with totally distinct factors, namely, pickled and salted fish or beans and also residence in areas with geochemical or agricultural sources of nitrate intake, not balanced by the presence of vitamin C, vitamin E, or certain phenolic antioxidants and nitrite traps such as pyrogallol or tannins (Correa *et al.* 1982; Weisburger & Horn, 1982; Joossens & Geboers, 1983). The possible genotoxic carcinogen may be a nitrosamide or aryldiazonium salt. The formation of such compounds is inhibited by vitamin C, vitamin E and certain antioxidants (Mirvish, 1983). This fact can be used to decrease the risk of gastric cancer deliberately.

Epigenetic or promoting agents play a major role in the development of cancers of the colon, breast and prostate (Reddy *et al.* 1980; Hill, 1983; Wynder *et al.* 1983). 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. These stem from the intake of appreciable amounts of dietary fat which are responsible for the endogenous production of specific non-genotoxic, epigenetic agents associated with increased risk.

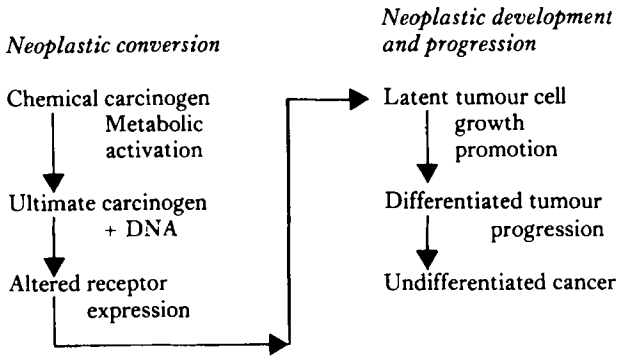

Fig. 1. Sequence of steps in the initiation, development and progression of human cancer.

For colon cancer, the major controlling dietary elements, relevant through studies in man and in animal models, are the amounts of dietary fat and fibre (Modan *et al.* 1975; Reddy *et al.* 1980; Wynder *et al.* 1983). One of the best arguments for this concept is the changing incidence of colon cancer in Japan in recent years as the Japanese nutritional intake became progressively westernized (Hirayama, 1979). 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 the risk of heart disease. An interesting exception to this rule is Finland where the risk of heart disease is high and that of colon cancer low. There is some evidence that the lower risk of colon cancer in Finnish people, despite a high fat intake, is due to their consumption of foods high in fibre, especially cereal bran fibre (I.A.R.C. Microecology Group, 1977; Reddy *et al.* 1978, 1980; Wynder *et al.* 1983).

Research by a number of groups, particularly by Reddy *et al.* (1980) and by Nigro (1981), has yielded insight into the mechanism whereby fat and cholesterol promote the risk of colon cancer and fibre 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, leads to increased bile acid biosynthesis and excretion through the intestinal tract. Certain bile acids have been shown to be colon tumour promoters in both germ-free and conventional rats. Bile acids do not act as complete carcinogens, and their role is to act as promoters in the overall carcinogenic process (Reddy & Watanabe, 1979; Reddy *et al.* 1980) Reddy & Watanabe (1979) found that cholesterol metabolites, including the α-epoxide or neutral sterols, not only did not by themselves, or by their metabolites produced by colonic bacteria, induce tumours in the colon of germ-free and conventional rats, but also had no promoting activity. Further studies are needed on the mechanisms whereby the bile acids enhance cell proliferation, and possibly also affect the functional differentiation of colonic cells during their upward migration in a crypt (Deschner, 1983; Lipkin, 1983).

The effect of some dietary fibres, such as cereal bran, is to increase intestinal and stool bulk, thereby reducing the concentration of promoters, effectively lowering

the risk of development of colon cancer. The lower incidence of colon cancer in populations such as the Mormons and the Finns, who consume fried meat and other sources of genotoxic carcinogens and eat appreciable amounts of fat which lead to promotion, 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. Recently, Wargovich *et al.* (1983) have made the interesting finding, which has the potentially important application of reducing colon cancer risk, that dietary intake of calcium salts, a simple, easily carried out dietary change, decisively lowers the incidence of chemically-induced colon cancer in mice (Table 1).

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 risk of colon cancer, remains to be defined (Graham & Mettlin, 1979; Wattenberg, 1983). 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 production or further metabolism, or in the metabolism of other, as yet unknown, epigenetic-promoting agents.

