Possible Role of Nutrients in Neoplasia

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Summary

The relationship between cancer and diet is supported by epidemiological evidence suggesting that diet is a factor in the development of cancer of various organs including the esophagus, stomach, liver, and large bowel. The role of depressed immunocompetency, especially during critical periods of growth and development, is stressed as a possible important consequence of nutritional insults leading to carcinoma. Study of the relationships among nutritional factors, host-defense mechanisms, and carcinogens to carcinogenesis is significant since, theoretically, manipulation of diet could suppress or prevent chemically induced cancers. The distinction should be emphasized, however, between "nutrients," those elements of one's intake that are essential because the body is unable to synthesize them de novo, and "diet," which refers to everything that is ingested. It is the components of diet, chemicals in particular, that are most convincingly implicated as carcinogens, while it is doubtful that nutrient deficiencies or excesses have a direct causal relationship with the onset or development of cancer. Rather, nutrition probably exerts its carcinogenic effects indirectly; nutrients possibly enhance chemical carcinogenesis multifactorially by mechanisms linked to their ability to: (a) act as carriers of carcinogens or their precursors; (b) alter intestinal flora so that carcinogenic reactions are facilitated; (c) enhance levels and reactivity of cocarcinogens; (d) influence absorptive properties or morphology of tissues so that carcinogenic activity is enhanced; and/or (e) modify host-defense mechanisms that normally protect the organism.

In discussing the role of nutrition in carcinogenesis, it is necessary first to define the term nutrition. To some, nutrition has never been shown to play the slightest role in carcinogenesis or neoplasia, while others might lead one to believe that nutrition is the single most important environmental factor in the causation of almost all of the major malignant diseases, including coronary heart disease. I herewith offer my personal views, substantiated, it is hoped, with pertinent references.

To be provocative, one can begin by saying that nutrition has absolutely nothing to do with carcinogenesis. That would be sophism at its worst. To say that nutrition has a great deal to do with carcinogenesis would be equally simplistic, sophist, and terribly naive.

There are statements that can be made about nutrition and carcinogenesis and about their relationship. A few definitions are in order. Nutrition, when used in this text, refers to the 50 or 60 or more known essential nutrients such as amino acids, iron, zinc, vitamin A, riboflavin, folic acid, ascorbic acid, etc. Diet is another phenomenon. What people eat in their diet is made up of nutrients and also of additives, preservatives, coloring matter, residues, fiber, chemicals, plasticides; fungal, bacterial and viral contaminants; and perhaps hundreds of additional compounds known as "peaks" on someone's gas chromatogram that may have carcinogenic activity in animals and perhaps in man. If other internal and external factors are added to them, such as hormones, steroids, ionizing radiation, and air pollutants, one is hard pressed to know with any degree of accuracy what role nutrients play, either directly or indirectly, in carcinogenesis. Since there is little or no evidence of a direct effect of nutrient deficiencies or excesses (save calories) on the formation or promotion of cancer, it is assumed that whatever effect they exert is indirect.

I believe that the available evidence seems to suggest that a major cause of cancer, if such a factor can be identified, is a result of the ingestion or inhalation of chemicals, rather than viruses or ionizing radiation (39). With the exception of the spontaneous tumors one sees in certain strains of animals or in aged animals, the feeding of purified or semipurified, nutritionally adequate or inadequate diets has not been shown to induce neoplasia in animals unless they are also fed a procarcinogen or a carcinogen, i.e., a chemical. Nutrients or diet must exert their major effect in I or several ways: (a) as carriers of a procarcinogen or carcinogen (e.g., nitrates in meat); (b) by altering flora that act on procarcinogens to convert them to carcinogens; (c) by increasing the level of cocarcinogens such as certain fatty acids and sterols; (d) by altering tissue morphology so that it is more susceptible to the action or penetration of the carcinogen as well as the cocarcinogen (e.g., diets that increase the concentration of sterols in the intestinal lumen and that have been implicated in enhancing chemical carcinogenesis); and (e) by influencing the host-defense system or I of its components, rendering the animal and/or organ more susceptible to both the chemical carcinogen and