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 (Wynder & Cohen, 1982). When the postmenopausal use of oestrogen drugs such as Premarin was

Table 1. *Comparison of high and low risk dietary factors for cancer in specific organs*

	High risk		Lower risk	
Organ	Population	Dietary factors	Population	Dietary factors
Stomach	Japan, Chile, Columbia	Salted, pickled food, nitrate	USA	Fresh fruit salad, vitamins C and E
Colon	USA, Western Europe, New Zealand, Australia, Denmark	High fat, low fibre, fried food	Japan	Low fat
			Mormons	Higher fibre
			Seventh Day Adventists	Low or no fried food, higher fibre
			Finland	Higher fibre, lower fried food
Breast	USA, Western Europe, New Zealand, Australia	High fat, low fibre, fried food	Japan	Low fat
Prostate	USA, Scandinavia, Western Europe	High fat	Japan	Low fat

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Table 2. *Nutritional factors involved in certain human cancers (Weisburger & Horn, 1982)*

Source of genotoxic carcinogen	Enhancing factors	Inhibiting factors	Organs affected
Nitrite + specific foods (Fish, beans, *not* meats)	Salt	Vitamin C Vitamin E Propyl gallate Tannins	Stomach Oral cavity Oesophagus
Fried foods	Fat	Fibre, vitamins, minerals (Se salts, Zn ion, Ca ion, others?), microwave cooking, antioxidants or soya-bean protein in cooking	Colon Breast Prostate Pancreas

discontinued, there was a rapid decline in endometrial cancer (Austin & Roe, 1982), witness 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 (Pariza *et al.* 1983; Weisburger *et al.* 1983). Furthermore, and importantly, if colon cancer risk is indeed associated with the level of dietary fat and inversely with the amount of cereal fibre, with the 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 fibre consumption as tools to lower disease risk (Table 2). Along these lines, research on optimal levels of vitamins, minerals and other micronutrients, as well as antioxidants and certain

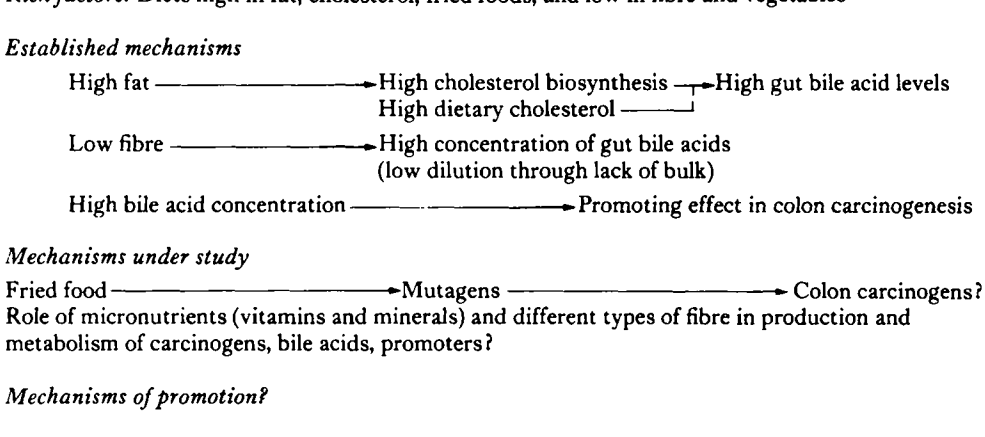

Fig. 2. Current concepts on colon cancer causation and development

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. Fig. 2 shows some of the underlying mechanisms involved in the development of colon cancer. An understanding of these mechanisms should provide a basis for the prevention of colon cancer and the long term goal of disease prevention.

REFERENCES

Austin, D. F. & Roe, K. M. (1982). *American Journal of Public Health* **72**, 65–68.

Barnes, W. S., Spingarn, N. E., Garvie-Gould, C., Vuolo, L. L., Wang, Y. Y. & Weisburger, J. H. (1983). In *The Maillard Reaction in Foods and Nutrition. ACS Symposium Series* no. 215, pp. 485–506 [G. R. Waller and M. S. Feather, editors]. Washington DC: American Chemical Society.

Correa, P., Haenszel, W. & Tannenbaum, S. R. (1982). *National Cancer Institute Monograph* **62**, 129–134.

Deschner, E. E. (1983). In *Precancerous Lesions of the Gastrointestinal Tract*, pp. 219–221 [P. Sherlock, B. C. Morson, L. Barbara and U. Veronesi, editors]. New York: Raven Press.

Doll, R. & Peto, R. (1981). *Journal of the National Cancer Institute* **66**, 1191–1308.

Graham, S. & Mettlin C. (1979). *American Journal of Epidemiology* **109**, 1–15.

Hiatt, H. H., Winsten, J. D. & Watson, J. (1977). *The Origins of Human Cancer*. Cold Spring Harbor, New York: Cold Spring Harbor Laboratories.

Hill, M. J. (1983). In *Precancerous Lesions of the Gastrointestinal Tract*, pp. 1–22 [P. Sherlock, B. C. Morson, L. Barbara and U. Veronesi, editors]. New York: Raven Press.

Hirayama, T. (1979). *Nutrition and Cancer* **1**, 67–78.

I.A.R.C. Microecology Group (1977). *Lancet* **ii**, 207–211.

Joossens, J. V. & Geboers, J. (1983). In *Precancerous Lesions of the Gastrointestinal Tract*, pp. 97–114 [P. Sherlock, B. C. Morson, L. Barbara and U. Veronesi, editors]. New York: Raven Press.

Lipkin, M. (1983). In *Precancerous Lesions of the Gastrointestinal Tract*, pp. 241–254 [P. Sherlock, B. C. Morson, L. Barbara and U. Veronesi, editors]. New York: Raven Press.

Magnus, K. (editor) (1982). *Trends in Cancer Incidence*. New York: Hemisphere Publications.

Mirvish, S. S. (1983). *Journal of the National Cancer Institute* **71**, 629–647.

Modan, B., Barell, V., Lubin, F., Modan, M., Greenberg, R. A. & Graham, S. (1975). *Journal of the National Cancer Institute* **55**, 15–18.

Nigro, N. D. (1981). *Fat, Fiber, and Other Modifiers of Intestinal Carcinogenesis A Strategy for Prevention. Banbury Report* no. 7, pp. 83–94. New York: Cold Spring Harbor Laboratories.

Pariza, M. W., Loretz, L. J., Storkson, J. M. & Holland, N. C. (1983). *Cancer Research* **43**, 2444s–2446s.

Reddy, B. S., Cohen, L. A., McCoy, G. D., Hill, P., Weisburger, J. H. & Wynder, E. L. (1980). *Advances in Cancer Research* **32**, 237–345.

Reddy, B. S., Hedges, A. R., Laakso, K. & Wynder, E. L. (1978). *Cancer* **42**, 2832–2838.

Reddy, B. S. & Watanabe, K. (1979). *Cancer Research* **39**, 1521–1524.

Sugimura, T., Sato, S. & Takayama, S. (1983). In *Environmental Aspects of Cancer: The Role of Macro and Micro Components of Foods*, pp. 167–186 [E. L. Wynder, G. A. Leveille, J. H. Weisburger and G. E. Livingstone, editors]. Westport, Connecticut: Food and Nutrition Press.

Wargovich, M. J., Eng, V. M. S., Newmark, H. L. & Bruce, W. R. (1983). *Carcinogeneis* **4**, 1205–1207.

Wattenberg, L. V. (1983). In *Environmental Aspects of Cancer: The Role of Macro and Micro Components of Foods*, pp. 157–166 [E. L. Wynder, G. A. Leveille, J. H. Weisburger and G. E. Livingstone, editors]. Westport, Connecticut: Food and Nutrition Press.

Weisburger, J. H. & Horn, C. L. (1981). *Bulletin of New York Academy of Medicine* **58**, 296–312.

Weisburger, J. H. & Horn, C. L. (1982). In *Nitrosamines and Human Cancer, Banbury Report* no. 12, pp. 523–529 [P. N. Magee, editor]. New York: Cold Spring Harbor Laboratories.

Weisburger, J. H., Horn, C. L. & Barnes, W. S. (1983). *Seminars in Oncology* **10**, 330–341.

Weisburger, J. H. & Williams, G. M. (1981). *Science* **214**, 401–407.
Wynder, E. L. & Cohen, L. A. (1982). *Nutrition and Cancer* **3**, 195–199.
Wynder, E. L., Leveille, G. A., Weisburger, J. H. & Livingstone, G. E. (1983). *Environmental Aspects of Cancer: The Role of Macro and Micro Components of Foods*. Westport, Connecticut: Food and Nutrition Press.

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