\(^1\) Presented at the Conference on Nutrition in the Causation of Cancer, May 19 to 22, 1975, Key Biscayne, Fla. Supported by Grants AA00213 from the National Institute of Alcohol Abuse and Alcoholism, CA16750 from the National Cancer Institute, 3057-41 from the General Research Support, Boston City Hospital, 508 from the Nutrition Foundation, Inc., and Contract HSM-42-72-195 from the National Institute of Alcohol Abuse and Alcoholism.
It seems that most experimentalists investigating the relationship between nutrition and cancer use chemical carcinogenesis as the means of studying the relationship. Certainly, the impetus for much of this research, I believe, has come from the epidemiological studies implicating diet as an important environmental factor in the pathogenesis of colon cancer as well as cancer of other organs (5, 7, 12, 51, 52, 54, 55). As Eastwood et al. have pointed out, "the epidemiologist first looks for the differences in the incidence of disease in different groups of people, and then, if the differences are large, he searches for causative factors. But such an association is not necessarily indicative of cause and effect. It may be merely fortuitous, although this is less likely the better the correlation. It may be indicative of some third independent factor affecting both disease and supposed agent, as in the non-causative association between ownership of radios and breast and bowel cancer" (13).

Burkitt suggested "that carcinogens produced by action of an abnormal bacterial flora when held for a prolonged period in a concentrated form in contact with the bowel mucosa may account for the high incidence of these diseases in economically developed countries" (7). For example, Africans have a low incidence of colonic cancer as compared with residents of industrial communities. Europeans and Americans, Burkitt contends, have a higher frequency of colonic cancer because they consume relatively small quantities of unrefined cereals, while the rural Africans ingest large quantities. The suggestion is that the high fiber content of unrefined grains promotes rapid evacuation of the fecal content and thereby affords protection against prolonged contact of the ingested procarcinogens or carcinogens with the colonic mucosa. Ackerman (1) supports this view by observing that the high incidence of colonic cancer in North Americans correlates with the substitution of refined sugar in the diet for unrefined carbohydrates. However, Glober et al. recently reported marked differences in bowel transit times in 2 populations experiencing similar colon cancer risks (15).

Scotland, Denmark, Canada, United States, New Zealand, and Ireland have the highest rates of colonic cancer, while Japan, Chile, Israel, and certain South African countries have the lowest rates. In general, the incidence parallels the proportion of meat consumed in the diet. Various studies of migratory populations provide additional circumstantial evidence that meat consumption in some manner contributes to the incidence of colonic carcinoma (54, 56). The Japanese, for example, who ingest diets principally composed of vegetables and fish, have a low incidence of colonic cancer. Japanese living in Hawaii, however, retain the low incidence of colonic carcinoma only if they adhere to original cultural dietary habits. Similarly, Japanese residing in California show a greater frequency of colonic carcinoma than in their home land when they change to "industrialized" diets. Berg2 implies that beef rather than meat per se more closely correlates with the incidence of colorectal and other cancers. Wynder et al. (54) believe that the association is linked closely with fat intake and state that the typical American diet of 45% fat results in the excretion of high quantities of fecal cholesterol and bile acids. These steroids may act as cocarcinogens. Moreover, they are found in relatively low quantities in fecal excretions of American vegetarians and Orientals, who have a low incidence of colorectal and other cancers.

Geographical variations in dietary habits have been associated with differences in the composition of the bacterial flora. Certainly, diet affects the composition of the intestinal flora, and an excellent review on this subject has been published recently (14). Hill et al., (19) postulate that the intestinal bacteria produce cocarcinogens from dietary fats or from bile steroids. For example, the fecal flora of residents of the United States and Britain is comprised of approximately 1 log greater numbers of Bacteroides sp. and 1 log less of enterococci than in residents of Uganda, South Africa, and Japan. It has also been demonstrated that the concentration of fecal steroids is greater in Western countries than in Africa and Eastern countries. Equally important, perhaps, but not as yet evaluated are quantitative changes associated with host diet and various bacterial populations in the gut, i.e., the relative numbers of a given population that possess the necessary degradatory enzymes to effect conversion of procarcinogens to carcinogens or to increase the production of cocarcinogens from endogenously produced substances, such as certain fatty acids and sterols (6, 14, 19, 23, 32-34).

There seems to be little question about the importance of bacterial flora in the induction of chemical carcinogenesis since, in its absence, adenomas are produced rather than adenocarcinomas (32). In addition, chemical carcinogens in the germ-free animal, while not producing cancer of the colon, have been shown to produce cancer in other organs. However, germ-free animals are morphologically, physiologically, and, most importantly, immunologically ill-equipped to survive in a normal environment when compared to conventional animals.

Thus, it seems quite clear that diet and bacterial flora are somehow involved in the pathogenesis of cancer of the colon and perhaps of cancer in other sites. What is not clear is the role of specific nutrients in this relationship and the mechanisms by which they exert their effect. From both experimental and clinical observations it appears to me that a possibly fruitful route of investigation would be to look at the effect of various nutritional deficiencies or excesses on the immune system and chemical carcinogenesis. Chart 1 is an attempt to illustrate the relationships between a number of factors related to chemical carcinogens: (a) procarcinogens and their conversion to carcinogens; (b) the probable effect of the carcinogen on the normal cell and the latter’s transformation to a precancerous cell; (c) the role of the host-defense system in preventing the development of cancer; and (d) the role that nutrition might play in altering both host-defense and bacterial flora that results in cancer.

Most investigators would agree that all of us are probably harboring “cancer” cells but that their proliferation

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and subsequent development into clinical carcinoma are held in check either by the cells being "killed" or arrested within their development by a competent immune or host-defense system. It is possible that chemical carcinogens or other carcinogens transform cells, and these in turn are killed or arrested by immune or defense mechanisms. Nutritional deficiencies, not of the order that result in any gross morbidity but of sufficient magnitude to affect the immune system or 1 of its components adversely, might be expected to favor carcinogenesis and, indeed, this has been demonstrated and/or suggested (16, 25, 27, 29, 36–38, 44, 47).

Observations from human studies strongly suggest that loss of function or defects in cell-mediated immunity are associated with carcinogenesis (e.g., use of immunosuppressive agents and the increased incidence of neoplasia) and that spontaneous remission of many tumors is associated with the return of normal cell-mediated immune function (43). The observation by some that immunosuppression correlates better with myeloproliferative diseases than with other types of neoplasia does not negate the strong circumstantial evidence, both clinically and experimentally derived, that the immune system plays some role in the pathogenesis of carcinoma. Animal experiment studies support the observation that loss of cell-mediated immunity is associated with tumorogenesis. Underfeeding rats (low calorie intake with all of the known essential nutrients added, not to be confused with diets deficient in 1 or more essential nutrients), from weaning until but not after maturity, results in a smaller but healthy, normal adult animal, a 35% increase in longevity, a slower rate in the maturity in cell-mediated immunity, a slower fall-off in immune competency, and a delay in the onset of spontaneous tumors (57). Several specific essential nutrient deficiencies have been shown to enhance experimental chemical carcinogenesis. These include deficiencies of vitamin A, methionine, choline, folic acid (or use of folic acid antagonists), vitamin C, and protein (16, 25–27, 29, 36–38, 47). All of these specific deficiencies that have been shown to enhance chemical carcinogenesis have also been shown to alter adversely immune competency and/or the morphology of various tissues and, perhaps, the gut flora (4, 6, 11, 36).

Conversely, the addition of chemical procarcinogens to the diet of animals has been shown adversely to affect the metabolism of essential nutrients, including folic acid (31). Poirier and Whitehead (31) demonstrated that the administration of diethylnitrosamine to rats resulted in folate deficiency that could only be mitigated by the administration of high dietary levels of the methyl donors, methionine, betaine, and choline. High dietary levels of folate and vitamin B₁₂, either alone or in combination, had no significant effect on the elevated formiminoglutamic acid secretion, pathognomonic of folic acid deficiency caused by diethylnitrosamine.

This observation by Poirier and Whitehead may have some special significance to our own studies with the Buffalo rat. The Buffalo rat is peculiar in its response to dimethylhydrazine, a chemical carcinogen, in that it develops only colonic cancer. It has other differences that relate to immunocompetence and carcinogenesis and these are: (a) it develops autoimmune disease spontaneously (42); (b) its thymocytes and T-cells are highly sensitive to mitogen in contrast to other strains of rats (45); (c) it is extremely sensitive to diets that are low but not deficient in lipotropes, and it develops renal and liver changes associated with severe lipotrope deficiency including cirrhosis and hepatitis (20), (d) it has a pronounced defect in methyltransferase enzymes and cannot transfer methyl groups sufficiently (20, 48); and, (e) it develops pronounced defects in cell-mediated immune function under conditions of mild iron deficiency, as evidenced by a decreased response of its lymphocytes to concanavalin A and its delay in the rejection of allogeneic skin grafts (preliminary results from this laboratory).

The manner in which nutritional deficiencies enhance chemical carcinogenesis may be multifaceted. It is possible that the effects of the various nutritional deficiencies that have been studied are mediated not only through their action on the host-defense systems but on the integrity of the organ or tissue affected by the chemical carcinogen. For example, vitamin A deficiency has been shown to enhance chemical carcinogenesis, and it is known to produce metaplasia (11) and to depress cell-mediated immunity. Indeed, the administration of vitamin A has been shown to mitigate the effect of an immunosuppressive agent (corticosteroid) (10) and enhance cell-mediated immunity with an associated remission of tumors (9, 25). Conversely, deficiencies of some nutrients may be beneficial. Parsons et al. reported the regression of malignant tumors with magnesium and potassium deficiencies induced by hemodialysis (30). The role of nutritional deficiencies or excesses (including calories) in the treatment of cancer or in tumor-bearing animals is another exciting subject. Nonetheless, the literature on the nutritional therapeutic aspects of cancer is probably more uncertain than that dealing with the role of nutrition as a causative factor in carcinogenesis.

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[31 Second National Carcinogenesis Conference. San Antonio, Texas, National Cancer Institute, 1973.](#)
A review of the literature dealing with the association between nutritional status and immune competency is pertinent to our discussion. Although the data are not conclusive, an association has been established between malnutrition and the increased susceptibility of an organism to infectious agents. However, it is a medical fact that an infectious disease in malnourished individuals does run a more serious course (40). Early fetal or neonatal malnutrition has been shown adversely to affect other organ systems, including subsequent brain size and brain cell number as well as general growth (53). In addition, studies on maternal or fetal malnutrition suggest that nutritional insults in utero or during the neonatal period have long-lasting effects extending into adulthood (3, 4, 28, 53, 57). A greater susceptibility to infectious disease as well as to neoplasia has been witnessed in patients with congenital or acquired immunodeficient diseases (40, 42). It may be that at least part of the accepted phenomena of individual variations in response to infectious agents, oncogenic viruses (e.g., Burkitt’s lymphoma), or procarcinogens can be attributed not only to genetic influences but also to nutritional deficiencies or nutritional excesses in early life.

A variety of studies has been undertaken to explain the role that iron plays in immune responses, and a relationship has been found to exist. Baggs and Miller (3, 4) conducted studies in which rats were fed iron-deficient diets only in the gestational and neonatal periods and immediately repleted after those stages. Hence, the animals were overtly indistinguishable from control animals fed adequate diets who were never anemic or iron deficient. Two months later, all the animals were challenged with Salmonella typhimurium, and only those who had been iron deficient in early life developed the more severe signs and symptoms of infection, including high morbidity and mortality rates. The authors attributed the observation to: (a) decreased myeloperoxidase activity, an iron-containing enzyme found in macrophages and required in optimal amounts for the killing of engulfed bacteria by polymorphonuclear leukocytes and macrophages, and (b) decreased numbers of polymorphonuclear leukocytes and macrophages. These observations would suggest that early neonatal malnutrition notwithstanding, subsequent repletion has long-lasting effects reaching into adulthood. They also suggest that iron deficiency plays some role in the synthesis of macrophages or perhaps in the differentiation of stem cells into macrophages. Iron deficiency has been shown to effect folate utilization, and thus the observations by Baggs and Miller may be due to secondary adverse changes induced in the metabolism of folic acid (49, 50).

Experiments with patients with chronic mucocutaneous candidiasis, a fungal disease, have indicated that their abnormal immunological status can be linked to disturbances in their iron metabolism (18). Joynson et al. (21) have shown that iron deficiency depresses the incorporation of [3H]thymidine into DNA of human proliferating lymphocytes. In other studies utilizing HeLa cells, it was noted that, during mitosis, iron present in the nucleolus is normally transferred to the chromosomes, but when the iron-chelating agent, deferoxamine, is introduced to the culture of the living cells, DNA synthesis is inhibited (35). It has been verified that the same defect in normal synthesis is found in patients with iron deficiency anemia (17). In our own earlier studies with protein-calorie-deficient children, we demonstrated that host-defense systems were affected not by the status of iron nutriture at any given moment but rather by shifts in iron metabolism (2, 24).

The mere presence of iron deficiency does not seem to affect the bactericidal rates by polymorphonuclear leukocytes or myeloperoxidase activity of malnourished children. However, when the subjects begin to eat, grow, and synthesize hemoglobin (when they begin to utilize iron), their bactericidal rates are adversely affected; each child’s ability to develop a positive delayed hypersensitivity reaction is depressed (2, 8). Also noteworthy is the observation that the major infection occurring in protein-calorie- and iron-deficient subjects is candidiasis.

Pertinent to this discussion of iron metabolism and host defense mechanisms is the review by Weinberg (51). Clearly, the extent to which an infectious agent results in “illness” may be the outcome of competition between the host and the infectious agent for available iron as well as other nutrients. The nutritional status of the individual can alter this competition between host and agent. For example, in vitamin C deficiency or in subclinical scurvy, there is a defect in the transport of iron from the reticuloendothelial cells into the parenchymal cells, with a concomitant increased susceptibility to infectious agents (22).

Turning to available data on protein deprivation and immune competency, studies do exist that demonstrate that protein-calorie malnutrition in children and in adults produces defects in cell-mediated immunity (8, 47). Interestingly, protein deficiency does not appear to affect bactericidal rates by polymorphonuclear leukocytes or, according to some, humoral immunity. Polymorphonuclear leukocytes isolated from protein-deficient rats or from children with kwashiorkor were normal with respect to their ability to engulf and kill bacteria (47). It has been found that animals or children with protein-calorie malnutrition have normal or elevated levels of immunoglobulins (47). However, there are reports that suggest that the response of malnourished subjects to antigenic stimulation measured by antibody production may be normal or abnormal (41, 47). However, more comprehensive studies are essential for the clarification of the role protein nutriture plays in humoral immune competence.

Although protein-calorie malnutrition in adults and children has been shown to produce defects in cell-mediated immunity, the effect of protein nutriture on cell-mediated immunity or on humoral immunity is quite difficult to ascertain from clinical material. Children or adults with protein deficiency present with a host of problems, including infections, decreased transferrin levels, and numerous other complications that conceivably profoundly affect immune competency. Protein deficiency produces hypoplasia (inhibition of all proliferating mechanisms) and the concomitant decreased utilization of all essential nutrients. Consequently, it is a complex matter to attempt to delineate the precise role that protein-calorie deficiency and its accom-
panying abnormal physiological states may play in the host's response to any infectious agent.

Various other nutritional deficiencies, including pyridoxine, biotin, iron, folate, vitamin A, vitamin C, and pantothenic acid, have been defined as factors resulting in decreased immunocompetence in experimental animals (41, 47). Thus these various observations linking diet to intestinal flora, diet or nutrients to immunocompetence, and immunocompetence to neoplasia suggest that nutritional status, perhaps as early as pregnancy and neonatal life, may have profound effects not only on subsequent growth and development but also on the response of infectious agents, including oncogenic agents and chemical carcinogens.

It would be fallacious to argue that malnutrition or a nutritional deficiency has nothing to do with the development of cancer, on the basis that cancer has a low prevalence or low incidence in areas of the world where malnutrition or nutritional deficiencies are quite prevalent. The fact is that such people in less developed countries die from other causes, and many do not reach the age at which some cancers develop. Moreover, in countries where iron deficiency is prevalent, the incidence of gastric cancer is 4 to 5 times that of the United States. Associated with gastric cancer is intestinalization of the stomach, achlorhydria, and achylia (46), conditions in which substantial bacterial colonization of the stomach and proximal small bowel occurs. It is quite possible that bacterial overgrowth seen in these patients may act on ingested procarcinogens in the proximal end of the gastrointestinal tract and play a role in the pathogenesis of cancer in the upper gastrointestinal tract rather than in the colon.

In summary, a review has been made of the current epidemiological and geographical evidence implicating diet and the microbial flora in the development of chemically induced cancer. While carcinoma must be multifactorial, the implication of many studies is that it may be preventable to a large degree by manipulation of diet, environment, or microbial flora. In any event, the statistical evidence underscores the need for a systematic approach in animal models toward understanding the role the specific nutrients in the diet play in the development of cancer and whether these effects are mitigated by, or merely reflected in, alterations in the host gut microbial flora and/or the changes in immune competency or tissue integrity.

Acknowledgments

The author wishes to express his appreciation to his working colleagues, Dr. Selwyn A. Broitman and Dr. Leonard S. Gottlieb, for their assistance and advice in the preparation of this manuscript and to Geraldine Rankin and Heidi VanArsdell for their editorial assistance.

References

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